REVIEW ARTICLE

Buccoadhesive Drug Delivery System: A Review

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ABSTRACT

Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases.Furthermore, films have improved patient compliance due to their small size and reduced thickness, compared for example to lozenges and tablets. The development of mucoadhesive buccal films has increased dramatically over the past decade because it is a promising delivery alternative to various therapeutic classes including peptides, vaccines, and nanoparticles. The "film casting process" involves casting of aqueous solutions and/or organic solvents to yield films suitable for this administration route. Over the last decade, hot-melt extrusion has been explored as an alternative manufacturing process and has yielded promising results. Characterization of critical properties such as the mucoadhesive strength, drug content uniformity, and permeation rate represent the major research areas in the design of buccal films. This review will consider the literature that describes the manufacture and characterization of mucoadhesive buccal films.

Key words: Buccal drug delivery, Oral mucosa, Mucoadhesion, Permeation, Mucoadhesive polymers, Buccal patches

Introduction:

Amongst the various routes of drug delivery, oral route is the most preferred to patient and clinician alike. Peroral administration of drugs has disadvantages such as first pass metabolism and enzymatic degradation within the GI tract, that prohibit 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 offer distinct advantages over peroral administration for systemic drug delivery [10].

Buccal mucosa as a site for drug delivery [1, 3]

There are two permeation pathways for passive drug transport across the oral mucosa: Paracellular and transcellular routes. Permeants may traverse these two routes simultaneously, but one route usually is more effective than the other, depending on the physicochemical properties of the diffusant. Because the intercellular spaces are less lipophilic in character than the cell membrane, hydrophilic compounds have higher solubility's in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient. Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds. Because the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

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Delivery of drugs within the oral mucosal cavity [3]

It is classified into three categories

1) Sublingual delivery: Is the administration of drug via sublingual mucosa (membrane of the ventral surface of the tongue and floor of the mouth) to

systemic circulation. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are most often one of two designs: those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa.

2) Buccal delivery: is the administration of drug via buccal mucosa (the lining of cheek) to the systemic circulation. The buccal mucosa is considerably less permeable than sublingual area, and is generally not able to provide rapid absorption and good bioavailability seen with sublingual administration.

3) Local delivery: for the treatment of conditions of oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time.

Even though sublingual mucosa is relatively more permeable than buccal mucosa, it is not suitable for a retentive oral transmucosal delivery system. The sublingual region lacks an expanse of smooth and immobile mucosa and is constantly washed by a considerable amount of saliva, making device placement difficult. The preferred site for retentive oral transmucosal delivery systems and for sustained- and controlled-release delivery devices is the buccal mucosa, mainly because of differences in permeability characteristics between the two regions and the buccal mucosa's expanse of smooth and relatively immobile mucosa.

Overview of Buccal Mucosa [3]

A. Structure: The oral mucosa is anatomically divided into

1) Epithelium

2) Basement membrane and Connective tissues

1) Epithelium:

The epithelium consists of approximately 40–50 layers of stratified squamous epithelial cells having thickness 500-800µm. The epithelium of oral mucosa serves as a protective covering for tissues and a barrier to the entry of foreign materials.

2) Basement Membrane and Connective Tissue

The basement membrane (BM) is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues. Connective tissue, along with basement membrane, is not considered to influence the diffusion of most compounds of pharmacological interest although these two regions may limit the movement of some macromolecules and complexes.

B. Buccal Mucosa Environment [2,3]:

The oral cavity is marked by presence of saliva produced by salivary glands and mucus which is secreted by major and minor salivary glands as part of saliva.

Role of Saliva:

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

Role of Mucus:

- Made up of proteins and carbohydrates
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

Pathways of Drug Absorption from buccal mucosa [2]: Two major routes are involved: Transcellular (intracellular) and Paracellular (intercellular) . The transcellular route may involve permeation across the apical cell membrane, intracellular space and basolateral membrane either by passive transport (diffusion, PH partition) or by active transport (facilitated and carrier-mediated diffusion, endocytosis). The transcellular permeability of drug is a complex function of various physicochemical

properties including size, lipophilicity, hydrogen bond potential, charge and conformation. Transportation through aqueous pores in cell membranes of epithelium is also possible for substances with low molar volume (80 cm^3/mol).

The second route, available to substances with a wide range of molar volumes, is the intercellular route (paracellular route).within the intercellular space, hydrophobic molecules pass through the lipidic bilayer, while the hydrophilic molecules pass through the narrow aqueous regions adjacent to the polar head groups of the lipids.

Structure and Design of Buccal Dosage Form [2]:

Buccal Dosage form can be of;

1. Matrix type: The buccal patch designed in a matrix configuration containing drug, adhesive, and additives mixed together.

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

Factors affecting drug delivery via buccal route [3]

Oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

1. Membrane Factors

These involve degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

2. Environmental Factors

A. Saliva: Thin film of saliva coats lining of buccal mucosa throughout and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. Thickness, composition and movement of this film affects the rate of buccal absorption.

B. Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa.

They constantly secrete mucus on surface of buccal m ucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

C. Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

3. Formulation related factors [3]:

A. 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 buccal epithelium, making this route more suitable for delivery of larger molecules.

B. Partition coefficient: partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in lipid-water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility.

C. pH: partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decrease,

while that of basic drugs increase. Partition coefficient is also an important indicator of drug storage in fat deposits. Obese individuals can store large amounts of lipidsoluble drug in fat stores. These drugs are dissolved in lipid and are a reservoir of slow release from these fat deposits.

D. pKa: 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.

Attractiveness of Buccoadhesive drug delivery system [4]:

- Permits the localization of delivery system.
- Patients are well adapted to oral administration of drugs.
- Patient acceptance and compliance is good compared to other drug delivery system.
- Ability to easily recover after local treatment is prominent.
- Allows a wide range of formulations that can be used e.g. buccoadhesive patches and ointments.

Advantages of buccoadhesive drug delivery system: -

Drug administration via the buccoadhesive drug delivery offers several advantages such as [1- 6]:-

- Drug is easily administered and extinction of therapy in emergency can be facilitated.
- Drug release for prolonged period of time.
- Drug can be administered in unconscious and trauma patients.
- Drugs bypass first pass metabolism so increases bioavailability.
- Drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption by passive diffusion.
- Flexibility in physical state, shape, size and surface.
- Maximized absorption rate due to close contact with absorbing membrane.
- Rapid onset of action.
- Formulation can be removed if therapy is required to be discontinued
- Large contact surface of the oral cavity contributes to rapid and extensive drug absorption
- Extent of perfusion is more therefore quick and effective absorption.
- Nausea and vomiting are greatly avoided.
- 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.[1]
- Transmucosal delivery occurs is less variable between patients, resulting in lower intersubject variability as compaired to transdermal patches
- Excellent accessibility
- Presence of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa
- Painless administration
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions
- Thin film is more stable, durable and quick dissolving than other conventional dosage forms.
- Thin film enables to improve dosage accuracy

relative to liquid formulations, since every strip is manufactured in such a way that it contains a precise amount of drug.

- Buccal films has the ability to dissolve rapidly without the need for water, which provides an alternate way to the patients to swallow and to patients who do not want suffering from nausea, such as those patients receiving chemotherapy.

Limitations of buccoadhesive drug delivery system [1-5]: -

There are some limitations of buccal drug delivery system such as-

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which cause allergic reactions, discoloration of teeth cannot be formulated.
- If formulation contains antimicrobial agents, which affects the natural microbes in the buccal cavity.
- Buccal membrane has low permeability, specifically when compared to the sublingual membrane.
- Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
- Drug with small dose can only be administered.
- Drugs which are absorbed by passive diffusion can only be administered by this route.
- Eating and drinking may become restricted.
- 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.[1]
- 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.

Design of Buccal Mucoadhesive Patches:

The different components of Buccal Mucoadhesive Patches are:

1. Drug
2. Polymers (Mucoadhesive polymers, polymers controlling rate of release and Polymers to prepare backing membrane).
3. Backing membrane.
4. Plasticizer
5. Penetration enhancer.

1. Drug [2, 3]: The important drug properties that affect its diffusion through the patch as well as buccal include molecular weight, chemical functionality and melting point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties.

Following are the critical properties for candidature to Buccal Mucoadhesive Drug Delivery [2, 3]:

- Conventional single dose of drug should be low.
- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
- Drug should not adversely affect the natural microbial flora or oral cavity.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.
- Drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
- Tmax of the drug shows wider-fluctuations or higher values when given orally.
- Drug absorption should be passive when given orally.

4. Mucoadhesive polymers [3]: As the contact between formulation and buccal mucosa is one of the key factors in successful buccal delivery, more emphasis is now given to the use of mucoadhesive polymers in the formulation of buccal drug delivery systems. Mucoadhesive polymers are used to improve drug delivery by enhancing the dosage form's contact time and residence time with mucous membranes. Mucoadhesion may be defined as the process where

polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface.

Adhesion of materials with mucosa can be considered as the result of following steps: Polymer hydration, wetting of mucosa, diffusion into mucus and chemical bonding with glycoprotein. Hydrated polymer wets the mucus when interatomic and intermolecular forces occur at the interface. The formulation of an assembly is determined by a liquid - solid contact step and thus, the criteria of good wetting and free energy of interaction between the two materials should be considered. After initial contact between hydrated polymer and mucus, the mucoadhesion strength is determined by formation of secondary chemical bonds due to polymer chain/mucin interpenetration, which is affected by polymer flexibility and mobility. Hence, the ideal bioadhesive polymer should have satisfactory surface energy and chain flexibility favouring its spread and diffusion into mucus and functional groups forming secondary chemical bonds (for examples, ionic and hydrogen bonds). Appropriate materials for bioadhesion are mostly hydrogel-forming polymers that are cellulose derivatives such as sodium carboxymethyl cellulose, methylcellulose, methyethylcellulose and hydroxyethyl cellulose. Natural gums such as karaya and pectin and other polymers such as starch, sodium alginate and poly vinyl pyrrolidone can also be used. The high molecular weights of polyethylene oxide (PEO) and polyethylene glycol (PEG) show good mucoadhesive characteristics because of their linear flexible molecular structure and ability to form physical bonds entangling the mucus.

The bioadhesive properties of a polymer is affected by following factors.

A. Molecular Weight and Polymer Conformation

The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer.It is generally understood that the threshold required for successful bioadhesion is at least100000 molecular weight. It is obvious that the polymer molecule must have an adequate length to allow chain interpenetration. It is also necessary to consider the size and configuration of polymer molecule. For example, with polyethylene oxide the adhesive strength increases even up to molecular weights of 4000000. These polymers are well known to contain molecules for highly linear configuration which contribute to interpenetration with dextran.

Cross-linking density

An increase in cross linking is found to decrease the strength of mucoadhesion, due to decreasing diffusion coefficient, chain segment flexibility and mobility. Therefore, the extent of interpenetration was reduced.

B. Charge and Ionization

Using a cell culture fluorescent probe technique, polymers were studied for their bioadhesive potential. It appears that charge density is an important element for bioadhesion. Carboxylated polyanions are good potential bioadhesives for drug delivery.

C. Concentration of Polymer

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

D.pH

pH was found to have a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross linked with COOH groups. pH influences charge on the surface of both mucus and polymers.

An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics [3, 24].

- Should be inert and compatible with environment

- Polymer and its degradation products should be non-toxic, non-irritant, free from leachable impurities and absorbable from mucous layer.
- Should adhere quickly to moist tissue surface and possess some site specificity.
- Must not decompose on storage or during the shelf life of dosage form.
- Should be easily available in the market and economical.
- Should allow easy incorporation of drug in to the formulation
- Should have good spreadability, wetting, swelling, solubility and biodegradability properties.
- Should adhere quickly to buccal mucosa and possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Criteria followed in polymer selection [3]

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

Classification of various mucoadhesive polymers [4]:

(I) Natural polymers:

- Tragacanth
- Sodium alginate
- Guar gum
- Xanthan gum
- Soluble starch
- Gelatin
- Chitosan

(II) Synthetic polymers:

- Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxy ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
- Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
- Poly hydroxyl ethyl methylacrylate.
- Poly ethylene oxide.
- Poly vinyl pyrrolidone.
- Poly vinyl alcohol.

3. Polymers used to prepare Backing Membrane:

The polymer whose solution can be casted into thin poreless uniform water impermeable film can be used to prepare backing membrane of patches. It should have good flexibility and high tensile strength and low water permeation. It should be stable on long storage maintaining its initial physical properties per se. cellulose acetate in concentration of 2.4% w/v in acetone with 10% plasticizer (PEG 4000 or glycerol) of total polymer weight when air dried produces a thin film suitable for backing membrane purpose. Similarly, 2-4% w/v solution of ethyl cellulose in 1:4 mixture of alcohol: toluene with suitable plasticizer can be casted into film.

The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for backing membrane must be inert and impermeable to drugs and penetration enhancers. Thickness of backing membrane must be

thin and should be around 75-100 microns. The most commonly used backing materials are Polyester laminated paper with polyethylene. Other examples include cellophane- 325, multiphor sheet and polyglassine paper.

4. Plasticizer: These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. Usually the percentage of polymer falls in the range of 10-50% of total polymer weight. Plasticizers help in release of drug substance from the polymer base as well as act as penetration enhancers. The choice of plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer- polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity.

5. Penetration Enhancers in Buccal Drug delivery [2, 3, 24]: Substances that help to promote drug permeation through buccal epithelium are referred as penetration enhancer, permeation promoters or absorption enhancer. The chemical used as penetration enhancers should ideally be safe and nontoxic, pharmacologically and chemically inert, non irritant and non-allergenic.

Mechanisms of action of permeation [3, 24]:

1) Changing mucus rheology:

- By reducing the viscosity of mucus and saliva overcomes this barrier.

2) Increasing the fluidity of lipid bilayer membrane:

- Disturb the intracellular lipid packing by interaction with either lipid or protein components.

3) Acting on components at tight junctions:

- By inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming enzymatic barrier.
- In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

4) Increasing the thermodynamic activity of drugs:

- Some enhancers increase the solubility of drug there by alters the partition coefficient

Example: Anions such as sodium laurate and sodium lauryl sulfate, cations such as cetylpyridium chloride and nonions such as poloxamers, brij, span, myrj and tween are known to disrupt the intercellular lipid domain and protein domain integrity, thus enhancing the penetration of hydrophilic molecules. Bile salts are believed to act by the extraction of membrane fluidization and reverse micellisation in the membrane, creating aqueous channels. Fatty acids such as oleic acid and carpylic acid increase the fluidity of phospholipids in the intercellular lipid domain, cyclodextrins act as drug penetration enhancers by including membrane components. Cationic polymers such as chitosan and poly-L-arginine are known to act by neutralizing the charge of mucosal surface and by opening the tight junctions. Because of the similarities between buccal mucosa and the skin, chemical enhancers and vehicles that increase transdermal delivery have also been used on the buccal mucosa. Ethanol at different concentrations (5% and 30%), propylene glycol, n-methylpyrrolidone and dimethylsulfoxide have been used as penetration enhancers in buccal dosage forms. Protease inhibitors such as aprotinin, bestatin, puromycin and bile salts, which have been tested and shown to stabilize peptides again buccal mucosal enzymes, have also been used.

Characteristics of patch [3]

- Size of the flexible buccal patch may be as large as 10–15cm^2 in area.
- Mucoadhesive buccal patches with a surface area of 1–3 cm^2 are most acceptable.
- It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2-cm^2 system in 1 day is approximately 10–20 mg.

- Shape of the delivery system may also vary, although for buccal drug administration, an ellipsoid shape appears to be most acceptable.
- Thickness of the delivery device is usually restricted to only a few millimeters. The location of delivery device also needs to be considered
- Maximal duration of buccal drug retention and absorption is approximately 4–6 h because food and/or liquid intake may require removal of delivery device.
- Physiology of mucus membrane under disease condition need to be accounted (for e.g.: Cancer patients suffer from oral candidosis)

Methods of preparation of buccal patches [6]

1. Solvent casting
2. Direct milling
3. Solid dispersion extrusion
4. Semisolid casting
5. Rolling method
6. Hot melt extrusion

1. Solvent casting

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of desired size and geometry.

2. Direct milling

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, resultant material is rolled on a release liner until desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by two processes, solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

3. Solid dispersion extrusion:

In this method immiscible components are extrude with drug and then solid dispersions are prepared.Finally the solid dispersions are shaped in to films by means of dies.

4. Semisolid casting:

In semisolid casting method first a solution of water soluble film forming polymer is prepared.The resulting solution is added to a solution of acid insoluble polymer (cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide.Then appropriate amount of plasticizer is added so that a gel mass is obtained.Finally the gel mass is casted in to films or ribbons using heat controlled drums. Thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble forming polymer should be 1:4.

5. Rolling Method:

In rolling method solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers and cut in to desired shapes and sizes.

6. Hot melt extrusion:

In hot melt extrusion method, first the drug is mixed with carriers in solid form.Then the extruder having heaters melts the mixture.Finally the melt is shaped in to films by dies.There are certain benefits of hot melt extrusion,

Fewer operation units, Better content uniformity, An anhydrous process.

Evaluation of buccal patches (9, 10)

1.) Surface pH

For the determination of surface pH combined glass electrode are used. The patches are kept in contact with 5 ml of distilled water for 1 hr. The pH can be noted by bringing the electrode near the surface of formulations and allowing it to equilibrate for 1 min.

2.) Weight Uniformity and thickness

Three samples of each patch (1.5 cm×1.9 cm) are randomly taken and each patch is weighed individually. The data is analyzed for mean weight and

standard deviation. Thickness of samples from each patch is measured in triplicate and average values are reported.

3.) Content Uniformity

Drug content uniformity is determined by dissolving each patch in 10 ml of solvent and filtering it with Whatman filter paper (0.45 µm). The filtrate is evaporated and drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution is diluted with phosphate buffer (pH 6.8) up to 20 ml, filtered through a 0.45-µm Whatman filter paper, and absorbance is measured using a UV Spectrophotometer against pH 6.8 phosphate buffer use as blank. The experiments are performed in triplicate, and average values are reported.

4.) Folding Endurance

The folding endurance of patches is determined by repeatedly folding one patch at the same place till it break or up to 300 times without breaking. The experiments are performed in triplicate, and average values are reported.

5.) Percentage moisture loss

This test is carried out to check the integrity of films at dry condition. Three 1-cm diameter films are cut out, weighed accurately, and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours, the films are removed and weighed. Average percentage moisture loss of three films is found out.

$$\text{Percentage Moisture Loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \text{X100}$$

6) Water absorption capacity test

Circular Patches, with a surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature till constant weight is recorded. Water uptake (%) is calculated using the following equation

$$\text{Water uptake (\%)} = (W_w - W_f) / W_f \times 100$$

Where, Ww is the wet weight and W_f is the final weight.

7. *Characterization of Drug Release*

Two methods are used to characterize drug release from patches one is simple dissolution using a modified paddle method. Special flasks containing 100 ml of dissolution medium are used. A second method uses a diffusion cell for determining drug release and considered an improvement over dissolution in that only one face of patch is in contact with the medium via a hydrated hydrogel, a situation that more closely mimics the moist surface of buccal cavity.

(a). In Vitro Methods

Beaker method

The dosage form in this method is made to adhere at the bottom of beaker containing the medium and stirred uniformly using overhead stirrer. Volume of medium used in the literature for study varies from 50-500 ml and the stirrer speed from 60-300 rpm.

Dissolution apparatus

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution

Other methods

Other methods involve plexiglass sample blocks placed in flasks, agar gel method, Valia-Chien cell, USP 2 dissolution apparatus, etc.

Although a number of methods have been reported, the ideal method would be one where sink condition

is maintained and dissolution time *in vitro* simulates dissolution time *in-vivo*.

(b). In Vivo Methods

The most desirable *in vivo* approach is to perform experiments in human volunteers or patients. However, it is very difficult to begin with this approach, because of difficulties of cost, time, toxicity of drug and ethical considerations. Therefore, animal models are being usually used for this purpose. The most important and difficult aspect of experimental design is the choice of animal species. Animal models such as dog, cat, rabbit, rat and sheep have been used to determine the oral mucosal absorption characteristics of drugs. Very few, and certainly no extensive *in vivo* (animal) *in vivo* (human) correlation have been reported, which would allow investigator, to compare oral mucosal absorption characteristics of a particular animal with those of its human counterpart. However, the methods used in *in vivo* studies are absorption cells and perfusion cells.

Disc methods

These methods have advantage that the absorption across a defined oral cavity mucosa can be studied. A polytef disc with a diameter of approximately 3.5 cm and height of 1 cm is used for the study. The disc has a central depressions depth of 4 mm. A water soaked filter paper disc is placed in the depression and known amount of drug spread onto it. Once the drug has dissolved the device is placed onto defined oral mucosal surface and maintained in place for 5 min. After removal, a non impregnated disc is used to wipe the oral mucosa, the discs combined and analysed[26].

Disc techniques allow investigators to study drug loss across a fixed area of defined oral cavity membrane. Major limitations of this technique include adherence of disc to the membrane, leakage of drug form disc and interference from salivary secretions.

Perfusion cells for animal studies

Veillard et al. developed perfusion cell, which is made from a medical grade silicon polymer. The cell has a volume of 0.075 cm^3 and exposed area of 0.25 cm^2. Barshun et al. constructed a pliable cell made of a hydrophilic vinyl polysiloxane polymer which has an internal volume of 1 ml and allowed a 1.8 cm^2 area of buccal membrane to be per fused. The design also incorporates sealing lip to prevent leaks. Ranthbone reported a buccal perfusion cell design constructed from inflexible material such as nylon or Teflon. Buccal perfusion cells of the types mentioned above offer fixed (known) interfacial areas over which transfer can take place into a defined oral cavity membrane.

(c). Human Techniques

Animal models play an important role in the development of an oral mucosal drug delivery system, but these models are appropriate to use only for screening of a series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations, if one is certain that the route of penetration,structure and composition of permeation barrier for both drug and excipients are an exact mimic of its human counterpart.

8. *Ex-Vivo* Buccal Permeation Study

The in vitro buccal permeation study through goat buccal mucosa is performed using a Keshary-Chien type glass diffusion cell at 37°C ± 0.2. Goat buccal mucosa is obtained from a local slaughterhouse and used within 2 hours of slaughter. Freshly obtained goat buccal mucosa is mounted between donor and receptor compartments. The patch is placed on the mucosa, and compartments are clamped together. The donor compartment is filled with 2 ml of phosphate buffer (pH 6.8). The receptor compartment (10-mL capacity) is filled with isotonic phosphate buffer (pH 7.4), and hydrodynamics in the receptor compartment are maintained by stirring with a magnetic bead at 50 rpm. At predetermined time intervals, a 1-ml sample is withdrawn and analyzed for drug content.

9. *Ex-Vivo* Mucoadhesive Strength

Fresh goat buccal mucosa is obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane is separated by removing the

underlying fat and loose tissues. The membrane is washed with distilled water and then with phosphate buffer (pH 6.8) at 37 °C ±1.

The patch's bioadhesive strength is measured on a modified physical balance. Fresh goat buccal mucosa is cut into pieces and washed with phosphate buffer (pH 6.8). A piece of buccal mucosa is tied in the open mouth of a glass vial; filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted in the center of a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1) so that it just touches the mucosal surface. The patch is stuck to lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of balance are balanced with a 5 g weight on the right-hand side pan. The 5 g weight is then removed from the left-hand side pan, which lowers the pan along with patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detaches from the mucosal surface. The weight, in grams, require to detach the patch from mucosal surface provides the measure of mucoadhesive strength. The experiments are performed in triplicate, and results are reported.

10. Measurement of mechanical properties

Mechanical properties of films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with dimensions of 60 x 10 mm and without any visual defects are cut and positioned between two clamps separated by a distance of 3 cm. Clamps are designed to secure the patch without crushing it during test, the lower clamp held stationary and strips are pulled apart by upper clamp moving at a rate of 2 mm/sec until the strip breaks. The force and elongation of film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula.

$$T = \frac{m \times g}{b \times t} kg/mm2$$

Where,

M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec 2

B - is the breadth of the specimen in cm

T - is the thickness of specimen in cm. Tensile strength (kg/mm2) is the force at break (kg) per initial cross- sectional area of the specimen (mm2).

11. Stability study in human saliva

In this the stability study of bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age18-50years). Buccal patches are placed in separate petridishes containing 5 ml of human saliva and kept in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the films are examined for changes in colour, shape, collapse and physical stability.

12. *Ex Vivo* Residence Time

The ex vivo mucoadhesion time Is studied (n = 3) after application of patches on freshly cut goat buccal mucosa.Which is fixed on the inner side of a beaker, about 2.5 cm from bottom, with cyanoacrylate glue. One side of each patch is wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker is filled with 200 ml of phosphate buffer (pH 6.8) and is kept at 37°C ± 1. After 2 minutes, at 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. Time requires for the patch to detach from goat buccal mucosa is recorded as the mucoadhesion time.

13. Swelling study

Buccal patches are weighed individually (designated as W_1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from gel plates and excess surface water is removed carefully using filter paper. The swollen patches are then reweighed (W_2) and swelling index (SI) is calculated using the following formula.

$S_1 = (W_2 - W_1) / W_{1 \times 100}$

14. Water vapor transmission rate:

For this study, vials of equal diameter are used as transmission cells. These cells are washed thoroughly and dried in an oven. About 1 g of calcium chloride is taken in the cell and polymeric films measuring one cm^2 area are fixed over the brim with the help of an adhesive. The cells are weighed accurately and initial weight is recorded, and kept in a closed desiccators containing saturated solution of potassium chloride. The humidity inside desiccators is found to be in between 80-90% RH. The cells are taken out and weighed after 18, 36, 54, and 72 hrs. Water vapour transmission rate is calculated by using the following formula.

Water Vapour Transmission Rate = WL/S

Where, W is water vapour transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm^2 .

Summary of the studies showing buccal films formulated using different polymers

Active ingredient	Polymers used	Investigators [Ref.]
Aceclofenac	Gelatine,NaCMC and PVA	D.Bavistar *et al.*[14]
Amiloride	HPMC K4M,CP 934P and Ethyl cellulose	P.Kumar *et al.*[21]
Atenolol	Ethylcellulose, Sodium alginate, and Carbopol	B.K Satishbabu *et al.*[22]
Carvedilol	HPMC, CP 934, Eudragit RS 100 and Ethyl cellulose	J. Thimmaasetty *et al.* [29]
Chlorpheniramine Maleate	Hydroxyethylcellulose	K.C Sekhar *et al.*[36]
Domperidone	HPMC, PVP K30,Eudragit RLPO, Polyethylene oxide	C .R Palem *et al.* [35]
Etophylline	HPMC	R.R Narasimha *et al.*[6]
Famotidine	Carbopol 934P; HPMC, PVP	M.Alagusundaram *et al.* [39]
Flufenamic acid	Chitosan,kollicoat IR and hydroxypropyl β-cyclodextrine	P. Mura *et al.* [38]
Flurbiprofen	HPMC, SCMC and PVA	S.K Mishra *et al.* [37]
Glipizide	HPMC E15, CP 934P, Eudragit RL100,and SCMC 1500-400 cps	M. Semalty *et al.*[8]
Ibuprofen	PVP and SCMC	L. Perioli *et al.* [34]
Insulin	SCMC DVP , IPA	J. Sahni *et al.* [33]
Methotrexate	EC,Sodium alginate and CP 934	R.Chaudhary *et al.*[16]
Miconazole nitrate	Hydroxypropyl methyl cellulose (HPMC), Hydroxyethyl cellulose, Chitosan, Sodium carboxy methyl cellulose and Polyvinyl alcohol	N. A Nafee *et al.*[12]
Montelukast	HEC,NaCMC,Eudragit RL100	R.N.G Rao *et al.*[17]
Nimodipine	Chitosan lactate, SCMC, PVP, CP, Sod. alginate and Eudragit RS 30D	N. Hassan *et al. [31]*
Nitredipine	Sodium alginate,HPMC K100, PVP K30, SCMC ,HPC , CP 934P and PVA	M. Nappinnai et al. [32]
Ondansterone	Chitosan and PVP K30	M. Koland *et al. [30]*
Pimozide	HPMC,PVA,PVP and CP 934	B.Basu *et al.*[18]
Prochlorperazine	HPMC	C.S Kolli *et al.*[19]
Propranolol HCl	Chitosan and PVP K 30	V.M Patel *et al. [26]*
Progesterone	Chitosan	S.K Jain *et al.*[25]
Resperidone	HPMC,PVA,PVP and Chitosan	B.Manasa *et al.*[13]
Salbutamol sulfate	Water soluble Chitosan, Acid soluble Chitosan, PVP and HPMC	A.Puratchikody *et al.*[27]
Sumatriptan	Chitosan,Gelatine and PVP K30	S.S Shidhaye *et al.* [28]
Tetracycline	CP 934,Ethyl cellulose	R.M Obaidat *et al.* [40]
Verapamil HCl	Chitosan and PVP K30	S.V Deshmane *et al.*[15]
Valsartan	Chitosan,HPMC,and PVP	P.B Anjankumar *et al.*[23]
Zidovudine	HPMC,Eudragit and CP	S.Rakesh Reddy *et al.*[20]

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