

**COMPREHENSIVE REVIEW ON BUCCAL DELIVERY**

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**ABSTRACT**

The main aim for the oral delivery of most of the drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parenteral route of administration is the only established route that overcomes all these drawbacks associated with these orally less/inefficient drugs. But, these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress and the near absence of langerhans cells. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability.

**Keywords:** Buccal cavity, proteins, presystemic metabolism and bioavailability

**INTRODUCTION**

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration particularly in overcoming deficiencies associated with latter mode of dosing, problems such as high first pass metabolism, and drug degradation in the harsh gastrointestinal environment, can be circumvented by administering the drug via the buccal route. Moreover, buccal drug delivery offers a safer method of drug utilization. Since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal delivery<sup>1</sup>. Buccal drug delivery is most advantageous because it abundant blood supply in buccal mucosa, bypassing the hepatic firstpass effect and accessibility<sup>2</sup>.

The buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the

sublingual route<sup>3</sup>. Oral cavity has been investigated for number of applications including the treatment of periodontal disease bacterial and fungal infection, aphthous and dental stomatitis. Over the last two decades mucoadhesion has become of interest for its systemic delivery by retaining a formulation intimate contact with buccal cavity<sup>4</sup>. The term bio adhesion has been used to define the attachment of a synthetic natural macromolecule to a biological tissue for an extended period of time. When a substrate is a mucosal system adheres and interacts primarily with the mucus layer, this phenomenon being referred to as mucoadhesion<sup>5</sup>. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane<sup>6</sup>. Adhesion of bioadhesive drug delivery devices to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improved bioavailability dosage forms have been used to target local disorder at the mucosal surface to reduce the overall dosage required and

minimize side effects that may be used by systemic administration of drugs. Compounds with partition coefficient in the range 40-20000 and PKa 2-10 are considered optimal to be absorbed through buccal mucosa<sup>7</sup>.

The driving force for transport across buccal mucosa is the concentration gradient which depends upon concentration of drug in saliva<sup>8</sup>. A suitable buccal drug delivery should be flexible and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response. Development of non-injection ways for proteins introduction is currently the most attractive route of non-injection way. Buccal way provided constant, predictable level of drug concentration in blood<sup>9</sup>. The effectiveness of mucoadhesive formulation is greatly determined by the nature of the polymer composition used<sup>10</sup>.

#### **ADVANTAGES OF BUCCAL DRUG DELIVERY<sup>11</sup>**

Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract. Improved patient compliance due to the elimination of associated pain with injections; a relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued. Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa. 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.

#### **LIMITATIONS OF BUCCAL DRUG DELIVERY<sup>12</sup>**

For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of food stuffs may lead to the requirement for frequent dosing. Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows. 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. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

#### **ANATOMY OF BUCCAL MUCOSA**

A stratified, squamous epithelium lines the oral cavity. Three different types of oral mucosa can be identified, i.e., masticatory, lining, and specialized mucosa as shown in Fig1. and Fig. 2. *Masticatory mucosa* covers those areas that are involved in mechanical process such as speech. It comprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissue and as such is able to withstand the abrasion and shearing forces of the masticatory process. It covers the 25% of oral cavity<sup>13</sup>. *Specialized mucosa* of the dorsum of the tongue is characteristic of both the masticatory and lining mucosa in that it consists of epithelium partly keratinized and partly nonkeratinized. This epithelium is bound to the muscle of the tongue. The specialized mucosa covers 15% of oral cavity<sup>14</sup>. *Lining mucosa* covers all other areas except the dorsal surface of the tongue and is covered by a nonkeratinized and hence more permeable epithelium. It is consisting of the inner cheeks, floor of the mouth, and underside of the tongue<sup>13, 14</sup>. The lining mucosa covers 60% of oral cavity. This mucosa is capable of elastic deformation and hence stretches to accommodate speech and mastication requirements. The buccal mucosa covers the inner cheeks and is classified as part of lining mucosa covers 40-50 cell layers resulting in an epithelium 500-600µm thick. The epithelium attached to underlying structures of lamina propria, separated by a basal lamina. The lamina propria contains the blood vessels that drain into lingual, facial, and retromandibular veins, which then open into internal jugular vein. Once a given drug molecule reaches the connective tissue, it may be readily distributed, thus the permeation barrier is across the whole thickness of the stratified epithelium<sup>14</sup>(Figure 1).

A gel-like secretion known as mucus, which contains mostly water-insoluble glycoproteins, covers the entire oral cavity. Mucus is bound to the apical cell surface and acts as a protective layer to the cells below. It is also a visco-elastic hydrogel, and primarily consists of 1-5% of the above-mentioned water-insoluble glycoproteins, 95-99% water, and several other components in small quantities, such as proteins, enzymes, electrolytes, and nucleic acids. This composition can vary based on the origin of the mucus secretion in the body<sup>15</sup>. The effective

permeability coefficient ( $P_{\text{eff}}$ ) values reported in the literature across the buccal mucosa for different molecules range from a lower limit of  $2.2 \times 10^{-9}$  cm/s for dextran 4000 across rabbit buccal membrane to an upper limit of  $1.5 \times 10^{-5}$  cm/s for both benzylamine and amphetamine across rabbit and dog buccal mucosa, respectively. This range clearly demonstrates the presence of a permeability barrier in the oral mucosa, which is mostly imposed by the oral epithelium acting as a protective layer for the tissues beneath, and as a barrier to the entry of foreign material and microorganisms. However, this range is estimated to be 4–4000 times more permeable than that of skin. Several proteolytic enzymes (aminopeptidases, endopeptidases, carboxypeptidases, deamidases), were found in various buccal epithelium (human, pig, monkey, rat, rabbit and cultured hamster buccal cells). Saliva, which ranges in pH from 6.8 to 7.2, contains a variety of enzymes such as esterases and carboxylesterase which could cause degradation of peptides and their prodrugs.

#### **BARRIERS TO PENETRATION ACROSS BUCCAL MUCOSA<sup>16</sup>**

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium.

**Membrane coating granules:** Membrane coating granules or cored granules in non-keratinized epithelia, the accumulation of lipids and cytokeratins in the keratinocytes is less evident and the change in morphology is far less marked than in keratinized epithelia. The mature cells in the outer portion of non-keratinized epithelia become large and flat retain nuclei and other organelles and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia. As cells reach the upper third to quarter of the epithelium, membrane-coating granules become evident at the superficial aspect of the cells and appear to fuse with the plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in non-keratinizing epithelia are spherical in shape, membrane-bounded and measure about 0.2  $\mu\text{m}$  in diameter. Such granules have been observed in a variety of other human non-keratinized epithelia, including uterine cervix and esophagus. However, current studies employing ruthenium tetroxide as a post-fixative indicate that in addition to cored granules, a small proportion of the granules in non-keratinized epithelium do contain lamellae, which

may be the source of short stacks of lamellar lipid scattered throughout the intercellular spaces in the outer portion of the epithelium. In contrast to the intercellular spaces of stratum corneum, those of the superficial layer of non-keratinizing epithelia contain electron lucent material, which may represent non-lamellar phase lipid, with only occasional short stacks of lipid lamellae.

**Basement membrane:** Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

**Mucus:** The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40  $\mu\text{m}$  to 300  $\mu\text{m}$ . Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Different types of mucus are produced, for example G, L, S, P and F mucus, which form different network of gels. Other substances such as ions, protein chains, and enzymes are also able to modify the interaction of the mucus molecules and, as a consequence, their biophysical properties. The oral cavity<sup>17-20</sup> is lined with mucous membranes with a total surface area of 100  $\text{cm}^2$ .

#### **DRUG TRANSPORT MECHANISM**

The drug transport mechanism through the buccal mucosa involves two major routes: transcellular (intracellular) and paracellular (intercellular) pathways. The transcellular route involves the crossing of the cellular membranes with a polar and a lipid domain whereas the paracellular route essentially implicates the passive diffusion through the extracellular lipid domain. It is generally

recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway. This was observed in Fig. 3.

### 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. Bioadhesive 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 excipient(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 bioadhesive 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 bioadhesive 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 bioadhesive 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 lipophilic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the paracellular route. Chemical modification may increase drug penetration through buccal mucosa. Increasing non-ionized fraction of ionizable 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 solubilize and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa.

### FORMULATION DESIGN

Buccal adhesive drug delivery systems with the size 1-3 cm<sup>2</sup> and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6 h. To fulfill the therapeutic requirements, formulations designed for buccal administration should contain the following functional agents: mucoadhesive agents, to maintain an intimate and prolonged contact of the formulation with the absorption site; penetration enhancers, to improve drug permeation across mucosa (transmucosal delivery) or into deepest layers of the epithelium (mucosal delivery); and enzyme inhibitors, to eventually protect the drug from the degradation by means of mucosal enzymes.

**Mucoadhesive polymers:** Different situations for buccal mucoadhesion are possible depending on the dosage form. In the case of dry or partially hydrated formulations, polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favor polymer chain flexibility and interpenetration between polymer and mucin chains. The spreading coefficient and the capability to form physical or chemical bonds with mucin (which results in a strengthening of the mucoadhesive interface)

increase when fully hydrated dosage forms (e.g. aqueous gels or liquids) are considered. So, depending on the type of formulation, polymers with different characteristics have to be considered. The polymers most commonly used in buccal dry or partially hydrated dosage forms include.

**Semi-natural/natural:** Agarose, chitosan, gelatin, Hyaluronic acid various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)

**Synthetic Cellulose derivatives:** CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC,

**Methylhydroxyethylcellulose Poly (acrylic acid) - based polymers:** CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid, PEG and poly(alkylcyanoacrylate).

To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as

- I. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups
- II. Suitable surface property for wetting mucus/mucosal tissue surfaces
- III. Sufficient flexibility to penetrate the mucus network or tissue crevices

**Permeation enhancer:** Due to limited permeability of buccal mucosa compared to that of intestinal epithelium, the use of permeation enhancers has been widely investigated in dosage forms of buccal delivery. Optimal control of buccal drug delivery would require the vehicle to be the rate-limiting domain rather than the epithelium. It is expected that this goal can be achieved with the help of effective permeation enhancers<sup>21</sup>. Penetration or absorption enhancers are substances that facilitate the transport of solutes across biological membranes. Permeation enhancers are pharmaceutical ingredients included in a formulation in order to improve the permeation characteristics of the drug through target mucosa and is desired to demonstrate null or very limited toxicity or tissue damage. These must be non-irritant and have a reversible effect: the epithelium should recover its barrier properties after the drug has been absorbed. Penetration enhancement to the buccal membrane is drug specific. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal

mucosa. Bioavailability of 5% after buccal co-administration of insulin with sodium glycocholate in rats, compared to negligible absorption without an absorption enhancer. Lysalbinic acid is a possible absorption enhancer for the buccal transfer of interferon and insulin. A bioadhesive tablet formulation for buccal delivery was designed using a mixture of hydroxypropyl methylcellulose and carbomer, incorporated with a penetration enhancer, sodium glycodeoxycholate (GDC). In vitro bioadhesion property of the formulated tablet was examined and histological study was carried out to examine an in vivo interaction between the tablet and tissue<sup>22</sup>. Table 1 gives list of permeation enhancers used in buccal delivery. The most promising agents for buccal delivery are surfactants. Their widespread use has created considerable interest; however, depending on the type of surfactant used, the concentration and exposure time, they can induce side effects such as protein denaturation or extraction, enzyme inactivation, swelling of tissue and extraction of lipid components. Experiments were conducted to evaluate the effect of permeability enhancers i.e.  $\beta$ -cyclodextrin, sodium lauryl sulphate, sodium glycocholate, sodium deoxycholate, sodium laurate and glyceryl monolaurate on insulin permeability through the buccal mucosa.

**Enzyme inhibitors:** The coadministration of a drug with enzyme inhibitors is another strategy for improving the buccal absorption of drugs, particularly peptides. Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including affecting the activities of the enzymes, altering the conformation of the peptides or proteins and/or rendering the drug less accessible to enzymatic degradation.

## THEORIES OF BIOADHESION<sup>14-16</sup>

The theories of polymer-polymer adhesion can be adapted to polymer-tissue adhesion or bioadhesion by recognizing that bioadhesion is different only because of the differing properties of the tissue as opposed to those of the polymer.

**Electronic theory:** According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface.

**Absorption theory:** According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the

atoms in the two surfaces. There are two types of chemical bonds resulting from these forces. *Primary chemical bonds* are of covalent nature, which are undesirable in bioadhesion because their strength may result in permanent bonds. *Secondary chemical bonds* are having many different forces of attraction, including electrostatic forces, Vander Waal forces and hydrogen bonds.

**Wetting theory:** is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over a biological system.

**Diffusion theory:** According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact.

**Fracture theory:** This theory attempts to relate the difficulty of separation of two surfaces after addition.

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

Where E is the Young's

$\varepsilon$  is the fracture energy

L is the critical crack length

## BUCCAL DOSAGE FORMS

Delivery of various therapeutic agents via the buccal route using conventional matrix tablets, disks, gel, films, patches, strips, ointment, laminated systems and buccal cups systems has been studied and reported by several research groups<sup>24</sup>.

**Buccal patch:** Buccal patch is a non dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time<sup>25</sup>. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments<sup>26</sup>. An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties

of buccal patches are critical and essential to be evaluated.

### Types:

**1. Matrix type (Bi-directional):** The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in the mucosa and the mouth.

**2. Reservoir type (Unidirectional):** 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.

**Buccal films:** Buccal films are preferable over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed and removed by saliva. Moreover, buccal films are also suitable for protecting wound surfaces, thus reducing pain and increasing the treatment effectiveness<sup>27</sup>. An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good bioadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film, if it occurs, should not be too extensive in order to prevent discomfort.

**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) Deaeration of solution
- 3) Transfer of appropriate volume of solution into the mold
- 4) Drying the casting solution
- 5) Cutting the final dosage form to contain desired amount of drug
- 6) Packaging

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 a handful articles have reported the use of hot melt extrusion for manufacturing mucoadhesive buccal films. Table 2 gives suitable polymers and drugs for buccal delivery.

**Buccal tablets:** Monolithic, two-layered and three layered matrix tablets have been designed for buccal delivery of drugs. Monolithic tablets in their simplest version consist of a mixture of drug with a swelling bioadhesive/sustained release polymer with a bidirectional release. They can be coated on the outer or on all sides but one face with water impermeable hydrophobic substances to allow a unidirectional drug release for systemic delivery. Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties, e.g. enhanced activity and prolonged drug release. Some newer approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. *Two layered tablets* comprise an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bidirectional release but mainly a local action. In the case of systemic action, the drug is loaded into the inner bioadhesive layer whereas the outer layer is inert and acts as a protective layer. Alternatively, the drug is loaded into a controlled release layer and

diffuses towards the absorbing mucosa through the bioadhesive layer, whereas a water impermeable layer assures the monodirectional release. Different drugs have been loaded in matrix tablets, such as propranolol, timolol, metronidazole, metoclopramide, morphine sulphate, nitroglycerin and codein. Peptides, such as insulin, calcitonin and glucagon-like peptide were also loaded in buccal mucoadhesive tablets.

**Three layered buccal compact**<sup>33</sup>: Buccoadhesive drug delivery offer distinct advantages over peroral administration and the selection of appropriate mucoadhesive polymer plays a crucial step for the development of controlled release buccal compact containing highlywatersoluble drug. Multilayered matrix tablet are proving to be more potential among the various formulations in the development of oral controlled release dosage form containing highly water-soluble drug to prevent the faster release and dose dumping. The backing layer contains EC and Mg stearate. EC was selected because of its hydrophobic nature and has low water permeability, moderate flexibility, thus preventing drug loss by backward diffusion. Mg stearate was included as anti-adherent MT, sodium alginate and HPMC K4M comprises the core layer. HPMC K4M is a water swellable polymer which controls the release of drug from the core layer by forming a matrix or gel layer. Peripheral layer which adhere to the mucosa should possess good bioadhesive strength and also control the release. Hence, carbopol 934P a potential mucoadhesive polymer along with HPMC K4M was included in peripheral layer.

**Bioadhesive progressive hydration tablets**<sup>38</sup>: A bioadhesive controlled, extended release progressive hydration composition wherein the active ingredient may be protected from water or the surrounding environment, thereby protecting it from metabolism or from other degradation caused by moisture, enzymes, or pH effects and making it bioavailable only at a controlled rate. The active ingredient may be protected from moisture during the manufacturing process, as necessary or desired, and more importantly may be protected from moisture and the immediate septic environment until well after the patient has applied the composition, and then only at a slow and controlled rate. It is by this process of progressive hydration that the active ingredient remains protected for many hours after administration. It is also by the process of progressive hydration that controlled and sustained release is achieved because only that part of the active ingredient that is the hydrated aqueous fraction of the composition is available for absorption.

**Buccal gels and ointments:** Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations. Certain bioadhesive polymers, e.g. poloxamer 407, sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from a liquid to a semisolid. The application of bioadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability. A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth. Buccal administration of triamcinolone acetonide gels containing sodium deoxycholate as an enhancer to rabbits showed a relatively constant, sustained blood concentration with minimal fluctuation. Candidiasis is opportunistic infections the reason for incomplete eradication of candidacies in most cases may be due to the short residence time of antifungal agents in the oral cavity. The other reason may be degradation of antifungal agents in salivary fluid. Therefore, researchers have prepared and reported new formulation such as buccal bio adhesive gels<sup>36</sup>. Bioadhesive ointments have not been described in the literature as extensively as other dosage forms, especially when compared to tablets and patches. HPMC has been used as an adhesive ointment ingredient.

**Buccal chewing gums:** Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of diseases in the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market<sup>34</sup>. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness.

It is absorbed at a significantly faster rate and its bioavailability was comparable to that in capsule formulation. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) have been marketed for smoking cessation. The permeability of nicotine across the buccal mucosa is faster than across the skin. However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking. Possible

swallowing of considerable amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum due to first-pass metabolism and gastrointestinal discomfort.

It is a major challenge to optimize the dose-response relationship of nicotine administered in a chewing gum<sup>35</sup>. Some currently available marketed buccal formulations in UK were given in Table 3.

## EVALUATION OF BUCCAL DELIVERY SYSTEM

In addition of weight variation, thickness, content uniformity, bioadhesive strength, dissolution tests some specific tests for patches/films, tablets, gels

### Specific tests for patches/films

**Folding Endurance:** Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on three patches.

**Swelling study:** Swell on the surface of agar plate kept in an incubator maintained at 37 °C. Increase in the weight and diameter of the patches (n = 3) was determined at preset time intervals (1–5 h). The percent swelling, %S, was calculated using the following equation:

$$\%S = (X_t - X_o/X_o) \times 100$$

Where  $X_t$  is the weight or diameter of the swollen patch after time  $t$ ,

And  $X_o$  is the original patch weight or diameter at zero time.

**Tensile strength of the film:** Tensile strength of the film is total weight, which is necessary to break or rupture the films and this was done by a device has rectangular frame with two plates made up of Plexiglas.

The one plate is in the front and is the movable part of the device and can be pulled by loading weights on the string, which is connected to the movable part. The required diameter of films containing dose were fixed between the stationary and movable plate. The force needed to fracture the films was determined by measuring the total weight loaded in the string.

Tensile strength = Breaking load (N) / Cross sectional area of the film

### Specific tests for tablets

**Friability:** Five tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula.

$$\% F = \{1 - (W/W_0)\} \times 100$$

Where, % F = friability in percentage

W<sub>0</sub> = Initial weight of tablet

W = weight of tablets after revolution

**Hardness:** Hardness was measured using Monsanto hardness tester. For each batch two tablets were tested.

### Measurement of bioadhesive strength of buccal dosage forms

**Modified physical balance test:** Bioadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in Fig. No. 5 The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side.

This was kept in beaker filled with phosphate buffer pH 6.8, which was then placed below right side of the balance. Goat buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. The goat buccal mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media phosphate buffer pH 6.8.

It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer pH 6.8 up to the upper surface of the goat buccal mucosa to maintain buccal mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and buccoadhesive dosage form was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between buccoadhesive tablet and goat buccal mucosa.

The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when Buccoadhesive tablet was detached from the goat buccal mucosa. The weight of water required to detach buccoadhesive tablet from buccal mucosa was noted as bioadhesive strength in grams. From the bioadhesive strength following parameter was calculated.

$$\text{Force of adhesion (N)} = \text{Bioadhesive strength (g)} \times 9.81/1000$$

$$\text{Bond strength (Nm}^{-2}\text{)} = \text{Force of adhesion/Disk surface}$$

### Measurement of dissolution and drug release form bioadhesive dosage forms

**Dissolution apparatus:** Standard USP or IP dissolution apparatus have been used to study in vitro release profile using both basket and rotating paddle. Place the tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study was 900ml phosphate buffer pH 6.8 during the course of study whole assembly was maintained at 37±0.5°C. Withdraw a 5 ml of sample at specific time interval and replaced with 5 ml of fresh dissolution medium. The withdrawn samples were dilute with dissolution medium and then filter it with whattman filter paper and assayed.

**Franz diffusion cell:** The release of drug from tablets was studied using modified Franz diffusion cells. The dissolution medium was phosphate buffer saline (PBS) at 37 °C. uniform mixing of the medium was provided by magnetic stirring at 300 rpm. To provide unidirectional release, each bioadhesive tablet was embedded into paraffin wax in a die with a 12mm central hole, which was placed on top of the tissue. Samples of 1ml were taken from the medium at certain time intervals and replaced with the same amount of PBS. The samples were filtered and assayed for drug<sup>37</sup>. Mumtaz and Ch'ng introduced another method for studying the dissolution of buccal tablets. The device that they introduced is based on the circulation of pre-warmed dissolution medium through a cell as shown in Fig.8. Here the buccal tablet was attached on chicken pouches. Samples were removed at different time intervals for drug content analysis. They stated "the results obtained by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns"

**CONCLUSION**

Novel buccal adhesive delivery systems, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. 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. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa.

Table 1: List of permeation enhancers used in buccal delivery

Permeation enhancer	Proposed mechanism of action	Preferred route enhanced	Examples
Surfactants	Lipid extraction from the mucosa	Paracellular	Sodium dodecyl sulfate, sodium lauryl sulphate
Bile salts	Lipid extraction from the mucosa	Paracellular	Sodium glycholate, sodium taurocholate, sodium glycodeoxycholate, and sodium taurodeoxy cholate, sodium deoxycholate
Fatty acids	Increase fluidity of intercellular lipids	Paracellular	
Ethanol	Disrupt arrangement of intercellular lipids	Paracellular	
Chitosan	Increase retention time of drug in contact with mucosa and disruotion of intercellular lipid organization	Paracellular	

Table 2: Some drugs as Buccal patch

Drug	Polymer	Plasticizer	Reference
Aceclofenac	Gelatin, Sodium carboxy methyl cellulose, Polyvinyl alcohol	Poly ethylene glycol	10
Carvedilol	Hydroxypropylmethylcellulose K15, Carbopol – 940,	Glycerin	28
Carvedilol	Carbopol 934, Hydroxypropylmethylcellulose, Eudragit RS100	Glycerin	29
Insulin	Sodium carboxymethylcellulose	Propylene glycol (0.25 ml)	23
Metoprolol tartrate	Eudragit NE40D, Hydroxypropylmethyl Cellulose (Methocel K4M and K15M), Sodium carboxymethyl Cellulose, Carbopol (cp 934p, cp 971p and cp 974p)		1

Miconazole nitrate	Sodium carboxymethyl cellulose, Polyvinyl alcohol, hydroxypropylmethyl Cellulose 4000 cp, HPMC, And Hydroxyethyl cellulose, Polyvinyl pyrrolidone.	5% v/v glycerol	30
Montelukast sodium	Eudragit RL-100, PVP	Propylene glycol	31
Propranolol hydrochloride	EudragitL-100cp 934, PVP k30	Propylene glycol (5% vol/vol)	25
Verapamil hcl	Carbopol 934 p, Eudragit RL100 and PVP K-30	Propylene glycol (5%, v/v)	6

Table 3: Some currently available marketed buccal formulations in UK

Product	Company	Bioadhesive agent	Pharmaceutical form
Buccastem®	Reckitt Benckiser	PVP, Xanthum gum	Buccal tablet
Corlan pellets®	Celltech	Acacia gum	Oromucosal pellets
Suscard®	Forest	HPMC	Buccal tablet
Gaviscon liquid®	Reckitt Benckiser	Sodium alginate	Oral liquid
Orabase®	Convatech	Pectin, Gelatin	Oral paste
Corsodyl gel®	GalaxoSmithKline	HPMC	Oromucosal gel

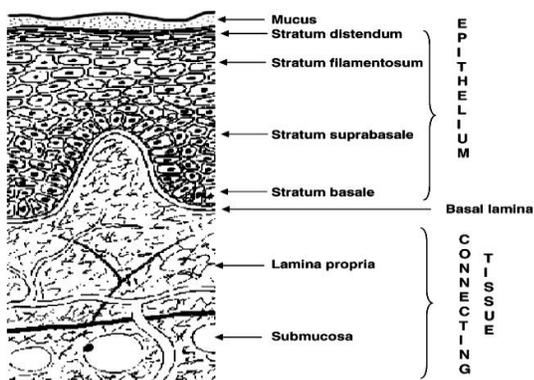


Fig 1: Cross-section of buccal mucosa

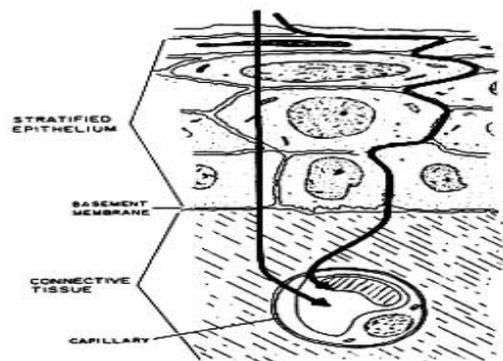


Fig 3: Routes of transepithelial penetration; transcellular route vs. intercellular Pathway

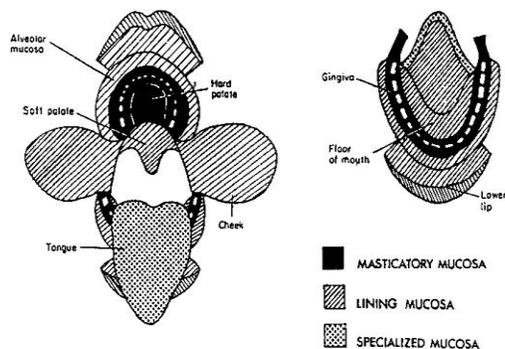


Fig 2: The distribution of masticatory, lining, and specialized mucosae within the oral cavity

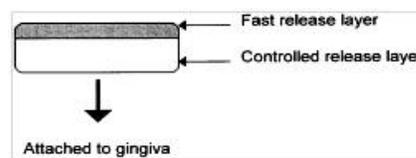


Fig 4: Two layered buccal tablet

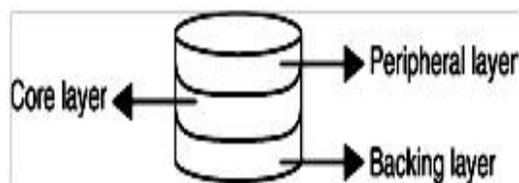


Fig 5: Three layered buccal tablet

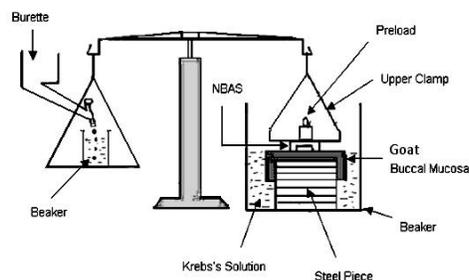


Fig 6: Physical Balance for measurement of adhesive strength

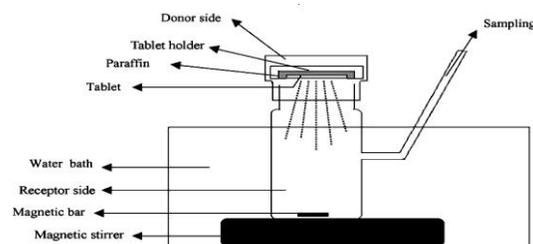


Fig 7: Franz diffusion cell

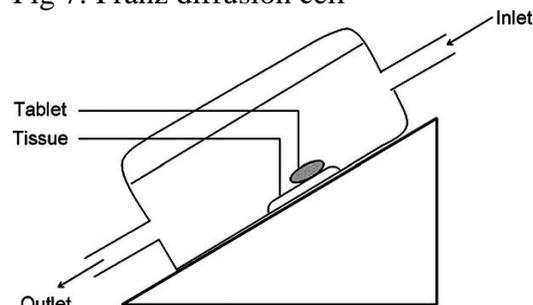


Fig 8: Schematic drawing of the dissolution apparatus used by Mumtaz and Ch'ng for studying the dissolution of buccal tablets

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