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Evaluation Parameters of Mucoadhesive Drug Delivery System

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Abstract

Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. Mucoadhesive drug delivery systems are available in the form of tablets, films, patches, and gels for oral,buccal, nasal, ocular, vaginal, rectal and topical routes for both systemic and local effects. This paper lays main emphasis on evaluation parameters of mucoadhesive drug delivery system. This review article presents the theories of mucoadhesion, factors affecting mucoadhesion and techniques for *in-vitro* and *in-vivo* evaluation of mucoadhesive dosage forms.

Key-Words: Mucoadhesion, polymers, evaluation parameters

Introduction

The termmucoadhesion (bioadhesion)is used to describe adhesion interactions between polymers and mucus or mucosal surfaces (Suresh *et al.*, 2013).Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. 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 (Muraleedhara*et al.*, 2013).Mucoadhesive drug delivery systems are available in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, vaginal, rectal and topical routes for both systemic and local effects. These are evaluated by *ex vivo* and *in vivo*.Mucous membranes (mucosae) are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal and respiratory tracts (Khan *et al.*, 2014). They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer.

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The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the oesophagus, vagina and cornea) (Boddupalli*et al.*, 2015). The mucoadhesive drug delivery system may include the following systems.

I. Buccal delivery system
II. Sublingual Delivery system
III. Nasal delivery system
IV. Ocular delivery system.
V. Gastro Intestinal delivery system.
VI. Vaginal delivery system.
VII. Rectal delivery system (Alexander *et al.*, 2011).

Factors affecting mucoadhesive drug delivery system

There are three factors of mucoadhesion drug delivery system are:-

Polymer related factors

a) **Molecular weight-** With the increase in the molecular weight (MW) of the polymer chain, the mucoadhesiveness of a polymer becomes significantly increases (Dharmendra*et al.*, 2012).

b) Chain length- With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer (Khan *et al.*, 2014).

c) Spatial arrangement- Spatial conformation of a molecule is also important factor.Besides molecular weight or chain length, spatial conformation of a molecule is also important. The helical confirmation of dextran may shield many adhesively active groups primarily responsible for adhesion, unlike PEG polymers which have a linear confirmation. (Nikalje*et al.*, 2012).

d) Flexibility- Flexible polymer chains helps in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bioadhesive property. The flexibility of the polymer chains is generally affected by the crosslinking reactions and the hydration of the polymer network. Higher the crosslinking density, lower is the flexibility of the polymer chains (Harsulkar*et al.*,2011).

e) Hydration of polymer- In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. Hence highly crosslinked polymeric matrix limits the interpenetration of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength (Trivedi et al., 2011).

f) Hydrogen bonding- In general, stronger the hydrogen bonding stronger is the adhesion. The functional groups responsible for such kind of interaction include hydroxyl, carboxyl and amino groups (Gandhi *et al.*,2011).

g) Charge and degree of ionization of polymer- The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion. Anionic polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers (Asane., 2007).

h) Polymer concentration- In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications (Shijith*et al.*, 2013).

Environmental factors

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion.

a) pH-Some studies have shown that the pH of the medium is important for the degree of hydration of cross link (Rajput *et al.*, 2010).

b) Applied strength- The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction with mucins(Mythri*et al.*, 2011).

c) Contact time- With the initial increase in the contact time there is an increase in the hydration of the polymer matrix and subsequent interpenetration of the polymer chains. The physiology of the mucosal layer may vary depending on the patho-physiological nature of the human body (Madhav*et al.*, 2014).

d) Swelling- Swelling depends both on polymer concentration and on water presence. When swelling is too great, decrease in bioadhesion (Lahoti*et al.*, 2011).

Physiological factors

The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa.

a) Mucin Turnover- The mucin turnover is expected to limit theresidence time of the mucoadhesive on the mucus layer. No matter how high the mucoadhesive strength is (Siddhapara*et al.*, 2011).

b) Disease state -The physicochemical properties of the mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, etc (Shaikh*et al*., 2011).

Theory of mucoadhesive drug delivery system

The concept of mucoadhesive drug delivery system is based upon the following six theories.

- **Electronic theory**

  In the electronic transfer theory, mucoadhesion occurs as the result of the transfer of electrons between mucus and the mucoadhesive platform. The electronic transfer between two different layers results in the formation of a double-layered electronic charge at the interface. This theory suggests that the electrostatic forces are critical in generating bond adhesions rather than high joint strength (Hägerström*et al.*, 2003).

- **Adsorption theory**

  This theory states that bio adhesion bond formed between an adhesive substrate and tissue as a mucus is due to vanderwall interactions, hydrogen bonds and related forces. Although these forces individually weak, the sheer number of interactions a whole produce intense adhesive strength (Lee*et al.*, 2000).

- **Diffusion theory**

  Interpenetrations and entanglement of bio-adhesive polymer chains and mucus polymer chains produced semi permeable adhesive bonds and is separated by diffusion theory. It is believed that the bond strength increases with degree of penetration

of the polymer chains in to the mucus layer. Penetration of polymer chains into the mucus network and vice versa is depends upon the concentration gradients and diffusion coefficients. Interpretation is required to produce an effective bio adhesion bond, it has not been determined exactly, but it is believed to be in the range of 0.2-0.5µm.

The penetration of depth (l) = (t-Db)1/2

where, t = time of contact ; Db= diffusion coefficient of the bio adhesive material in mucus (Peppas*et al.*, 1996).

- **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 (sm) is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force (Fm) and the total surface area (Ao) involved in the adhesive interaction.

Sm= Fm/Ao

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains (Vinod*et al.*, 2012).

- **Mechanical Interlocking Theory**

The mechanical interlocking theory only considers the adhesion between liquid and a rough surface or a surface rich in pores and essentially proposes that the adhesion between the two substrates is due to mechanical interlocking of the adhesive into the irregularities of the substrate surface. Adhesion between the mucoadhesive system and the rough surface typically occurs within a diverse biological environment and accordingly this theory does not fully explain the adhesive properties in vivo (Carvalho*et al.*, 2010).

- **Wetting theory**

The ability of a bioadhesive or mucous to spread and develop intimate contact with its corresponding sub-strate is a major factor in bond formation. The affinity between the liquid systems and the mucus membrane can be determined by measuring the contact angle. As a general rule, lower the contact angle, greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. Thespreadability coefficient (SAB) can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in equation:

$$SAB = \gamma B - \gamma A - \gamma AB$$

Greater the individual surface energy of mucus and device in relation to the interfacial energy, greater is the adhesion work, WA(Andrews *et al.*, 2009).

$$WA = \gamma A + \gamma B - \gamma AB$$

Techniques to evaluate mucoadhesion

Mucoadhesive polymers and drug delivery systems can be evaluated by testing theiradhesion strength by both *ex vivo* and *in vivo* tests.

a) *Ex vivo* Study

1. Tensile strength measurement.
2. Falling liquid film method
3. Viscometric method.
4. Thumb test
5. Colloidal gold staining method
6. Method of shear strength
7. Fluorescent probe method
8. Flow channel method
9. Electrical conductance
10. Mucoadhesive strength
11. Stability Studies
12. Adhesion mumber
13. Swelling index
14. Microbalance method.
15. Wash off test
16. Drug permeation.
17. Mucoadhesion time.
18. Surface pH study.
19. Scanning Electron microscopy. (SEM)
20. Atomic Force Microscopy (AFM)

b) In vivo methods

1. Use Of Radioisotopes
2. Gamma Scintigraphy Technique
3. *In vivo* bio adhesive study (Xray studies)
4. In vivo evaluation of gastric mucoadhesion of microspheres
5. Rat gut loop studies of mucoadhesion

Tensile strength measurement

Tensile strength can be defined as the strength of material expressed as the greatest longitudinal stress it can bear without tearing apart. As it is the maximum load applied in breaking a tensile test piece divided by the original cross-sectional area of the test piece, it is measured as Newton's/sq.m. Specifically, the tensile strength of a material is the maximum amount of tensile stress that it can be subjected to before failure. The definition of failure can vary according to material type and design methodology.

There are three typical definitions of tensile strength:

▪ **Yield Strength** — the stress a material can withstand without permanent deformation.

▪ **Ultimate Strength** — the maximum stress a material can withstand.

▪ **Breaking Strength** — the stress coordinates on the stress strain curve at the point of rupture (Nielsen *et al.*, 1998).

Falling liquid film method

Small intestine segments from rats were placed at inclination of a tygon tube flute. The adhesion of particles to this surface was monitored by passing the particles suspension over the surface. By comparing the fraction of particles adheres to the tissue the adhesion strength of different polymers can be determined (Rao*et al.*, 1989).

Viscometric method

Katarina Edsman has studied the dynamic rheological measurements on gels containing four different carbopol polymers and the corresponding mixtures with porcine gastric mucin and bovine submaxillarymucin. The method does not give the same ranking order when two different comparison strategies were used (Chowdary*et al*., 2004).

Thumb test

This is a very simple test used for the qualitative determination of peel adhesive strength of the polymer and is useful tool in the development of buccal adhesive delivery systems. The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time (Kumar *et al*., 2014).

Colloidal gold staining method

Park proposed the colloidal gold staining technique for the study of bioadhesion. The technique employs red colloidal gold particles, which were adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesives hydrogels develops a red color on the surface. This can be quantified by measuring at 525 nm either the intensity on the hydrogel surface or the conjugates (Krishna *et al.*, 2006).

Method of shear strength: The measurement of the shear stress gives a direct correlation to the adhesion strength. In a simple shear stress measurement based method two smooth, polished plexi glass boxes are selected; one block is fixed with adhesive Araldite® on a glass plate, which is fixed on leveled table. The level is adjusted with the spirit level. To the upper block, a thread is tied and the thread is passed down through a pulley, the length of the thread from the pulley to the pan was 12 cm. At the end of the thread a pan of fixed is attached. More weights can be added to it. A recent method involves the measurement of mucoadhesion by use of a stainless steel rotating cylinder which is coated with freshly excised porcine intestinal mucosa to which polymer discs were attached. The cylinder is placed in a dissolution apparatus and rotated at 125 RPM. It is analysed every 30 mins for the attachment of the polymers discs (Latheeshjala*et al.*, 2011).

Fluorescent probe method

In this method the membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion (Senthil*et al.*, 2010).

Flow channel method

They study was done in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesives polymers for oral use. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescence isothiocyanate, respectively. The cells were then mixed with candidate bioadhesives and the change in florescence spectra was monitored. This gave an indication of polymer binding and its influence on polymer adhesion(Tangri*et al*., 2011).

Electrical conductance

The rotational viscometer was modified to determine electrical conductance of various semi-solid mucoadhesive ointments and found that the electrical conductance was low in the presence of adhesive material (Krupashree*et al*., 2014).

Mucoadhesive Strength

Mucoadhesive strength of the dosage form can be measured on the modified physical balance.The apparatus consists of a modified double beam physical balance in which the right pan is replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon® block of fixed diameter and height is fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This is kept in beaker filled with buffer media 0.1N HCl pH 1.2, which is then placed below right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer media 0.1N HCl pH 1.2 can be used as moistening fluid. The one side of the dosage form is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive dosage form and goat or rat stomach mucosa. The preload and preload time are kept constant. After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when

mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams (Gupta *et al.*, 1992).

Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. ICH guidelines can be followed in this regard(Cafaggi*et al.*, 2005).

Adhesion number

Adhesion number for mucoadhesive microspheres is determined as the ratio of the number of particles attached to the substrate to the total number of applied particles, expressed as a percentage. The adhesion strength increases with an increase in the adhesion number (Collins *et al.*, 1989).

Swelling index

Swelling of excipients of mucoadhesive dosage form involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of% weight gain by the mucoadhesive dosage form.(Margeta*et al.*, 2009).

One mucoadhesive dosage form is weighed and placed in a beaker containing 200 ml of buffer media. After each interval the dosage form is removed from beaker and weighed again up to 8 hours. The swelling index is calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo)/Wo

Where, S.I. = Swelling index

Wt = Weight of the dosage form at time t

Wo = Weight of the dosage form before placing in the beaker

Microbalance Method

The microforce balance technique is used to measure the specific adhesion force of microparticles. This involves the use of a microtensiometer and a microforce balance, yielding both contact angle and surface tension. The mucous membrane is placed in a small mobile chamber with both pH and physiological temperature controlled. A unique microsphere is attached by a thread to the stationary microbalance. The chamber with the mucous membrane is raised until it comes into contact with the microsphere and, after contact time, is lowered back to the initial position (Botagataj*et al*., 1999).

Wash-off test

Wash-off test is used to determine the mucoadhesive property of dosage form. In this test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the dosage form is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 370C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined % adhesive strength = (Ns/No)*100.

whereNo = Initial number of the dosage form spread over the mucosal surface.

Ns = Number of the dosage form detaching from the mucosal surface (Keely*et al.*, 2005).

Drug Permeation

The in vitro buccal drug permeation study of buccal tablet through the sheep buccal mucosa is performed by using Keshary-Chien type glass diffusion cell at 37°C ± 0.2°C. Fresh sheep buccal mucosa is mounted between the donor and receptor compartments. The buccal tablet is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment (15-mL capacity) is filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. A 1-mL sample is withdrawn at predetermined time intervals and analyzed for drug content at 290 nm using aUVspectrophotometer (Alexander A *et al*., 2011).

Mucoadhesion Time

It is measured by modified balance method. The fresh sheep buccal mucosa is tied on the glass slide, and a mucoadhesive core side of each tablet is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 mL of the phosphate buffer pH 6.8, and kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and tablet adhesion is monitored for 12 hours. The time for the tablet to detach from the sheep buccal mucosa is recorded as the mucoadhesion time (Takeuchi *et al*., 2005).

Surface pH Study

The surface pH of buccal tablets are determined in order to investigate the possibility of any side effects *in-vivo*, as an acidic or alkaline pH may cause irritation to the buccal mucosa.The method adopted, is used to determine the surface pH of the tablet. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH is measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute (Patel *et al*., 2007).

Scanning Electron Microscopy (SEM)

The microbeads are previously mounted on a brass stub using double-sided adhesive tape and then coated under vacuum with a thin layer of gold (3~5nm) for 75 sec and at 40W to make them electrically conductive. Afterwards, the stub containing the sample is placed in the scanning electron microscopechamber. The surfacemorphology of blank microbeads, drug loaded microbeads before and after dissolution are studied by photomicrographs at an excited

voltage of 20 KV, specific chamber pressure (in mm Hg) under different magnification (Kumar *et al.*, 2009).

Atomic Force Microscopy (AFM)

Generally, Atomic Force Microscopy for the use in bioadhesionstudies bases on the change in surface roughness by polymer bindingto a biological tissue. Forming bonds between polymer and tissuelead to higher surface roughness.Atomic Force Microscopy can be used to study the surface propertiesas well as the force which is needed to remove the adhesiveformulation or polymer from a tissue. The method to characterisethe surface structure bases on visualisation of atoms depicted astridimensional images. Determining the adhesive force betweena polymer and a suitable tissue AFM is used in the force–distancemode.Cleary et al. determined the bioadhesive force between Pluronic–PAA copolymer and mucin-coated surfaces. A colloidal-sizedspherical particle was attached to an AFM cantilever which wasbrought in contact with mucin, which was in turn attached to anepoxy adhesive layer positioned on a glass microscope slide. Itwas noticeable that the surface structure was quite heterogeneous,so different locations of measurement led to differences in the results.Furthermore, changes in measurement time, pretest speed aswell as withdrawal speed had a significant influence on the results. The authors found out that the slowest speed possible should be used for the measurements, which is limited by loss of water due to evaporation and a potential instrumental drift using too long time intervals. A speed of 0.02 lm/s was chosen for further measurements. An advantage of this method is the possibility to study the surface properties as well as determining the bioadhesive forces. Disadvantages are the time dependency and the missing adaptability for various dosage forms (Woertz*et al*., 2013).

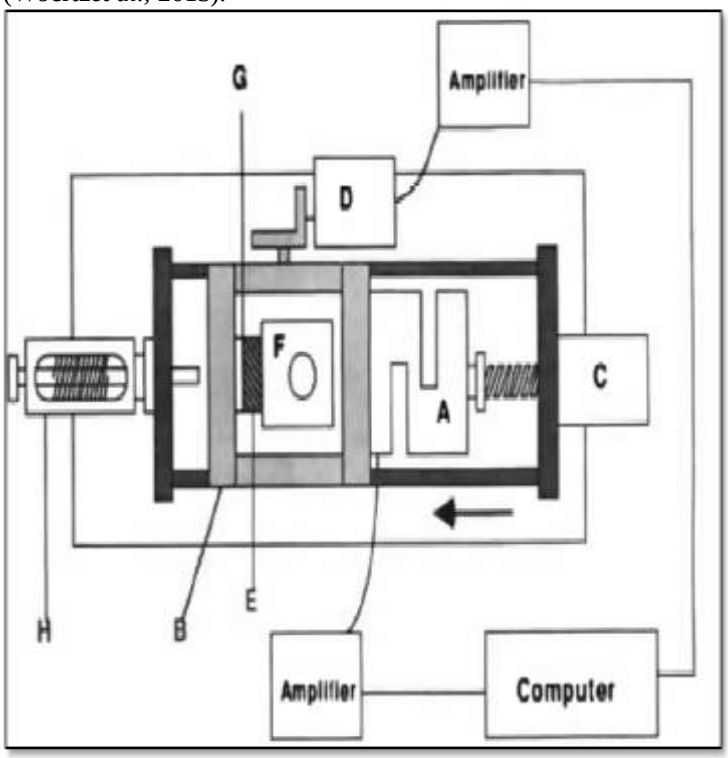

Figure 1:- Atomic Force Microscopy

b) Measurement of the Residence Time/*In Vivo* Techniques

Measurements of the residence time of mucoadhesive at the application site provide quantitative information on their mucoadhesive properties. The GI transit times of many mucoadhesive preparations have been examined using following techniques.

Use of Radioisotopes

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. Faeces collection(using an automated faeces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesiveslabeled with Chromium-51(Cr-51), Technitium-99 (Tc-99m), Indium-113(In-113m), or Iodine-123(I-123) have been used to study the transit of the tablets in the GItract (Davis *et al.*, 1984).

Gamma Scintigraphy Technique

It is a valuable tool used in the development of pharmaceutical dosage forms. With this methodology, it is possible to obtain information non-invasively. This technique gives information in terms of oral dosage forms across the different regions of GI tract, the time and site of disintegration of dosage forms, the site of drug absorption, and also the effect of food, disease, and size of the dosage form on the in vivo performance of the dosage forms. Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomachmucoadhesive tablets (Krishnaiah*et al.*, 1988).

***In-vivo* bio adhesive study (X-ray studies)**

To study the bioadhesive character and mean residence time of the natural polymer in the stomach, barium sulphate loaded tablet was used. Two healthy rabbits weighing 2.5 kg are selected and administered orally with the tablet. X-ray photograph is taken at different time intervals (Senthil*et al*., 2011).

In vivo evaluation of gastric mucoadhesion of microspheres

Male Wistar rats, 200–250 g, are fasted for 24 hbefore the experiments, but are allowed free

access to water. Labeled microspheres (2 mg) that are filled in capsules are administered to rats using a gastric sonde. Two hours after administration, the rats are sacrificed, and the stomach is removed and washed with phosphate-buffered saline (pH 7.4) to recover the remaining microspheres.The amount of labeled microspheres that remained in the stomach isdetermined (Burgalassi*et al.*, 1996).

Rat gut loop studies of mucoadhesion

The everted gut sac technique is an example of an ex-vivo method.Male Wistar rats, with a mean weight about 300 g, are anesthetized and killed with an overdose of barbiturate. The small intestine is removed and washed with physiological saline with a syringe 5–10 ml/min for 10 min, then 20– 30 ml/min for about 20 min. At least 500 ml of the saline is used for cleaning the intestine. The cleaned tissues are used immediately or kept at −15°C until use. A required amount of microspheres are suspended in physiological saline and sonicated. The microsphere suspension is filled into lengths of small intestine (about 15 cm in length) and sealed. These tubes are incubated in saline at 37°C for 60 min. The microsphere suspension is then removed and the number of microspheres present in the suspension before and after the adhesion study is counted using a Coulter Counter method.The percentage of microspheres adhered to the tissue is calculated from the difference of the counts (Santos *et al.*, 1999).

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