Section A-Research paper

REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM: AN ESSENTIAL MEANS IN DESIGNING OF INNOVATIVE CONTROLLED DRUG DELIVERY SYSTEM FOR THE EFFECTIVE DELIVERY OF PHARMACEUTICALS

Prashanta Kumar Panda[1], Prasanna Kumar Dixit[2] and Uma Shankar Mishra[3]

[1]Department of Pharmaceutics, College of Pharmaceutical sciences, Mohuda, Berhampur-760002, Ganjam, Odisha, India

[2]Department of Zoology, Berhampur University, Berhampur- 760007, Ganjam, Odisha, India

[3]Department of PA&QA, Royal College of Pharmacy & Health Sciences, Berhampur-760002, Ganjam, Odisha, India

Abstract

Since the previous four decades, the idea of mucoadhesion has attracted a great deal of attention in the many pharmaceutics sectors. The mucoadhesive drug delivery system has many benefits that make it an innovative method for the local and systemic administration of various medications. This medication delivery system's primary benefit is that it extends the dosage form's stay in residence at the application site. The phenomenon of interfacial molecular attractive forces between a biological membrane's middle layer and natural or synthetic polymers, which enables the polymer to cling to that membrane's surface for an extended as well as protracted period of time, is known as bioadhesion. 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. To design an effective particulate drug delivery system having mucoadhesive function, several mucoadhesion tests for polymers and for the resultant delivery systems should be developed. This paper lays main emphasis on the mechanism of bioadhesion, various bioadhesion theories, various types of mucoadhesive dosage forms, various types of mucoadhesive polymers, and various evaluation methods.

Keywords: Mucoadhesive Drug Delivery Systems, mucoadhesion, mucoadhesive dosage forms, and evaluation methods.

Corresponding Author

Prashanta Kumar Panda
Department of Pharmaceutics,
College of Pharmaceutical Sciences, Mohuda, Berhampur-760002,
Odisha, India
Tel.: +91-9938822541
E-mail:pkpanda35@gmail.com

Introduction

The notion of mucoadhesion has been used extensively over the past 40 years to extend the residence length as well as the controlled release impact of numerous bioadhesive dosage forms via various mucosal routes. The mucoadhesive drug delivery system-based formulations have demonstrated the increased bioavailability of numerous medications. The development of prolonged, extended, and sustained release dosage forms has seen a substantial increase in interest in the usage of various mucoadhesive polymers. Due to the huge surface area and increased blood flow in the mucosal cavities, the mucoadhesive drug administration offers better absorption and enhanced bioavailability of dose forms. When compared to alternative drug delivery methods, distribution over the mucus membrane has a number of advantages, including the ability to avoid hepatic first pass metabolism and drug degradation by a variety of gastrointestinal enzymes and intestinal flora [1].

There are numerous mucoadhesive polymers that can be utilised depending on the required mucoadhesive strength of the mucoadhesive dosage forms. These macromolecules, known as polymers, can stick to the mucosal surfaces whether they are made of natural or manufactured materials. The usage of various mucoadhesive polymers has generated a lot of attention in the pharmaceutical technology industry during the past three decades. Today, it is widely acknowledged that using mucoadhesive polymers is a key tactic for extending the residence time and improving the localised effects of drug delivery systems on diverse mucous membranes within a biological system [2].

Oral, gastrointestinal, nasal, ophthalmic, vaginal, and rectal delivery routes for mucoadhesive dosage forms of medication are among the potential choices. These locations for drug delivery were briefly compared. Due to its relatively static and flat surface, which may accommodate a variety of mucoadhesive dosage forms, the buccal route has been found to be more suited for the delivery of pharmacological agents employing mucoadhesive polymers [3].For drug distribution over the buccal mucosa, a variety of dosage forms including films, pills, gels, ointments, and patches can be employed. The medications that have a short biological half-life, poor solubility and permeability, are susceptible to enzymatic degradation, and may achieve sustained release effect may be good candidates to be given via the oral cavity.

Mucoadhesive drug delivery systems can be delivered by various routes such as

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

These approaches provide a number of benefits, including a reduction in hepatic adverse effects, which are highly common when administered via the parenteral route, as well as the avoidance of discomfort, tissue damage, and first pass metabolism [4].

Advantages[5,6]

- The buccal drug delivery has a high level of patient acceptability since, in comparison to other non-oral routes, it offers a relatively quick onset of action.
- Better patient compliance as a result of dosage forms' ease of use compared to injections and lack of unpleasant side effects
- Because of the mucosal membranes' high vascularization, administering and removing dosage forms is simple.
- The use of mucoadhesive polymers of "SR" grades can result in sustained medication delivery.
- The rate of drug absorption is quicker due to the great amount of perfusion.
- The potential negative effects of oral delivery, such as nausea and vomiting, can be fully avoided
- Drugs with low oral bioavailability can have their bioavailability increased by designing their mucoadhesive delivery methods, making them easier to administer to unconscious and uncooperative patients.

Disadvantages[7]

- The rate of drug absorption is quicker due to the great amount of perfusion.
- The potential negative effects of oral delivery, such as nausea and vomiting, can be fully avoided.
- Drugs with low oral bioavailability can have their bioavailability increased by designing their mucoadhesive delivery methods
- Making them easier to administer to unconscious and uncooperative patients.

Mechanism of Mucoadhesion[8,9]

An interfacial phenomena known as mucoadhesion occurs when two materials- one of which may be artificial, such a mucoadhesive polymer, and the other of which may be the mucin layer of the mucosal tissues are drawn together by attractive forces at the interface. An artificial substance that may interact with mucus membranes and be maintained on them or hold them together for a lengthy or protracted amount of time is referred to as a "mucoadhesive." The two steps that have typically been recognised during the adhesion process are listed below. Figure 1 depicts these stages of mucoadhesion as well.

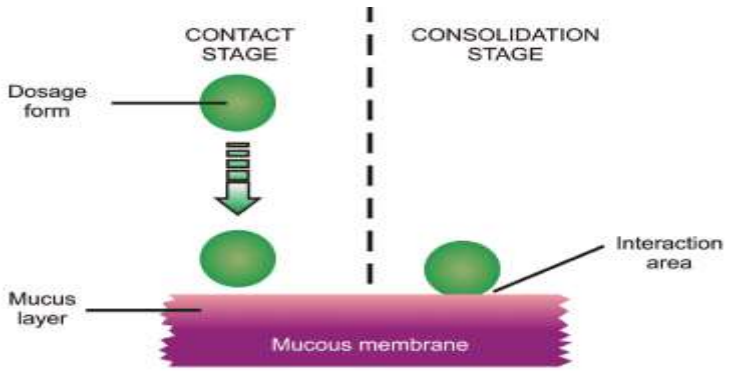

Figure 1: Mechanism of Mucoadhesion

Contact stage: An intimate wetting between the mucoadhesive material and mucous membrane takes place at this stage when the mucoadhesive material comes into touch with the mucous membrane. The mucus in the mucosal membrane does this wetting of the mucoadhesive.

Consolidation stage: By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion. This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

Theories of Mucoadhesion

The examination of mucoadhesion has been adopted from six general hypotheses of adhesion: According to the **electronic theory**, adhering surfaces transfer electrons when they come into touch because of the disparities in their electrical structures [10]. According to the theory, this would cause an electrical double layer to form at the interface, followed by adhesion brought on by attraction forces.

The **wetting theory** takes surface and interfacial energy into account and is mostly used to liquid systems. In order for adhesion to form, a liquid must have the capacity to spread spontaneously onto a surface [11]. It is possible to determine a liquid's affinity for a surface using methods like contact angle goniometry, which measures the liquid's contact angle with the surface. In general, the lower the contact angle, the higher the liquid's affinity to the solid.

The **adsorption theory** describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. These forces are thought to be the primary causes of the sticky contact. The chemisorption hypothesis, a branch of this, postulates that an interaction across the interface happens as a result of strong covalent bonding [12].

The **diffusion theory** describes inter-diffusion of polymers chains across an adhesive interface. Concentration gradients drive this process, which is also influenced by the mobility's of the available molecular chain lengths [13]. The diffusion coefficient and the duration of contact affect the interpenetration's depth. A semi-permanent adhesive bond is made when there is sufficient depth of penetration.

According to the **mechanical theory**, adhesion results from a liquid adhesive's interlocking (after it sets) into surface imperfections [14]. Though it is believed that a viscoelastic and plastic effect, rather than a mechanical one, plays a more significant role in the adhesion process, rough surfaces also offer an increased surface area that is available for interaction and an enhanced viscoelastic and plastic dissipation of energy during joint failure.

The **fracture theory** is a little different from the other five in that it connects the strength of the adhesive to the forces necessary to separate the two involved surfaces after adhesion [15].

Factors affecting mucoadhesion

The bioadhesive polymer and the surface it is present on affect mucoadhesion capabilities. The following list of variables summarises how a polymer's mucoadhesive characteristics are affected.

Molecular weight: For linear polymers, but not for non-linear ones, molecular weight increases mucoadhesion strength [16]. For instance, the mucoadhesive strength of polyethylene glycols rises in the following order as their molecular weight increases: $2x10^4$, $2x10^5$, and $4x10^5$. While low molecular weight polymers favoured higher mucus layer penetration, high molecular weight polymers encourage physical entanglement.

Hydrophilicity: Because they expand in aqueous conditions and include hydrophilic functional groups with little hydrogen bonds to the substrate, mucoadhesive polymers facilitate mucoadhesion by maximising exposure to their mucoadhesive sites[17]. Furthermore, the maximal distance between the chains of swollen polymers and their disentangled condition result in high chain flexibility and effective penetration.

Flexibility: The flexibility of the polymer chain is crucial for enabling mucoadhesive polymer to connect to mucus and penetrate it. The diffusion of polymer chains at the interfacial regions leads to mucoadhesion, and the more flexible the polymers are, the more readily they will diffuse into the mucus network [18]. As a result, the viscosity and diffusion coefficients of the polymers may be related to their flexibility.

Concentration of polymer: This factor is crucial for creating a reliable adhesive bond between the polymer and mucus. The relationship between polymer and mucus will be unstable if the polymer concentration is too low, and there will be few invasive polymer chains per mucus unit. Due to the polymer's seemingly coiled form, which occurs at a critical concentration, the adhesion property decreases in high polymer concentrations [19]. As a result, the polymer's ability to access solvents declines, which in turn reduces the polymer's chain penetration.

Hydrogen bonding capacity: Hydrogen bonding is another factor that has a significant impact on the bioadhesion of polymers. The polymers must have functional groups (OH, COOH, etc.) that may create hydrogen bonds in order for mucoadhesion to occur, and the polymer's flexibility will increase its hydrogen bonding potential [20].

Cross linking density and Swelling: The usual pore size, crosslink density, and the quantity and average molecular weight of the cross-linked polymers are three important and connected structural factors of a polymer network. According to a study by Flory, the cross-linking of a polymer and its swelling are inversely connected [21]. Therefore, it seems fair that as crosslinking density rises, polymer swelling declines because of slowly absorbed water, leading to a lower rate of interpenetration between mucin and polymer.

Charge and pH: From literature,it was observed that non-ionic polymers were shown to adhere less strongly than anionic polymers. Particularly in a neutral or to some extent in an alkaline solution, some cationic polymers, like chitosan, have enhanced bioadhesive characteristics [22]. There isn't much information in the literature about how the charge of the

membrane affects mucoadhesion, although the pH of the membrane can have an impact on the polymer's ionised or non-ionized forms, which may have an impact on mucoadhesion.

Mucoadhesive Polymers[23,24]

In order to localise the active agents to a specific region or site, mucoadhesive delivery techniques are being investigated. Both water-soluble and water-insoluble polymers are used in mucoadhesive polymers.

It is practical to categorise mucoadhesive polymers that stick to the mucin-epithelial surface into three major groups:

- Polymers that, when submerged in water, become sticky and owe their mucoadhesion to stickiness.
- Polymers with non-specific, non-covalent interactions that are largely electrostatic in nature attach to one another (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to a particular receptor on the self-surface of tiles. For drug delivery, any of the three types of polymers can be employed.

Characteristics of an ideal Mucoadhesive Polymer [25]

- They should be nontoxic and should be non-absorbable from the gastrointestinal tract.
- It shouldn't irritate the mucous membrane in any way.
- It should stick easily to most tissues, have some site-specificity, and ideally form a strong non-covalent link with the mucin-epithelial cell surfaces.
- It should not obstruct the drug's release and permit daily integration.
- Neither during storage nor the dosage form's shelf life may the polymer degrade.
- The price of the polymer shouldn't be too high to keep the prepared dosage form affordable.

Classification of Mucoadhesive Polymers [26,27]

I. Based on Origin

Synthetic mucoadhesive polymers

Cellulose derivatives, Poly (acrylic acid) polymers, Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

Natural mucoadhesive polymers

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

II. Based on Nature

Hydrophilic polymers

When placed in an aqueous medium, matrices made with these polymers swell, leading to the matrix's eventual dissolution. The mucoadhesive properties of the polyelectrolytes are increased. For their mucoadhesive qualities, substances including poloxamer, hydroxypropyl

methyl cellulose, methyl cellulose, poly (vinyl alcohol), and poly (vinyl pyrrolidone) have also been utilised.

Polysaccharides and its derivatives

Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxy propyl methylcellulose, hydroxy propyl cellulose, sodium carboxymethyl cellulose,Xanthan gum, gellan gum, guar gum, and Carrageenan gum,

Hydrogels

Three-dimensionally cross-linked polymer chains having a porous structure that can hold water are known as hydrogels. Mucoadhesive hydrogel-based formulations for increasing the bioavailability of the poorly water-soluble drug are used in addition to drug targeting.

Mucoadhesive Dosage Forms

Powders

The use of powder-based mucoadhesive formulations for nasal drug delivery has been widely used. In comparison to liquid formulations, these formulations, which include a medication and mucoadhesive components (often polymers), tend to increase the drug's bioavailability by prolonging its stay at the site of absorption or the target site [28]. Spraying rats' oral mucosa's with HPC and beclomethasone in powder form results in a noticeably longer residence period than an oral solution and a 2.5% retention of beclomethasone on the buccal mucosa for up to 4 hours.

Tablets

Tablets have a diameter of about 5-8 mm and are tiny, flat, and oval. Mucoadhesive tablets, in contrast to traditional tablets, enable for speaking and drinking without any significant discomfort. They become softer, stick to the mucosa, and remain there until the disintegration or release is finished. Generally speaking, mucoadhesive tablets have the potential to be used for controlled release drug delivery. However, coupling mucoadhesive properties to tablets has additional benefits. The ability to target any mucosal tissue, including those in the stomach, with mucoadhesive tablets allows for both localised and systemic controlled medication release. Due to its longer drug release, decreased frequency of drug administration, and increased patient compliance, mucoadhesive tablets are widely used. Mucoadhesive tablets' main flaw is that they aren't physically flexible, which results in poor patient compliance for prolonged and repeated use [29]

Bioadhesive Micro/Nanoparticles

The benefits of bioadhesive micro/nanoparticles are similar to those of tablets, but because of their physical characteristics, they can intimately contact a larger mucosal surface area. These are often applied as aerosols, mixed into pastes or ointments, or supplied as an aqueous suspension. Bioadhesive polymeric microparticles of carbopol, polycarbophil, chitosan, or Gantrez are to stick to swine oesophageal mucosa; particles made from polyacrylic acids showed better mucoadhesive strength in tensile testing trials. However, it was discovered in

elution investigations that chitosan or Gantrez particles remained on mucosal tissue for longer lengths of time [30]. Drugs that are poorly soluble and hence cannot be effectively given from a solid dosage form can be substituted with liposomes. In comparison to free medication powder, silamyrin liposomal buccal administration demonstrated steady state penetration into a chicken buccal pouch for 6 hours. Microparticles are less likely to induce local irritation at the point of adhesion than tablets because of their smaller size, and they also lessen the unpleasant sensation of a foreign object in the mouth.

Films

Because they are more flexible and comfortable, mucoadhesive films may be preferable to adhesive tablets. Additionally, they can get around the mucosa's very brief length of residence for oral gels, which is readily washed away and eliminated by saliva. Additionally, the films assist in protecting the wound surface in the local delivery of oral illnesses, which helps to lessen pain and improve the effectiveness of treatment. The perfect film should be soft, pliable, elastic, and sturdy enough to resist breaking under the strain of mouth movements. To stay in the mouth for the necessary amount of time and have the desired effect, it must also have strong mucoadhesive strength. If film swelling does develop, it should not be too severe to avoid discomfort. [31]

Patches

Patches are laminates made up of a mucoadhesive surface for mucosal attachment, an impermeable backing layer, and a reservoir layer that contains the medicine and releases it gradually. The technologies used for transdermal drug delivery are comparable to patch systems. Solvent casting and direct milling are two techniques used to make adhesive patches. The intermediate sheet from which patches are punched is created using the solvent casting process by pouring a drug and polymer solution onto a backing layer sheet and then letting the solvent(s) evaporate. In the direct milling procedure, formulation ingredients are uniformly combined and compacted to the correct thickness before being cut or punched into patches of a specific size and shape [32].To regulate the direction of drug release, stop drug loss, and lessen the device's distortion and disintegration throughout the application time, an impermeable backing layer may also be used.

Bioadhesive Wafers

By freeze-drying the polymer gels in dispersion or solution, bioadhesive wafers are highly porous structured solid formulations. Wafers are more prone to disintegration than standard formulations because of their porous texture. The delivery system is a composite wafer made up of bulk layers of antimicrobials, biodegradable polymers, and matrix polymers, and surface layers with sticky characteristics. It has been reported on a conceptually innovative periodontal drug delivery system designed to treat microbial infections brought on by periodontitis [33].

Bioadhesive Lozenges

The potential for longer drug release with increased patient compliance is provided by bioadhesive lozenges. Drugs that work in the mouth, such as antibiotics, corticosteroids, local anaesthetics, and antifungals, can be delivered via bioadhesive lozenges. Antifungal medicines can be administered to the oral cavity via a bioadhesive lozenge, according to a report. Since these bioadhesive lozenges disintegrate within 30 minutes, the total amount of the medicine that may be administered is constrained [34]. This short residence time at the site of absorption is dependent on the size and type of formulation. Lozenges usually dissolve or dissolve into the mouth depending on how aggressively the patient suctions. Uncontrolled swallowing and increased salivation lead to medication loss down the GI system. As a result, the inter- and intra-individual variability in absorption and bioavailability is often substantially higher for solid dosage forms. Additionally, these systems are unable to deliver medication release that is unidirectional. Another significant barrier to the efficacy of such dose formulations is continuous salivation.

Gels and ointments

As opposed to tablets, patches, or films, semisolid dosage forms may not provide the most precise drug dosage. The use of mucoadhesive formulations has improved the gels' poor retention at the application site. Hyaluronic acid, carbopol, sodium carboxymethylcellulose, and xanthan gum are a few mucoadhesive polymers that experience a phase change from liquid to semisolid. This alteration increases viscosity, which causes medications to release slowly and under control. Another interesting dosage type for buccal medication administration is hydrogel. They are made of polymers that physically entrap drug molecules for later gradual release via diffusion or erosion. The local delivery of pharmaceuticals for the treatment of periodontitis, an inflammatory and infectious condition that results in pockets forming between the gum and the tooth and can ultimately result in tooth loss, is a significant application of adhesive gels. When included in formulations with antimicrobials that are simple to inject with a syringe into the periodontal pocket, mucoadhesive polymers may be helpful for treating periodontitis. [35] HPMC has been utilised as a component in adhesive ointments. Additionally, a highly viscous gel that could stay on the tissue for up to 8 hours was created using carbopol and hydroxyl propylcellulose for ointment dosage forms.

Medicated chewing gums

Despite the challenges in controlling the dose supplied, medicated chewing gums nevertheless offer some benefits as drug delivery systems, particularly in the treatment of dental disorders and in nicotine replacement therapy [36]. Stay Alert®, a caffeinated chewing gum, was created lately to reduce drowsiness. It absorbs much more quickly and has a bioavailability that is comparable to that of the capsule formulation. For the purpose of quitting smoking, nicotine chewing gums like Nicorette® and Nicotinell® have been sold.

Pastes

Pastes have been used to deliver controlled release in oral care formulations as well as antibacterial agents for enhanced extraction socket healing following tooth extractions in

patients with HIV illness. Using a carbomer polymer, mucoadhesive pastes containing methylprednisolone hydrogen succinate have been identified [37].

Liquid dosage forms

They consist of medication solutions or suspensions in appropriate aqueous carriers. Such dosage forms are frequently used to deliver localised effects to the oral cavity, and mouthwashes and breath fresheners with antibacterial properties are readily accessible in the market for this use [38]. The drawback of these liquid dose forms is that they can release relatively uncontrolled amounts of medication throughout the oral cavity and are not easily retained or targeted to the buccal mucosa. Chitosan exhibits the highest level of binding among the diverse spectrum of polymer solutions, followed by methylcellulose, gelatin, carbopol, and polycarbophil. Viscous liquids may be applied to the mucosal surface of the buccal cavity as either protective coatings or drug delivery vehicles. Artificial saliva solutions are used to treat dry mouth in order to lubricate the mucosal surfaces. As a bioadhesive polymer, sodium CMC is included in these solutions.

Recent innovations [39,40]

Gel Forming Liquids

This kind of formulation, which is liquid when applied, transforms into a viscoelastic gel in response to stimuli like temperature, ionic strength, or pH. As the pH rises, carbomers become more viscous. Alginate and gellan gum both produce gel when exposed to stronger ions, especially Ca^{+2} ions. At about body temperature, smart hydrogel® (Advanced medical solution) and poloxamers gel.

Slowly disintegrating buccal mucoadhesive plain tablet (SDBMPT)

The preparation of SDBMPTs involves using a significant amount of HPC. For instance, a tablet with 20 mg of medication, 20 mg of HPC, 20 mg of CMC, and 60 mg of lactose would be mixed and compressed with an 8 mm-diameter flat sided die. The one drawback is that it loses its shape and softens over time, making it difficult to regulate disintegration over an extended length of time.

BCTS (Buccal Covered Tablet System)

S-DBMP-T system is positioned between two sheets of polyethylene. Lower sheet is constructed of adhesives, while above sheet has a hole to absorb water. Drugs are transported by way of this mechanism over the mucosal membrane. ionisation and solubilization take place because the based on effervescent technology as described in is smaller than pKa for a weak base.

TECHNIQUES TO EVALUATE MUCOADHESION

[A] In-vitro methods.

[B] In-vivo methods

[C] In-vitro as Well as in-vivo method

A. In-vitro / Ex-vivo methods

In vitro tests were initially designed to screen potential bioadhesion, because an evaluation of bioadhesive properties is fundamental to the development of new bioadhesives [41]. The most commonly employed in vitro techniques are

1. Tensile Strength Measurement

a) Wilhelmy Plate Technique

A small glass plate (2×5cm) was coated with 1% w/v of the mucoadhesive agent. The mucus gel was taken from goat intestine kept in a suitable container, where the above mentioned glass plate can be kept in contact with gel in a balanced condition and the temperature was maintaining at30°C. Nylon thread was attached at one end of the glass plate. Provision was given to raise the weight at the other end.At specified intervals, weight was added to detach the coated glass plate from gel and the force required to pull the plate out of the gel was determined under experimental condition. Six plates were tested for each material and the average weights required were calculated [42].

b) Tensile Tester

It is used to measure the adhesive force of the polymer complexes with a plastic (PolyVinylChloride) plate. Polymers and plastic plates were cut with the area 1 cm sq. (thickness: 0.8 mm). The polymer wasprewetted with water and placed on the surface of the plastic plate. They were kept in contact with the plate under the force of "fingertip for 2 min before themeasurement [43]. The peak force required to detach the polymer from the plastic plate was measured

c) Electromagnetic Force Transducer (EMFT)

The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer microsphere from a tissue sample. It has the unique ability to record simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force [44].

2. Shear Stress Measurement

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their place of contact of adhesion. Two smooth, polished plexi glass box were selected; one block was fixed with adhesive araldite on a glass plate, which was fixed on levelled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was passed down through a pulley. At the end of the thread a pan was attached into which the weights can be added [45].

3 Modified Physical Balance

A modified balance method was used to determine the ex vivo mucoadhesive strength. Fresh sheep buccal mucosa or goat stomach mucosa or rat stomach mucosa or porcine gastric mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter.

The two sides of the balance were made equal before the study, by keeping a 5-gm weight on the right-hand pan. A weight of 5 gm was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gives the mucoadhesive strength of the buccal tablet in grams. [46] The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams.

From the mucoadhesive strength following parameter was calculated.

$$\text{Force of Adhesion (N)} = \frac{\text{Bioadhesive strength (gm)} \times 9.8}{1000}$$

4 Microbalance Method

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 [47]. 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.

5 Ex-vivo Mucoadhesive Strength Determination

This technique is specific for microspheres and in this technique four number of Albino rats were fasted overnight and then 25 number of microspheres (N_0) were ingested to these rats through an oral feeding needle [48]. These were then sacrificed at an interval of 0, 4, 8, 12 hours respectively to isolate their stomach and intestine region. Thestomach and intestine regions are cut and opened longitudinally to note the number of microspheres adhering to these regions (N_S)

$$\% \text{ Adhesive strength} = (Ns/No) * 100.$$

No =Number of microspheres

Ns = Number of microspheres adhered

6 Swelling Index

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 [49]. The swelling index is calculated using following formula.

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

Where,

Wt = Weight of the dosage form at time t

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

7 Viscometer method

A simple viscometric method is used to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15 %w/v porcine gastric mucin dispersion in 0.1M HCl (pH 1) or 0.1M acetate buffer (pH 5.5) is measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion are calculated [50].

8 Fluorescent probe method

In this method the membrane lipid bilayer and membrane proteins are labelled with pyrene and fluorescein isothiocyanate, respectively. The cells are then mixed with candidate bioadhesive, and the changes in fluorescence spectra should be monitored [51]. This gives a direct indication of polymer binding and its influence on polymer adhesion.

B. Measurement of Residence Time (In Vivo Methods)

1. Use of Radioisotopes

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulphate, 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 GIT.

Approximately 2 gm of each formulation to be tested is radiolabelled by the addition of 3-4 drops (20MBq) of technetium-99m DTPA (diethylenetriaminepentaacetic acid). The gel to be tested is then carefully and thoroughly mixed with the technetium. The average final activity per dose and per subject, at the time of administrationsranged from 0.92 to 1.14MBq.After the subject had been asked to swallow his saliva, an amount of approximately 100 mg accurately weighted of the formulation is applied topically with a syringe on the right lower premolar region and spread with a small teflon spatula on anarea of approximately 1 cm^2 of the oral mucosa.Each test formulation is applied only once throughout the trial [52]

2. Gamma Scintigraphy Technique

Three groups of five healthy male volunteers are taken for gamma scintigraphic studies. A capsule containing the granules is administered with 180 ml of water, with the subject in a sitting position, at 8 a.m. or 12 p.m., after the volunteer had fasted overnight for at least 12 hr. The volunteers are not allowed toeat or drink during the imaging period. One minute after

administration gamma images, each of 1-min duration, are recorded continuously for 30 min, after which six images, each of 1-min duration, are recorded every 15 min for the next 3–4 hr. During imaging each subject is in a supine position beneath thegamma camera. At all other times they are able to move freely.Gamma counts are detected using a dual-head gamma). camera equipped with collimators. [53]

3. 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 [54]

4. **In vivo evaluation of gastric mucoadhesion of microspheres**

Male Wistar rats, 200–250 gm, are fasted for 24 hr before 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 is determined. [55]

5. Rat gut loop studies of mucoadhesion

Male Wistar rats, with a mean weight about 300 gm, 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 is 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 microspheresuspension 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. [56]

C. In-vivo as well as in-vitro Technique

BIACORE

Recently mucoadhesion 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 thesame. 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. [57,58]

The most widely used sensor chip is CM5 (BIACORER) whose surface is modified with a carboxymethylated dextran layer. In general, the ligand can covalently bind to the sensor chip surface via carboxyl moieties on the dextran. Functional groups on the ligand that can be used for coupling include NH_2, SH, CHO and COOH.

Conclusion

Drug delivery systems created with the goal of enhancing patient compliance and convenience are more crucial than ever now. Therefore, there is a lot of work being done to create innovative dosage forms to meet the growing patient demand for more practical dosage forms. Oral mucosal delivery provides a practical method of administering medication to the general public as well as to particular populations with swallowing issues. When compared to alternative dosage forms, mucoadhesive dosage forms are more affordable, have good patient compliance, and provide prolonged contact time at the attachment site. This controlled release delivery technique is made possible by the use of mucoadhesive polymers. Although there have been substantial improvements made in the field of mucoadhesives, there are still numerous problems that have not been solved. However, this medication delivery mechanism has been the subject of extensive research. However, in order to understand how to practically distribute medication for the treatment of both systemic and localised disorders, much more study must be done on these innovative mucoadhesive formulations.

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