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BUCCO-ADHESIVE DRUG DELIVERY SYSTEM: A NOVEL DRUG DELIVERY TECHNIQUE

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ABSTRACT

The main aim of pharmaceutical research is steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effectiveness in terms of therapeutic action, patent protection, patient compliance and reduced adverse effects. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. This system of drug delivery is called mucoadhesive drug delivery system. The buccal region of oral cavity is an attractive target for administration of drug of choice. Buccal drug delivery involves the administration of desired drug through the buccal mucosal lining of the oral cavity. Other than the common advantages of novel drug delivery systems, buccal mucosa has several specific advantages like, faster and richer blood flow, lesser thickness of the buccal mucosa and increased permeability, low enzymatic activity in the buccal mucosa and versatility in designing unidirectional release systems to overcome the first-pass metabolism and subsequent low bioavailability of the drug.

KEYWORDS

Buccal mucosa, Mucoadhesion, Permeation enhancers and Novel drug delivery system.

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INTRODUCTION[1-10]

Bio adhesion is defined as the state in which two bodies one or both of adherents are of a biological nature and are held together for extended periods of time by interfacial forces. A bio adhesive can therefore be defined as a substance, which has an ability to interact with biological materials, and is capable of being retained on the biological substrate for a period of time. One distinctive feature of bio

adhesion is that adhesion almost always occurs in the presence of water. There are a variety of mechanisms that have been described in the literature to explain bio adhesion. Any mechanism of adhesion requires the establishment of an intimate molecular contact between the bio adhesive and mucin/epithelial cell surface, often referred as wetting of the substrate. The attachment can be specific (receptor site involved) or non-specific and can involve covalent or non covalent bonds. The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential route for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery Figure No.1 and 2.

Advantages of Drug Delivery via the Buccal Lining

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to p H and digestive enzymes of the middle gastrointestinal tract.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
3. Sustained drug delivery.
4. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5. Increased ease of drug administration.
6. Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
7. In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration. Hence transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches,
8. Transmucosal delivery occurs with fewer variables between patients, resulting in lower intersubject variability as compared to transdermal patches.

Limitations of Buccal Drug Delivery

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel" is an issue. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

MECHANISM OF BUCCAL DRUG DELIVERY SYSTEM

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. It is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism (Figure No.3 and 4):

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon also called as contact stage).
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration or consolidation stage).

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption.

A. Bio adhesive Interface

Adhesive bonds between a polymer and a soft tissue require contributions from the surface of the potentially bio adhesive polymer. The first layer of the natural tissue and the interfacial layer between adhesive and tissue. Mucus is highly a viscous product, which coats lining of hollow organs in contact with external media. The main components of the mucous layer are glycoproteins or mucins, inorganic salts, proteins, lipids and muco polysaccharides and its composition Varies depending on its source. The mucin composition also depends on the pathological conditions. It was found those mucins secreted by abnormal tissues are histo chemically different from the corresponding mucins produced by the normal tissues.

B. Chemical and Physical Interactions

Adhesion of polymers to tissues may be achieved by:

1. Primary ionic or covalent chemical bonds.
2. Secondary chemical bonds or
3. Physical or mechanical bonds.

Primary chemical bonds are the result of chemical reaction of functional groups of the adhesive material with the substrate' they are hardly desirable for most soft tissue uses where a semi-permanent adhesive bond strength is needed lasting from a few minutes to a few hours. Secondary chemical bonds contribute to bio adhesive bonds through Vander walls dispersive interactions or hydrogen bonding. Hydrogen bonds are also important in bioadhesion as in other form of adhesion. Physical or mechanical bonds are obtained by inclusion of the adhesive material in the crevices of the tissue. Thus the surface roughness of the substrate becomes an important factor in bioadhesion. Only highly fluid materials or suspensions that can be incorporated within these anomalies of the tissue can be considered successful adhesive systems.

OVERVIEW OF THE ORAL MUCOSA[11-20]

The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and sub mucosa. It also contains many sensory receptors including the taste receptors of the tongue.

A. Structure

The oral mucosa (Figure No.5) is composed of outermost layer of stratified epithelium. Below lies a basement membrane, a lamina prairie followed by the sub mucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelkiml8. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium. It has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 um, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200 um.

B. Role of Saliva

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

C. Role of Mucus

- Made up of carbohydrates and proteins (Figure No.6).
- Lubrication.
- Bioadhesion of mucoadhesive drug delivery systems.

D. Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the

permeability of the buccal mucosa is 44000 times greater than that of the skin. In general, the perm abilities of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

E. Permeability of Drugs through Buccal Mucosa

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

1. **Transcellular** (intracellular, passing through the cell) and
2. **Paracellular** (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the Paracellular route through the intercellular lipids produced by membrane-coating granules. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability. Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions (Figure No.7).

F. Buccal Drug Delivery and Mucoadhesivity

In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element. The term [u] mucoadhesive" is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as:

1. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
2. Suitable surface property for wetting mucus/mucosal tissue surfaces and
3. Sufficient flexibility' to penetrate the mucus network or tissue crevices.

The polymers which have been tried and tested over the years include Carboxymethyl cellulose, Carbopol, Polycarbophil. Poly (acrylicacid/ divinyl benzene), Sodium Alginate. hydroxyethyl cellulose. Hydroxypropyl methylcellulose, Hyaluronic acid, Gelatin, Guar Gum, Thermally modified Starch, Pectin, Polyvinyl pyrrolidone. Acacia, Polyethylene glycol, Psyllium, Amberlite-200 resin. Hydroxypropyl cellulose, Chitosan, Hydroxy ethyl methacrylate.

There are some Novel Mucoadhesive Polymers under development, these include Copolymer of PAA and PEG monoethylethermonomethacrylate, PAA complexed with PEGylated drug conjugate, Hydrophilic pressure-sensitive adhesives (PSAs), AB block copolymer of oligo(methyl methacrylate) and PAA, Polymers with thiol groups (cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator.

G. Factors Affecting Drug Delivery via Buccal Route

The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this

route to be more suitable for the delivery of larger molecules.

H. Toxicity and Irritancy Associated With Buccal Drug Delivery

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is particularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods. Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation.

THEORIES OF BIOADHESION

The theoretical framework for polymer- polymer adhesion can be easily extended to describe the bioadhesion of polymeric materials with biological surfaces. The theories include the electronic, the adsorption, the wetting, the diffusion and the fracture theory.

A. Electronic Theory

The electronic theory indicates that there is likely to be electron transfer on contact of the bioadhesive polymer and the glycoproteinic network which have different electronic structures, which will in turn lead to the formation of a double layer of electrical charge at the bioadhesive interface.

B. Adsorption Theory

According to the adsorption theory, bioadhesive systems adhere to tissue because of vander walls, hydrogen bonding, and related forces.

C. Wetting Theory

Intimate molecular contact is a pre - requisite for development of strong adhesive bond, requiring examination of the wetting equilibrium and dynamic behavior of the bioadhesive candidate material with the mucus. Some important characteristic for liquid bioadhesive materials include:

i. A zero or near zero contact angle

ii. A relatively low viscosity and

iii. An intimate contact that exclude air entrapment.

The specific work of adhesion between bioadhesive controlled release system and the tissue is equal to the sum of the two surface tensions and less than the interfacial tension.

D. Diffusion Theory

Interpenetration of the chains of polymer and mucus may lead to formation of a sufficiently deep layer of chains. The diffusion mechanism is the intimate contact of two polymers or two pieces of the same polymer. During chain interpenetration the molecules of the polymer and the dangling chains of the glycoproteinic network are brought in intimate contact. Due to the concentration gradient, the bioadhesive polymer chains penetrate at rates that are dependent on the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient. In addition, good solubility of the bioadhesive medium in the mucus is required in order to achieve bioadhesion. Thus the difference of the solubility parameters of the bioadhesive medium and the glycoprotein should be as close to zero as possible. Thus the bioadhesive medium must be of similar chemical structure to the glycoproteins.

E. Fracture Theory

The facture theory of bioadhesion relates the difficulty of separation of two surfaces after adhesion to the adhesive bond strength.

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM

Buccal Dosage form can be of two types

1. Matrix type

The buccal patch designed in a matrix configuration contains drug, adhesive and additives mixed together (Figure No.8).

2. Reservoir type

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Transmucosal drug delivery systems can be bi-directional or unidirectional or multi-directional.

Type I (Multidirectional)
This device has a single layer with drug release multiple directions. The disadvantage of this type of dosage form is that it suffers from significant drug loss due to swallowing.

Type II (Bi-layered)
In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Type III (Unidirectional)
This is a uni-directional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa (Figure No.9).

A number of related buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides like thyrotropin-releasing hormone (TRH), insulin, protirelin, buserelin and oxytocin, have been administered via the buccal route, although with relatively low bioavailability (0.1-5%) pertaining to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa.

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

1. Absorption Enhancers
Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism (Figure No.10).

2. Prodrugs
Hussain et al delivered opioid agonists and antagonists in bitterness prodrug forms and found that the drug exhibited low bioavailability as prodrug.Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of Nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

3. pH
Shqjaeict al evaluated permeability of acyclovir at pi 1 ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8). as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

4. Patch design
Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

FACTORS AFFECTING DRUG DELIVERY VIA BUCCAL ROUTE

The Mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors (Figure No.11).

1. The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal

epithelium, causing this route to be more suitable for the delivery of larger molecules.

2. Only the non ionized forms of molecules have the ability to cross-lipoidal membranes in significant amounts. The more lipid soluble a compound is, the higher its permeability. The permeabilities for these compounds are direct functions of their oil-water partition coefficients. The partition coefficient is a useful tool to determine the absorption potential of a drug.
3. The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.
4. In short one can say that the lipid solubility of drugs is an important factor in Transmucosal Drug Delivery system. Along with lipid solubility, drugs selected for Transmucosal Drug Delivery system must have physiochemical properties, including size and pKa that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentrations. The drug must resist, or be protected by salivary and tissue enzymes that could cause inactivation. Additionally, the drug and adhesive materials must not damage the teeth, oral cavity, or surrounding tissues (e.g. by keratinolysis, discoloration, and irritation).

CLASSIFICATION OF BUCCAL SYSTEMS

Recent buccal mucoadhesive formulations prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Mucoadhesive adhesive drug delivery systems using tablets, films, layered systems, discs, micro particles, ointments, wafers, lozenges and hydrogel systems has been studied by various research groups.

1. Buccal Tablets

Bioadhesive tablets may be prepared using different methods such as direct compression or wet granulation technique. For delivery of drug via buccal route, the tablets which are inserted into the buccal pouch may dissolve or erode; therefore, they must be formulated and compressed with sufficient pressure only to give a hard tablet. To enable or to achieve unidirectional release of drug, water impermeable materials, like ethyl cellulose, hydrogenated castor oil, etc. may be used either by compression or by spray coating to coat every face of the tablet except the one that is in contact with the buccal mucosa. Bilayered and multilayered tablets are already formulated using bioadhesive polymers and excipients. If necessary, the drug may be formulated in certain physical states, such asmicrospheres, prior to direct compression in order to achieve some desirable properties e.g. enhanced activity and prolonged drug release.

2. Buccal semisolid dosage forms

These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa over the other type of dosage forms. Bioadhesive formulations have been used to overcome the poor retention of gels on the buccal mucosa. Certain bioadhesive polymers for example, sodium carboxy methylcellulose undergo a phase change from a liquid to a semisolid. This change enhances or improves the viscosity, resulting in sustained or controlled release of drugs. Buccal bioadhesive semisolid dosage forms consists of finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution, like Arabase.

3. Buccal films

In recent years, numerous bioadhesive dosage forms for delivery of drug via the buccal route have been developed such as films, tablet, patches, discs, gels and ointments. Buccal films are preferable over mucoadhesive discs and tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments and thereby sustaining drug action. Buccal films also reduce pain

by protecting wound surface and increasing drug effectiveness.

4. Buccal Powders

Buccal bioadhesive powders are a mixture of Bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of nifedipine.

5. Micro particles

Micro particles have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

6. Wafer

Wafer is a novel periodontal drug delivery system. This is used for the treatment of microbial infection.

7. Lozenges

Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. In lozenges multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline to the subtherapeutic levels.

8. Buccal patches

These are flexibles which deliver the drugs directly in to systemic circulation through mucus membrane thereby by passing the first pass effect. Buccal patch formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

CHARACTERISATION OF BUCCAL PATCHES[20-31]

1. Mass uniformity

Mass uniformity was tested in 10 different randomly selected patches from each batch.

2. Thickness

Thickness was measured at 5 different randomly selected spots on patches using a screw gauge.

3. Folding endurance

Folding endurance of patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times without breaking.

4. Drug content uniformity

Drug content uniformity was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 7.4) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 7.4 up to 20 ml, and the resulting solution was filtered through a 0.45 u.m Whatmann filter paper. The drug content was then determined after proper dilution at UVspectrophotometer. The experiments were carried out in triplicate.

5. Surface pH Determination

The surface pH was determined by the method similar to that used by Bottenberg et al. 1991. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.5±0.1) for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patch close to the neutral pH.

***In vitro* Swelling Studies of Mucoadhesive patch**

The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of mucoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 7.4 at 37^{o}C.

Buccal patch was weighed, placed in a 2% agar gel plate and incubated at 37±1^{0}c. At regular one-hour time intervals (upto 3 h), the patch was removed from the petri dish and excess surface water was removed carefully using the filter paper. The swollen patch was then weighed again and the swelling index was calculated.

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

***In vitro* release Studies**

In order to carry out *In vitro* release studies dissolution test apparatus type II (USP) rotating paddle method was used. The studies were carried out for all formulation combination in triplicate, using 900 ml of isotonic phosphate buffer (pH 7.4) as the dissolution medium. The release was performed at 37^{0}C, at 50rpm. To provide unidirectional release, one side of buccal patch was attached to a glass disk with the help of two sided adhesive tape then disk was put in the bottom of the dissolution vessel so that patch remained on the upper side of the patch remained on the upper side of the disk. An aliquot of 5ml sample was withdrawn at predetermined time intervals and similar volume was replaced with fresh phosphate buffer (pH 7.4) maintained at same temperature. Samples were then analyzed with the help of UV spectrophotometer.

***Ex vivo* Mucoadhesion time**

The selected batch was subjected to *ex vivo* mucoadhesion test. The disintegration medium was composed of 800 ml isotonic phosphate buffer pH 7.4 maintained at 37^{o}C. A segment of porcine cheek mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded. The experiment was carried out in triplicate.

Permeation studies

The *in vitro* study of venlafaxine permeation through the sheep buccal mucosa was performed using a Franz diffusion cell at 37 ± °.2°C. Sheep buccal mucosa was obtained from a local slaughterhouse (used within 2 h of slaughter). Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of isotonic phosphate buffer pH 7.4. The receptor compartment (15 mL capacity) was filled with isotonic phosphate buffer pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 1 rpm. One mL sample was withdrawn at predetermined time intervals and analyzed for drug content at 224 nm.

Bioadhesion strength

The tensile strength required to detach the bioadhesive patch from the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled. The device was mainly composed of a two-arm balance.

METHODS TO STUDY MUCOADHESION[20-31]

The evaluation of mucoadhesive properties is fundamental to the development of novel Bioadhesive drug delivery system. Measurement of the mechanical properties of a Bioadhesive material after interaction with a substrate is one of the most direct ways to quantify the Bioadhesive performance. Testing is essential for the development, quantification, processing and proper use of the Bioadhesive. Several methods have been developed for the determination of Bioadhesive bond strength. These tests are also important during the design and development of Bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis, and Bioadhesive strength. The test methods can be classified into two major categories:

***In vitro/Ex vivo* methods -*In vivo* methods**

***In vitro/Ex vivo* methods**

The *in vitro* methods are based on the measurements of either tensile stress or shear stress.

Methods based on measurement of tensile strength

In these methods the force required to break the adhesive bond between a model membrane and the test polymer is measured.

Tensinometer

This instrument consists of two jaws from flat glasses. The upper glass was fixed, but the lower glass had been mounted on a screw-elevating surface. The upper fixed glass was attached to a sensitive digital balance. Tablets from each formulation were suspended in water (pH 7) for 15 min. Then these adhesive tablets were located on the surface of lower glass and were elevated until they contact the surface of upper glass. The lower glass was then lowered until the tablet clearly was pulled free from the upper glass. The maximum tensile force needed to detach the jaws was recorded in gram/cm and mean values were calculated and recorded (Figure No.12).

Modified balance method

Modified double beam physical balance was used as the Bioadhesion test apparatus. The right pan of the balance was replaced with lighter one and pan was prepared with the Teflon ring hanging by a number of metallic rings. A cylinder at whose base a tablet was attached was hung from this ring. The two sides of the balance were then balanced with a fixed weight on the right hand side. The mucus membrane was tied with mucosal side upward using a thread over a Teflon block. The block was then lowered into the jacketed beaker which was then filled with phosphate buffer such that buffer just reached the surface of the balance. The balance beam was raised by removing the fixed weight kept on the right side of the pan. This lowered the Teflon cylinder along with the tablet over the mucosa. The balance was kept in this position for a fixed time and then slowly increased on the right pan till the tablet separated from the mucus surface. The excess weight on right hand side gave the Bioadhesive strength of the tablet in grams. It was observed that assembly gave reproducible results and performed efficiently.

***In vitro* methods**

Adhesion weight method

A system where suspension of an exchange resin particles flowed over the inner mucosal surface of a section of guinea pig intestine and the weight of adherent particles was determined. Although the method has limited value due to poor data reproducibility resulting from fairly rapid degradation and biological variation of the tissue, it was possible to determine the effect of particle size and charge on the adhesion after 5 minutes contact with the adverted intestine.

Flow channel method

Mikos and Peppas developed this method which utilizes a thin channel made up of glass which is filled with 2% w/w aqueous solution of bovine submaxillary mucin, thermostated at 37°C. Humid air at 37°C was passed through glass channel. A particle of Bioadhesive polymer was placed on the mucin gel, and its static and dynamic behaviour was monitored at frequent intervals using a camera, thereby calculating its adhesive property.

Fluorescent probe method

In order to examine a large number of polymers for their Bioadhesive potential, the technique of labelling the lipid bilayer and memberane protein with the fluorescent probes namely pyrene and fluorescein isothiocynate, respectively, was used. Addition of polymers to this substrate surface compressed the lipid bilayer or protein causing a change in fluorescence, as compared to control cells. By using the fluorescent probes, it was possible to compare charge type and density and backbone structure and their influence on polymer adhesion. Charged carboxylated polyanions were found to have a good potential for Bioadhesive drug delivery.

Mechanical spectroscopic method

Mechanical spectroscopy was used to investigate the interaction between glycoprotein gel and polyacrylic acid, and the effect of pH and polymer chain length on this. Mortazavi et al. used a similar method to investigate the effect of carbopol 934on the rheological behaviour of mucus gel. They also

investigated the role of mucus glycoproteins and the effect of various factors such as ionic concentration, polymer molecular weight and its concentration, and the introduction of anionic, cationic and neutral polymers on the mucoadhesive mucus interface.

Thumb test

It is simple test method used to quantify mucoadhesiveness. The difficulty of pulling the thumb from the adhesive as a function of pressure and contact time gives a measure of adhesiveness. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are nonspecific and not mucin specific and like mucin the skin has also many hydroxyl groups for interaction with Bioadhesive systems. Although the thumb test may not be conclusive, it provides useful information on mucoadhesive potential.

Colloidal Gold Staining

This technique employed red colloidal gold particles, which were stabilized by the absorbed mucin molecules to form mucin gold conjugates. Upon interaction with mucin-gold conjugates, Bioadhesive hydrogel developed a red colour on the surface. Thus the interaction between them could easily be quantified, either by measurement of the intensity of the red colour on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at wavelength.

Electronic conductance

This method is used to test the semisolid mucoadhesive ointments. The adhesion of Orabase, carbopol, eudispert, guar gum and methylcellulose to artificial membranes in artificial saliva was studied by using a modified rotational viscometer capable of measuring electrical conductance. In the presence of adhesive the conductance was comparatively low, as the adhesive was removed, the value increased to final value, which corresponds to the conductance of saliva, which indicates the absence of adhesion.

NEWER TECHNOLOGIES

Buccal drug delivery by novel aerosol sprays for insulin delivery was developed by generex pharmaceuticals with a brand name of ORAL-LYN (Figure No.14).

DISSOLUTION AND DRUG RELEASE FORM BIOADHESIVE DOSAGE FORMS

USP 29 states the use of disintegration test for ergoloidmesylate and ergotamine tartrate sublingual tablets and apparatus 2 with water as dissolution medium for by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns" Mumtaz and Ch'ng introduced another method for studying the dissolution of buccal tablets. The device that they introduced is based on the circulation of pre-warmed dissolution medium through a cell as shown in Figure below. Here the buccal tablet was attached on chicken pouches. Samples were removed at different time intervals for drug content analysis. They stated "the results obtained.

Slug mucosal irritation assay

Those formulations remain in contact with the mucosal surface for a longer time period, therefore it is important to assess their mucosal irritation potency. The Slug Mucosal Irritation (SMI) assay was developed at the University of Ghent (Belgium) in the Laboratory of Pharmaceutical Technology. The slug mucosal irritation assay can be used as an alternative test to predict the mucosal and ocular tolerance of new pharmaceutical early in the research and development phase, thereby replacing the use of laboratory mammals. The principle of this assay is that the body wall of slug (Arionlustanicus) has a highly mucosal surface as a test organism. Slugs that are placed on an irritant substance will produce mucus and tissue damage results in the release of proteins and enzymes. Based on estimation of the levels of protein and enzymes irritation potency can be predicted. The irritation potency is predicted based on the total amount of mucus produced (total MP) during the repeated 30-min contact periods. The mucus production is expressed as a percentage of the body weight of the slugs (Figure No.13).

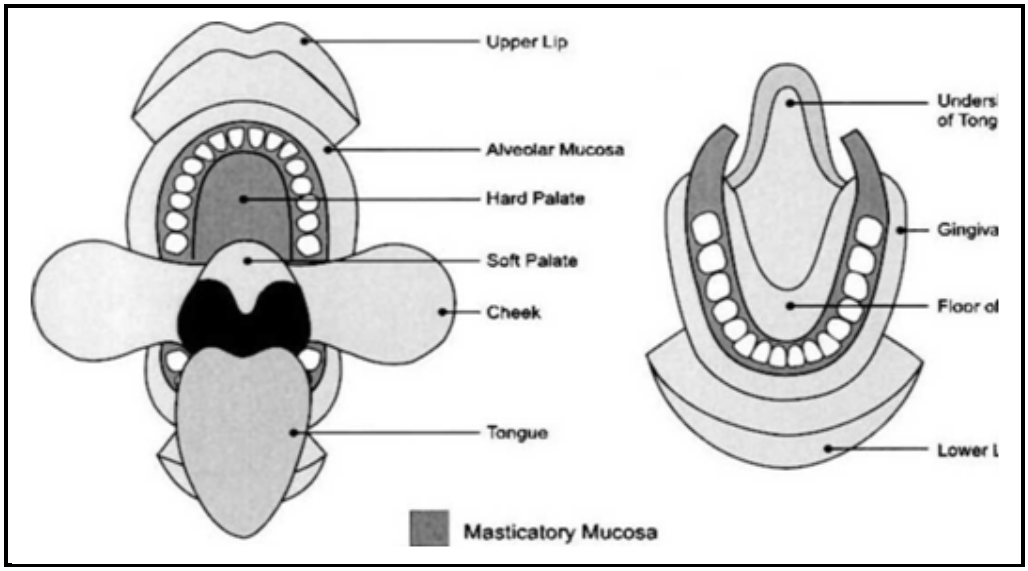

Figure No.1: Schematic representation of the different linings of mucosa in mouth

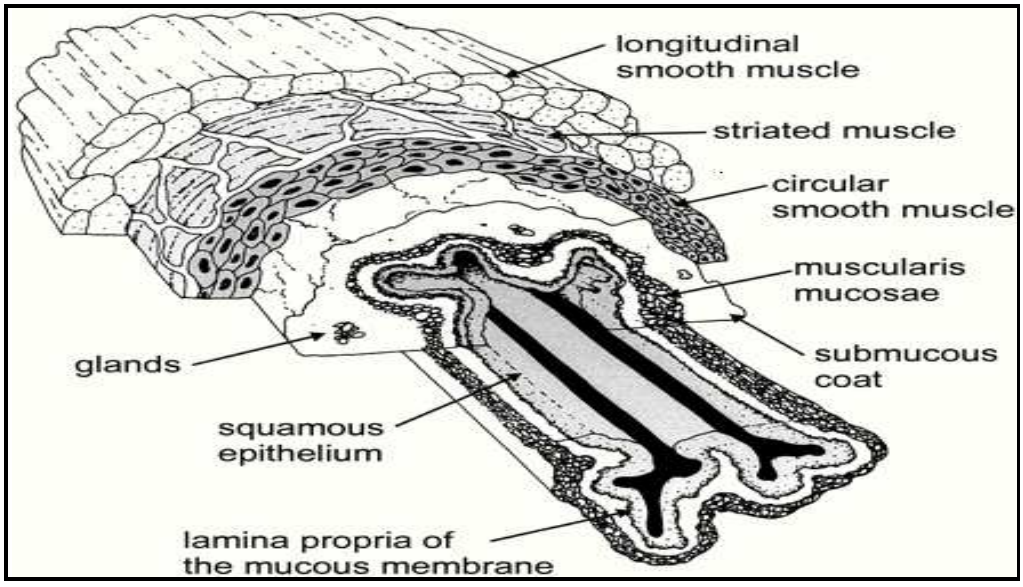

Figure No.2: General Structure of Oral Mucosae

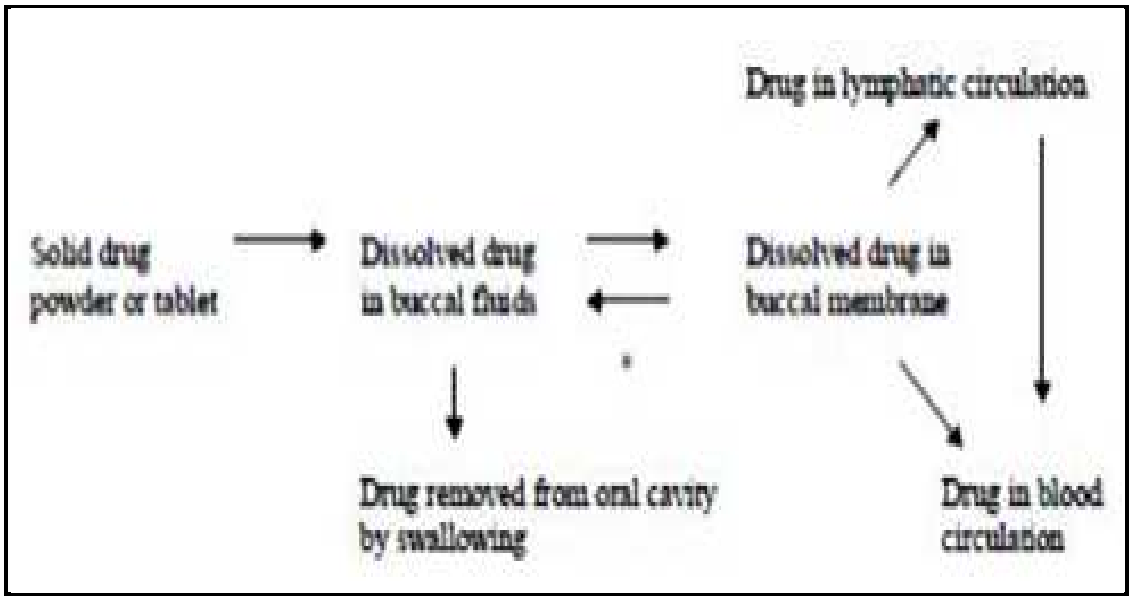

Figure No.3: Representation absorption kinetic of Buccal presented drugs

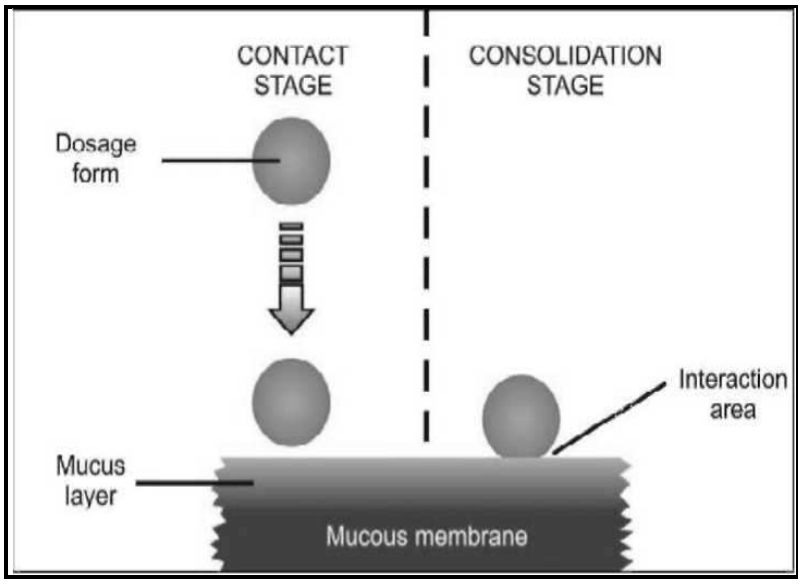

Figure No.4: Two steps of the process of Mucoadhesion

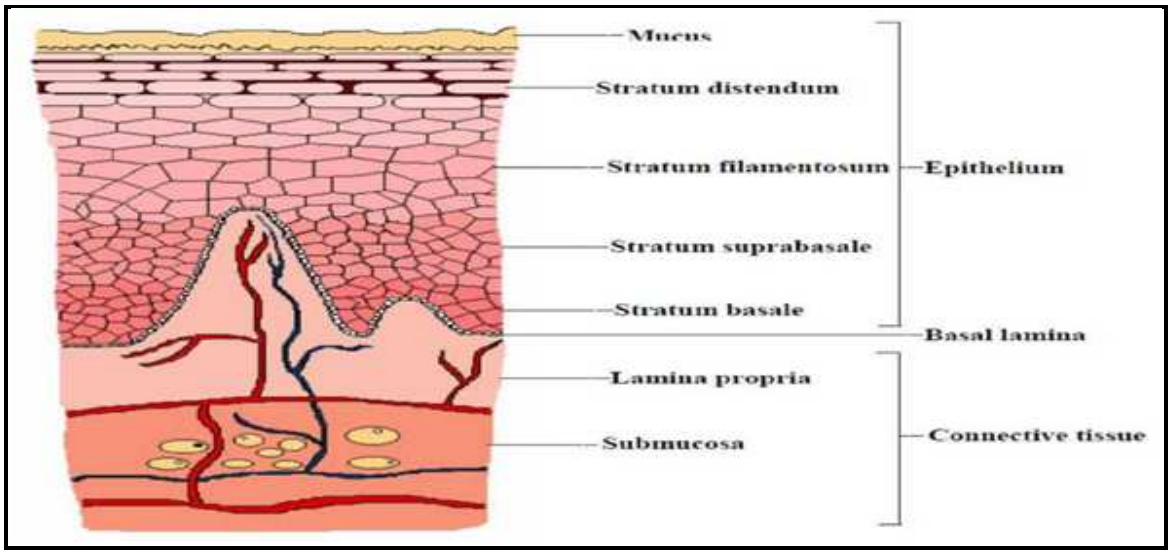

Figure No.5: Histology of oral mucosa

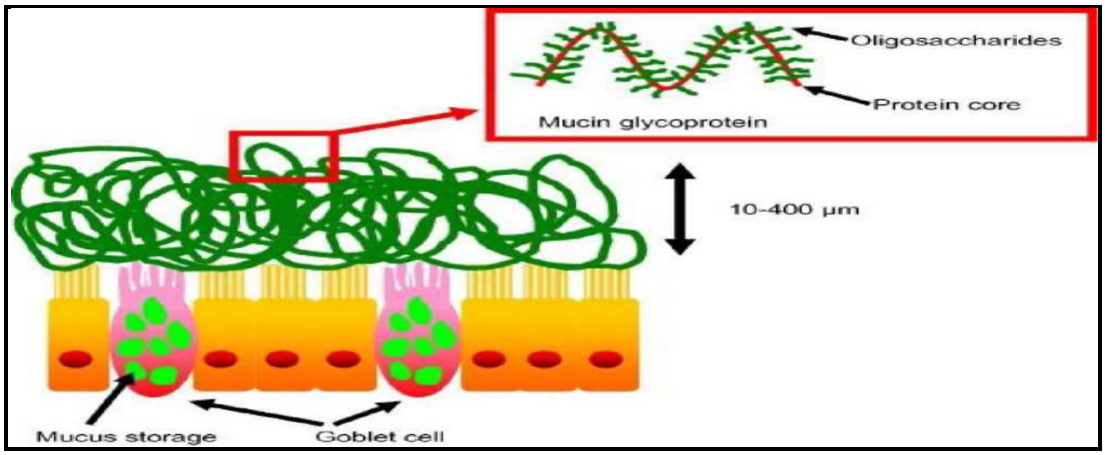

Figure No.6: The composition and interaction of glycoprotein chains within

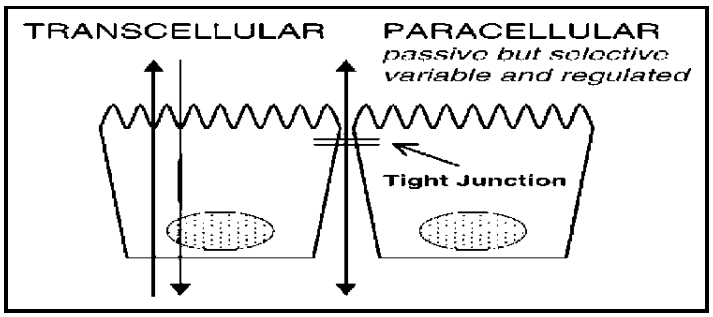

Figure No.7: Permeability Mechanism

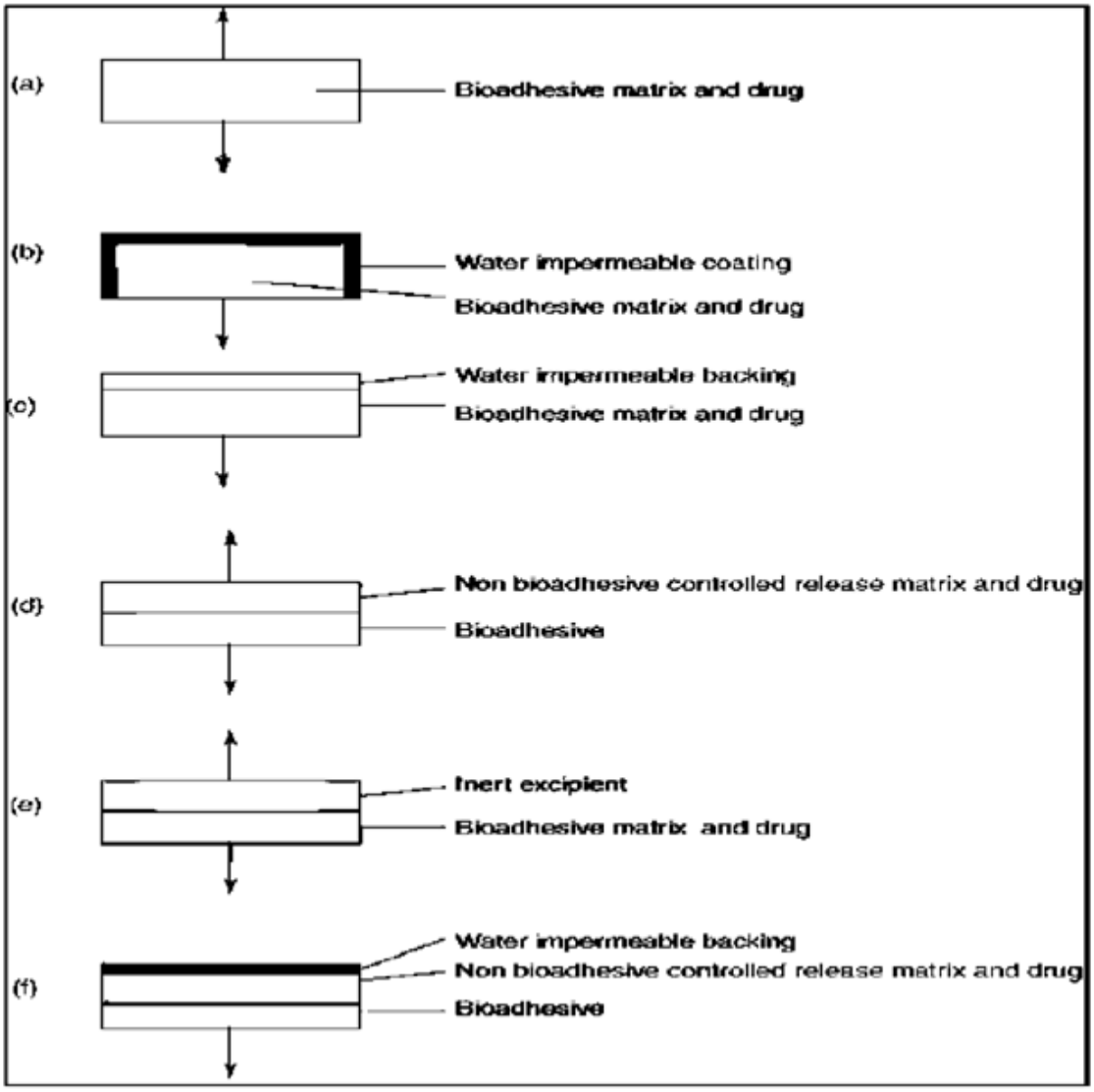

Figure No.8: Matrix Type Buccal dosage forms

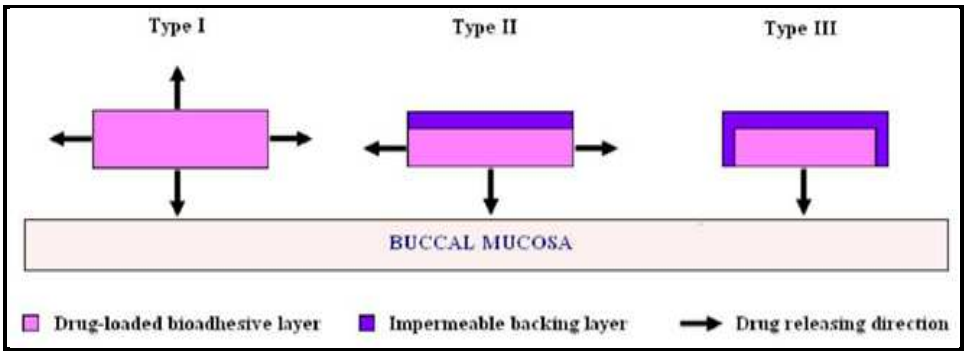

Figure No.9: Reservoir type buccal mucoadhesive dosage forms

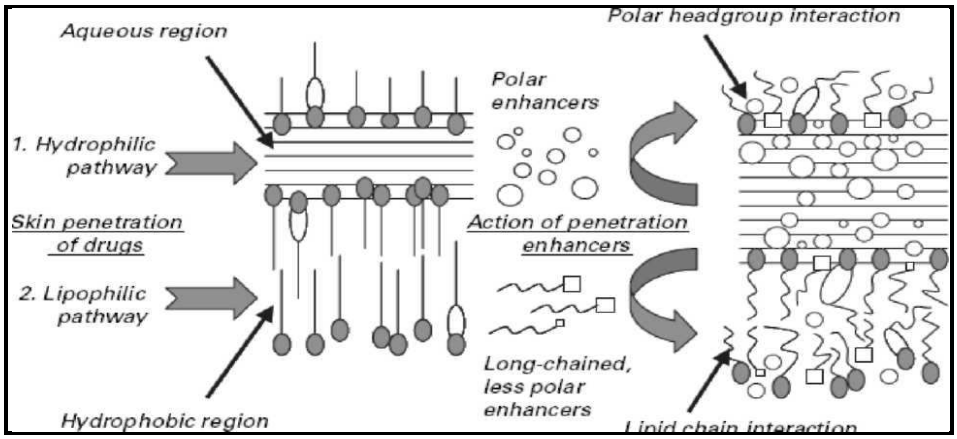

Figure No.10: Penetration enhancing mechanism

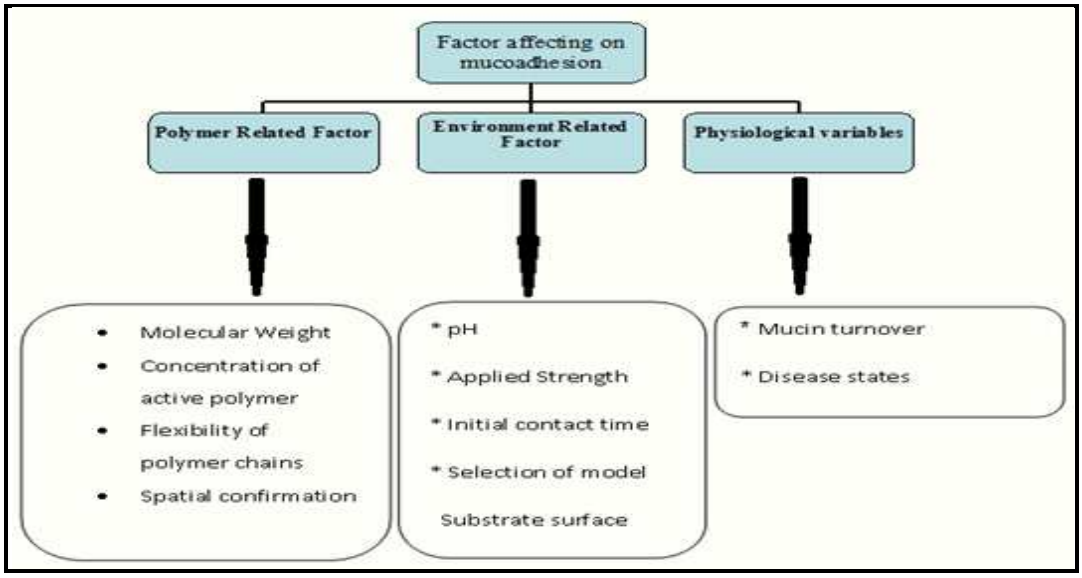

Figure 11: Factors Affecting Mucoadhesion

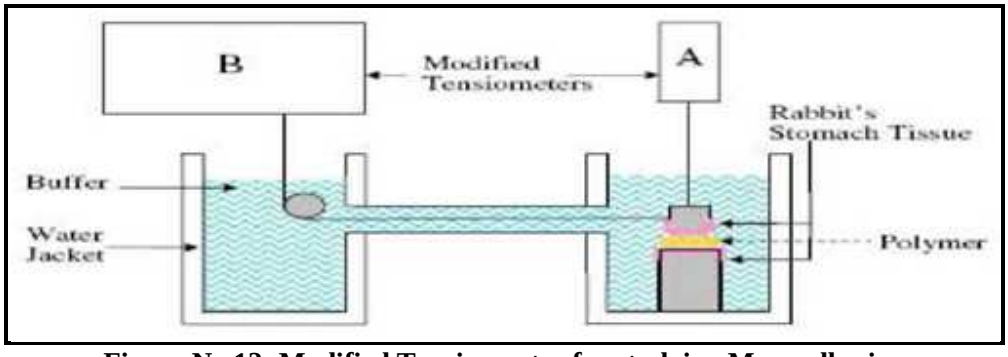

Figure No.12: Modified Tensinometer for studying Mucoadhesion

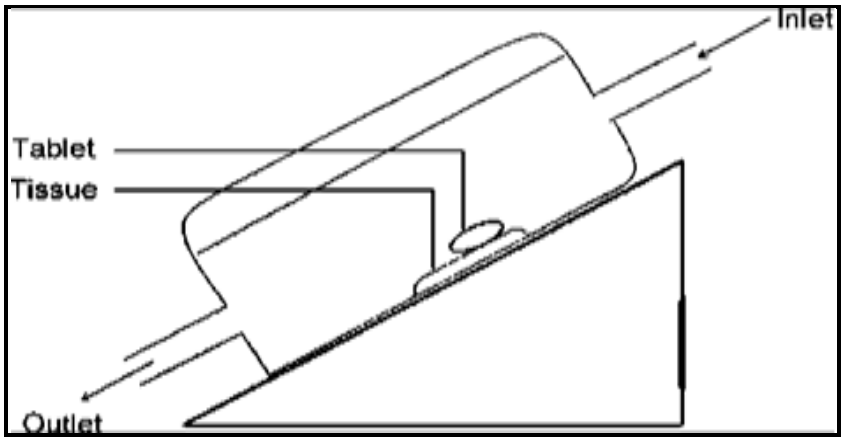

Figure No.13: Schematic drawing of the dissolution apparatus used by Mumtaz and Ch'ng

Figure No.14: Generex ORAL-LYN

CONCLUSION

Novel drug release through trans-mucosal and transdermal, would be of huge worth, because through such routes, the pain factor coupled with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer countless advantages in provisions of convenience, management and pulling out, retentivity, short enzymatic activity, cost effective and elevated enduring fulfillment. Mutually an economic and universal healthcare viewpoint, determining ways to formulate injectable medications is expensive and a number of time leads to grave harmful effects. Consequently various cost effective novel drug delivery formulations with improved bioavailability are essential.

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