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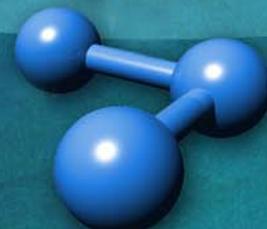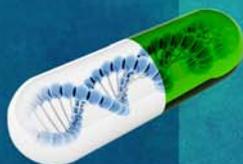
Review Article

RECENT ADVANCES IN MUCOADHESIVE/ BIOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW

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The current article has been focused on the mucoadhesive drug delivery system may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Application of dosage forms to mucosal surfaces may be of benefit 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, factors affecting mucoadhesion, evaluating methods, and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal) based on literatures were reported so far.

Keywords: Bioadhesive, Transmucosal, Bioavailability, Transdermal

INTRODUCTION

The oral mucosa has many properties which make it an attractive site for drug delivery but also provides several challenges for researchers investigating novel delivery techniques to overcome many different formulations including sprays, tablets, mouthwashes, gels, pastes and patches are presently used for delivery into and/ or across the oral mucosa (Hearnde *et al.*, 2011; Mathiowitz, 2000). The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which

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presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption (Miller *et al.*, 2005). A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1-5%), (Veuillez *et al.*, 2001) owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

MUCOADHESION

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces (Good, 1983). In biological systems, bioadhesion can be classified into 3 types:

- Type 1, adhesion between two biological

phases, for example, platelet aggregation and wound healing.

- Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio-film formation on prosthetic devices and inserts.

- Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydro gels to soft tissues (Henriksen *et al.*, 1996) and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Leung and Robinson (Leung and Robinson, 1988) described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane and if the

Figure 1: Schematic Representation of Approaches to Oral Mucoadhesive Drug Delivery System
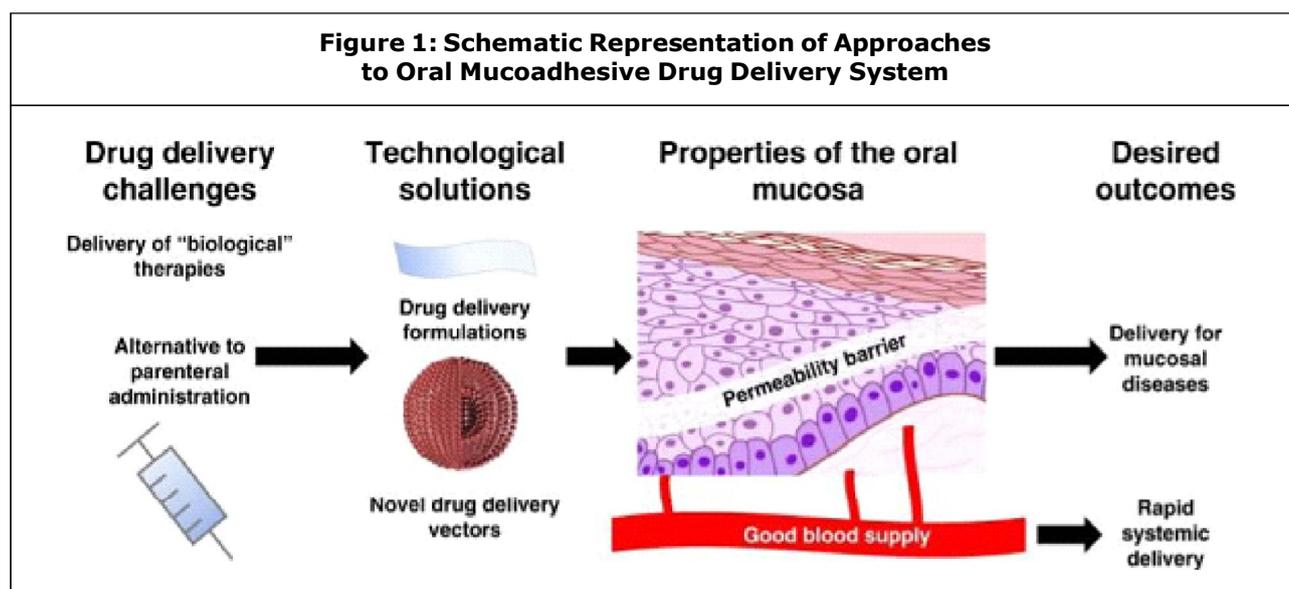
substrate is mucus membrane the term mucoadhesion is used.

Hydrocolloids are believed to adhere to mucosa upon hydration, as the synthetic polymer molecules become more freely mobile and are able to orientate adhesive sites favorably with those of the substrate. As the level of hydration increases, adhesive strength was found to decrease, since mucoadhesive bonds become overextended. It is proposed that the hydrogen bond-forming capacity of the polymer is important in this effect, and may emphasize the well-documented mucoadhesive properties of polymers possessing numerous carboxyl groups such as carbopol and polycarbophil. However, the greater swelling properties of the polymer increased ionisation may lead to a reduction in mechanical strength and concomitant reduction in mucoadhesive properties. Based on the mucoadhesion theories, it may be concluded that the most efficient mucoadhesive polymers have physiochemical properties that are closely related to those of the mucus substrate.

ADVANTAGES (Asane, 2007; Sudhakar Yajaman and Ketousetuo Kuotsu, 2006)

• Prolongs the residence time of the dosage form at the site of absorption

• To avoid the first pass metabolism

• Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug

• Excellent accessibility

• Rapid absorption because of enormous blood supply and good blood flow rates

• Increase in drug bioavailability due to first pass metabolism avoidance

• Drug is protected from degradation in the acidic environment in the GIT

• Improved patient compliance & ease of drug administration

• Faster onset of action is achieved due to mucosal surface

MECHANISM OF MUCOADHESION

The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must be dominated. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water (Lee *et al.*, 2000).

Due to its relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. Lee, Park, Robinson, 2000 had described the mechanism of mucoadhesion in four different approaches.

These include

• Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity)

• Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many mucoadhesive that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract)

- Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina)

- Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the esophagus or eye)

It is unlikely that the mucoadhesive process will be the same in each case (Chowdary and Srinivas, 2000). In the study of adhesion, generally, two stages in the adhesive process supports the mechanism of interaction between mucoadhesive materials and a mucous membrane Thus, the mechanism of mucoadhesion is generally divided in two stages, the contact stage and the consolidation stage.

Stage 1: Contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucus membrane.

Stage 2: Consolidation stage: Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

THERIOS OF MUCOADHESION

Various therios exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond (Longer and Robinson, 1986). However five main theories can be distinguished.

- Wettability theory

- Electronic theory

- Fracture theory

- Adsorption theory

- Diffusion theory

Wetting Theory of Mucoadhesion

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesive. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion (McBain and Hopkins, 1925).

The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre's equation (Pritchard, 1970);

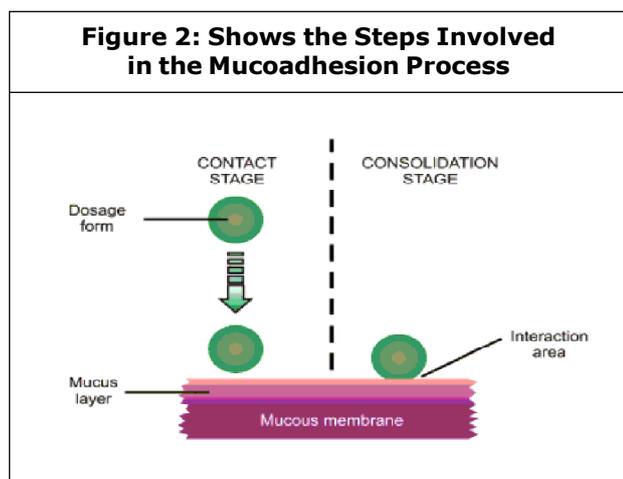$$\omega_A = \gamma_b + \gamma_t - \gamma_b \qquad \ldots(1)$$

where ω_A is the specific thermodynamic work of adhesion and γ_b, γ_t, and γ_{bt} represent, respectively, the surface tensions of the bioadhesive polymer, the substrate, and the interfacial tension. The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases (Wake, 1982). Figure 2 a drop of liquid bioadhesive spreading over a soft-tissue surface.

A liquid bioadhesive spreading over a typical soft tissue surface

Horizontal resolution of the forces gives the Young equation:

$$\gamma_{ta} = \gamma_{bt} + \gamma_{ba} \cos\theta \qquad \ldots(2)$$

where θ *is* the angle of contact, γ_{bt} is the surface tension between the tissue and polymer, γ_{ba} is

Figure 2: Shows the Steps Involved in the Mucoadhesion Process

the surface tension between polymer and air, and γ_{ta} is the surface tension between tissue and air. Equation 3 states that if the angle of contact, θ is greater than zero, the wetting will be incomplete. If the vector γ_{ta} greatly exceeds $\gamma_{bt} + \gamma_{ba}$, that is (Wake, 1982):]

$$\gamma_{ta} \geq \gamma_{bt} + \gamma_{ba} \qquad ...(3)$$

Then θ will approach zero and wetting will be complete. If a bioadhesive material is to successfully adhere to a biological surface, it must first dispel barrier substances and then spontaneously spread across the underlying substrate, either tissue or mucus. The spreading coefficient, S_b, can be defined as shown in

$$S_b = \gamma_{ta} - \gamma_{bt} - \gamma_{ba} > 0 \qquad ...(4)$$

which states that bioadhesion is successful if S_b is positive, thereby setting the criteria for the surface tension vectors; in other words, bioadhesion is favored by large values of γ_{ta} or by small values of γ_{bt} and γ_{ba}

Electrostatic Theory of Mucoadhesion
(Ahuja A *et al.*, 1997)

According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Diffusion Theory of Mucoadhesion

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semi permanent bond. The process can be visualized from the point of initial contact (Alur H H *et al.*, 1999). The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved as shown in

a. Schematic representation of the diffusion theory of bioadhesion. Blue polymer layer and red mucus layer before contact; (b) upon contact; (c) The interface becomes diffuse after contact for a period of time

The exact depth needed for good bioadhesive bonds is unclear, but is estimated to be in the range of 0.2-0.5 μm (Alur H H *et al.*, 1999). The mean diffusional depth of the bioadhesive polymer segments, *s*, may be represented by

$$S = \sqrt{2tD} \qquad ...(5)$$

where *D* is the diffusion coefficient and t is the contact time. Duchene *et al.* (1988) adapted Equation 5 to give Equation 6, which can be used to determine the time, *t*, to bioadhesion of a particular polymer:

$$t = \frac{l^2}{D_b} \qquad ...(6)$$

in which *l* represents the interpenetrating depth

and D_b the diffusion coefficient of a bioadhesive through the substrate.

Once intimate contact is achieved, the substrate and adhesive chains move along their respective concentration gradients into the opposite phases. Depth of diffusion is dependent on the diffusion coefficient of both phases. Reinhart and Peppas (Reinhart and Peppas, 1984) reported that the diffusion coefficient depended on the molecular weight of the polymer strand and that it decreased with increasing cross-linking density.

Adsorption Theory of Mucoadhesion

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces.[21] When polar molecules or groups are present, they reorient ate at the interface (Leung S H and Robinson J R 1988). Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding) (Huntsberger, 1967; Kinloch, 1980; Yang and Robinson, 1998).

Fracture Theory of Adhesion

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

$$\sigma = \left(E \times \varepsilon / L \right)^{1/2} \qquad ...(7)$$

where σ is the fracture strength, ε fracture energy, E young modulus of elasticity, and L the critical crack length (Ahuja *et al.*, 1997).

FACTORS AFFECTING MUCOADHESION (Chen J L and Cyr G N, 1963; Ch'ng *et al.*, 1985)

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

Polymer Based Factors

1. Molecular weight of the polymer, concentration of polymer used of polymer chain.

2. Swelling factor stereochemistry of polymer.

Physical Factors

pH at polymer substrate interface applied strength, contact time

Physiological Factors

Mucin turnover rate diseased state

IDEAL MUCO POLYMER CHARACTERSTICS

A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva. As understood earlier, that various physical and chemical exchanges can affect the polymer/ mucus adhesion, so as polymer should be carefully selected with the following properties in mind (Deraguin B V and Smilga V P 1969).

• Polymer must have a high molecular weight up to 100.00 or more this is necessary to promote the adhesiveness between the polymer and mucus (Allur *et al.*,1990)

• Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion

becomes a problem (Huang *et al.*, 2000)

• High viscosity

• Degree of cross linking- it influences chain mobility and resistance to dissolution

• Highly cross linked polymers swell in presence of water and retain their structure. Swelling favors controlled release of the drug and increases the polymer/mucus interpenetration. But as the cross linking increases, the chain mobility decreases which reduces the muco adhesive strength

• Spatial conformation (Huang *et al.*, 2000)

• Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network (Sudhakar *et al.*, 2006)

• Concentration of the polymer-an optimum concentration is required to promote the muco adhesive strength. It depends however, on the dosage form. For solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi solid dosage forms an optimum concentration so essential beyond which the adhesive strength decreases (Imam *et al.*, 2003)

• Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. In this work, various chemical entities were attached to chitosan and the mucoadhesive strength was evaluated. Cationic chitosan HCl showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadhesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low

charge. Hence the mucoadhesive strength can be attributed as anion>cation>non-ionic (Ugwoke *et al.*, 2005).

• Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.

• Optimum pH – mucoadhesion is optimum at low pH conditions but at higher Ph change in the conformation occurs into a rod like structure making them more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces (Bernkop-Schnurch and Freudl, 1999; Hagerstrom *et al.*, 2000; Sigurdsson *et al.*, 2006; Lee *et al.*, 2000).

• High applied strength and initial contact time

• It should non toxic, economic, biocompatible preferably biodegradable

POLYMERS USED FOR MUCO-ADHESIVE DRUG DELIVERY

(Shojaei and Li, 1997)

1. PAA derivatives carbomer- carbopol noveon- polycarbophil

These are polymers of acrylic acid cross linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 2-6 micron diameter. Each primary particle exists as a network structure of polymer cahains interconnected by cross links. Carbopol polymers along with pemulen and noveon polymers are all cross linked. They swell in water upto 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0 the glass transition temperature is about 105°C. Due to presence of carboxylate group and an pKa of 6.0 to 0.5,

repulsion between the negative charges occurs leading to is swelling and hence increased mucoadhesive strength of the polymer (Park and Robinson, 1984).

Today, a large number of companies are using carbopol polymers because of the following merits.

- Good tableting formulation, flowability
- Long drug release profiles
- Can give drug releases profiles similar to carbopol 971 NF, with better handling characteristics.
- Are safe and effective for oral administration
- Are bioadhesive and providing increased bioavailability
- Are approved by many of the world. Pharmacopoeias
- Protect protein and peptides from degradation and hence increase the bioavailability of proteins or peptide based formulations

2. Chitosan

It is a cationic polymer (polysaccharide) (Jian-Hwa *et al.*, 2003), it is produced by the deactivation of chitin. Chitosan is gaining importance in the development of mucoadhesive drug delivery system because of its good biocompatibility, biodegradability and non toxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear provides greater polymer chain flexibility. Onishi and Machida showed that chitosan and its metabolized derivatives are quickly eliminated by the kidney (He *et al.*, 1998).

3. Newer second generation polymers

They have the following advantages

- More site specific hence called cytoadhesives.

- Are least effected by mucus turn over rates.
- Site specific drug delivery is possible.

Lectins

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues (Onishi and Machida, 1999). After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis. They hence allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic.

Thiolated Polymers

These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking (Clark *et al.*, 2000).

E.g. chitosan iminothiolane

PAA homocystiene

PAA cystiene

Alginate cystiene

Polyox WSRA

Class of high molecular weight polyethylene molecular weight polyethylene oxide homo polymers having the following properties (Lehr , 2000),

- Water soluble.
- Hydrophilic nature.

- High molecular weight.

- Functional group for hydrogen bonding.

- Biocompatible and non toxic.

- Can be formulated into tablets, films, gels, microcapsules, syrups.

NOVEL POLYMERS

- Tomato lectin showed that it has binding selectivity to the small intestine epithelium (Bottenberg *et al.*, 1991).

- Shajaei and Li have designed and characterized a co polymer of PAA and PEG monoethylether mono methacrylate (PAA-co-PEG) for exhibiting optimal buccal adhesion (Carreno-Gomez *et al.*, 1999).

- Leleetal, investigated novel polymers of PAA complexed with PEGylated drug conjugate (Shojaei and LI, 1997).

- A new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends.

- Bogataj *et al.*, prepared and studied Mucoadhesive microspheres for application in urinary bladder (Lele and Hoffman, 2000).

- Langath N *et al.* investigated the benefit of thiolated polymers for the development of buccal drug delivery systems (Alur *et al.*, 1999)

- Alur et al. Studied the transmucosal sustained delivery of chlorphenazine maleate in rabbits using a novel natural mucoadhesive gum from hakea as an excipient in buccal tablets. The gum provided sustained release and sufficient mucoadhesion (Langoth *et al.*, 2003).

RECENT APPLICATIONS IN AN ORAL MUCOADHESIVE DRUG DELIVERY

Oral mucoadhesive drug delivery has widespread applications for many drugs which on oral administration result in poor bioavailability and are rapidly degraded by the oral mucoadhesive drug delivery provides advantages of high accessibility and low enzymatic activity.

Earlier the hydrophilic polymers like SCMC, HPC and polycarbophil were used for the treatment of periodontal diseases, but now the trend is shifting towards the effective utilization of these systems to the delivery of peptides, proteins and polysaccharides (Park K and Robinson J R, 1984).

The buccal cavity has additional advantages of high patient compliance. Orabase, a first generation mucoadhesive paste has been used as barrier system for mouth ulcers. Semisolids offer more ease in administration, but tablets have also been formulated. Tablets include matrix devices or multilayered systems containing a mucoadhesive agent. The tablet is kept under the upper lip to avoid clearance mechanism of the salivary gland. Buccostem, an adhesive antiemetic tablet containing prochloroperazine is usually administered in this manner (Patel V M *et al.*, 2007 and Peppas N A and Buri P A, 1985).

Buccal mucoadhesive dosage forms may be classified into three types,

- A single layer device with multidirectional drug release.

- A dosage form with impermeable backing layer which is superimposed on top of a drug loaded bioadhesive layer, creating a double layered device and preventing loss from the top

surface of the dosage form into the oral cavity.

- Unidirectional release device, the drug is released only from the side adjacent to the buccal mucosa.

METHODS OF EVALUATION

Mucoadhesive polymers can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

IN VITRO METHODS

The importance is laid on the elucidation of the exact mechanisms of bioadhesion. These methods are (Botagataj *et al.*, 1999),

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Filling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- In vitro drug release studies
- Muco retentability studies

In Vivo Methods

- Use of radioisotopes (Sam *et al.*, 1989)
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic resonance (EPR) oximetry

- X ray studies
- Isolated loop technique

CURRENTLY USED FORMULATIONS

Representative drugs with transmucosal dosage former with type of release and manufacturer are shown in table. Many novel formulations have been advanced to various stages of development and approval and have met with varying manufacturing and marketing successes.

a. Tablets (Alur *et al.*, 1999)

Lozenges, troches and tablets for systemic delivery across the oral mucosa are currently commercially available for drugs including nitroglycerin and fentanyl. Solid formulations such as tablets and lozenges dissolve into the saliva utilizing the whole surface area of the oral cavity for absorption.

Drawbacks of tablets and lozenges include variation due to differences in saliva production and sucking intensity, accidental swallowing and short exposure time, usually no greater than 30 min. Mucoadhesive tablet formulations are better in this respect as they adhere to the mucosa-increasing exposure time. One example of this is a mucoadhesive tablet under development shown to deliver therapeutic doses of flurbiprofen to the saliva for 12 h. This mucoadhesive tablet allowed patients to eat and speak without discomfort and caused no irritation, bad taste or pain. When compared to delivery of the same drug via lozenges such as Benactiv® or orally in Froben® the daily dosage requirement was reduced as the drug release was sustained within the oral cavity. Striant™ is a commercially available mucoadhesive tablet for testosterone replace-

ment therapy.

b) Sprays (Palermo *et al.*, 2011)

Glyceryltrinitrate is a small molecule that can be rapidly delivered across the sublingual oral mucosa using a spray for angina relief. The Generex Biotechnology Corporation has developed a RapidMist™ spray which is capable of delivering large molecules, such as insulin across the oral mucosa. The Generex Oral-lyn™ spray uses micelles and generally recognised as safe GRAS like surfactants as permeability enhancers to improve the permeability of the drugs across the buccal epithelium. The product is currently available for purchase in India and Ecuador and awaiting approval elsewhere in the world. Other applications of the RapidMist™ system in development include vaccination against influenza and cancers, pain management and weight loss.

c) Mouthwashes (Battino *et al.*, 2002)

The current literature on mouthwashes and oral rinses predominantly focuses on their use in the local delivery of antimicrobial agents. Chlorhexidine gluconate is one such antimicrobial with literature supporting its use in the management of gingival and periodontal disease, caries and as prophylaxis for oral candidiasis in the immunosuppressed. The substantivity allows significant antibacterial effect up to 7 h after the mouth rinse. Several naturally occurring antimicrobials such as lactoperoxidases, lysozymes and lactoferrin have also been investigated in a mouthwash form. The effectiveness of essential oil containing antimicrobial mouthwashes is thought to relate to their antioxidant properties with current literature demonstrating variable levels of

effectiveness. More recently, the use of antimicrobial mouthwashes have also been proposed for reduction of viral contamination (HIV-1 and HSV-1) of bio-aerosols during the delivery of dental care. The management of vesiculo-ulcerative conditions frequently involves the topical delivery of various steroid preparations and antimicrobials in mouthwash form. Numerous other studies have utilized mouthwash vehicles to deliver established therapeutic agents in the management of various conditions, some of these have been referenced however extensive review of these is outside the scope of this review.

d) Gels (Peppas and Sahlin, 1996)

Gels have been investigated as a means of controlled drug delivery since the 1980s. The primary goal of bioadhesive controlled drug delivery is to localise a delivery device within the body to enhance the drug absorption process in a site-specific manner. Bioadhesion is affected by the synergistic action of the biological environment, the properties of the polymeric controlled release device, and the presence of the drug itself. Overall, more than half of the therapeutic agents and vehicles being formulated are in the development stage (bioavailability, distribution, safety and adherence stages). Others are at the stage of animal or ex-vivo studies. Few clinical trials have been performed and those that have are often small in size. None-the-less, gels applied to the oral mucosa have been trilled for the delivery of systemic analgesics, anti-hypertensive's and drugs for treating cardiovascular disease as well as topical delivery of antifungal agents, anti-inflammatories and mucoprotective agents to the oral mucosa.

e) Pastes (Ortega *et al.*, 2007)

The use of pastes as a drug delivery vehicle is a

relatively under investigated method with most current literature focussing on the intra-canal delivery of antimicrobial pastes in endodontics; however this is beyond the scope of this review. One currently commercially available muco-adhesive paste is Orabase® an oral adhesive paste that is available as a carrier alone or containing 0.1% triamcinoloneacetonide (Kenalog in Orabase®) for treating immunologically mediated oral mucosal conditions. Liposomes have been investigated as drug delivery carriers both as a solution and in a paste formulation. One study suggests that liposome encapsulated corticosteroids applied topically in a paste form may enhance symptom remission in the treatment of oral lichenplanus and an anti-inflammatory paste incorporating amlexanox has been found to accelerate healing of aphthous ulcers. Pastes have been utilised in the delivery of antimicrobial agents for improved extraction socket healing after tooth extractions in patients with HIV disease and for the delivery of controlled release triclosan in oral care formulations. Pastes are also being used for the local delivery and retention of slow release minocycline in the

gingival crevice surrounding teeth in the treatment of periodontal disease. Allen et al. investigated the topical delivery of an antiviral agent in paste form. The drug was delivered topically to oral and genital lesions. Only genital lesion response was measured and was found to have some effect. One might consider topical oral delivery for the treatment of oral HSV lesions.

f) Patches (Gibson *et al.*, 2007)

Several different patch systems that adhere to the oral mucosa and are designed to deliver drugs have been developed. There are basically three different types of oro-adhesive patches: patches with a dissolvable matrix for drug delivery to the oral cavity. These patches are longer acting than solid forms such as tablets and lozenges and can produce sustained drug release for treating oral candidiasis and mucositis. They slowly and completely dissolve during use leaving nothing to remove. However significant amounts of drug will be lost to the oral cavity. They are better used, therefore, for delivering drugs more generally into the oral cavity than into the oral mucosa to which they are applied. Non-dissolvable backing patches

Table 1: Shows Some Commercially Available Oral Mucoadhesive Drug Delivery Systems				
Drug	**Dosage form**	**Type of release**	**Product Name**	**Manufacturer**
Fentanyl citrate	Lozenge	Quick	Actiq	Cephalon
	Tablet	Quick	Fentora	Cephalon
	Film	Quick	Onsolis	Meda Pharmaceutical Inc
BuprenorphineHcl	Tablet	Quick	Subutex	Reckitt Benckiser
BuprenorphineHcl and naloxone	Tablet	Quick	Subutex	Reckitt Benckiser
Proclorperazine	Tablet	Controlled	Buccastem	Reckitt Benckiser
Testosterone	Tablet	Controlled	Striant SR	Columbia pharmaceuticals
Nitroglycerine	Tablet	Quick	Nitrostate	W lambert-pDavis
	Spray	Quick		pfizer pharmaceuticals
Glyceryltrinitrate	Spray	Quick	nitromist	NovaDel
Zolpidem	Spray	Quick	Zolpimist	NovaDel
	Tablet	Quick	Suscard	Forest laboreteries
Nicotine	Chewing gum	Quick	Nicorette	GSK Consumer Helth
	Lozenge	Quick	Nicotinelle	Novartis Consumer.

systems for systemic drug delivery that offer protection from saliva. The patches deliver a controlled concentrated dose of the drug into the oral mucosa for 10–15 h. Drawbacks include that the patch can only deliver to a small area of the mucosa, limiting the dose which can be delivered, and the patch has to be removed by the patient after the dose is delivered.

g) Wafers/Films (IntelGenxCorp., 2006)

Thin strips of polymeric films, capable of loading up to 20 mg of drugs, dissolve on the tongue in less than 30 s and deliver drugs(which are able to cross the permeability barrier) directly to the blood supply for rapid treatment of conditions such as impotence, migraines, motion sickness, pain relief and nausea. Similar wafer technology is already used in the treatment of migraines and it is hoped the fast dissolution of the wafers, the self-administrable nature of the technology and the high blood supply of the oral mucosa will enable fast effective treatments for many more conditions in the future.

CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. With the appropriate technologies, delivery techniques and the choice of the polymer for the oral mucosa could, in the future, be utilized for the treatment of many diseases both mucosal and systemic and the catalogue of drugs which can be delivered via the mucosa could be greatly increased. Further advances in muco-buccal adhesive

technology and sustained local drug release also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

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