WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 2, 267-278. Review Article ISSN 2277– 7105

TEST METHODS OF BIOADHESIVE SYSTEM

Prajapati Twinkle Kantibhai*, Kaushika S. Patel and Dr. Shreeraj Shah

M.Pharm Candidate, Assist Professor, HOD (Pharmaceutical Technology),
L.J Institute of Pharmacy Ahmedabad, Gujarat, India.

Article Received on
19 November 2017,
Revised on 10 Dec. 2017,
Accepted on 01 Jan. 2018
DOI: 10.20959/wjpr20182-10636

***Corresponding Author**
Dr. Prajapati Twinkle Kantibhai
M.Pharm Candidate, Assist Professor, HOD (Pharmaceutical Technology), L.J Institute of Pharmacy Ahmedabad, Gujarat, India.

ABSTRACT

The term bioadhesion commonly defined as adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery system. Bioadhesion often refers to the adhesive between the excipients and biological tissue. Application of dosage forms to mucosal surfaces may be of benefits to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. This review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive, materials, factor affecting mucoadhesion, evaluating methods and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

KEYWORDS: Bioadhesion, tensile strength, retention time, adhesion number, mucosa.

INTRODUCTION

Mucoadhesive based topical and local systemhave shown enhanced bioavaibility. Bioadhesive drug delivery gives good bioavaibility due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. Thus mucosal drug delivery system could be of value in delivering a growing number of high molecular weight sensitive molecules such as peptide and oligonucleotides. In mechanism of bioadhesive system wetting and swelling of polymer to permit intimate contact with biological tissue and formation of weak chemical bonds between entangled chain.

EVALUATION METHODS

1) Ex vivo methods

a. Methods based on measurement of tensile strength

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh goat mucosa was obtained and used within 2h of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with 0.1N HCL at 37□C. The mucosa was cut into the pieces and washed. A piece of mucosa was tied to the Teflon piece, which was kept in beaker filled with HCL pH 1.2, at 37□C ± 1□C. The Teflon pieces was tightly fitted into a glass beaker so that it just touched the mucosa surface. The bioadhesive tablet was stuck to the lower side of a pan. The weight of 5 g was kept in the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 min to provide contact time for bioadhesion. The weight was removed. The water (equivalent to weight) was added slowly drop by drop with an infusion set to the left hand pan until the tablet detached from the mucosal surface. The mucoadhesive strength of the bioadhesive tablet is calculated by formula:

Detachment stress $\left(\frac{dyne}{cm2}\right) = m.g/A$

Where, m = the weight added to the balance in gram,

g= acceleration due to gravity taken as 980 cm/sec2,

A= area of tissue exposed and is equal to $\pi r2$

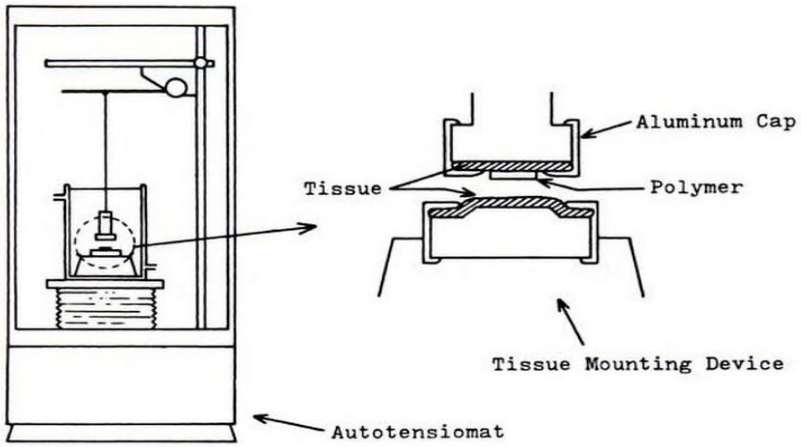


Figure 1: Automatic surface tensiometer.

b. Methods based on measurement of shear strength

The shear stress measures the force that causes mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. The shear mucoadhesive strength is measured by flow channel method where force necessary for the detachment of a particle placed on the mucin gel was determined by passing humid air through the flow cell.

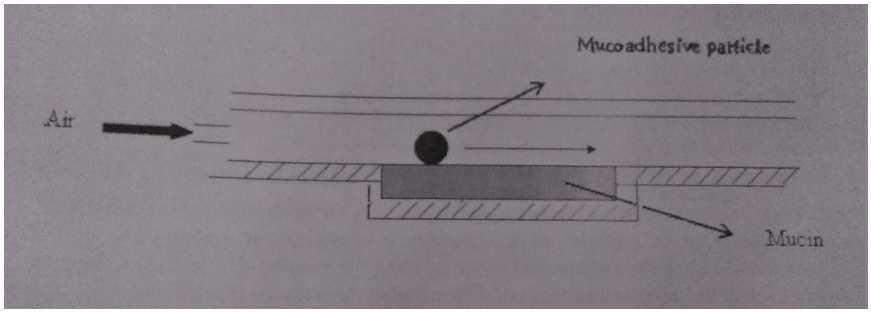


Figure 2: measurement of shear strength.

c. Method based on measurement of peer strength

The peel test involves the application of stress over a fine line at the edge rather than over the entire area of contact sites.

d. Bioadhesion retention time

Measured at site of application. Provides quantitative information on mucoadhesive properties. The GI transit time of many mucoadhesive have been examined using radioisotopes e.g.[51] Cr and the time dependent distribution of the radioactivity in the GIT is measured. As same, radionuclides such as ^{99m}Tc, ^{113m}In or ^{123}I are used and their transit through the GIT is measured by ϒ scintigraphy.

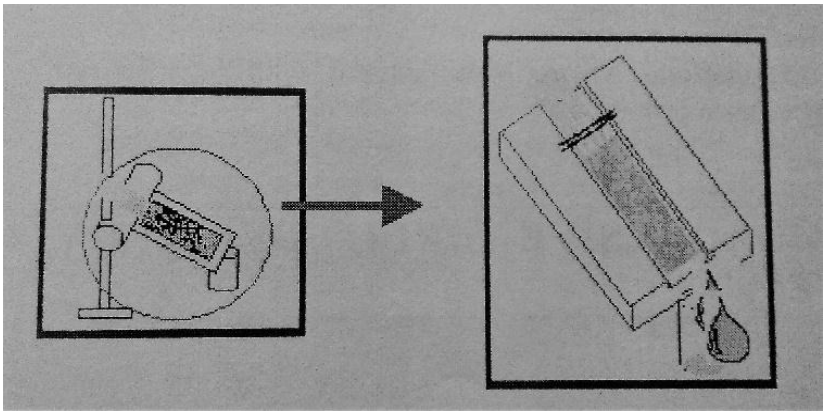


Figure 3: measurement of retention time.

If we want to test the oesophageal bioadhesive retention, then longitudinal sections of porcine oesophageal tissue is used and sections are equilibrated to 37®C in a humidity chamber immediately prior to use. The tissue is washed at a rate of 1ml/min to simulate saliva flow. 1.5 ml of formulation was mixed with -0.2MBq Tc99m as a radioactive label and it is spread evenly over the mounted tissue surface and washing initiated. Eluate was collected into tubes at regular intervals up to 30 min. The radioactivity in each tube was measured to determine the percentage of the dose washed off at each time point.

2) In vitro methods

a) Adhesion weight method

Smart and kellaway developed a test system where suspensions of ion exchange resin particles flowed over the inner mucosal surface of a section of guinea pig intestine, and the weight of the adherent particles determined. Although the method was of limited value due to poor data reproducibility resulting from fairly rapid degeneration and biological variation of the tissue, it was possible for them to determine the effect of particle size and charge on to the adhesion after 5min contact with everted intestine. A sieve size fraction (63 to 178µm) showed a significant increase in the weight of the intestine. No weight changes were observed with smaller sieve size fractions.

b) Fluorescent probe methods

Park and Robinson studied polymer interaction with the conjunctival epithelial cell membrane using fluorescent probes. The study was done in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesive polymers for oral use. The membrane lipid bilayer and membrane proteins were labelled with candidate bioadhesive and the changes in fluorescence spectra were monitored. The fluorescence spectra were monitored. The fluorescence spectrum of pyrene in the cell membrane showed two distinct bands known as monomer and excimer bands. It was known that the ratio of excimer/ monomer was dependent on the viscosity of the environment. Thus the idea was to detect the change in membrane viscosity by measuring the excimer/monomer ratio. The fundamental assumption of this approach was that the change in membrane viscosity was directly related to adhesive strength of the test polymer. Polymer binding to membrane protein was examined using fluorescence depolarization. This technique is useful to quantitatively compare interactions of various soluble polymers with the cell membrane.

c) Flow channel method

Mikos and Peppas have developed a flow channel method that utilizes a thin channel made of glass and filled with 2%(w/w) aqueous solution of bovine submaxillary mucin, thermostated at 37®C. Air was used as model fluid to test the adhesive characteristics of polymers for nasal application. A gas cylinder containing air was used for the gas flow. The gas stream was passed through a humidifier, where it was saturated at 37®C. the flow cell(C), consisting of two parallel plexiglass plated 15cm long and 4cm wide, was constructed with a jacket(E) connected to a water bath (F) and outside insulating fiberglass (G). The temperature of the cell was measured using a thermometer (L). A particle of a bioadhesive polymer (size in the range of 10 and 200µm) was placed on the mucin gel (D), which had a depth of 0.5 cm through the top of the flow cell (H). Both the static and dynamic bioadhesive behaviour of the particle were determined by taking pictures of the motion of the particle at frequent intervals using a permanently attached micro meter (K). The flow rate of the air was increased slowly and at a constant rate using a regulating valve with gauge (B), and the time corresponding to the particle detachment was recorded. As pointed out by the authors, this experiment can be done using freshly excised mucus layer or gastrointestinal tissue.

The bioadhesive force is equal to the hydrodynamic force necessary for the particle detachment, assuming no cohesion failure occurs. In the simplest case of a rigid particle interacting to a rigid force, the hydrodynamic force (F) exerted on the sphere is

$F = 6\pi fuvR$

WHERE, f= 1.7009, u is the air viscosity,

R is the particle radius, and v is a characteristic velocity.

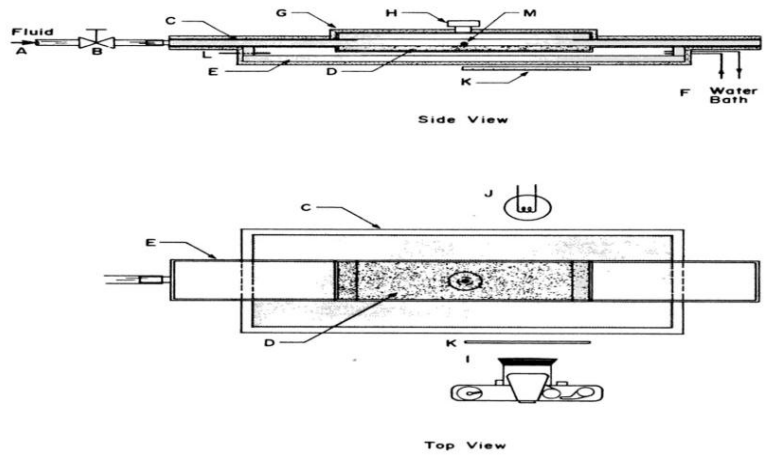


Figure 2: flow channel method.

d) Falling liquid film method

Teng and Ho developed a technique that used excised segment and micro size particles. Polymer coated latex particles were prepared by adding a known volume of 1% polymer solution to the cleaned latex particles (5×10^8 particles/ml) in water and stirring at least for 2 h. To further prepare the polymer coated particles in the buffer solutions varying in ionic strength, an aliquot of the polymer coated particles in water was directly transferred into a beaker containing the desired buffer solution to give about 5×10^6 particles/ml. The suspension was subsequently sonicated for 30s and used 15 min later. The small intestine obtained from Sprague-Dawley rats was cut into segments of desired length, and the lumen was cleaned with normal saline. The intestinal segment was cut lengthwise with surgical scissors and immediately spread out on the flute prepared by cutting open the Tygon tubing (1 in. internal diameter). The Tygon flute was supported by a platform composed of a plastic foam board. The angle of inclination was adjusted by a laboratory jack to 78®. The prepared intestinal segment mounted on the Tygon flute was perfused using a perfusion pump and a sample syringe for 10min with a buffer to remove any loosely held mucus. With the aid of the pump, a liquid film of the buffer solution was established on the intestinal segment. In the next 2min, sample of the eluent solution were collected and used as a control solution for the particle counting. They observed a constant sloughing of an extraneous substance, presumably mucus, with time. To test the adhesion of polymer coated particles to the intestinal surface by the perfusion of the particle suspension, 0.5 ml samples of the eluent particle solution were collected, and the number of particles remaining in the sample was coated using an electronic particle counter (Coulter). The fraction of particles adsorbed on the mucous layer (F_a) was measured using the following equation.

$F_a = 1- N_l/N_o$

Where,

N_o and N_l are the particle concentration entering the intestinal segment from the dilute suspension reservoir and leaving the segment.

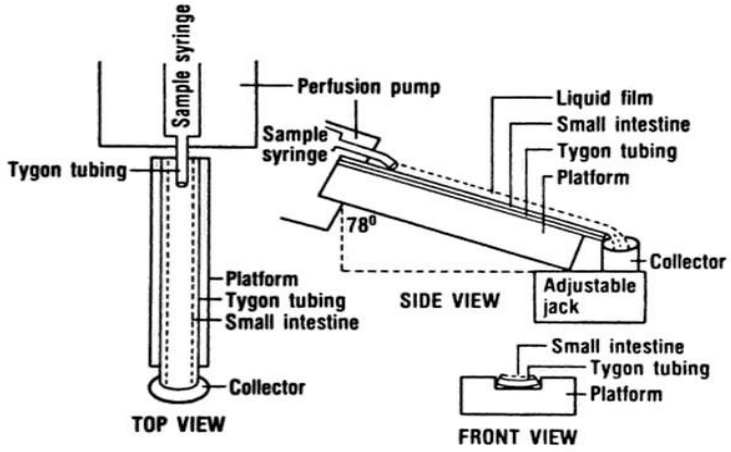


Figure 3: falling liquid film perfusion system.

e) Colloidal gold staining method

Colloidal gold staining techniques have been used widely to study protein-protein or protein polymer interactions. Colloidal gold particles with an average diameter of 18nm were prepared by boiling HAuCl4 in the presence of trisodium citrate. The formation of the monodisperse colloidal gold particles was indicated by a colour change from dark blue to red. The concentration of colloidal gold particles can be easily calculated by measuring the absorbance at 525nm. The absorbance of 1.0 at 525 nm corresponds to 8.5×10^{11} particles per millilitre. The colloidal solution was cooled and centrifuged. The colloidal gold particles were resuspended in the buffer solution of the desired pH. The buffer concentration was always less than 5mm. To this solution was added bovine submaxillary mucin solution dialysed against deionized distilled water. Mucin molecules adsorbed onto the gold particles and stabilized them. The total amount of the mucin necessary to stabilize the colloidal gold particles depends on the pH. We varied pH and the total amount of added mucin, and found that the conjugates were very stable if 0.2 ml of mucin (at least 0.112 mg/ml) was added to a 2ml of the colloidal gold solution (7.7×10^{11} particles per millilitre or absorbance of 0.9 at 525nm) at pH 1.3. The colloidal gold and mucin were gently mixed using a rotary mixer foe 15 min at 10rpm. The mixture was then centrifuged at 20,000g for 45min to remove unadsorbed mucin molecules. The sedimented mucin-gold conjugates were resuspended in the desired buffer solution. Once conjugates are formed, they are very stable under all conditions so that the p H and ionic strength of the solution can be varied. The advantage of using the mucin-gold conjugates is that the red colour is formed on the bioadhesive hydrogels as the hydrogels interact with the conjugates. Thus the adhesive interaction between them can be easily quantified either by measuring the intensity of the red colour on the hydrogel

surface or by measuring the decrease in the concentration of the conjugates from the absorbance change at 525nm.

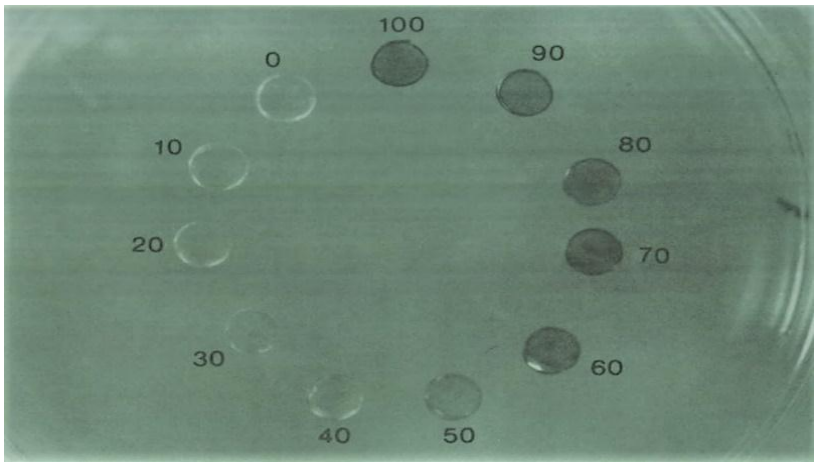


Figure 4: colloidal system.

f) Thumb test

Here, the adhesiveness is qualitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. It provides useful information on mucoadhesive potential.

g) Adhesion number

With a mucoadhesive in the form of small particles, the adhesion number can be used as a parameter for Mucoadhesion.

The adhesion number (Na) is,

Na = (N/No)*100

Where,

No= total no. of applied particles

N= no. of particles attached to the substrate

It is assumed that as the adhesion strength increases, the adhesion number also increases.

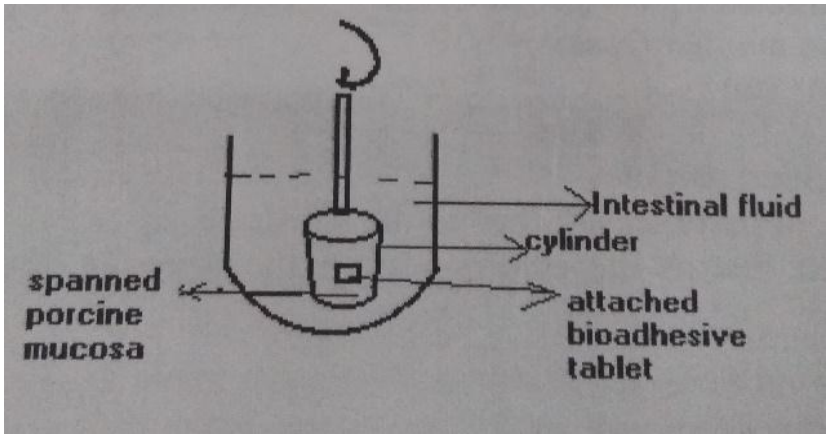
3) In vivo methods

Used for evaluation methods are based on administration of polymers to a laboratory animal and tracking their transit through the GI system. Administration methods include forced oral gavage, surgical stomach implantation and infusion through a loop placed in situ in the small intestine. Tracking generally followed with the help of X-ray studies, radio opaque markers and radioactive elements etc. for e.g. X-ray studies for monitoring GI transit time for

bioadhesive tablet made of $BaSO_4$ and radiolabelled microspheres and nanoparticles is carried out.

a) Mucoadhesive studies

Bernkop-schnurch and steininger et al. have established a new method to evaluate the binding to the mucosa as well as the cohesiveness of the tablet. The prepared tablets were attached to freshly excise intestinal porcine mucosa, which has been spanned on stainless steel cylinder (apparatus 4 cylinder, USPXXII).



Thereafter, the cylinder was placed in the dissolution apparatus according to the USP containing 100 mm Tris-HCl buffered saline (TBS). The fully immersed cylinder was agitated with 250rpm. The detachment, disintegration or erosin of tablet were observed and recorded within a time period of 10h.

CONCLUSION

Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. The various sites where mucoadhesive polymers have played an important role include buccal cavity, soft palate, gingival, nasal cavity, rectal lumen, vaginal lumen and gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents. Advantages such as mucoadhesion, an increase in the residence time of the polymer, penetration enhancement, and enzymatic inhibition. This class of polymers has enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines. Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has

shown dramatic improvement in both specific therapies and more general patient compliance. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future. Drug delivery through the numerous gastro retentive approaches has opened a new horizon for effective way of increasing patient compliance and increasing bioavailability of variety of drugs through oral rout. Many approaches with use of different polymers and other constituents can produce different range of gastro retentive systems. Especially the floating drug delivery system is the most widely used in gastro retentive dosage forms. However a lot of work is still needed to be done to overcome the different physiological and pharmaceutical barriers to develop the more effective gastro retentive dosage forms.

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