CHAPTER II

LITERATURE REVIEW

1. Polysaccharide Gel (PG)

Durian (*Durio zibethinus* Murr.), a tropical fruit native to Southeast Asia, is one of the most highly valued and desired fruits among Southeast Asians due to its distinct flavour and unique taste. Its powerful odor has two distinct notes, one very strong and onion-like, the other more delicate and fruity. When the fruit is kept in a box a more fetid note also becomes evident. The fruit is ovoid-oblong to nearly round shape with an average size weighing between 2 and 4.5 kg depending on their varieties. The rind which usually weighs more than half of the total fruit weight is green to yellowish brown, thick and semi-woody with sharply pointed pyramidal thorns (Pongsamart and Panmaung, 1998).

Polysaccharide gel (PG) consisting of water-soluble polysaccharides is isolated from dried fruit-hulls of durian and has been found potential as pharmaceutical excipients. PG is composed principally of galacturonic acid, rhamnose, galactose, arabinose, and xylose. PG structurally consisted of long chain acid sugar and neutral sugars side chains. Its chemical composition was investigated by using CHNS-O Elemental Analyzer (EA) and carbon:hydrogen:oxygen at an atomic ratio of 2.88:5.33:3.09 were found, however, nitrogen and sulfur were not found (Pongsamart and Panmaung, 1998; Hokputsa et al., 2004).

Their applications as a tablet binder, tablet disintegrator and gelling agent have been well reported (Umprayn, Kaitmonkong, and Pongsamart, 1990). Further investigation have also shown that the crude PG have antibacterial activities against certain strain of gram positive bacteria, *Staphylococcus aureus*, and gram negative bacteria, *Escherichia coli* (Lipipun, Nantawanit, and Pongsamart, 2002).

2. Etiology and Management of Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is defined as the presence of recurring ulcers confined to the oral mucosa in patients with no other signs or symptoms of underlying disease. The classical presentation of RAS in the oral mucosa consists of painful, shallow, round ulcerations covered by a yellowish-tan pseudomembrane with a surrounding erythematous halo. The lesions are self-limiting, lasting 1 or 2 weeks. RAS is classified according to clinical characteristics in three categories; minor RAS, major RAS, and herpetiform aphthous stomatitis (Table1).

Table 1 Classification of RAS

	Minor RAS	Major RAS	Herpetiform aphthous stomatitis
Incidence	most common (75-85% of patients)	mainly in childhood and aldolescence (10-15% of patients)	least common (5-10% of patients)
Ulcer	less than10 mm in diameter; round erythema	more than10 mm in diameter; larger, deeper ulcer	multiple small, clustered lesions

Multiple hypotheses exist regarding the etiology of RAS. Current research in the area of RAS involves local immune dysfunction that triggers the molecular events responsible for mucosal injury creating the ulcers, a periodic syndrome with fever and pharyngitis, various nutritional deficiencies with or without underlying gastrointestinal disorders, some other primary immunodeficiencies, and infection with human immunodeficiency virus. Rarely, drugs such as nonsteroidal anti-inflammatory drugs or nicorandil can give rise to oral ulcers, similar to RAS. Food hypersensitivity, although rare, is related to RAS and manifests as part of the gluten sensitivity enteropathy complex or celiac disease. Zinc

deficiency, menstrual change, psychological illness and genetic factors associate with RAS. Patients with RAS consume some kinds of food such as Japanese radishes, seaweed, spinach, calcium, iron, vitamin B1, and vitamin C less frequently than the controls. In addition, vitamin C is required for the synthesis of collagen, and vitamin C deficiency might lead to the breakdown of already healed wounds (Ogura et al., 2001).

A Systemic Review of the Management of RAS (Porter et al., 2000).

1. Non-pharmacological therapy, i.e., oral hygiene, trauma prevention, avoidance of certain food/drinks.

2. Pharmacological therapy for minor to major RAS.

2.1 Over-the-counter conservative treatment; liquid antacids or 3% hydrogen peroxide/water solution.

2.2 Covering agents; orabase, 5% aphthasol, Zilactin® (Rodu, and Russell, 1988).

2.3 Antiseptics mouthwashes; benzydamine HCl, chlorhexadine gluconate.

2.4 Low potency topical steroid pellets and ointments; 0.1 % triamcinolone in carboxymethylcellulose paste and 0.1% triamcinolone in orabase.

2.5 Aerosal; beclomethasone dipropionate aerosol.

2.6 Steroid mouthwashes; betamethasone sodium phosphate, fluocinonide, and clobetasol.

2.7 Buccal tablets; Aftach® (bilayer tablet with triamcinolone acetonide), and poly acrylic acid and hydroxyl propyl cellulose tablet absorbed with citrus oil composition and magnesium salts

2.8 Buccal patch; Manapol® patch (OraPatch® with acemannon hydrogel).

3. Pharmacological therapy for severe RAS.

3.1 Systemic drugs; oral prednisolone, thalidomide, colchicine, and azathioprine.

3.2 Tetracycline capsules or topical.

3.3 Topical immunomodulatory agent; azelastine, human alpha-2 interferon cream, deglycyrrhizinated licorice.

4. Pharmacological therapy for children under age of 12

4.1 First line therapy; benzydamine, lidocaine gel, and local anesthetics.

4.2 In more severe cases; hydrocortisone sodium succinate, or 0.1% triamcinolone in carboxymethylcellulose paste.

5. Treatment for HIV-associated ulcers; antifungal treatment in conjunction with steroids, biopsy.

3. Pharmaceutical Aspects of Bioadhesive Systems

Bioadhesion or mucoadhesion may be defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time (Duchene, Touchard, and Peppas, 1988).

3.1 Mucous Layer

Mucus is a thick liquid layer covering the mucosa. It is secreted by goblet cells. It is a highly viscous liquid, adhering to the epithelium.

3.1.1 Chemical Composition

Besides water, which represents more than 95% of the mucus, its major components are glycoproteins (0.5 to 5%), lipids in low proportions, mineral salts (1%) and free proteins (0.5 to 1%). Glycoproteins are the main mucus components, responsible for its viscosity, adhesive and cohesive properties. Basically, glycoproteins consist of a protein core on which oligosaccharide chains are attached (diagram (a) in Figure 1). A lot of terminal residues in the oligosaccharide side chains are sialic acids, which are negatively charged at pH greater than 2.8, thus making the protein an anionic polyelectrolyte. Sulphate residues contribute equally to this negative charge. The mucus gel structure is the consequence of the intermolecular association of glycoproteins in a polymeric network (diagram (b) in Figure 1). Salivary mucin is a mixture of several secretions from major and minor salivary glands with distinct protein compositions and different rheological properties. The secretion from the sublingual gland displays a very high elastic behavior, in addition to its high viscous property; the high mucin concentration can cause the elastic behavior although it is not the only reason. The high

elastic component of these secretions at very low viscosities may be of importance for the retention of the salivary fluid film onto the oral mucosa (Slomiany et al., 1996).

(a) glycoprotein chain (b) glycoprotein tetramer

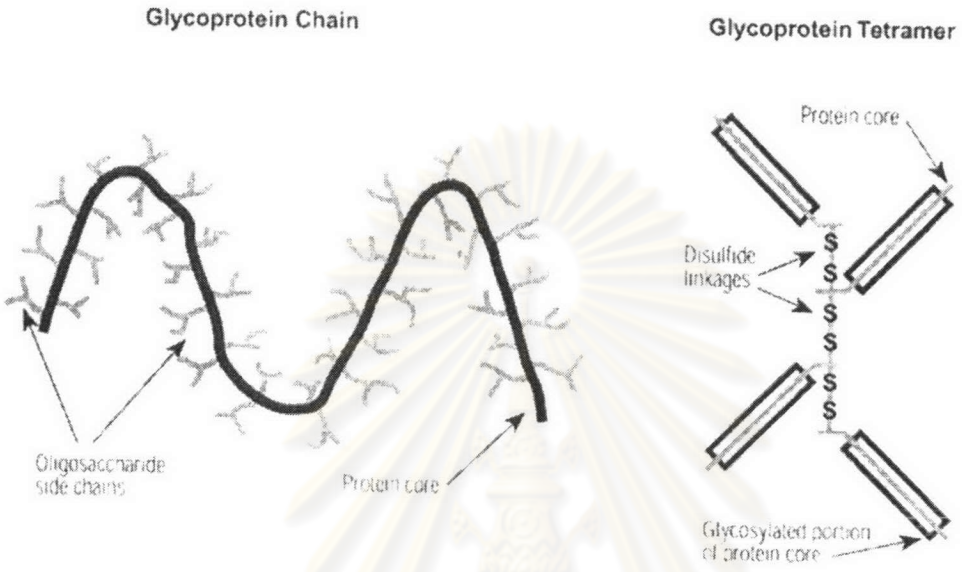

Figure 1 Schematic representations of the mucus (Duchene, Touchard, and Peppas, 1988).

3.1.2 Diffusion Barrier

The mucus covers the epithelial surface with a layer of heterogeneous thickness, varying between 5 and 200 μm with an average of 80 μm. The mucus protective role is evident at the stomach level. Besides its gastric protection role against hydrochloric acid, the mucus constitutes, generally speaking, a diffusion barrier for molecules, and especially against drug absorption. Salivary mucin plays an important role in the oral cavity. These large glycoproteins play a major role in the formation of protective coating covering tooth enamel and oral mucosa, which act as a dynamic functional carrier capable of modulating the untoward effects of oral environment, and are of significance to the processes occurring within the epithelial perimeter of mucosal defense (Slomiany et al., 1996).

3.2 Bioadhesion Mechanism (Mathiowitz, Chickering, and Lehr, 1999; Lee, Park, and Robinson, 2000).

The bioadhesion mechanism involves the following theories:

3.2.1 The Electronic Theory

The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come into contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

3.2.2 The Adsorption Theory

The adsorption theory states that the bioadhesive bond formed between adhesive substrate and mucosa is due to secondary surface forces such as van der Waals forces, hydrogen bonds, or hydrophobic interactions.

3.2.3 The Wetting Theory

For liquid bioadhesive systems, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetted surface is controlled by structural similarity, degree of cross-linking of the adhesive polymer.

3.2.4 The Diffusion Theory

The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semipermanent adhesive bond (Figure 2). The penetration rate depends on the diffusion coefficients of both interacting polymers, and the diffusion coefficient is known to depend on the molecular weight crosslinking density.

3.2.5 The Fracture Theory

This theory analyzes the forces required to separate two surfaces after adhesion. The maximum tensile stress produced during detachment can be determined by dividing the maximum force of detachment by the total surface area involved in the adhesive interactions (Nair, and Chien, 1996).

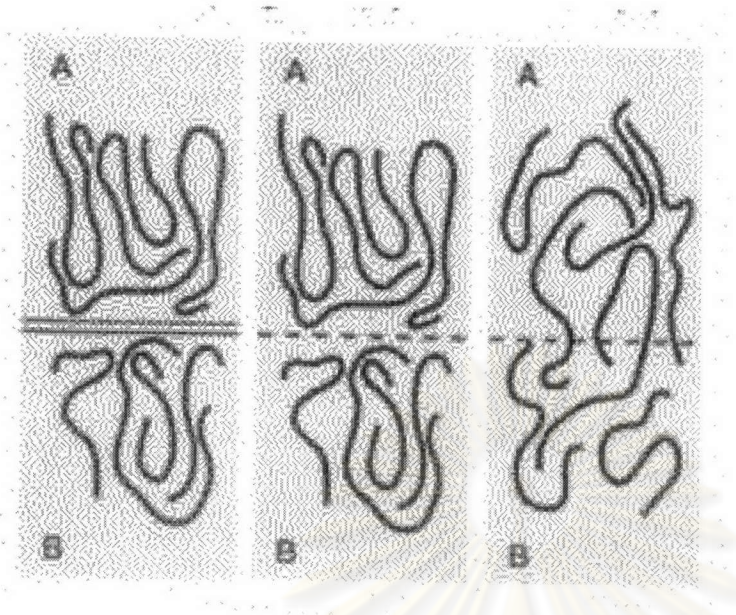

Figure 2 Chain interpenetration during bioadhesion of polymer A with the mucus B (Duchene, Touchard, and Peppas, 1988).

4. Factors Influencing Bioadhesion

4.1 Bioadhesive Polymer-related Factors

4.1.1 Molecular Weight

The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is at least 100,000 dalton of molecular weight.

4.1.2 Concentration

There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops. In concentrated solutions, the coiled molecules become solvent-poor, and the chains available for interpenetration were not numerous.

4.1.3 Chain Flexibility

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become crosslinked, mobility of individual polymer chains decrease

and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

4.2 Environment-related Factors

4.2.1 pH

pH can influence the formal charge on the surface of mucus as well as certain ionizable bioadhesive polymers. For example, polycarbophil does not show a strong bioadhesive property above pH 5 because it is uncharged, rather than ionized.

4.2.2 Initial Contact Time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the polymer. Moreover, bioadhesive strength increases as the initial contact time increases.

4.2.3 Swelling

During the dynamic process of bioadhesion, maximum bioadhesion *in vitro* occurs with optimum water content. Overhydration results in the formation of a wet slippery mucilage without adhesion (Lee, Park, and Robinson, 2000)

4.3 Formulation-related Factors

To cure a disease on buccal mucosa, a system that can be retained on the mucosa for a certain time period such as a mucoadhesive tablet and patch should enhance the drug efficacy. However, patient acceptance is likely to be an obstacle in many cases, particularly for retentive delivery systems, since we are dealing with an unconventional delivery route. Furthermore, salivary flow is probably even more important an issue in the context of local delivery (Harris, and Robinson, 1992).

5. Methods to Study *In Vitro* Bioadhesion

Bioadhesion is a difficult phenomenon to measure. Results of bioadhesion tests vary widely depending on factors considered when designing the test. Most tests measure stress-strain curves and force of adhesion refers to peak height of the stress-strain curve, which represents the force required to separate the probe from the substrate. Work of adhesion is the area under the stress-strain curve (Eouani et al., 2001).

5.1 Wilhelmy Plate Method

Smart, Kellaway, and Worthington (1984) developed a method for the measurement of mucoadhesion, which is a modification of the Wilhelmy method for the measurement of superficial tension. A polymer coated glass plate is suspended from a microbalance into homogenized guinea-pig mucus. After an equilibration time of 10 min, the plate is withdrawn from the mucus. One approach to quantify the bioadhesion is to calculate the fracture energy. In 1992, Sam, Van den Heuij, and Tukker also used this apparatus with native Yorkshire pig mucus instead of homogenized guinea-pig mucus (Figure 3).

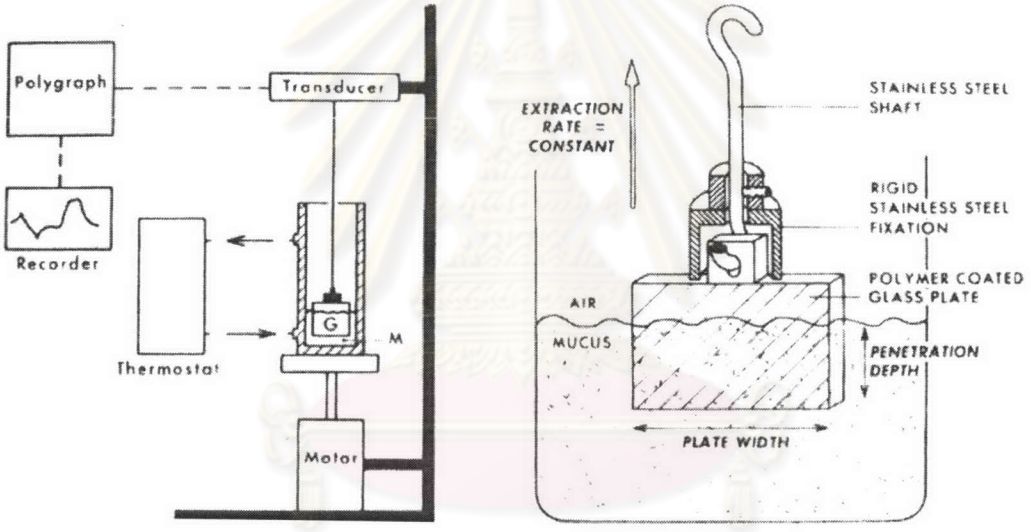

Figure 3 Schematic representation of the Wilhelmy plate apparatus; G. glass plate, M. mucus gel (Smart, Kellaway, and Worthington, 1984).

5.2 Tensiometer Technique

In 1991, Smart developed an *in vitro* method for the assessment of the adhesive force between a disc of test material and a model mucous membrane. This technique measured the tensile force required to break the adhesive bond between rabbit gastric mucosa and a test polymer (Figure 4). This system showed reasonable and reproducibility

data (Mortazavi, and Smart, 1994 and 1995). This technique was also modified to measure maximum detachment force and duration of mucoadhesion

Figure 5 displays an apparatus which is composed of a model mucosal surface and test disc which was placed in contact with the mucosal surface for a period of 2 min in order to allow the mucoadhesive bonds to form and consolidate. Then, a constant tensile stress of 10 g is applied and the duration of mucoadhesion of the test discs are determined (Mortazavi, 1995 and 2002).

A similar method was used by Lehr et al. (1992) to measure the force of detachment for polymer-coated cover glasses from pig intestinal mucosa in various test fluids. The polymers were used to routinely screen for mucoadhesive properties by measuring the force of detachment of swollen polymer. Kockisch et al. (2003) also used this technique but porcine esophageal tissue was used.

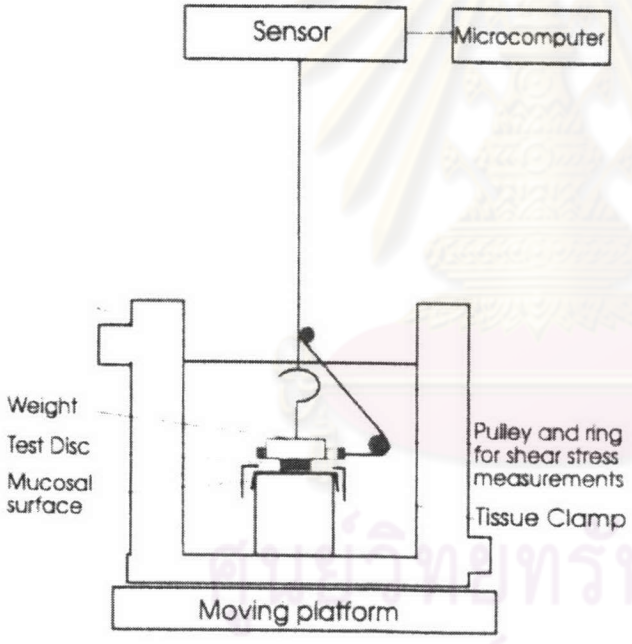

Figure 4 Schematic diagram of the mucoadhesion apparatus showing tensile and shear arrangements (Smart, 1991).

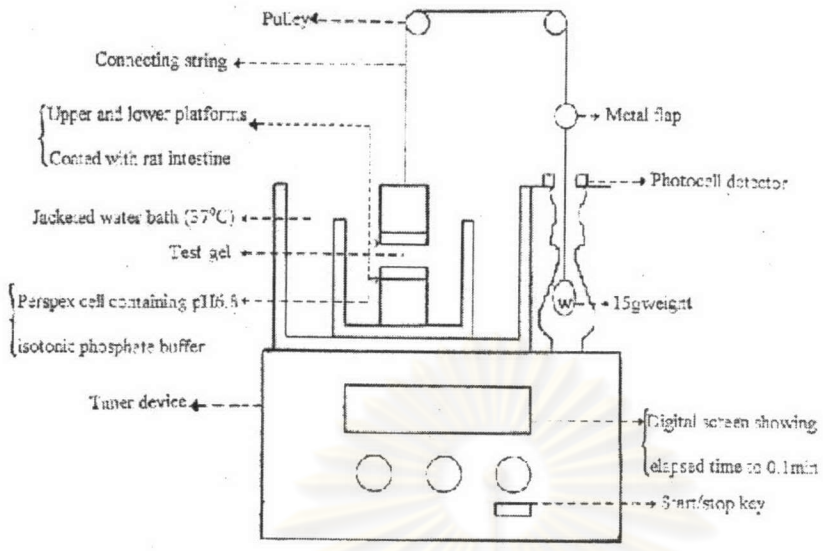

Figure 5 Schematic drawing of one compartment of the apparatus used for assessing the duration of mucoadhesion (Mortazavi, 2002).

A tensile stress tester was developed by Ferrari et al. (1996). The apparatus is assembled in a horizontal supporting base (Figure 6). At the beginning of the experiment, the carriage is moved until the adhesive side of the dressing comes into contact with the paper disc. After application for 3 min, the preload is removed and the movable carriage is moved forward, both displacement force and force of detachment are recorded.

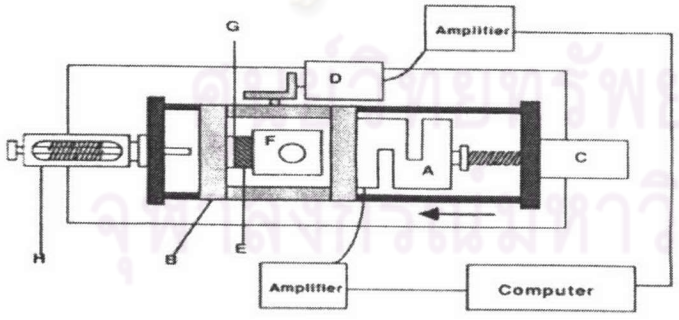

Figure 6 Schematic drawing of the tensile stress tester; A. load cell, B. movable carriage, C. motor, D. LVDT transducer, E. dressing, F. sample holder, G. paper filter, H. preload device (Ferrari et al., 1996).

Instron is also used as a tensile tester and illustrated in Figure 7. A sample is adhered to the upper holder of the tester, while a sample of mucosa is placed on the lower jaws. The two jaws are brought together and then separated at a constant rate. The detachment force is measured as a function of displacement, and the work of adhesion (work of fracture) is calculated as the area under the curve. The data are analyzed using Instron Corp. software (Guo, 1994; Li, Bhatt, and Johnston, 1998; Huang et al., 2000; Shojaei, Paulson, and Honary, 2000; Jug, and Becirevic-Lacan, 2004).

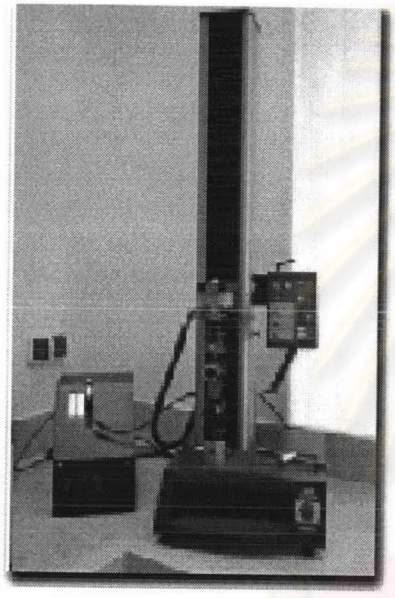

Figure 7 Schematic representation of the Instron apparatus (Jug, and Becirevic-Lacan, 2004).

TA.TX2*i* is another apparatus proposed to measure mucoadhesion tensile strength (Figure 8). It is capable of precisely quantifying a wide variety of the adhesive properties of adhesive sample. Adhesiveness and tensile strength can be quantified with the TA.TX2*i* Texture analyzer and its Texture Expert Exceed software packages. For mucoadhesive measurements, a sample of the prepared film is attached to the base of an aluminium probe which is fixed to the mobile arm of the TA.TX2*i*. A sample of mucosa is mounted on a platform within jacketed water bath containing artificial saliva. Upon making contact between the film and the mucus layer, the probe is withdrawn with a

constant rate. The maximum detachment force is determined by measuring the resistance to the withdrawal of the probe reflecting the mucoadhesion characterization of the films with mucus. The areas under the force/distance curves are also determined (Tamburic, and Craig, 1997; Nielsen, Schubert, and Hansen, 1998; Tan, Peh, and Al-Hanbali, 2000; Eouani et al., 2001).

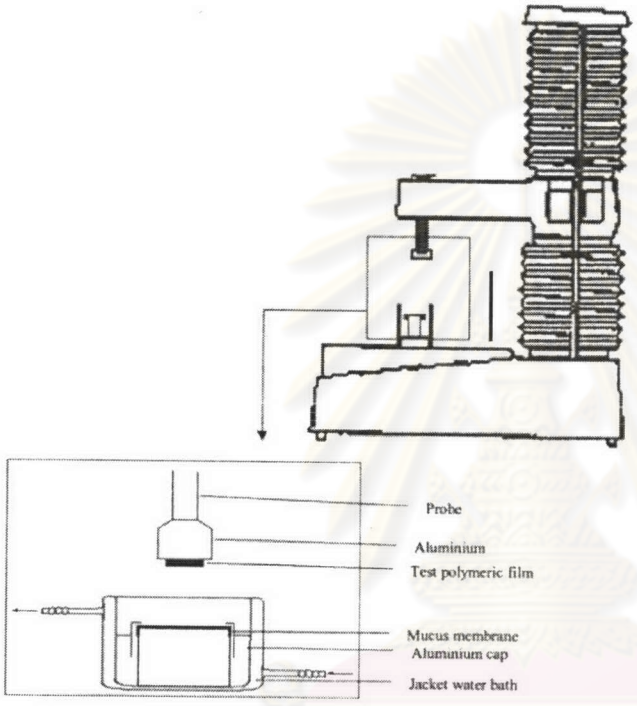

Figure 8 Diagrammatic representation of TA.TX2*i* for determining bioadhesive tensile strength (Eouani et al., 2001).

5.3 Organ Culture Technique

Organ culture technique is used to test adhesives on tissue *in vitro* over prolonged periods. Briefly, hamster cheek pouch mucosa on stainless steel grids is submerged in standard growth media. Duration of adhesion is assessed. The film is placed onto the adhesive using a constant application force of 15 g for 2 s. Prima Instruments applies this standardized force. Each cell is observed for the loss of retention of the film. The completed model cell tissue is shown in Figure 9 (Needleman, and Smales, 1995).

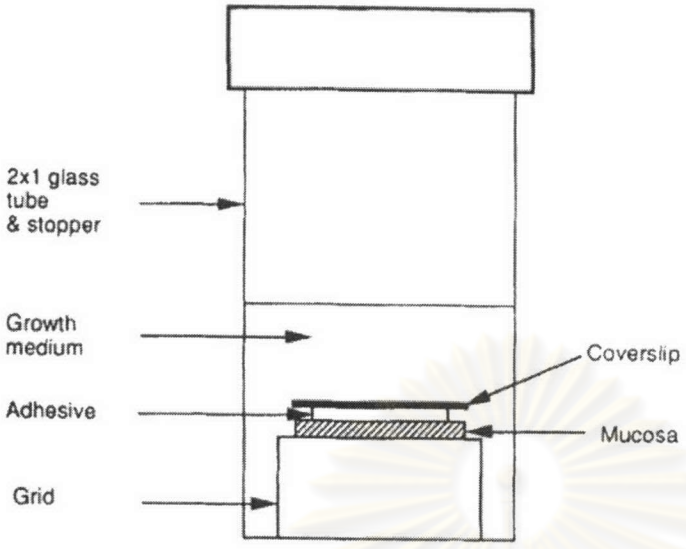

Figure 9 Diagram of organ culture cell (Needleman, and Smales, 1995).

5.4 Modification of USP XXII Dissolution Apparatus 4-Cylinder

Buccal tablets are attached to freshly excise intestinal porcine mucosa, which has been spanned on a stainless steel cylinder. Thereafter, the cylinder is placed in the dissolution apparatus containing 100 mM TBS medium according to the USP. The experimental set up is illustrated in Figure 10 (Schnurch, and Steininger, 2000).

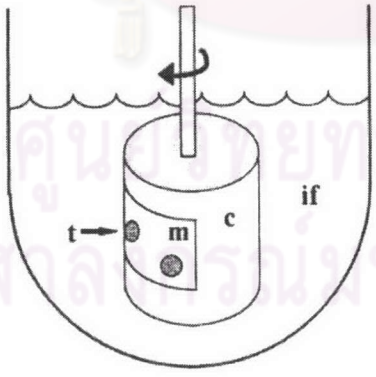

Figure 10 Schematic presentation of modified USP XXII dissolution apparatus 4-cylinder used to evaluate the mucoadhesive properties of buccal tablets; c. cylinder, m. porcine mucosa, t. tablet (Schnurch, and Steininger, 2000).

5.5 Dynamometer

The adhesion strength is assessed by a dynamometer using porcine mucosa. For mucoadhsive measurements, tablets are attached on a support and connected to the dynamometer. A piece of porcine buccal mucosa is glued on a support and kept in a vessel placed in a thermostatic bath. The free side of tablets is attached to porcine buccal tissues by applying a light force for 20 s. The vessel is filled with simulated saliva fluid. The maximum adhesive forces are also determined (Perioli et al., 2004).

6. Bioadhesive Polymers

Diverse classes of polymers have been investigated for their potential use an mucoadhesives. These include synthetic polymers such as monomeric α cyanoacrylate, polyacrylic acid, hydroxy propyl methylcellulose, and polymethacrylate derivatives as well as naturally occurring polymers such as hyaluronic acid, chitosan (Shojaei et al., 2001; Snyman, Hamman, and Kotze, 2003; Rossi et al., 2003), and tamarind gum, a polysaccharide obtained from the seeds of *Tamarindus indica* (Burgalassi et al., 1996). In a more functional type of classification, bioadhesive polymers can be grouped into (1) water soluble, which are typically linear or random and (2) water insoluble, which are commonly a swellable network formed by covalent or ionic bonds via a crosslinking agent (i.e., polycarbophil). In the case of water soluble polymers, the duration of residence time on tissue surfaces is based on the dissolution rate of the polymer. In contrast, cross-linked polymers, given their lack of solubility in common solvents, have a residence time based on the rate of mucus/tissue turnover. Many types of forces can be used to anchor a polymer to mucus as shown in Table 2 (Lee, Park, and Robinson, 2000).

Table 2 Potential Bioadhesive Forces

Type of Force	Example
Covalent bond	Cyanoacrylate
Hydrogen bond	Carbopol, polycarbophil, acrylates
Electrostatic interaction	Chitosan

Eudragit® is methacrylic acid-ethyl acrylate copolymer (1:1) having a mean relative molecular mass of about 250,000 (Lehmann, 1989; Rowe, Shesky, and Weller, 2003). The ratio of carboxylic groups to ester groups is about 1:1. Three types (type A, type B, and type C) are defined base on their methacrylic acid content and solution viscosity. Type A (Eudragit® RL) and type B (Eudragit® RS), are also referred to as ammonio methacrylate copolymers. They are fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Type C may contain suitable surfactants. The structural formula of Eudragit® is shown in Figure 11.

Eudragit® RL 100 is a copolymer of acrylic and methacrylic acid esters with 10 % of quaternary ammonium groups. Whereas, Eudragit® RS 100 is a copolymer of acrylic and methacrylic acid esters with 5 % quaternary ammonium groups and less water permeable than Eudragit® RL 100. Eudragit® NE 30D is a neutral poly (ethylacrylate methylmethacrylate) copolymer prepared by emulsion polymerization. Their applications are film former, tablet binder, and tablet diluent.

The addition of the Eudragit® RL 100 is required to achieve a control over the remarkable dissolution of polycarbophil films and regulate mechanical properties of films. The incorporation of at least 50 %w/w Eudragit® RL 100 into polycarbophil films significantly reduced the mucoadhesion ability of the films. However, no effect is observed when less than 20 %w/w Eudragit® RL 100 is used (Tirosh et al., 1997). In addition, films containing carbopol 934P with Eudragit® NE 30 D or Eudragit® RL 100 exhibited good physical and mechanical properties (Khanna, Agarwal, and Ahula, 1997).

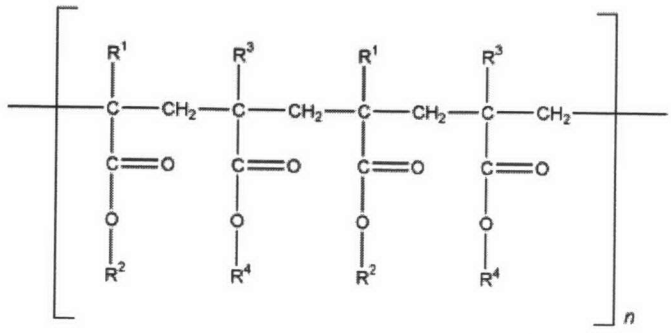

Figure 11 The structural formula of Eudragit® (Rowe, Shesky, and Weller, 2003).
For Eudragit® RL and Eudragit® RS; R^1 = H, CH_3, R^2 = CH_3, C_2H_5, R^3 = CH_3, R^4 = $CH_2CH_2N(CH_3)_3^+Cl^-$.
For Eudragit® NE 30 D; R^1, R^3 = H, CH_3, R^2, R^4 = CH_3, C_2H_5.

Kollicoat® SR 30 D is an aqueous dispersion of polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate. Its chemical structure is illustrated in Figure 12. Its applications are for the production of pH-independent sustained release formulations and film former (Lehmann, 1989; Rowe, Shesky, and Weller, 2003).

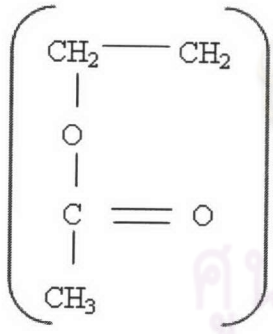

Figure 12 The chemical structure of Kollicoat® (Rowe, Shesky, and Weller, 2003).

7. Buccal Mucoadhesive Dosage Form

In general, dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by patients (Shojaei,

1998). Dosage forms such as mouthwashes, erodible chewable buccal tablets, and chewing gums allow only a short period of release, and the reproducibility of drug absorption is poor. An application of bioadhesive semisolid gels creates considerable technical problems. Bioadhesive buccal films/patches and tablets are the less developed type of dosage forms. The bioadhesive buccal films/patches and tablets are usually fabricated in different geometry, as shown in Figure 13. Type I is a single layer device, from which drug can be released multidirectionally. Type II device has an impermeable backing layer on top of the drug loaded bioadhesive layer, and drug loss into oral cavity can be greatly decreased due to backing layer on top of the bioadhesive layer. Type III is a unidirectional release device, from which drug loss will be avoided and drug can penetrate only via the buccal mucosa (Hao, and Heng, 2003).

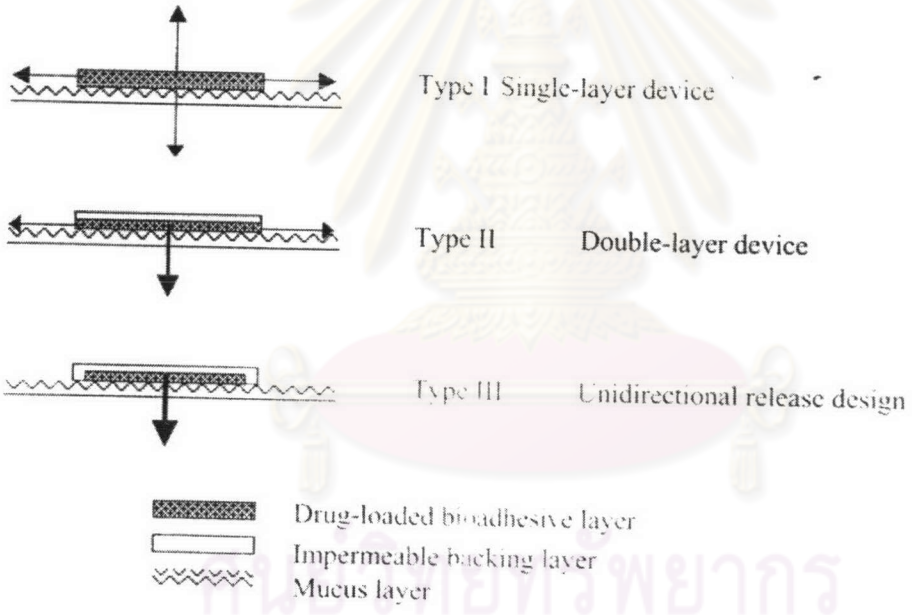

Figure 13 Schematic representation of buccal dosage form design (Hao, and Heng, 2003).

Based on the mechanism by which a drug is released, the devices can be classified into one of the following two categories; monolithic (matrix) systems and reservoir (membrane) systems. In the monolithic systems, the drug is dissolved or dispersed in the polymer system and the diffusion of drug from the drug/polymer matrix controls the overall rate of its release from the device. In the case of reservoir systems, the diffusional

resistance across a polymeric membrane controls the overall drug release rate (Jasti, Li, and Cleary, 2003).

The bioadhesive tablets are usually prepared by direct compression. Bioadhesive buccal tablets containing triamcinolone acetonide has been investigated in the buccal mucosa of healthy human volunteers. The tablets seem to provide a suitable compromise for good bioadhesion and prolonged release of drug (Mumtaz, and Ch'ng, 1995). *In vivo* bioavailability performed in dogs showed that the perorally administered danazol-sulfobutylether 7 complex and the danazol-sulfobutylether 7 in matrix buccal tablets had absolute bioavilability greater than the commercial formulation (Jain, Aungst, and Adeyeye, 2002).

Flexible adhesive films and laminated patches are used as buccal delivery systems. These require a bioadhesive to facilitate intimate contact with the mucosa and increase residence time, a vehicle that releases the drug at an appropriate rate, and additives such as penetration enhancers and/or enzyme inhibitors. The films are commonly manufactured by solvent casting methods using adhesive coating machines. This method involves dissolving a drug in a casting solution, casting film, and drying and laminating with a backing layer or a release liner (Hao, and Heng, 2003). The film dosage forms containing lidocaine and glycyrrhizic acid are successfully manufactured by the solvent evaporation method. Placing hydroxy propyl cellulose, lidocaine and glycyrrhizic acid solutions in a reduced pressure minimizes the time needed to remove the solvents. The hydroxy propyl cellulose film dosage forms are elastic (Okamoto et al., 2001). Bioadhesive films of triamcinolone acetonide exhibit an *in vitro* adhesion time of 3.24 hr are accepted well by healthy human volunteers, and no irritation of buccal mucosa is reported (Ali, Khar, and Ahuja, 1998). The processing technology is quite similar to pressure sensitive adhesive based patch manufacturing. A hot melt extrusion method is reported to fabricate hot melt extruded films for buccal delivery, which overcomes the disadvantages associated with a solvent casting method such as environmental concerns, long processing times, and high costs. The extruded films demonstrate excellent content uniformity and exhibit good bioadhesive strength (Repka, Prodduturi, and Stodghill, 2003).

8. Methodology in Evaluation of Buccal Delivery Systems

8.1 Drug Release from Dosage Forms

The determination of drug release can be carried out according to the official pharmacopoeias. They require a large volume of dissolution medium and are operated under sink conditions. These methods do not simulate conditions prevailing for buccal administration where low liquid environment exists and a non sink condition is more appropriate for a poorly permeable drug. Hence, the *in vitro* dissolution tests for buccal delivery systems should be performed in small volumes of dissolution medium. The apparatus is fabricated with the capability of adjusting the flow of water over the tablet which is adhered to a tissue. The USP dissolution apparatus is used to maintain the temperature of the medium and to supply medium via a peristaltic pump to the testing cell. A constant flow rate of 4 ml/min of medium is allowed to flow over the tablet in the assembly in order to simulate the flow of saliva in humans (Mumtaz, and Ch'ng, 1995). An automated method is performed using the Enhancer Cell™, a modified USP apparatus 2 using the Enhancer Cell™ in 200 ml capacity flasks instead of the standard 900 ml flasks. This study demonstrates the use of Enhancer Cell™ as an automated qualify control tool in the *in vitro* release testing (Rege, Vilivalum, and Collins, 1998).

8.2 Kinetics of Drug Release (Gohel, and Panchal, 2001)

Mathematical models used to describe the kinetics of drug release from the test formulation include zero-order, first-order, Higuchi's, Hixson-Crowell's, Weibull's, and Korsmeyer and Peppas's models. The criterion for selecting the most appropriate model is chosen on the basis of a goodness-of-fit test.

The zero order kinetic (Equation 1) describes the systems in which the drug release rate is independent of its concentration.

The first order kinetic describes the release from the systems in which the release rate is concentration dependent.

Higuchi model describes the release of drugs from an insoluble matrix as a square root of time dependent process on the basis of Fickian diffusion (Equation 2)

The Hixson-Crowell cube root law (Equation 3) describes the drug release from systems in which there is a change in the surface area and the diameter of the particles present in the tablet.

Dissolution data can be analyzed with the Korsmeyer and Peppas equations (power law) (Equation 4):

$$Q_t = k_0 .t \quad (1)$$

$$Q_t = K.S.\sqrt{t} = k_H .\sqrt{t} \quad (2)$$

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = k_{HC} .t \quad (3)$$

$$M_t / M_\infty = kt^n \quad (4)$$

Q_t is the amount of drug released in time t.

Q_0 is the initial amount of drug in the sample.

S is the surface area of the sample.

k_0, k_H, k_{HC} are release rate constants for zero order, Higuchi, and Hixson-Crowell rate equations, respectively.

M_t is the amount of drug released at time t

M_∞ is the amount of drug release at infinite time

M_t / M_∞ is the fraction of drug released at time t

k is the kinetic constant

n is the diffusional exponent indicative of the release mechanism.

8.3 Toxicity and Irritation Studies

Evaluation of toxicity and irritation should be concerned with mucosal cells and their rate of recovery. Membrane damage to the mucosal cells can be examined histologically.

8.4 Bioadhesion Measurement

Methods available for measuring bioadhesion are limited, and method selection depends on applicability, reproducibility, and useful information provided. It is unnecessary to compare the absolute values obtained from different methods and is more meaningful to examine the relative bioadhesive performances using each technique.

8.4.1 Duration of Bioadhesion

The measurement of residence time of adhesive at the application site provides quantitative bioadhesive properties.

8.4.2 Tensile Test

The tensile test is based on the measurement of detachment force of the polymer layer from the mucus substrate. The detachment force and adhesion work are indicative of bioadhesion strength.

8.5 Mechanical Properties

An ideal buccal film should be flexible, elastic, durable and adequately strong to withstand breakage due to stress from oral cavities. Consequently, the mechanical properties are critical and needed to be evaluated. The tensile testing gives an indication of the strength and elasticity of the film reflected by the parameters such as tensile strength, % elongation and Young's modulus. The guidelines of the American Society for Testing Material method (ASTM D882-95a) define definition of the parameters. The ability of a material to resist breaking under tensile stress is one of the most important and widely measured properties of sample. The force per unit area (MPa) required to break a material in such a manner is the ultimate tensile strength. The ultimate elongation of the sample is the percentage increase in length that occurs before it breaks under tension. So, the combination of high ultimate tensile strength and high elongation leads to the materials of high toughness. Young's modulus shall be defined by drawing a tangent to the initial linear portion of the load extension curve, selecting any point on this tangent, and dividing the tensile stress by the corresponding strain. The result shall be expressed in force per unit area, usually MPa. Polymer are normally characterized by the mechanical parameters and described as the following:

A soft and weak polymer is characterized by a low tensile strength, % elongation and Young's modulus.

A hard and brittle polymer is defined by a moderate tensile strength, high Young's modulus, and low % elongation.

A soft and tough polymer is characterized by a moderate tensile strength, low Young's modulus, and high % elongation.

A hard and tough polymer is defined by a high tensile strength, Young's modulus, and % elongation.

Suitable buccal films should have a relatively high to moderate tensile strength, and high % elongation but low Young's modulus (Peh, and Wong, 1999). The tensile strength and % elongation are the critical parameters that should be considered.