BUCCAL PATCH AS DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, 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. It is also possible to administer drugs to patients who unconscious and less co-operative. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combinations of polymers, absorption enhancers. Natural polymers have recently gained importance in pharmaceutical field. Mucoadhesive polymers are used to improve drug delivery by enhancing the dosage form's contact time and residence time with the mucous membranes. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. 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. In addition to this, studies have been conducted on the development of controlled or slow release delivery systems for systemic and local therapy of diseases in the oral cavity.

Keywords: Buccal patches, Mucoadhesive polymers, Natural polymers and Synthetic polymers.

INTRODUCTION

Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity)[1]. Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva.

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action[2].

Advantages of buccal patches

- The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation.

- Buccal administration, the drug gains direct entry into the systemic circulation. There by bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.

- The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.

- Buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application painless and with comfort.

- Patients can control the period of administration or terminate delivery in case of emergencies.

- The buccal drug delivery systems easily administered into the buccal cavity.

- The novel buccal dosage forms exhibits better patient compliance.

Disadvantages of mucoadhesive buccal Patches

- Once placed at the absorption site & the dosage form should not be disturbed.

- The drug swallowed in saliva is lost.

- Properties like unpleasant taste or odour, irritability to the mucosa & stability at salivary pH posses limitations to the choice of drug.

- Only drugs with small dose can be administered.

- Eating and drinking may become restricted.

Limitations in buccal patches

- The area of absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.

- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.

- Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse

properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route. Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk.[3]

Ideal characteristics of mucoadhesive buccal drug delivery

a. Polymer and its degradation products should not be non-toxic, and free from leachable impurities.

b. Should have good spreadability, wetting and solubility and biodegradability properties.

c. pH should be biocompatible and should posses good viscoelastic properties.

d. Should adhere quickly to buccal mucosa and should posses sufficient mechanical strength.

e. Should posses peel, tensile and shear strength at the bioadhesive range.

f. Polymer should be easily available and its cost should not be high.

g. Should show bioadhesive properties in both dry and liquid state.

h. Should demonstrate local enzyme inhibition and penetration enhancement properties.

i. Should demonstrate acceptable shelf life.

j. Should have optimum molecular weight.

k. Should posses adhesively active groups.

l. Should have required spatial confirmation/

m. Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.

n. Should not aid in development of secondary infections such as dental caries.

Oral mucosal sites

Within the oral mucosal cavity, delivery of drugs is classified in to three categories

1. Sublingual delivery: is the administration of the drug via the sublingual mucosa (the Membrane of the ventral surface of the tongue and the floor of the mouth to the Systemic circulation).

2. **Buccal delivery**: is the administration of drug via the buccal mucosa (the lining of the

Cheek) to the systemic circulation.

3. **Local delivery**: for the treatment of conditions of the 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[4,5].

Overview of Buccal Mucosa

A. Structure[4,6,7]
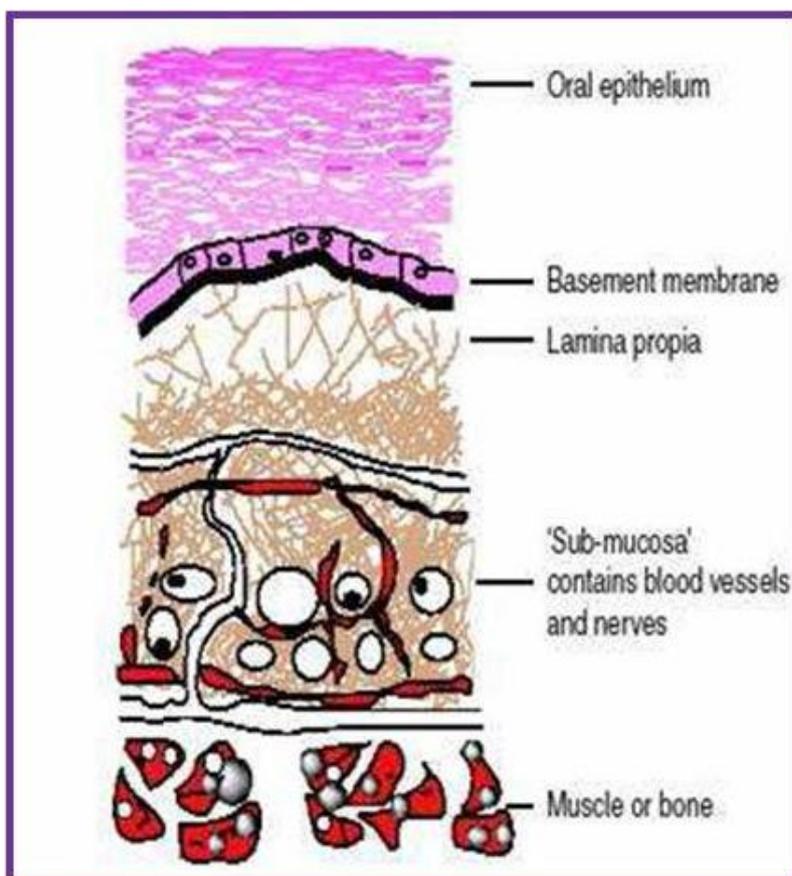
The oral mucosa is anatomically divided into

1) Epithelium

2) Basement membrane and Connective tissues

1) Epithelium[4,6]: The epithelium consists of approximately 40–50 layers of stratified squamous epithelial cells having thickness 500-800μm[4]. The epithelium of the oral mucosa serves as a protective covering for the tissues and a barrier to the entry of foreign materials. These functions are reflected in the organization of the epithelium in which individual epithelial cells are closely opposed and stratified so there are a number of layers that show a sequence of differentiation. The uppermost layers form a surface that is resistant to physical insult and to penetration by foreign substances[7]. Membrane Coating Granules (MCG) are spherical or oval organelles (100–300 nm in diameter). MCGs discharge their contents into the intercellular space and thus form the permeability barrier. Major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids[4]. Cells increase in size and become flattened as they progressively mature and migrate from the basal layer towards the epithelial surface, showing increasing levels of protein monofilaments and declining levels of some cytoplasm organelles[7].

2) Basement Membrane and Connective Tissue[4,7]: 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. This basal complex anchors the epithelium to the connective tissue and supplements the barrier function of the superficial layers of the epithelium to prevent some large molecules from Passing the oral mucosa. The bulk of connective tissue consists of a collagen fibre network, the organization of which determines mechanical stability, resistance to deformation, and extendibility of the tissue. Most likely, the connective tissue, along with the 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. Environment[8]

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

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.

Role of Mucus

• Made up of proteins and carbohydrates.

• Cell-cell adhesion

• Lubrication

• Bioadhesion of mucoadhesive drug delivery System

Buccal Mucosa and Pathways of Drug Absorption

The buccal mucosal tissues consist of a multilayered, stratified squamous epithelium covered with mucous. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual mucosa contains somewhat fewer layers[9]. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The basal lamina connects the epithelium to a connective tissue layer, the lamina propriya[10]. The thickness of the buccal mucosa is about 500-800 μm. The buccal epithelium is not keratinized and has small amounts of ceramide, neutral but polar lipids and cholesterol sulphate in the intercellular lipid region. Buccal epithelia have been found to be considerably more permeable to water than keratinized epithelia present in other regions of the oral mucosa[11].

Apart from the intercellular lipids, the basement membrane may present some resistance to permeation as well. The basic drugs transport mechanism for the buccal epithelium is the same as that for other epithelia in the body. Two major routes are involved:

Transcellular (intracellular) and Para cellular (intercellular)[12].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 a drug is a complex function of various physicochemical properties including size, lipophilicity, hydrogen bond potential, charge and conformation. Transportation through aqueous pores in the cell membranes of the epithelium is also possible for substances with low molar volume (80 cm^3/mol)[13].

The second route, available to substances with a wide range of molar volumes, is the intercellular route (par cellular 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[14].

Factors affecting buccal absorption

The 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[15].

1. Membrane Factors: This involves degree of keratinisation, 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: The thin film of saliva coats throughout the lining of buccal mucosa and is Called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect 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 mucosa. 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.

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Physiological aspects: Physiological considerations such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms. Constant flow of saliva and mobility of the involved tissues challenge drug delivery to the oral cavity. The residence time of drugs delivered to the oral cavity is typically short; in the range of 5-10 min. Buccal mucoadhesive formulations are expected to overcome this problem. Bio adhesive polymers offer a means by which a delivery system is attached to the buccal mucosa, and hence, provide substantially longer retention times at the absorption site.

They also provide a means to confine and maintain high local concentrations of the drug and/or excipients (s) to a defined, relatively small region of the mucosa in order to minimize loss to other regions and limit potential side effects. The mucus layer covering the buccal mucosa is necessary for bio adhesive systems. Unfortunately, it not only forms a physical barrier to drug permeation, but also prevents long-term bioadhesion and sustained drug release by its short turnover time. Interestingly, the presence of bio adhesive polymers on a mucous membrane might alter the turnover of mucin, since the residence time of mucoadhesives are usually longer than the reported mucin turnover time. Nevertheless, the maximum duration for buccal drug delivery is usually limited to approximately 4–6 h, since meal intake and/or drinking may require dosage form removal.

Pathological aspects: Some diseases or treatments may also influence the secretion and properties of the mucus, as well as the saliva. Changes at the mucosal surface due to these pathological conditions may complicate the application and retention of a bio adhesive delivery device. Therefore, understanding the nature of the mucosa under relevant disease conditions is necessary for designing an effective buccal delivery system. In addition, drugs with the potential of changing the physiological conditions of the oral cavity may not be suitable for buccal delivery.

Pharmacological aspects: A buccal dosage form may be designed to deliver a drug to the systemic circulation, or merely indicated for local therapy of the oral mucosa. Selection of dosage forms is affected by the intended application, target site of action, drug characteristics, and the site to be treated (periodontal pockets, gingival, teeth, buccal mucosa, or systemic). Drug absorption depends on the partition coefficient of the drugs. Generally lipophillic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the par cellular route. Chemical modification may increase drug penetration through buccal mucosa. Increasing non-ionized fraction of ionisable drugs increases drug penetration through transcellular route. In weakly basic drugs, the decrease in pH increases the ionic fraction of drug but decreases its permeability through buccal mucosa.

Pharmaceutical aspects: Regardless of dosage form types, the drug must be released from the delivery system and subsequently taken up by the oral mucosa. Poor drug solubility in saliva could significantly retard drug release from the dosage form. Cyclodextrin has been used to solubilise and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa.

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM[16]

Buccal Dosage form can be of following types

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive and additives mixed together. Tran mucosal drug delivery systems can be bidirectional or unidirectional.

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 .Unidirectional (Fig 3) patches release the drug only into the mucosa.

basic components of buccal drug delivery system

The basic components of buccal drug delivery system are

1) Drug substance

2) Bio adhesive polymers

3) Backing membrane

4) Permeation enhancers

1. drug substance: Before formulating mucoadhesive 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[17].

- The conventional single dose of the drug should be small.

- The drugs having biological half-life between 2-8 hrs are good candidates for controlled drug delivery.

- Tmax of the drug shows wider-fluctuations or higher values when given orally.

- Through oral route drug may exhibit first pass effect or presystemic drug elimination.

- The drug absorption should be passive when given orally.

2. bioadhesive polymer: The first step in the development of buccoadhesive dosage forms is the selection and Characterization of appropriate bio adhesive polymers in the formulation. Bio adhesive 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 control the duration of release of drugs[18]. Bio adhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment[16]. The drug is released into the mucous membrane by means of rate controlling layer or core layer. Bio adhesive polymers which adhere to the mucin/ epithelial surface are effective and lead to significant improvement in the oral drug delivery[19].An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics[17,20].

- 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

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 Bio adhesive in pharmaceutical applications are in **Table:1**

Bioadhesive polymers[21]: These are hydrophilic macromolecules that contain numerous hydrogen bond forming groups. These polymers become bioadhesive on hydration and are therefore called "wet adhesives".

The characteristic properties of ideal bioadhesive are

- It should have good mucoadhesive property.

- It should not chemically react with the drug and other excipients in formulation.

- Molecular weight, glass transition temperature and chemical functionality of polymer must allow proper diffusion and release of drug.

- It should be pharmacologically bland-free from irritancy, allerginicity, bad taste and adverse properties such as discoloration or erosion of teeth. Cost of polymer should not be excessive.

Examples of good bioadhesive polymers include hydroxyl propyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), carbopol 934P, gelatin, pectin, PVP 44,000, sodium alginate, hydroxy ethyl cellulose, PEG 6000, tragacanth, Gantrez-AN, methyl cellulose, carboxy methyl cellulose sodium, carboxymethyl cellulose, Gantrez AN-139, chitosan and diethylamino ethyl dextrin.

Polymer controlling rate of drug release from buccal mucoadhesive patches: The polymers which are insoluble in saliva or water can be used as efficient matrix systems through which rate of release of drug can be controlled as desired. Examples for this category include ethyl cellulose and butyl rubber. Water-soluble polymers can be used for controlling rate of release in which, rate of polymer dissolution will be release rate determining step.

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[22].

Polymers used to prepare backing membrane: The polymer whose solution can be casted into thin pore less 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. They should be stable on long storage maintaining their initial physical properties. The cellulose acetate in concentration of 2.4% w/v in acetone with 10% of 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 and suitable plasticizer can be casted into film.

The backing membrane can be of two types

- A polymer solution casted into thin film. It is biodegradable in nature.

- A polyester laminated paper with polyethylene. It is not biodegradable.

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 the backing membrane must be inert and impermeable to drugs and penetration enhancers. The thickness of the 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. permeation enhancers: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients.

Mechanisms of action of permeation

1. **Changing mucus rheology**: By reducing the viscosity of the mucus and saliva overcomes this barrier.

2. **Increasing the fluidity of lipid bilayer membrane:** Disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.

3. **Acting on the components at tight junctions:** By inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the 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.

Categories and examples of membrane permeation enhancers

1. Bile salts and other steroidal detergents: Sodium glycocholate, sodium taurocholate, sodium taurodihydro fusidate, and sodium glycol dihydro fusidate.

2. Surfactants: i) Non ionic: Laureth-a, polysorbate-9, sucrose esters and do-decyl maltoside.

ii) Cationic: Cetyl trimethyl ammonium bromide

iii) Anionic: Sodium lauryl sulphate.

3. Fatty acids: Oleic acid, lauric acid, caproic acid

4. Other enhancers: i) Azones

ii) Salicylates

iii) Chelating agents

iv) Sulfoxides e.g. Dimethyl sulfoxide (DMSO)

Methods to increase drug delivery via buccal route[23,24]

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 inters/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.

Prodrugs: Hussain et al delivered opioid agonists and antagonists in bitter less 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.

pH: The permeability of acyclovir at pH 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).

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.

Manufacturing methods of buccal patches/films

Manufacturing processes involved in making mucoadhesive buccal patches/films, namely solvent casting, hot melt extrusion and direct milling.

Solvent casting method: Solvent casting is widely used manufacturing process for making patches/ films. This is mainly due to ease of process and low cost that the system setup incurs at research laboratory scale, the process consist of six steps.

1) Preparation of casting solution

2) Deareation of solution

3) Transfer of appropriate volume of solution into the mould

4) Drying the casting solution

5) Cutting the final dosage form to contain desired amount of drug

6) Packaging

The buccal patches are preferably formulated using the solvent casting method. The required quantity of polymer was added in small quantities and mixed well to dissolve in distilled water. Drug dissolved in the above solution in small quantities. Plasticizer added to the above solution and mixed well. Solution was then casted on mercury into petridishes and kept in hot air oven for drying at 40° C. After drying patches were removed with the help of sharp blade and kept in desicator for 24 hrs then as per requirement cut into pieces of the desired shape and size.

The rheology of liquid to be casted will determine the drying rates and uniformity in terms of the active content as well as physical appearance of films. Patches cast from aerated solutions exhibit an uneven surface and heterogeneous thickness. The use of organic solvents generally questioned, not only due to problems related to

solvent collection and residual solvents, but also because organic solvents are undesired hazards for the environment and health.

Direct milling: In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described.

Hot melt extrusion of films: In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films. However, only hand full articles have reported the use of hot melt extrusion for manufacturing mucoadhesive buccal films. **Table 2** gives suitable polymers and drugs for buccal delivery.

Advantages of hot-melt extrusion for film formation include

- No need to use solvent or water

- Fewer processing steps

- Compressibility properties of the drug may not be of importance

- Good dispersion mechanism for poorly soluble drugs

- More uniform dispersion of the fine particles because of intense mixing and agitation.

- Improved bioavailability of the drug.

The hot-melt extrusion process has gained popularity because the formulators can extrude combination of drugs, polymers and plasticizers into various final forms to achieve desired drug-release profiles.

Evaluations of buccal patch/films

1. Surface pH: Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch[25].

2. Thickness measurements: The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer[26].

3. Swelling study: Buccal patches are weighed individually (designated as W1), 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 the gel plates and excess surface water is removed carefully using the filter paper[27].

The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated

using the following formula

$$SI = \frac{(W2-W1) \times 100}{W1}$$

4. Folding endurance: The folding endurance of patches is determined by repeatedly folding 1 patch at the times without breaking[28].

5. Thermal analysis study: Thermal analysis study is performed using differential scanning calorimeter (DSC).

6. Morphological characterization: Morphological characters are studied by using scanning electron microscope (SEM).

7. Water absorption capacity test: Circular Patches, with a surface area of 2.3 cm² are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na_2HPO_4, 0.19 gms KH_2PO_4, and 8 gms NaCl per litter 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 hrs), samples are weighed (wet weight) and then left to dry for 7 days in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.

Water uptake (%) = (Ww – Wi)/Wf x 100

Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.[29]

8. Ex-vivo bioadhesion test: The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the 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 detached from the mucosal surface.[30] The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength **(Fig 3).**
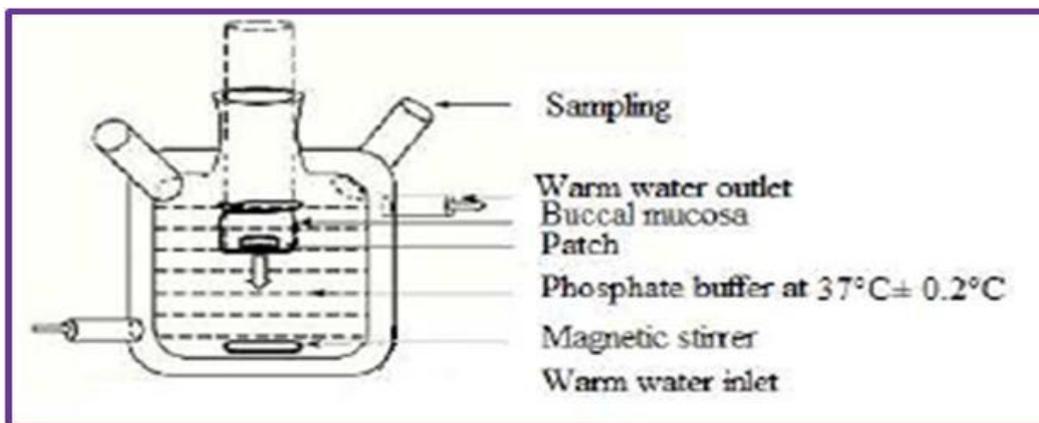

Fig. 3: measurement of mucoadhesive strength

9. In-vitro drug release: 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. The in-vitro buccal permeation through the buccal mucosa (sheep and rabbit) is

performed using Keshary-Chien /Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer **(Fig 4).**
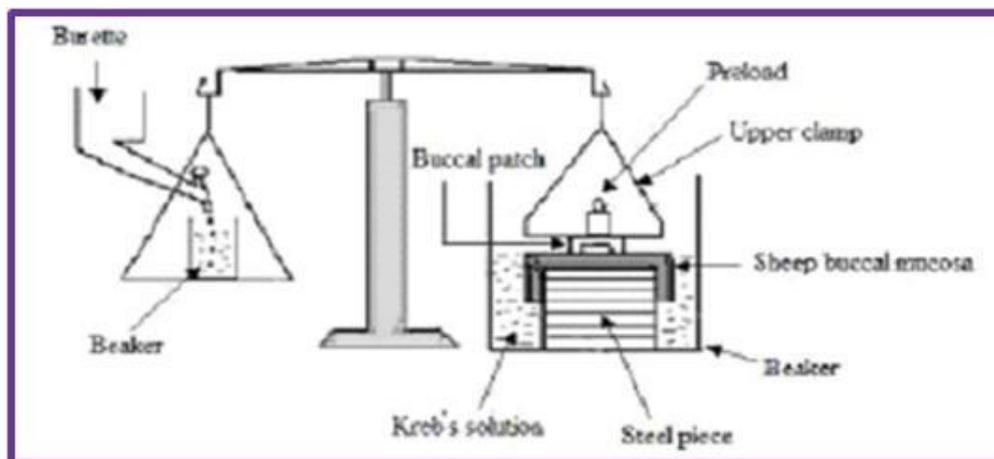

Fig. 4: schematic diagram of Franz diffusion cell for buccal patch

10. Permeation study of buccal patch: The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content[31].

11. Ex-vivo mucoadhesion time: The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit)[32].The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 secs. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 min, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch and drug content is noted[33-35].

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

$$T = m \times g/ b \times t \ Kg/mm^2$$

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/mm^2) is the force at break (kg) per initial cross-sectional area of the specimen (mm^2).

13. Stability study in human saliva: The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50 years). Buccal patches are placed in separate petridishes containing

5ml of human saliva and placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hrs. At regular time intervals (0, 1, 2, 3, and 6 hrs), the dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dose required and minimize side effects that may be due to systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

Future aspects

- In mucoadhesive placebo buccal patches we can use any potent drugs which fulfil the criteria for buccal patch as drug delivery system.

- We can perform the dissolution of medicated mucoadhesive buccal patch for drug release profile studies.

- We can further perform the in-vivo studies for the prepared mucoadhesive buccal patches.
- We can perform the stability test for the prepared mucoadhesive buccal patches.

REFERENCE

1. Giradkar KP, Chanwaar MA, Kajale AD, Sridhar E, Kambel RS, Bakde BV, Chandewar AV. Design development and in vitro evaluation of bioadhesive dosage form for buccal route, *International journal of pharma research & development*, 2010, 2.
2. Shidhaye SS, saindane NS, Sutar S, Kadam V, Mucoadhesive bilayered patches for administration of sumatriptan, *AAPS pharm sci tech*, 2009, 9(3).
3. Zhang J, Suyi Nui, Charles Ebert, Theodore, Stanley H. An In-Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancement without Tissue Damage, *Int. J. Pharm*, 1994, 101, 15–22.
4. Shojaei Amir H, Buccal Mucosa As A Route For Systemic Drug Delivery: A Review;J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1998;1 (1):15-30
5. Sevda Senel, Mary Kremer, Katalin Nagy and Christopher Squier, Delivery of Bioactive Peptides and Proteins Across Oral (Buccal) Mucosa, Current Pharmaceutical Biotechnology, 2001; 2: 175-186.
6. Miller NS, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews., 2005; 57:1666 - 1691.
7. Ghosh Tapash K, William R. Pfister, Drug Delivery to the Oral Cavity by Taylor & Francis, Preclinical Assessment of Oral Mucosal Drug Delivery Systems, Page no 46.
8. Marcos Luciano Bruschi and Osvaldo de Freitas, Oral Bioadhesive Drug Delivery Systems, Drug Development and Industrial Pharmacy, 31(3), 2005; 293-310.
9. Aungst BJ, and Rogers NJ. Site dependence of absorption-promoting actions of Laureth-9, Na salicylate, Na2EDTA, and Aprotinin on rectal, nasal, and buccal insulin delivery, *Pharm. Res.*, 1988;5:305-308..
10. Lee WE. Permeation enhancers for the nasal delivery of protein and peptide therapeutics, *Bio Pharm*, 1990; 3:22-25.
11. Tengamnuay P, and Mitra AK. Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength. Adjuvant composition and lipid structure on the nasal absorption of [D-Arg2] Kyotorphin, *Pharm. Res.*, 1990; 7:127-133.
12. Shao Z, and Mitra AK. Nasal membrane and intracellular protein and enzyme release by bile salts and bile salt-fatty acid mixed micelles: correlation with facilitated drug transport, *Pharm. Res.*, 1992; 9.
13. Shao Z, and Mitra AK. Bile salt fatty acid mixed micelles as nasal absorption promoters. III. Effects on nasal transport and enzymatic degradation of acyclovir prodrugs, *Pharm. Res.*, 1994; 11:243-250.
14. Ahagon A, Gent AN. Effect of interfacial bonding on the strength of adhesion, J. Polym. Sci. Polym. Phys. 1975; 13, 1285–1300.
15. Steward A, Bayley DLC, Howes, The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha Interferon, *Int. J. Pharm*, 104, 1994, 145–149.
16. Mitra AK, Alur HH, Johnston. Peptides and Protein- Buccal Absorption, Encyclopedia of Pharmaceutical technology, Marcel Dekker Inc., Edition 2002: 2081-2093.
17. Wise Donald L, Handbook of Pharmaceutical controlled release technology: 255-265.
18. Yajaman S, Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs, Journal of Controlled Release, 2006;114:15–40.
19. Jain NK. Controlled and novel drug delivery; 65- 75; 371-377.
20. www.controlled drugdelivery.com
21. Vyas SP, & Khar Roop K, Controlled drug delivery system; 257-295
22. Scrivener CA, Schantz CW, J AM Dental Assoc, 35, 1947, 644-647.
23. Wani MS, Parakh SR, Dehghan MH, Polshettiwar SA, Chopade VV, Pande VV. Current Status In Buccal Drug Delivery System, Pharmainfo.net, 5(2), 2007
24. Zhang J. An In-Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancement without Tissue Damage, *Int. J. Pharm*, 1994, 101,15–22.
25. Goudanavar PS, Bagali RS, Patil M, Chandhashakar S, Formulation and In-vitro evaluation of mucoadhesive buccal films of Glibenclamide, *Der pharmacialettre*, 2010, 2 (1), 382-387.
26. Choudhary A, Gulab Tiwari, Manisha Pandey, Koshy M. Kymolin, Shubini A. Saraf. Formulation and characterization of carvedilol buccal mucoadhesive patches, *www.ijrps.pharmascope.org*, 2010, 1(4), 396-401.
27. Kamel AH , Micromatricial metronidazole benzoate film as a local mucoadhesive delivery system for treatment of periodontal diseases, *AAPS pharmscitech*, 2007, 8 (3), 75.
28. Giradkar KP. Design development and in vitro evaluation of bioadhesive dosage form for buccal route, *International journal of pharma research & development*, 2010, 2.
29. Leung SS and Robinson JR. Polymer Structure Features Contributing to Mucoadhesion II, *J. Contr.Rel*, 1990, 12, 187–194.
30. Gandhi RE and Robinson JR, Bioadhesion in Drug Delivery, *Indian J. Pharm. Sci*, 1988, 50 (May/June), 145–152.
31. Sanzgiri YD, Elizebeth M Topp, Lucca Beneditti, Valentino J Stella. Evaluation of Mucoadhesive Properties of Hyaluronic Acid Benzyl Esters, *Int. J.Pharm*, 1994, 107, 91–97.
32. Park K and Robinson JR. Bioadhesive Polymers as Platforms for Oral Controlled Drug Delivery, Method to Study Bioadhesion, *Int. J. Pharm.,* 1984, 19, 107–127 .
33. Zhang J. An In-Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation.
34. Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancement without Tissue Damage, *Int. J. Pharm*, 1994, 101, 15–22.