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Bioadhesive Microspheres As A Controlled Drug Delivery System : A Review

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ABSTRACT

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes etc. which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate drug delivery system by virtue of their small size and efficient carrier characteristics. However, the success of these novel drug delivery system is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. It can be achieved by coupling bioadhesion characteristics to microspheres and developing novel delivery systems referred to as "bioadhesive microspheres". This article contains the bioadhesive microspheres which have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. This presents study includes the spectrum of potential applications of bioadhesive microspheres in controlled drug delivery ranging from the small molecules, to peptides, and to the macromolecular drugs such as proteins, oligonucleotides and even DNA. Some research work on bioadhesive microspheres and microcapsules. Various patents related to bioadhesive microsphere and developments in the techniques for in vitro and in vivo evaluation of bioadhesive microspheres have also been discussed. From this study concluded that the bioadhesive microsphere can be efficiently used as controlled or targeted drug delivery.

Keywords: Bioadhesive Microspheres; Controlled release drug delivery; Site Specific Bioadhesive Polymer, Application.

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INTRODUCTION

“Adhesion” can be defined as the bond produced by the contact between a pressure sensitive adhesive and a surface. “Bioadhesion” can be defined as attachment of a drug carrier to a biological location for extended period of time. The biological surface can be epithelial tissue. If adhesive attachment is to a mucous coat the phenomenon is referred as “Mucoadhesion”.

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder. Bioadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration, and hence can be used for targeting a drug to a particular region of the body for extended periods of time.

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. The last two decades in the pharmaceutical industry have witnessed an avant-garde interaction among the fields of polymer and material science, resulting in the development of novel drug delivery systems. Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Microspheres are one of the novel drug delivery system which posses several applications and are made up of assorted polymers. Microspheres are small spherical particles (typically 1 μm to 1000 μm), sometimes referred to as microparticles.

Generally microspheres posses’ potentiality to be employed for targeted and controlled/extended release of drug, but incorporating bioadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs. Bioadhesive microspheres enhance the intimate contact with the mucus layer, and drug targeting to the absorption site by anchoring bacterial adhesions , plant lectins, antibodies etc.

The present study include the potential of bioadhesive microspheres in controlled release systems, drug targeting and their administration through various routes. Other applications such as mucosal immunization and delivery of macromolecules, e.g. protein drugs as well as DNA, have been highlighted. A brief review of various polymers, microencapsulation techniques and recent developments in methods to evaluate bioadhesive microspheres is also included.

Advantages of Bioadhesive Microspheres⁶

1. Provide constant and longer therapeutic effect.
2. Reduces the frequency of daily administration and thereby improve the patient compliance.

3. Improve the absorption of drug hence improve the bioavailability of drug and reduce the chances of adverse effects.
4. The morphology of microspheres permits a controllable variability in degradation and drug release.

Disadvantages of Bioadhesive Microspheres ⁶

1. The release from the formulations may get modified.
2. The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.
3. Differences in the release rate can be found from one dose to another.
4. Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.
5. These kinds of dosage forms cannot be crushed or chewed.

MECHANISM OF BIOADHESION ^{3,6,7,8}

however most research has described bioadhesive bond formation as a three step process .

Step 1

The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. Swelling of polymers occur because the components within the polymers have an affinity for water.

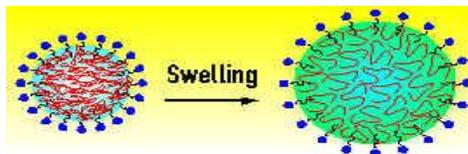
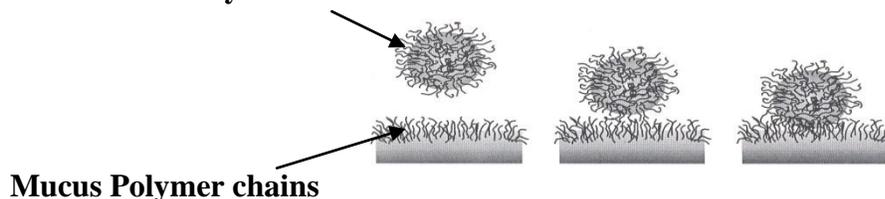


Figure 1 : The wetting and swelling step

Step 2

The surfaces of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In step 2 of the bioadhesive bond formation, the bioadhesive polymer chains and the mucosal polymer chains intermingle and entangle to form semi permeable adhesive bonds. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

Bioadhesive Polymer chains



Mucus Polymer chains

Figure 2 : Bioadhesive Bond Formation

Step 3

This step involves the formation of weak chemical bonds between the entangled polymer chains. The types of bonding formed between the chains include primary bonds such as covalent- bonds and weaker secondary interactions such as Van der Waals Interactions and hydrogen bonds.

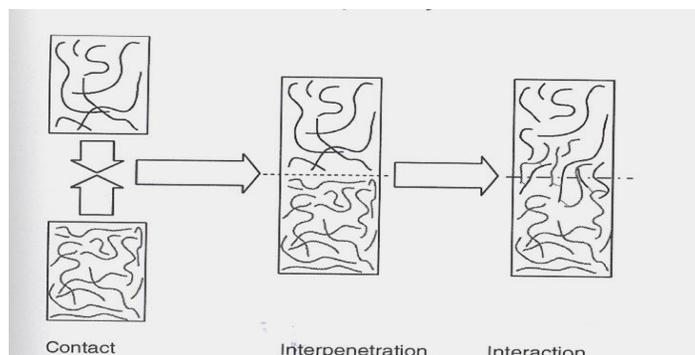


Figure 3 : Formation of weak chemical bonds

THEORIES OF BIOADHESION^{5,6,9,10}

a) Electronic theory:

According to this theory, an electronic transition occurs upon contact of adhering surfaces and due to differences in their electronic structure. This is proposed to result in the formulation of an electrical double layer at the interface with subsequent adhesion due to attractive forces.

b) Wetting theory:

This theory is predominantly applicable to liquid. It analyses adhesive and contact behaviour in terms of the ability of liquid or paste to spread over biological system. It postulates that the lower the contact angle of liquid on substrate surface there will be greater affinity for adhesion.

c) Adsorption theory:

According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces. Two types of chemical bonds can be distinguished:

I. Primary chemical bonds of covalent nature which are undesirable in Bioadhesion because their high strength may result in permanent bond.

II. Secondary chemical bonds having many different forces of attraction, including electrostatic force, van der Waals forces, hydrogen and hydrophobic bonds.

d) Mechanical theory:

According to this theory, adhesion arises from an interlocking of a liquid adhesive into irregularities on a rough surface. However, rough surfaces provide an increased 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.

e) Diffusion theory:

According to this theory, polymer chains and the mucus mix to a sufficient depth to form a semi-permanent bond. The depth of interpenetration depends on the diffusion coefficient and time of contact. This diffusion coefficient depends on the molecular weight between cross-links and decreases significantly as the cross linking density decreases.

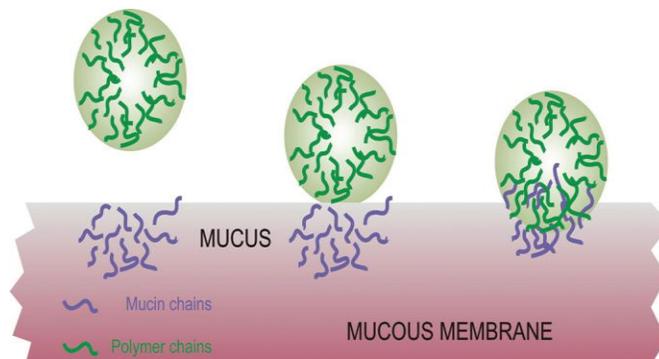


Figure 4: Secondary interactions resulting from inter diffusion of polymer chains of bioadhesive device and of mucus

f) Fracture theory:

This is the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum Tensile stress.

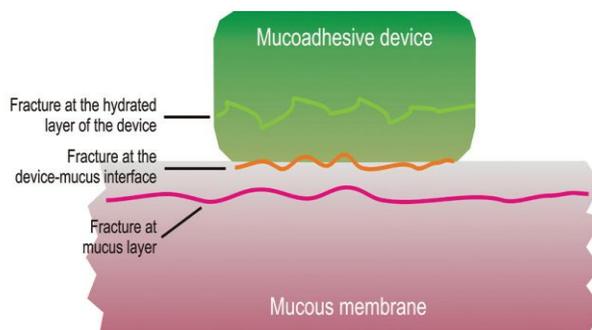


Figure 5: Regions where the Bioadhesive bond rupture can occur.

FACTORS AFFECTING BIOADHESION:^{11- 14}

1) Polymer-Related Factors

a) Molecular Weight:

Bioadhesive polymer at issue at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be a good bioadhesive,
- Entanglement is important for higher molecular weight polymers.

b) Concentration of active polymers:

There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In highly concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

c) Flexibility of polymer chains:

It is critical for interpenetration and entanglement. As water-soluble polymers become cross linked, mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

d) Spatial conformation:

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.

2) Environment Related Factors

a) Applied strength:

To place a solid bioadhesive system, it is necessary to apply a defined strength, the adhesion strength increases with the applied strength or with the duration of its application, upto an optimum the pressure initially applied to the bioadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become bioadhesive even though they do not have attractive interaction with mucin.

b) pH:

It can influence the formal charge on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a decrease as alkalinity and ionic strength increases.

c) Initial Contact Time:

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases.

d) Swelling:

It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.

3) Physiological Variables

a) Mucin Turnover:

the mucin turnover is expected to limit the residence time of the Bioadhesive on the mucus layer. No matter, how high the adhesive strength, Bioadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules.. Mucin turnover may depend on other factors such as presence of food.

b) Disease State:

The physiochemical properties of mucus are known to Change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections.

BIOADHESIVE MICROSPHERES^{5,11}

Bioadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1–1000 μm in diameter and consisting either entirely of a bioadhesive polymer or having an outer coating of it, respectively.

Advantages

- efficient absorption
- 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 drugs to the absorption site achieved by anchoring plant lectins, bacterial adhesins and antibodies, etc. on the surface of the microspheres.
- The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion.
- Drug is protected from degradation in the acidic environment in the GIT.
- compared with the tablets uncomfortable sensation of a foreign object within the oral or nasal cavity is reduced.

Polymers used for Bioadhesive Microspheres

Ideal Bioadhesive Polymer Characteristics :^(15,19,20)

1. The polymer and its degradation products should be nontoxic and nonabsorbable.
2. It should be nonirritant.
3. It should preferably form a strong noncovalent bond with the mucus or epithelial cell surface.
4. It should adhere quickly to moist tissue and possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains competitive.
8. Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
9. polymer must have a high molecular weight upto 100.00 or more this is necessary to promote the adhesiveness between the polymer and mucus
10. polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.
11. Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
12. Concentration of the polymer- an optimum concentration is required to promote the bioadhesive strength.

CLASSIFICATION OF POLYMERS ^{11,12,16,17,18}

A)Based on Origin

1) Synthetic Polymers

Cellulose derivatives (methylcellulose, ethylcellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose, Poly (acrylic acid) ,polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

2) Natural polymers,

Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan.

Table1: Bioadhesive Polymers And Their Bioadhesive Property ⁽¹³⁾

Polymer	Bioadhesive Property
CMC Sodium	+++
Carbopol 934	+++

Polycarbophil	+++
Tragacanth	+++
Poly(acrylic acid/divinyl benzene)	+++
Hydroxy Ethyl Cellulose	+++
HPMC	+++
Gum Karaya	++
Gelatin	++
Guar Gum	++
Thermally Modified Starch	+
Pectin	+
PVP	+
Acacia	+

Excellent = + + +, *Fair* = + +, *Poor* = +

B) Based on Nature

1) Hydrophilic polymers:

These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution possess excellent bioadhesive properties. These are

- PVP(poly vinyl pyrrolidine),MC(methyl cellulose),Hydroxyl propyl cellulose

2)Thermoplastic polymers:

These polymers include the non-erodible neutral polystyrene and the semi crystalline bioerodible polymers, which generate the carboxylic acid groups as they degrade,

- polyanhydrides and polylactic acid,polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters, halides, polymethacrylic acid, polymethyl methacrylic acid,methylcellulose,ethyl cellulose, hydroxypropyl cellulose,hydroxypropyl methylcellulose,

Various biocompatible polymers used in bioadhesive formulations include

- cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate and esters of hyaluronic acid.

Various biodegradable polymers used in bioadhesive formulations are

- poly (lactides), poly(glycolides), poly (lactide-co-glycolides), polycaprolactones, and polyalkyl cyanoacrylates,Polyorthoesters, polyphosphoesters, polyanhydrides, polyphosphazenes are the recent additions to the polymers.

3) Hydrogels polymers:

These are water swellable materials, usually a cross-link polymer with limited swelling capacity,

- poly (acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate,
- guar gum, modified guar gum, etc.

SPECIFIC SITE DIRECTED BIOADHESIVES —*THE NEW GENERATION***Table 2 Specific ligands corresponding to the glycosyl groups on cell membranes, which can be used for targeting the bioadhesive microspheres to a specific site**

S. no.	Glycosyl groups on cell membranes	Specific ligands	Specific site
1	Mannose	<i>Galanthus nivalis</i> agglutinin (GNA)	Epithelial cells in stomach, caecum, and colon
2	<i>N</i> -Acetyl glucosamine	Wheat germ agglutinin (WGA) or tomato lectin (LEA)	Epithelial cells in stomach, caecum, colon and absorptive enterocytes in small intestine Strong binding to M cells
3	<i>N</i> -Acetyl galactosamine	Lectin ML-1 from <i>Viscum album</i>	Endocytosed by villus enterocytes and goblet cells Strong binding to epithelial cells in small intestine
4	Phytohaemagglutinin	<i>Phaseolus vulgaris</i> isoagglutinin	Surface cells of the stomach
5	Fucose	<i>Aleuria aurentia</i> agglutinin (AAA)	Specific binding and transcytosis by M cells

1). Lectins

Lectins can be defined as proteins of non-immune origin that bind to carbohydrates specifically and non covalently. According to the molecular structure, three groups of lectins distinguished :

1. Merolectins: lectins having only one carbohydrate recognising domain;
2. Hololectins: lectins with two or more carbohydrate recognising domains;
3. Chimerolectins: lectins with additional unrelated domains.

2) Bacterial adhesions

Bacteria are able to adhere to epithelial surfaces of the enterocytes with the aid of fimbriae. Fimbriae are long, lectin like proteins found on the surface of many bacterial strains. Their presence has been correlated with pathogenicity, e.g. adherence of *Escherichia coli* to the brush border of epithelial cells mediated by K99 fimbriae is a prerequisite for subsequent production and cellular uptake of *E. coli* enterotoxin. Thus, the DDS based on bacterial adhesion factors could be an efficient mechanism to increase adhesion of bioadhesive microspheres to epithelial surfaces.

3) Amino acid sequences

Certain amino acid sequences have complementary parts on the cell and mucosal surfaces and when attached to microparticles can promote binding to specific cell surface glycoproteins. The cell surface glycoproteins are altered in the presence of disease conditions and these altered protein sequences can be targeted by complementary amino acid sequences attached to the drug

delivery device.

4) Antibodies

Antibodies can be produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibody can be a rational choice as a polymeric ligand for designing site-specific bioadhesives. This approach can be useful for targeting drugs to tumor tissues

Preparation of Bioadhesive Microspheres^{5,11}

Bioadhesive microspheres can be prepared using any of the following techniques.

Table 3 Comparison of the various processes used for the preparation of bioadhesive microspheres

Process used	Particle size (µm)	Polymers	Comments
Solvent evaporation	1–100	Relatively stable polymers, e.g. polyesters, polystyrene	Labile polymers may degrade due to the presence of water
Hot-melt microencapsulation	1–1000	Water labile polymers, e.g. polyanhydrides, polyesters; with a MW of 1000–50000	Smooth and dense external surfaces of the microspheres
Solvent removal	1–300	High melting point polymers especially polyanhydrides	Avoids use of water, only organic solvents are used
Spray drying	1–10	–	Primarily for microspheres used for intestinal imaging
Ionic gelation and size extrusion	1–300	Chitosan, CMC, alginate	Used for encapsulation of live cells

EVALUATION OF THE BIOADHESIVE MICROSPHERES^{5, 6, 7, 9, 11, 18, 21}

Various *in vivo*, *ex vivo* method for evaluating the Bioadhesive microspheres.

1. Measurement of adhesive strength (*in vitro* techniques)

Bioadhesive strength of microspheres can be evaluated and indicated by quantifying Bioadhesive forces between the polymeric microspheres and the mucosal tissue. Several *in vitro* techniques had been used to test the effectiveness of polymeric microspheres against a variety of synthetic and natural mucus, frozen and freshly excised tissue, etc. Important *in vitro* adhesive strength determination methods were as follows.

a. Falling liquid film method:

It was a simple, quantitative *in situ* method, involves flowing down the suspension of microspheres. on the intestinal strip (obtained by cutting the excised intestinal segment, lengthwise) that was spread on a plastic flute, and kept at an inclined position. Particle concentrations entering the intestinal segment and leaving the segment, determined suitably

(mostly with coulter counter), to quantify the steady state fraction of microspheres. adhered to the intestinal mucosa; and reported in percent, as an index of bioadhesion .

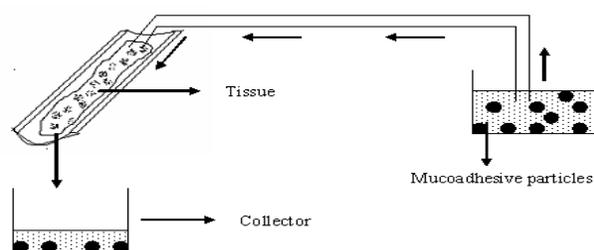


Figure 6: Schematic representation of *in vitro* model of Falling liquid film method.

b. Novel electromagnetic force transducer:

The electromagnetic force transducer measures tissue adhesive forces by monitoring the magnetic force required to detach a magnetic loaded polymer microspheres from a tissue sample. The microspheres firstly attached to the sample of tissue; then the magnetic force generated by an electromagnet mounted on the microscope vertically above the tissue chamber. The position of microspheres was determined by computer, and then the tissue chamber was slowly moved down, away from the magnet tip. The slow descending movement of the tissue away from the magnet was continuously video analyzed to calculate the position of microspheres until the latter was completely pulled free of the tissue. making it suitable to perform accurate bioadhesive measurements on the small microspheres. Evaluation of the bioadhesion of polymers to specific cell types can be done with this technique.

c. Tensile stress measurement by Wilhelmy plate technique:

Modified CAHN dynamic contact angle analyzer is used to perform adhesive micro force measurements. The bioadhesive force between the mucosal tissue and a single microspheres mounted on a small diameter metal wire suspended from the sample loop in microtensiometer was measured by the instrument . The tissue was mounted within the tissue chamber containing Dulbecco's phosphate buffered saline containing 100 mg/dl glucose, maintained at the physiologic temperature. Contact of the tissue with the suspended microspheres was achieved by raising the chamber that was rested on a mobile platform. The contact was held for 7 min, subsequently the mobile stage was lowered, and the resulting force of adhesion was recorded as a plot of the load on microspheres versus mobile stage distance or deformation. The plot displays both the compressive and the tensile portions of the experiment. Using CAHN software system, three essential bioadhesive parameters; the fracture strength, the deformation to failure, and the work of adhesion; can be analyzed.

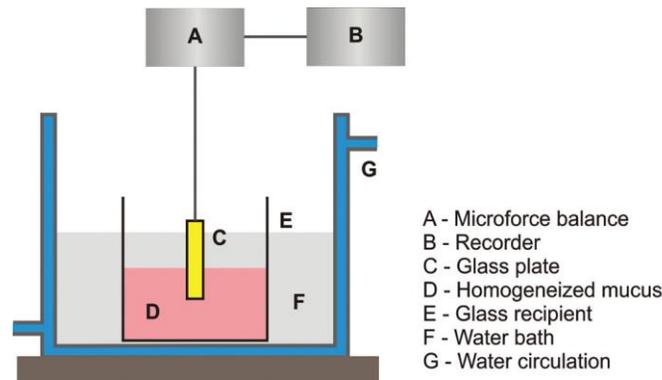


Figure 7 –Apparatus to determine bioadhesion *in vitro*, using Wilhemy's technique.

d. Everted sac technique:

It is a passive test of bioadhesion; and carried out using a section of intestinal tissue excised from the rat that should everted and ligated at the ends followed by filling with saline. The sac is then introduced into a tube containing known amount of microspheres in saline, and incubated for 30 min with occasional agitation. microspheres contained in the tube washed and lyophilized, after removing the sac, and the percent binding to the sac calculated from difference in the weight of the residual microspheres from that of initial .This technique does not utilize any external force.

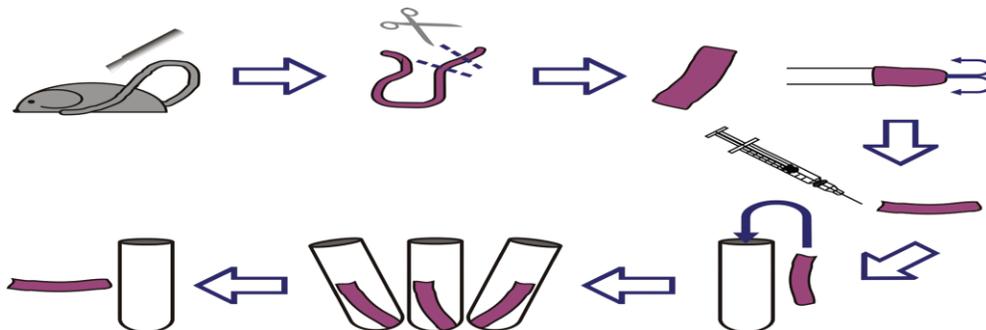


Figure 8 – Everted gut sac procedure.

e. Adhesion number:

Adhesion number was determined as the ratio of the number of microspheres attached to the substrate with respect to the total number of applied microspheres. and was expressed in percent. An increase in the adhesion number indicates increase in adhesion strength .

2. Measurement of adhesive strength (*in vivo* techniques)

a. Measurement of the residence time:

Quantification of bioadhesive properties of microspheres achieved by measuring their residence time at application site and examined using radioisotopes and fluorescent labeling techniques.

b. Gamma scintigraphy technique:

This technique can enumerate the distribution and retention time of the intra-vaginal bioadhesive

microspheres. Combination of sheep model and gamma scintigraphy method had been proved to be an extremely useful tool for evaluating the distribution, the spreading, and the clearance of vaginally administered bioadhesive drug delivery system .

3.Swelling index

Swelling index enumerates the ability of the bioadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption. From the size of dried microspheres ($D0$) and those after incubation (DT), in suitable fluid for stipulated period of time, the percent swelling value can be determined using following equation.

$$\text{Percent swelling} = [DT - D0] / D0 \times 100$$

4.Particle size and size distribution, and flow property study

Particle size and size distribution study was done by photon correlation spectroscopy with the dispersions of microspheres in suitable non-solvent system. bioadhesive microspheres Flow property of the bioadhesive microspheres was determined from the result of study parameters namely Angle of repose, Carr's index, and Hausner ratio.

5. Surface characterization of the bioadhesive microspheres

The scanning electron microscopy, the electron microscopy, and the scanning tunneling microscopy data provides insight to the surface morphology of microspheres.

6. In *vitro* release study

Standard IP/BP/USP dissolution apparatus had been used to study *in vitro* release profile in the dissolution media similar to fluid present at the absorption site, using rotating basket or paddle.

7) Recent Bioadhesion test

Recently Bioadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer-mucin interaction is measured by an optical phenomenon called Surface Plasmon Resonance (SPR), which measures the change in the refractive index when mucin binds on the polymer surface.

RESEARCH WORK ON BIOADHESIVE MICROSPHERES

Table 4: Research Work on Bioadhesive Microspheres and Microcapsules^{16,23}

Drug	Route of Administration	Bioadhesive Polymers use	Comments/results	Ref.
Acyclovir	Ocular	Chitosan	Slow release rate increased AUC	(24)
Methyl prednisolone	Ocular	Hyaluronic acid	Slow release rates sustained drug concentration in tear fluids.	(25)

Gentamicin	Nasal	DSM+LPC	Increased nasal absorption	(26)
Insulin	Nasal	DSM+LPC	Efficient delivery of insulin into the systemic circulation via nasal route	(26)
Human growth hormone (hGH)	Nasal	DSM+LPC	Rapid and increased absorption	(27)
Desmopressin	Nasal	Starch	Addition of LPC causes a five folds increase in Cmax	(28)
Haemagglutinin (HA) obtained from influenza A virus	Nasal	HYAFF	With mucosal adjuvant serum IgG antibody response as compared to i.m. immunization	(29)
Furosemide	GI	AD-MMS (PGEFs)	Increased bioavailability Higher AUC effective absorption from the absorption window	(30)
Amoxicillin	GI	Ethyl cellulose-Carbopol-934P	Greater anti H. pylori activity	(31)
Delapril HCL	GI	AD-MMS (PGEFs)	MRT of drug is increased	(32)
Glipizide	GI	Chitosan	Prolonged blood glucose reduction	(33)
Glipizide	GI	Chitosan-alginate	Prolonged blood glucose reduction	(34)
Vancomycin	Colonic	PGEF coated with Eudragit S 100	Well absorbed even without absorption enhancers	(35)
Insulin	Colonic	PGEF coated with Eudragit S 100	Absorbed only in the presence of absorption enhancers, e.g. EDTA salts	(35)
Nerve growth factor (nGF)	Vaginal	HYAFF	Increased absorption from HYAFF microspheres as compared to aqueous solution of the drugs	(36)
Insulin	Vaginal	HYAFF	Increased absorption for HYAFF microspheres, compared to aqueous solution of the drugs	(37)
Salmon calcitonin	Vaginal	HYAFF	Increased absorption from HYAFF microsphere, compared to aqueous solution of the drugs	(38)
Pipedimic acid	Vesical	CMC as muco polysaccharide +Eudragit RL as matrix polymer	-	(39)

CMC: Carboxy methyl cellulose; DSM: Degradable starch microspheres;

EDTA: Ethylenediaminetetraacetic acid; GI: Gastrointestinal; HYAFF: Hyaluronic acid esters;

IgG: Immunoglobulin G; LPC: Lysophosphatidylcholine; PGEF's: Polyglycerol esters of fatty acids, PMMA: Polymethyl methacrylate

Patens Related To Bioadhesive Microspheres

Table 5: Patens Related To Bioadhesive Microspheres

Patent number	Assignee/inventor	Year of grant of patent	Title
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US7985430	Izun Pharmaceuticals Corporation	Jul, 2011	Solid mucoadhesive composition
US20100226855	Vaunnex, Inc.	Aug, 2009	Rate-controlled bioadhesive oral dosage formulations
US20090011019	Lupin Ltd	Jan, 2009	Pharmaceutical compositions for gastro-intestinal drug delivery
US20090232898	Orexo AB	Dec, 2007	New pharmaceutical compositions useful in the treatment of migraine
EP1784167 A2	Spherics, Inc	May, 2007	Multi-layer tablets and bioadhesive dosage forms
EP1133269 B1	Durect Corporation	Feb, 2007	Controlled release system for delivering therapeutic agents into the inner ear.
EP1569620 A1	Spherics, Inc.	Sept, 2005	Nanoparticulate bioactive agents
EP0671906 B1	Brown University Research Foundation	Jun, 2005	Bioadhesive microspheres and their use as drug delivery and imaging systems
EP 0671906A1	Brown University Research Foundation	March, 2005	Bioadhesive drug delivery systems comprising poly(fumaric-co-sebacic acid)
EP1328257 A4	Salvona L.L.C.	Oct, 2004	Biodegradable bioadhesive controlled release system of nano-particles
US 6207197	West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited	July, 2004	Gastroretentive controlled release microspheres for improved drug delivery system
US 20030152629	Salvona L.L.C.	July, 2003	Multicomponent biodegradable bioadhesive controlled release system
US 6368586	Brown University Research Foundation	April 2002	Methods and compositions for enhancing bioadhesive properties of polymers
WO 0203955	Roversi Francesco, Cilurzo Francesco	January 2002	Fast release bioadhesive microspheres for the sublingual administration of Proximate principles
US 6274175	Immunex Corporation	August 2001	Prolonged release of GM-CSF
US 6197346	Brown University Research Foundation	March 2001	Bioadhesive microspheres and their use as drug delivery and imaging system
US 6207197	West Pharmaceutical Services Drug Delivery and Clinical Research Centre	March 2001	Gastroretentive controlled release microspheres for improved drug delivery
CA 2060176	West Pharmaceutical Services Drug Delivery and Clinical Research Centre	January 2001	Small particle drug compositions
US 6123965	Brown University Research Foundation	September 2000	Methods and compositions for enhancing bioadhesive properties of

US 6156348	Brown University Research Foundation	December 2000	polymers Methods and compositions for enhancing bioadhesive properties of polymers using organic excipients
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CONCLUSION

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. Bioadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity and throughout the respiratory, urinary and gastrointestinal tract. The bioadhesive microspheres can be used not only for controlled release but also for targeted delivery of the drugs to specific sites in body. Therefore, it can be say that in future also Bioadhesive microspheres will play an important role in the development of new pharmaceuticals employing more advanced techniques and materials. Many studies have already been undertaken for exploring the prospects of bioadhesive microspheres in gene therapy, delivery of peptides (insulin, calcitonin, and desmopresin), localised and targeted release of antitumour agents and mucosal vaccination (influenza vaccine). Although significant advances have been made in the field of bioadhesives, 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 EMFT techniques for evaluation of bioadhesion strength of microspheres to specific cell types. Polymeric science needs to be explored to find newer bioadhesive polymers with the added attributes of being biodegradable, biocompatible, bioadhesive 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 bioadhesive microspheres as a cutting edge technology for site targeted controlled release drug delivery of new as well as existing drugs. The future direction of bioadhesive drug delivery lies in vaccine formulations that adhere to the mucosal surface and result in mucosal immunity.

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