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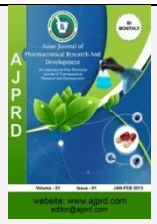

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Review Article

Review on a Oral Mucoadhesive Drug Delivery System

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A B S T R A C T

Since the previous four decades, the idea of mucoadhesion has attracted significant interest across a range of pharmaceutics domains.Because mucosal membranes are relatively permeable, the mucoadhesive drug delivery system is a well-liked innovative drug delivery technique, allowing for the rapid uptake of a medication into the systemic circulation and avoiding the first pass metabolism. Recent years have seen the development of a number of mucoadhesive drug delivery systems for nasal, buccal, oral, vaginal, and rectal routes for both local and systemic effects.The mucus membrane, which covers the mucin molecules and the mucosal epithelial surface, can interact with mucoadhesive drug delivery systems. This interaction increases the dosage form's residence time at the site of absorption, increasing medication bioavailability and effectiveness while also enhancing therapeutic results.

Keywords: Metabolism, Mucoadhesive, Buccal, Polymer,

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INTRODUCTION

The oral mucosa has a rich blood supply[1]. Oral route of drug administration is the most convenient and preferred route by patients but the main aim in the process of drug development is to obtain a drug product with a good oral bioavailability. The problem of bioavailability is dependent upon the formulation[2].

Traditional drug delivery methods[3] for the oral mucosa include liquids, erodible or chewable tablets, capsules, and buccal or sublingual tablets. Unfortunately, due to involuntary swallowing and a relatively short residence period caused by mastication, speaking, etc., a significant percentage of the medication in these systems may be inaccessible, making prolonged release generally out of the question[4].For mucoadhesive drug delivery, dosage forms must be small and flexible enough to be accepted by patients and not irritate them. The situation in which two materials, at least one of which is biological in nature, are kept together for a long time by interfacial forces is known as bioadhesion[5]. The most common mucosal dosage forms now on the market include chewing gum, ointment, gel, spray, and tablets. Oral drug administration is a potential method to apply a variety of therapeutic agents to the oral mucosal surface, according to several studies in the literature on clinical trials and registered patents of oral mucoadhesivemedicines[6].

Bio-adhesion, which is primarily used to explain the adhesion between polymers and soft tissue, is any bond formed between natural and synthetic materials with a biological surface.Despite the fact that there are numerous in vitro techniques for determining mucoadhesivity that are already in use, the higher cost and challenging installation of these techniques makes this task still perplexing[7].

Mucoadhesive DDS is required.

- Painless administration
- Rapid onset action
- Low enzymatic activity
- Avoid of first pass metabolism
- Rapid onset action
- Good bioavailability due to its significant surface area
- and strong blood flow
- Herbal mucoadhesive oral gel decreased the negative effect

- Oral mucosa has rich blood supply

Mucoadhesion mechanism

Typically divided into**:**

1) Contact stage

2) Stage of consolidation

The first stage is characterised by the mucoadhesion's contact with the mucous membrane, the formulation expanding and spreading, and the beginning of the formulation's deep contact with the mucous layer[8].

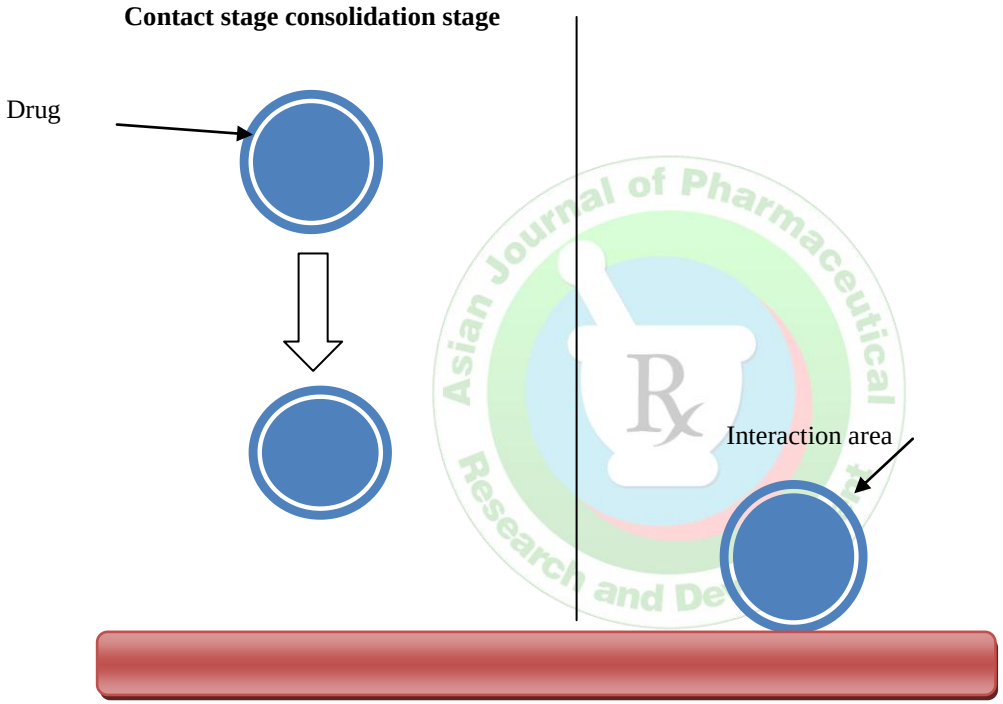
Molecules that are mucoadhesive can separate and form weak hydrogen and van der Waals bond[9]. Basically, the presence of moisture activates materials. There are two ideas that account for the consolidation phase: Moisture plasticizes the system.

1. The theory of diffusion

2. The hypothesis of dehydration

The inter-perforation of mucin and polymer chains up to a sufficient depth is described in the diffusion theory as being necessary to create a semi-permanent adhesive bond. Such a penetration rate would unquestionably depend on a number of factors, including the type of mucoadhesive chains, diffusion coefficient, flexibility, and motility in relation to contact time[10].

Dehydration hypothesis states that substances that easily gel in an aqueous environment might dehydrate mucus when they come into touch with it because of the osmotic pressure differential [5].



Polymer used in mucoadhesive DDS

Criteria	*Category*	*Example*
Based on Source	**Natural**	Tragacanth ,Alginate, Guar gum, Karayagum , Agarose, Carrageenan, Chitasan, Tamarind gum
	Synthetic	Cellulose derivatives, polyvinyl alcohol, Polyacrylic acid polymer, polyethylene oxide, polyvinylpyrrolidon, thiolated polymer

Based on solubility	***Water solubility***	Carbopol , sodium carboxy methyl cellulose, Pectin, Xanthum gum, Sodium alginate, HPMC
	Water insolubiity	Chitosan, Ethyl cellulose, Polycabophil

Based on charge	***Cationic***	Chitosan[11], dimethyl amino ethyl dextran, Amino dextran
	Anionic	Chitosan, EDTA, CMC, Xanthum gum, Alginate, carbophil
	Non – ionic	Polyvinyl alcohol, Hydroxy propyl cellulose, Hydroxy ethyl starch, polyvinyl pyrrolidone

Formulations of mucoadhesive drug delivery system

Tablets

The diameter of tablets, which ranges from 5-8 mm, is small, flat, and oval[12,13].Mucoadhesive tablets, in contrast to traditional tablets, don't significantly interfere with speaking and drinking. They liquefy, cling to the mucosa, and are held there until the dissolution or release is finished. Generally speaking, mucoadhesive tablets have the potential to be used for controlled release drug delivery, but coupling mucoadhesive properties to tablets has additional benefits. For instance, it offers effective absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer. Mucoadhesive tablets can be made to stick to any mucosal tissue, including those in the stomach, providing both localised and system[14].

Gel or Hydrogel

Gels and hydrogels are two different kinds of semi-solid adhesive systems. Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold

water within its porous structure[15]. To increase their absorption and lengthen their stay, they should be administered to the buccal mucosa or intra-periodontal pocket. Gels provide a perfect drug delivery system for the oral cavity because they have the advantage of being able to establish direct contact with the mucosa and release the medication quickly where it is applied. The effectiveness of gels is generally increased by carbomers because they prolong the duration of action and lengthen the residence period on mucous. Gels are superior to solutions because they have a longer release time and better bioavailability. is an oral mucoadhesive gel that is brushed on the teeth to stop plaque from forming and has chlorhexidinegluconate as an active ingredient, thus improving oral hygiene. It also contains the polymer Hydroxypropyl cellulose (HPC) which aids to keep the gel inside the oral cavity[6]. Polysaccharides have physicochemical properties that make it simple to create particles and hydrogels for transport reasons as well as a convenient handle for chemical modification when needed[16].

Films:

Flexible bioadhesive films can be utilised to deliver medications directly to particular mucosal membranes. They make very close contact with the membrane and can deliver a precise amount of medication to the absorption location. Zilactin®, which is used in the treatment of cold sores and mouth ulcers, is an illustration of a bioadhesivefilm[17].In order to imitate oral/peroral circumstances, mucoadhesive studies of Carbopol® polymers/PVA films were carried out utilising a modified in-vitro esophageal retention (IVOR) model[18].

Patches

A mucoadhesive surface for mucosal attachment, a drug reservoir layer from which the drug is dispensed in a regulated manner, and an impermeable waterproof backing layer make up patches. The technologies used for transdermal drug delivery are comparable to patch systems. To prepare adhesive patches, a variety of techniques are used, including direct milling and solvent casting techniques. The intermediate sheet from which patches are punched is set up using the solvent casting process by pouring the drug and polymer solution onto a backing layer sheet and then letting the solvent(s) evaporate. However, in the direct milling procedure, the component parts of the formulation are uniformly blended and compacted to the desired thickness before being cut or punched out into patches of a specific size and shape.The direction of drug release can be controlled, drug loss can be avoided, and the device's deformation and disintegration can be minimised by using an impermeable backing[19].Shermer[20]assessed the effectiveness and acceptability of a mucoadhesive patch and an oral painkiller for the treatment of aphthous stomatitis.The mucoadhesive patch was found to be more effective than the oral solution in terms of healing time and pain intensity after 12 and 24 h[21].

Solution

When administering the drug in the nasal cavity and eyes, the mucoadhesive formulation is administered in solution form. Polymers that are mucoadhesive are utilised in mucoadhesive formulation to increase the mucosal surface's resistance. When the mucoadhesive system is applied to the eye, it is referred to as the situ gelling system[22].

Measurement of mucoadhesivity

Tablet swelling study

Accurately weigh the mucoadhesive dose form, then put it in a beaker with 200 ml of buffer liquid.After each interval, take the dose form out and weigh it once more. Continue in this manner for up to 8 hours. You can use the formula below to determine

calculating the swelling index:

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

Where,

S.I.=Swelling index

Wt=Weight of the dosage form at time t

Wo=Initial weight of dry dosage form[10].

The Wilhelm plate method

This method is typically used to calculate the size of dynamic contact angles[24]. This involves the use of a microtensiometer or a microbalance. The CAHN dynamic contact angle analyzer (CAHN instruments, model DCA 322, Cerritos) is used to detect adhesive microforce. The DCA 322 setup includes a microbalance configuration and an IBM, well-matched CPU.46.Wilhemy's plate technique, or the microforce balance technique, can also be modified in order to measure the specific adhesion force of microparticles[25] and mucous tissue put on a metal wire with a tiny diameter that is strung from the microtensiometer's sample loop.47. Important bioadhesive properties, primarily the fracture strength,deformation to failure, and the work of adhesion,

can be analysed by applying the CAHN software technique. With the help of a physiological tissue chamber that replicates in vivo settings, this method enables the quantity of bioadhesive characteristics of a candidate material to be tested in the precise geometry of the proposed microsphere delivery device[24].

Fluorescent probes method

In order to better understand the structural requirements for bioadhesion and create more effective bioadhesive polymers for oral use, Park and Robinson (1984) used the fluorescence probe method to investigate the interaction of polymers with the conjunctival epithelial cell membrane(26). When mixing the cell with a potential bioadhesive, Sudhakar et al. (2006) tagged the membrane proteins and lipid bilayer with pyrene and fluorescein isothiocyanate, respectively, and observed the fluorescence spectra. This demonstrated clearly how polymer binding affects polymer adhesion. In this technique, pyrene and fluorescein isothiocyanate were used to mark the membrane proteins and bilayered membrane lipids, respectively. As the mucoadhesive agents and cells were combined, alterations in the fluorescence spectra were observed. This provided a clear evidence of the influence of polymer binding within the polymer. This approach has been used to assess the dose forms of corsodyl gel (oromucosal gel) and corlan pellets (oromucosal pellet)[27].

Modified USP disintegration apparatus

Using a modified USP disintegration device, Nakane et al. (1996) first calculated the in vitro residence time. At 37 °C, the 800 mL isotonic phosphate buffer pH 6.75 disintegration medium was kept constant. A vertically mounted glass slab had a 3 cm long section of rabbit intestinal mucosa adhered to its surface. Using 15 mL IPB, one surface of the mucoadhesive tablet was hydrated before the hydrated surface was brought in touch with the mucosal membrane.The tablet was entirely submerged in the buffer solution at the lowest point and was out at the highest point. The glass slab was mounted vertically to the device and permitted to move up and down. The amount of time required for the tablet to completely erode or separate from the mucosal surface was noted. This approach has been used to analyse the dose forms of Calcitonin tabs and Enapramil solution. The approach is more reliable because it complies with in vivo physiological conditions, although solid particles must first be hydrated before adhesion[24].

Colloidal gold staining method

An innovative in-vitro method for comparing the mucoadhesive properties of diverse hydrogels was described. Red colloidal gold particles are used in this method, and they are stabilised by partially or completely adsorbed mucin. The surface of the mucoadhesive turns red as a result of the contact. By comparing the intensity of the red hue, one can compare the mucoadhesive qualities of the mucoadhesivedevice[26].

Falling Liquid Film Method

Nielsen, Schubert and Hansen (1998) used a method proposed by RangoRao and Buri (1989) in which the chosen mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut. This support is placed inclined in a cylindrical cell with a temperature controlled at 37 ºC. An isotonic solution is pumped through the mucous membrane and collected in a beaker. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter (Chowdary, Rao, 2004). For semi-solid systems, the non adheredmucoadhesive can be quantified by high performance liquid chromatography (Nielsen, Schubert, Hansen, 1998). In this later case, porcine stomach, intestinal and buccal mucus were tested, and also jejunum from rabbits. The validation of this method showed that the type of mucus used does not influence the results. The release systems tested were precursors of liquid crystals constituted w24areaaby monoglycerides. This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy (Nielsen, Schubert, Hansen, 1998)[25].

Recent study of mucoadhesive drug delivery system

Many drug that are poorly bioavailable and quickly destroyed when administered orally have extensive uses for oral mucoadhesive drug delivery, which offers advantages of high accessibility and low enzymatic activity. Before, periodontal disorders were treated with hydrophilic polymers as SCMC, HPC, and polycarbophil; however, the current approach is to effectively utilise these systems to transport peptides, proteins, and polysaccharides[28].The mucoadhesivedevice's free mucophilic chains are anticipated to diffuse from the network into the mucous layer when the hydrogel system comes into contact with mucus over time due to the concentration gradient across the interface, whereas the mucus' glycoprotein chains are anticipated to diffuse into the polymer. The device's adherence to the mucus is strengthened by this event.To reduce the quantity of unreacted and crosslinked monomer that persisted in the networks after polymerization, a number of different ways of creating the polymers have been researched[17]. To provide prolonged drug release, a number of laminated devices have been created. It can be classifie as:-

Monolithic (or matrix) systems where the drug is dissolved or dispersed in the polymer system – diffusion of drug from the drug/polymer matrix controls the overall rate of its release from the device.

Reservoir (or membrane) systems, in which the overall rate of drug release is regulated by diffusional resistance through a polymeric membrane[5]. Recently, investigations on mucoadhesion employing BIACORE® integrated chip (IC) systems have been published. The technique entails immobilising the polymer (powder) before moving the mucin solution across the IC and onto the surface of the latter. The mucin then engages in interaction with the polymer's surface. An optical phenomenon called Surface Plasmon Resonance (SPR) evaluates the refractive index change that occurs when mucin clings to the surface of the polymer and analyses the interaction between the polymer and mucin[23].

CONCLUSION

This review comes to the conclusion that the mucoadhesive drug delivery mechanism is preferable to the traditional oral route. It is a special substitute for traditional drugs due to its capacity to circumvent hepatic metabolism, reduction in dose, frequency, and duration, and improving the bioavailability. This medication delivery device will demonstrate a regulated drug release.It is a growing field whose objectives include the production of novel device, more "intelligent" polymers, and new approaches to better understand the mucoadhesion phenomena.

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