



Buccal Drug Delivery System: A Review

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Abstract: Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. Bioadhesive polymeric systems have been used since extent in the development of products for various biomedical applications which include denture adhesives and surgical glue. Considerable attention has been focused in recent years on the delivery of drugs through the oral mucosa which have a high first pass metabolism or degrade in the gastrointestinal tract. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which 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. Mucoadhesive controlled-release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site.

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. Buccal dosage forms can be of Matrix or Reservoir types. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome.

Keywords: Bioadhesive; mucoadhesive; buccal; polymers; retention time; drug delivery system.

INTRODUCTION:

Mucoadhesive polymers are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes. Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of

certain classes of drugs especially peptides and proteins.

Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption. Within the oral mucosal cavity, delivery of drugs is classified into three categories. [1]

1) Sublingual delivery: Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth?

2) Buccal delivery: Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

3) Local delivery: Which is drug delivery into the oral cavity?

MECHANISM OF MUCOADHASIVE:

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer–polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the

mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.^[2-4]

IDEAL PROPERTIES/CHARACTERISTICS OF BUCCAL

ADHASIVE DRUG DELIVERY SYSTEM^[5]

- Should adhere to the site of attachment for a few hours
- Should release the drug in a controlled fashion
- Should provide drug release in an unidirectional way toward the mucosa
- Should facilitate the rate and extent of drug absorption
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

- 1) Bypass 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 pH 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.
- 8) Transmucosal delivery occurs is less-variable between patients, resulting in lower intersubject variability as compared to transdermal patches.
- 9) The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

DISADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

- 1) Low permeability of the buccal membrane: specifically when compared to the sublingual membrane.
- 2) Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm² of which ~50 cm² represents non-keratinized tissues, including the buccal membrane.
- 3) The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug.

- 4) Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form.

These are some of the problems that are associated with buccal drug delivery

LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

- 1) Drugs which are unstable at buccal pH cannot be administered.
- 2) Eating and drinking may become restricted.
- 3) There is an ever present possibility of the patient swallowing the dosage form.
- 4) Over hydration may leads to slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.
- 5) Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.
- 6) Only drug with small dose requirement can be administered.
- 7) Only those drugs which are absorbed by passive diffusion can be administered by this route.
- 8) Drugs contained in the swallowed saliva follow the pre-oral and advantages of buccal route are lost.

THEORIES OF MUCOADHASIVE:

1. 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 semi-permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on

molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.^[5]

2. Electronic Theory: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in 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. Adsorption Theory: The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from:

- (i) Primary bonds that is somewhat permanent and therefore undesirable in bioadhesion
- (ii) Vander Waals, hydrogen, hydrophobic and electrostatic forces, which form secondary chemical bonds.

4. Wetting Theory: Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion; expressed in terms of surface and interfacial tension (Y) being defined as energy per cm^2 released when an interface is formed.^[6]

According to Dupres equation work of adhesion is given by

$$W_a = Y_A + Y_B - Y_{AB}$$

Where, A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$W_c = 2Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

5. Fracture:

Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon / L)^{1/2}$$

Where: E=Young's modulus of elasticity

ε =Fracture energy

L=Critical crack length when two surfaces are separated

BIOADHASIVE POLYMERS:

Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance.^[7, 8]

FACTORS AFFECTING BIOADHESION

1) Polymer-Related Factors

➤ Polymer molecular weight

The optimum molecular weight for the maximum bioadhesion depends on the type of polymers. The bioadhesive forces increases

with the molecular weight of bioadhesive polymer.

➤ **Molecular flexibility**

It is important for interpenetration and enlargement. As water soluble polymers become cross linked, the mobility of the individual polymer chain decreases. As the cross linking density increases, the effective length of chain which can penetrate into the mucus layer decreases even further and mucoadhesive strength is reduced.

➤ **Concentration of active polymer**

There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated system, the adhesive strength drops significantly.

➤ **Polymer chain length**

The polymer molecule must have an adequate length.

2. Environment Related Factors

➤ **pH**

pH was found to have a significant effect of mucoadhesion are observed in studies of polyacrylic polymer cross linked with COOH group. pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone. Polycarbophil show the maximum adhesive strength at pH 3, the adhesive strength decreases gradually as the pH increases upto 5 polycarbophil does not show any mucoadhesive property above pH 5. This study, the first systematic investigation of the mechanism of mucoadhesion, clearly shows that the protonated carboxyl group rather than ionized carboxyl group react with mucin molecules

presumably by numerous simultaneous hydrogen bonds. [9]

➤ **Hydrogen bonding capacity**

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential.

➤ **Charge**

Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

➤ **Hydration (swelling)**

Hydration is required for a mucoadhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. [10, 11]

Permeation enhancers:

Permeation enhancers are substances added to pharmaceutical formulation in order to increase the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without

damaging the membrane and causing toxicity. Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination. [12]

Categories and examples of membrane permeation enhancers

- ❖ Bile salts: Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate,
- ❖ Surfactants : Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-Laurylether, Polyoxyethylene-20-cetylether, Benzalkonium chloride,
- ❖ Fatty acids : Oleic acid, Capric acid, Lauric acid/propylene glycol, Methylolate, Lysophosphatidylcholine, Phosphatidylcholi
- ❖ Chelators: EDTA, Citricacid, Sodium salicylate, Methoxy salicylates
- ❖ Non-surfactants: Unsaturated cyclic ureas
- ❖ Inclusion complexes: Cyclodextrins
- ❖ Others: Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides.
- ❖ Thiolated polymers: Chitosan-4-thiobutylamide, Chitosan- 4-thiobutylamide/gsh, Chitosan-cysteine, Chitosan- 4-thiobutylamide/gsh (where, gsh= Glutathione).

List of Active Ingredients delivered via a buccal route

Sr. No.	Active Ingredients	Sr. No.	Active Ingredients
1	Metronidazole	13	Chitosan
2	Nifedipine	14	Testosterone
3	Propranolol	15	Zinc sulphate
4	Danazol	16	Morphine sulphate
5	Nicotine	17	Acyclovir
6	Omeprazole	18	Metoprolol tartrate
7	Carbamazepine	19	Lignocaine
8	Arecoline	20	Oxytocin
9	Protirelin	21	Diclofenac sodium
10	Piroxicam	22	Pentazocine
11	Terbutaline sulphate	23	Ergotamine tartrate
12	Theophylline	24	Hydrocortisone acetate

BASIC COMPONENTS OF BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEM

The basic components of buccal bioadhesive drug delivery system are

1. Drug substance
2. Bioadhesive polymers
3. Backing membrane
4. Penetration enhancers
5. Adhesives

1. DRUG SUBSTANCE

Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties. The drug should have following characteristics: [13]

- The conventional single dose of the drug should be small.
- The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
- T_{max} of the drug shows wider-fluctuations or higher values when given orally. [14, 15]
- Through oral route drug may exhibit first pass effect or presystemic drug elimination.
- The drug absorption should be passive when given orally.

2. BIOADHESIVE POLYMERS

The first step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the

polymer matrix, which controls the duration of release of drugs. Bioadhesive polymers are by far the most diverse class and they have considerable benefits upon patient health care and treatment. The drug is released into the mucous membrane by means of rate controlling layer or core layer. A Bioadhesive polymer which adheres to the mucin/epithelial surface is effective and lead to significant improvement in the oral drug delivery.^[16]

An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics.

- It should be inert and compatible with the environment
- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.
- It should allow easy incorporation of drug in to the formulation.^[17]

Criteria followed in polymer selection

- It should form a strong non covalent bond with the mucin/epithelial surface
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

The polymers that are commonly used as bioadhesive in pharmaceutical applications are:

- Natural polymers
Ex: Gelatin, sodium alginate.
- Synthetic and semisynthetic polymers
Ex: PVA, PEG, HPMC, PVP, carbomers etc.^[18]

3. BACKING MEMBRANE

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.^[19]

4. PENETRATION ENHANCERS

Penetration enhancers are used in buccoadhesive formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are sodium lauryl sulphate, CPC, polysorbate -80, laureth -9, sodium fusidate, polmitoyl carnitine, azone, sodium glycocholate, dimethyl formamide etc.^[20]

5. BIOADHESIVES

Bioadhesives are the substances that are capable of interacting with the biological material and being retained on them or holding them together for extended period of time. Bioadhesive can be used to apply to any mucous or nonmucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane.^[20, 21] The commonly used bioadhesives are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

The bioadhesive should have the following characters,

- It should not produce any residue on mucosa layer.
- It should be inert and compatible with biological environment.
- It should adhere to the mucus membrane aggressively.
- It should preferably form a strong non-covalent bond with mucin/ epithelial cell surface.

CLASSIFICATION OF BUCCAL BIOADHESIVE DOSAGE FORMS

1. Buccal Bioadhesive Tablets
2. Buccal Bioadhesive Patches and Films
3. Buccal Bioadhesive Semisolids (ointments and gels)
4. Buccal Bioadhesive Powders

1. BUCCAL BIOADHESIVE TABLETS

Buccal bioadhesive tablets are dry dosage forms that are to be moistened prior to placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. The two buccal bioadhesive tablets commercially available buccoadhesive tablets in UK are **Bucastem** (Nitroglycerine) and **Suscard buccaP** (Prochloroperazine).

Examples:

- 1) Nitroglycerin bioadhesive tablets for the treatment of angina pectoris. ^[22]
- 2) Sumatriptan succinate buccal adhesive tablet which is effective in the acute treatment of migraine and cluster headache. ^[23]
- 3) Verapamil buccal tablet with compressed Verapamil (15ml) mucoadhesive polymer like

sodium alginate and HPC - EXF with standard tablet excipients.

2. BUCCAL BIOADHESIVE PATCHES AND FILMS

Buccal bioadhesive patches consists of two poly laminates or multilayered thin film round or oval as consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Example:

- 1) Isosorbide dinitrate in the form of unidirectional erodible buccal film are developed and characterized for improving bioavailability.
- 2) Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma.
- 3) Buccoadhesive film of clindamycin used for pyorrhea treatment. ^[24]

3. BUCCAL BIOADHESIVE SEMISOLID DOSAGE FORMS

Buccal bioadhesive semisolid dosage forms consist of finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution.

Example: Arabase. ^[25]

4. BUCCAL BIOADHESIVE POWDER DOSAGE FORMS

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa. ^[26]

Evaluation of bi-layered tablets:

All the above batches were evaluated for average thickness, average weight and weight variation, hardness, friability, swelling index, surface pH, in vitro drug release, mucoadhesive strength, residence time and in vivo bioavailability studies.

1. Weight variation:

Collect 10 tablets from each formulation of varying concentration of natural polymer. Weigh the tablets individually from all the selected formulations; calculate the average weight and comparing the individual tablet weights to the average.^[27]

2. Thickness:

Collect 3 tablets from each batch of formulation and the thickness of the tablets were measured with the help of vernier caliper. The average thickness is calculated.

3. Friability :

Friability of the tablets was determined by using Roche friabilator. From each batch, 6 tablets were weighed accurately which was W1 then placed in the friabilator and rotated at 25 rpm for 4 min. After completing the rotation weight of tablets were weighed which is W2. The percentage friability was determined.^[28]

4. Hardness:

Monsanto hardness tester was used for this purpose. The hardness of five tablets in each batch was measured and the average hardness was calculated.

5. In-vitro swelling studies:

The swelling rate of buccoadhesive tablets are evaluated using 2% w/v agar gel plate. For each formulation, 3 tablets are weighed and average weight of each 3 tablets are calculated (W1). The tablets are placed with the core facing the gel surface in Petridishes which are placed in an

incubator at 37±0.1°C. The tablets are removed at time intervals of 0.5, 1, 2, 3, 4, 5 and 6 hours, excess water on surface is absorbed using filter paper and swollen tablets are weighed. The average weight (W2) is determined and then swelling index is calculated using the formula.^[29]

$$\% \text{ Swelling index} = ((W2-W1)/W1) \times 100$$

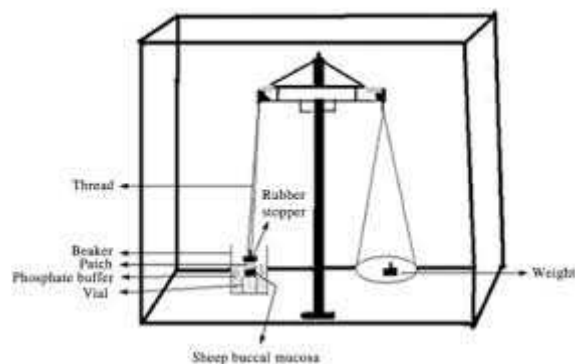
6. Determination of surface pH of tablets:

Buccoadhesive tablets are left to swell for 2hrs on surface of agar plate. The surface pH is measured using pH paper placed on core surface of the swollen tablet.

7. In-vitro mucoadhesion studies:

Mucoadhesive strength of the buccal tablets was measured on the "Modified Physical Balance method" which is shown in figure. The method used porcine buccal membrane as the model mucosal membrane. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. The both pans were balanced by adding an appropriate weight on the left-hand pan. A piece of mucosa was tied to the surface of the beaker and placed below the left pan which was moistened with phosphate buffer pH 6.8. The tablet was stuck to the lower side of left pan with glue. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The both pans were balanced by adding an appropriate weight on the left-hand pan. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated.^[30]

$$\text{Force of adhesion} = (\text{mucoadhesive strength}/100) \times 9.81.$$



8. In-vivo residence time:

The *in-vivo* residence time was examined in human volunteers. The placebo buccal tablets were prepared and given to the human volunteers and advised to administer the tablet in the buccal region. The time required for the tablet to detach from the buccal region is determined as residence time. [31]

9. In-vitro release studies:

The United pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2×2 cm glass slide with a solution of cyanoacrylate adhesive. In vitro drug release studies were carried out in 500 ml of phosphate buffer solution pH 6.6 for 8h using TDT 08L dissolution apparatus at 50 rpm and 37±0.5°C. At predetermined time intervals samples were withdrawn and replaced with fresh medium. The samples were filtered, diluted suitably then analyzed spectrometrically. All dissolutions were performed in triplicate. [32]

10. Surface pH:

The method used to determine the surface pH of the formulation was similar to that used by Bottenberg et al. a combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1 mL of

distilled water for 2hr. sand pH was noted by bringing the electrode in contact with the surface of tablet and allowing it to equilibrate for 1 min.

11. Ex-vivo Permeation Study:

In this study, porcine buccal mucosa was used as a membrane. Diffusion studies were carried out, to evaluate the permeability of drug across the porcine buccal mucosal membrane, by using glass surface Franz diffusion cell. Porcine buccal mucosa was obtained from local slaughter house and used within 2 hrs of slaughter. The tissue was stored in phosphate buffer pH 7.4 solution upon collection. The epithelium was separated from underlying connective tissues with surgical scissors clamped between donor and receiver chamber of diffusion cells for permeation studies. The smooth surface of mucosa should face the donor chamber and receiver chamber was filled with phosphate buffer of 7.4 pH. Whole assembly was placed in water bath maintained at 37±10°C. Buccal epithelium was allowed to stabilization for period of 1hr and hydrodynamic in receiver chamber was maintained by stirring with magnetic bead at 50 rpm. After the stabilization of buccal epithelium, the patch was kept on buccal epithelium and 3ml of phosphate buffer of 6.8pH was added in donor chamber. The sample of 1 ml were withdrawn at the time interval of 1 hour upto 8hrs and replaced with equal volume of fresh dissolution medium. The sink condition was maintained throughout the study. The withdrawn sample was diluted to 5ml. The amount of drug was determined by UV-VIS Spectrophotometer. [32, 33]

12. In-vivo oral bioavailability studies:

Albino white rabbits weighing about 1.5-2Kg were used for oral bioavailability studies. All the rabbits were fasted overnight before the experiments but had free access to water.

EVALUATION OF BUCCAL FILM:

1. Measurement of mechanical properties

Mechanical properties of the film were evaluated using Universal testing machine (Instron, India). The film strip in dimension of 50x15 mm, free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 5 cm. The strip was pulled by the top clamp at a rate of 300 mm/min till it broke. The force and elongation were measured when the film broke. The following equations were used to calculate mechanical properties of the film:

$$\text{Tensile strength (Kg/cm}^2\text{)} = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation at break (\%)} = \frac{\text{Increase in length (mm)} \times 100}{\text{Original length (mm)}}$$

2. Folding endurance

Three films of each formulation of size 2x2 cm were cut. Folding endurance was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times at the same place. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.^[34]

3. Measurement of film thickness

The thickness of the film was measured using a Screw gauge micrometer at 10 different spots from each batch. The mean and standard deviation were calculated.

4. Mass uniformity

The assessment of mass uniformity was done by weighing 10 randomly selected films from each batch. The test was performed on three films from each formulation then mean and standard deviation were determined.^[35]

5. Drug content uniformity

5 films were weighed and dissolved in 100 ml isotonic phosphate buffer pH 6.8 using magnetic stirrer. The solution was filtered and after suitable dilution analyzed for drug spectrometrically.

6. Surface pH

The agar plate was prepared by dissolving 2% w/v agar in isotonic phosphate buffer pH 6.8 and pouring the solution into the petridish till gelling at room temperature. Buccal films were allowed to swell on the surface of agar plate for 2 h. The surface pH was measured using pH indicator paper, the change in colour determined after 90s and compared with the standard colour scale.

7. Viscosity

The viscosity of the solution used for buccal films were determined using Brookfield viscometer.

8. Film swelling

The film swelling studies were conducted using two media, namely, distilled water and simulated saliva fluid. The buccal film was weighed and placed in a pre-weighed wire mesh with sieve opening 800 μ m. The mesh containing a film sample was submerged into 15 ml medium. Increase in weight of the film was determined at preset time intervals until a constant weight was observed. The degree of swelling was determined for three films of one type of formulation.^[36]

9. In-vitro residence time

The in vitro residence time was determined using a modified USP disintegration apparatus. 800 ml of isotonic phosphate buffer (IPB) maintained at 37°C was used as a medium. The segment of rabbit intestinal mucosa of 3 cm length was glued vertically to the glass slab. Then this glass slab was attached to the apparatus vertically. The film was hydrated on one surface using 50 μ l IPB and then this hydrated surface was applied to the rabbit mucosa with little pressure. The glass slab was then

allowed to move up and down so that patch was completely immersed in the buffer solution at the lowest and highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded. [37]

10. In-vitro release study

The release of drug from the buccal film was determined using Keshary-Chein diffusion cell. The diffusion medium was phosphate buffer pH 6.8, maintained at 37°C. The parchment paper was soaked in phosphate buffer pH 6.8 for 1h and then air-dried. It was mounted between the donor and receptor compartment and film was placed on it. Both the compartments were clamped together. The phosphate buffer pH 6.8 was filled in the receptor compartment (11ml capacity) and stirred using magnetic stirrer. At different time intervals samples were withdrawn and replaced with an equal volume of buffer. The samples were analyzed spectrophotometrically. [38]

11. In vitro bioadhesion strength

To evaluate the bioadhesion strength the tensile strength required to detach the bioadhesive film from mucosa was measured.

12. Measurement of adhesion force

The two sides of the balance were balanced with 5 g weight on the right hand side. The rabbit intestine excised and washed was tied tightly with the protrusion in the block. The block was then lowered into the glass container, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37±1°C, such that the buffer just reaches the surface of the mucosal membrane and keeps it moist. This was then kept below the left hand setup of the balance. The film was then stuck with a little moisture on to the cylinder hanging on the left hand side and the balance beam rose with 5 g weight on the right pan removed. This lowered the Teflon cylinder along with the film over the

mucosa with a weight of 5 g. The balance was kept in this position for 3 min and then slowly weights were increased on the right pan till the film separated from the mucosal surface, the total weight on the pan minus 5 g is the force required to separate the film from the mucosa. This gives the bioadhesive strength of the film in grams. [39]

13. In-vivo mucoadhesion studies

The in vivo mucoadhesion of the buccal films were determined in healthy human volunteers. The volunteers were asked to apply the film by gently pressing it in the buccal mucosa for 30 s. The volunteers were advised to perform their normal activity except eating food. They were asked to note down the retention time of the film as well as various criteria related to acceptability of the film for example irritation of mucosa, taste, dryness of mouth, comfort, salivary secretion etc. [40, 41]

CONCLUSION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. Bioadhesive polymeric systems have been used since extent in the development of products for various biomedical applications which include denture adhesives and surgical glue. Considerable attention has been focused in recent years on the delivery of drugs through the oral mucosa which have a high first pass metabolism or degrade in the gastrointestinal tract. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which 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. Mucoadhesive controlled-release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site.

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. Buccal dosage forms can be of Matrix or Reservoir types. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome.

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