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BUCCAL DRUG DELIVERY SYSTEM: THE CURRENT APPROACHES

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Abstract:

Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. As we all know that, the buccal cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.

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 mucosaldosage 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. 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. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. The studies of Mucoadhesive polymers provide a good approach of mucoadhesion and some factors which have the ability to affect the mucoadhesive properties of a polymer. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. 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.. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs.

Key words: Mucoadhesive buccal patch, Natural polymer, Bioadhesive polymers, Buccal formulations, Buccal Mucosa, first-pass effect, permeation enhancers.

Introduction:-

Novel drug delivery system:- Novel drug delivery systems, such as lipophilic gel, buccal spray and phospholipids vesicles have been recently proposed to deliver peptides via the buccal route. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been already developed. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.The oral cavity is used as a site for local and systemic drug delivery. Local therapy is used to treat conditions such as gingivitis, oral candidosis, oral lesions, dental caries, and xerostoma while systemic delivery delivers drugs into the circulation avoiding hepatic „first pass metabolism" effects. Delivery systems used include mouthwashes, aerosol sprays,chewing gums, bioadhesive tablets, gels and patches[1]. There are three major problems associated withdrug therapy within the oral cavity [2–5]. The first is the rapid elimination of drugs due to the flushingaction of saliva or the ingestion of foods-stuffs, which may lead to the requirement for frequent dosing. Thesecond is the non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system [6], which could mean that some areas of theoral cavity might not receive therapeutic levels ofdrug. The third is patient acceptability in terms of tasteand „mouth feel". This review will consider the use of lectins as ameans of enhancing therapy within (or delivered via)the oral cavity, by prolonging retention, targetingdelivery, and/or enhancing absorption.

Anatomy and physiology of the oral scavity

The oral cavity is divided into two regions, theouter and the interior oral vestibules. The outer oralvestibule is the space between the cheeks or lips andthe teeth while the interior oral vestibule (oral cavity proper) is situated between the teeth and the pharynx[7].The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propia and submucosa It also contains many sensory receptors including the taste receptors of the tongue [8]. There are three types of oral mucosa. Lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (beneath the tongue). Specialised mucosa is found on the dorsal surface of tongue, while masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The epithelium in masticatory mucosae is keratinized whilst those of the lining mucosae are non-keratinised. Keratinised and non-keratinised epithelium occupies about 50% and 30%, respectively, of the surface area of the mouth (mean area at rest being 214F12.9 cm2)[9]. The turnover time for cells in the oral mucosa has been reported to be 3–8 days [10] and 14–24 days [11]. The thickness of the mucosae varies form 500– 800 Am for the buccal mucosa (40–50 cell layers) to 100–200 Am for the sublingual mucosa and gingival[10]. The nature of the epithelial lining varies according to the tissue function, but generally it behaves as a lipophilic drug barrier [10]. The tongue consists of a mass of interlacing bundles of skeletal muscle fibre and is covered by mucosa. It is specialised for manipulating food, general sensory The ventral surface of the tongue and floor of the mouth

constitutes about 16% of the oral mucosa [9]. Adults have 32 teeth, 16 in the upper jaw and 16 in the lower. The outer surfaces of teeth are covered with enamel, which is one of the hardest materials in the body and contains over 96% calcium hydroxyapatite (a form of calcium phosphate). There are three major salivary glands (the parotid, submaxillary and sublingual), which secrete saliva into the oral cavity. These glands are situated away from the oral cavity but open into it by long ducts. Minor salivary or buccal glands are situated in or immediately below the oral mucosa. The parotid andsubmaxillary glands produce a watery secretion whereas the buccal and sublingual glands produce the mainly viscous saliva that contains mucin with Saliva has the function of lubricating the oral structures, facilitate the oral phase of swallowing by enhancing the formation of a slippery food bolus, preventing demineralisation of teeth, carbohydrate digestion (contains amylases) regulating the oral microbial flora [12,13], maintenance of oral pH and soft tissue repair. A salivary film (pellicle) is distributed over the surfaces of the mouth, coating epithelial cells and dental enamel [14]. The thickness of the salivary film is calculated to be only 70–100 Am [9], although its thickness and properties will vary in different area of the mouth, depending on the proximity to the ducts of the major and minor salivary glands. A human typically produces circa 1 l per day of saliva; the resting flow is 0.5 ml min_ 1, which can be increased to more than 7 ml min_ 1 upon maximal stimulation of the parasympathetic system (e.g. in anticipation of food). Saliva is viscous, colourless and opalescent, hypotonic compared with plasma, and has a specific gravity of about 1.003. It consists of circa 99.5% water with 0.15–0.25% dissolved protein or glycoprotein. The pH varies between 6.2 and 7.4 (from low to high rates of flow). The major ions present in saliva are calcium, sodium, potassium, chloride and bicarbonate, the concentration of each varying with the salivary flow rate. Saliva also contains enzymes (amylase and lysozyme), albumin, globulin, urea and uric acid [5]. Salivary mucins are high molecular weight glycoproteins that are comprised of apomucin enriched in hydroxyamino acids (threonine and/or serine) and proline, the oligosaccharides being linked O- glycosidically to this protein backbone. Several different mucin genes have been identified, termed the MUCgenes, and these encode for at least eight apomucins (e.g. MUC5b) [15]. Two unique sets of salivary mucins are present in human saliva, high molecular weight mucin (MG1) and low molecular weight mucin (MG2) [13]. MG1, has a molecular weight of over 103 kDa and is composed of hydrophobic, protease-vulnerable domains alternated with heavily glycosylated domains. MG2 contains short oligosaccharide chains and has a molecular weight of 200–250 kDa. It has been proposed that the enhanced rheological properties of MG1 lend themselves to a coating function while MG2 tends to interact with oral microorganisms in the soluble phase of saliva [16]. The oral cavity is a complex and dynamic environment, which contains a diversity of microorganisms (over 300 different species of bacteria have been isolated and identified). The density of microorganisms in the oral fluids is high; saliva, which derives its flora from oral surfaces, contains 107–108 bacteria ml_ 1 [17]. Most bacteria in the mouth are commensals and are considered to have a protective role against pathogenic bacteria. Nonetheless, infections mostly result from the activity of this „normal" flora. These bacteria can rapidly form a biofilm (dental plaque) on teeth and other surfaces within the oral cavity.

Advantage of drug delivery via the buccal lining:

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.

3. Sustained drug delivery.
4. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5. Increased ease of drug administration.

Limitations of buccal drug delivery :-

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

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drug within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and

„mouth feel" is an issue. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

Composition of the Oral Mucosae

For a fuller account of the structures and functions of the human oral mucosae, the reader is referred to Meyer et al.13 The oral mucosa consists of an outermost layer of stratified squamous epithelium, below which lies a basement membrane, and below this, in turn, a lamina propria and submucosa (see Figure **1).** Epithelium-Oral epithelium is broadly similar to stratified squamous epithelia found elsewhere in the body in that it consists of a mitotically active basal cell layer, progressing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The buccal epithelium is composed of **-40-50** cell layers, while the sublingual epithelia contain somewhat fewer. As cells mature and migrate from the basal layer towards the epithelial surface, they increase in size and become progressively flattened, while showing increasing levels of protein tonofilaments and declining levels of most other cytoplasmic organelles. The turnover time for the buccal epithelium has been estimated at &6 days, and this is probably representative of the oral mucosa as a whole. The thickness of the oral epithelium varies considerably between sites: in humans, dog, and rabbit, the buccal mucosa measures 500-800 pm in thickness, while the hard and soft

palates, floor of the mouth, ventral tongue, and gingivae measure -100-200 ***pm."16*** The composition of the epithelium also varies with its location in the oral cavity. Thus, mucosae of the gingiva and hard palate (areas subject to mechanical stress) are keratinized in a similar manner to the epidermis. Keratin is laid down in the superficial cells of the epithelium, and these cells become flattened in shape and virtually devoid of organelles. The mucosae of the soft palate and the sublingual buccal regions, on the other hand, are generally not keratinized. The superficial cells in these regions become less flattened and retain their nuclei and some cytoplasmic function.

Biochemical Composition:-

A reasonable account of the biochemistry of the oral mucosae is given by Gerson and Harris.17 A notable feature of the oral mucosae is the large amount of protein present in the form of tonofilaments in the cells of all layers, in both keratinized and nonkeratinized epithelia. These tonofilaments are composed of at least seven component proteins, termed keratins, with ***M,*** ranging from 40 to 70 kDa. Cells of "nonkeratinized" mucosae contain mostly the lower ***M,*** keratins, while in those of "keratinized mucosae, the higher ***M,*** keratins predominate.18 It thus

appears that keratinization is not an "all-or-nothing" process, but that these terms simply represent extremes of a spectrum of keratinization. Comparatively little is known about the lipid composition of the oral mucosae. Furthermore, the studies that have been reported have determined lipid profiles that differ markedlyfrom one another in certain respects."@-21 Wertzlo suggested that the lipid compositions of the various oral epithelia and the epidermis correspond with the water permeabilities of these tissues. In particular, the keratinized oral mucosae (gingiva and palate) and the epidermis contain sizeable amounts of acylceramides and ceramides, which have been associated with barrier function, while the nonkeratinized oral mucosae (buccal and floor of the mouth), which are also more permeable, contain smaller amounts of these components. The cells of the oral epithelia are surrounded by an intercellular ground substance, the principal components of which are carbohydrate:protein complexes, some of which may be intimately associated with particular sites on the cell surfaces. It is thought that this matrix may play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Another aspect of the biochemical composition of the oral mucosae is the so-called "membrane-coating granules", and their role in the biochemical changes which occur during the maturation of the epithelium; this subject is dealt with in some detail under the heading Membrane-Coating Granules.

Intercellular Junction-A number of different intercellular junctions are found in epithelia, principally gap junctions, tight junctions, and desmosomes and/or hemidesmosomes. In a gap junction, the plasma membranes of adjacent epithelial cells are separated by a gap of *2-5* nm, which is believed to be continuous with the intercellular space: a gap of this dimension would probably permit the passage of permeants of ***M,*** up to several thousand Da. These junctions are generally no > 1 pm in diameter and are probably confined to the basal and intermediate layers of the epithelium. In a tight junction, by comparison (macula occludens or zonula occludens), the membranes of adjacent cells appear to be fused together. These junctions are uncommon in oral epithelia, however, and appear to be confined to the more superficial cell layers, though they are not found in the very outermost layers. The remaining junctional complexes are desmosomes and hemidesmosomes, which are mechanical attachments between adjacent epithelial cells and between basal cells and the basement membrane, respectively. Basement Membrane and Connective Tissues-The basement membrane is a continuous layer of extracellular material, forming the boundary between the basal layer of the epithelium and the connective tissues of the lamina propria and submucosa. It is a trilaminar structure, consisting of an upper amorphous layer **(40-80** nm in thickness; the lamina lucida), a central dense layer of similar thickness (the lamina densa), and a broader region of fibrous material below. The lamina densa is the primary structural component of the basement membrane: it is composed of a form of collagen, thought to be arranged as a highly ordered network, which would impart considerable strength to the structure. Hemidesmosomes in the membranes of the basal cells connect across the lamina lucida with the lamina densa. The functions of the basement membrane are probably twofold: (1) to provide adherence between the epithelium and the connective tissues beneath and to provide mechanical support for the epithelium, and **(2)** to form a barrier to the passage of cells and some large molecules across the mucosa.

Below the basement membrane lies the lamina propria: this is a continuous sheet of connective tissue containing collagen and elastic fibers and cellular components in a hydrated ground substance. It also carries blood capillaries and nerve fibers that serve the mucosa. The uppermost elements of the lamina propria mesh with the anchoring fibrils of the basement membrane, and the lower layers border onto the submucosa, if present, or onto periosteum or muscle. The junction between the epithelium and the lamina propria is not flat, but is thrown into ridges and folds and drawn out into connective tissue papillae that project into the epithelium

Consequently, the area of the basement membrane is greater than that of the epithelial surface: this provides a broader area for attachment of the epithelium and for metabolic exchange between the epithelium and the lamina propria.

Mechanism of action of permeation enhancers [8] Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows. (Ganem et. al., 1996).

1) Changing mucus rheology Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

2) Increasing the fluidity of lipid bilayer membrane The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers 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 Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

4) By overcoming the enzymatic barrier These act 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.

5) Increasing the thermodynamic activity of drugs Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

Mechanism of drug absorption by buccal route

1. **Simple diffusion:** absorption path is based on random motion of molecules from a zone of higher concentration to one of low concentration to substance placed on mucosa.
2. **Facilitated diffusion:** absorption involves a carrier system which leads to more rapid absorption such a carrier system exhibit stereo specificity in D- glucose and L-arabinose. Absorption of nicotinic acid and nicotinamide across the buccal mucosa has been shown to depend upon the presence of sodium ions.
3. **Intercellular movements:** oral epithelium has loose junctions and is leaky therefore is likely to allow passage of substance through intercellular space. The basal lamina limits the passage of molecules with a molecular weight more than 70,000.
4. **Endocytosis:** although cells of oral mucosa are able to absorb substances by endocytosis it is likely that this mechanism has only a minor role in drug transport from oral cavity.

Factors affecting drug delivery via buccal route

(a) Nature of permeant

Most drug move extracellularly through the neutral lipids and glycolipids that separate the mucosal cells. There the lipid solubility of drugs is an important in TMDD suitability. Along with lipid solubility, drugs selected for TMDD must have physiochemical properties, including size and pka that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentration.

(b) Molecular size

For hydrophilic macromolecules such as peptides, absorption enhancers(see later section) have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules [26].

(c)Lipid solubility and partition coefficient

Only the nonionized forms of molecules have the ability to cross lipoidal membranes in significant amounts. The more lipids soluble a compound is, the higher its permeability. Thepermeabilities for these compounds are direct functions of their oil-water partition coefficient. The partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug‟s polarity by ionization or the addition of hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient.

(d) Ionization

The ionization of a drug is directly related to both its pka and ph at the mucosal surface . Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.

Methods to increase drug delivery via buccal route 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 enhancers are azone, fatty acids, bile salts, and surfactants such as sodium dodecyl sulfate. Solution/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 [1].

Table 1: List of permeation enhancers

SR. No	Permeation enhancers	SR. No	Permeation enhancers
1	2,3- lauryl ether	14	Phophatidylcholine
2	Aprotinin	15	Polyoxyethylene
3	Azone	16	Polysorbate 80
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Phophatidylcholine
6	Cetyltrimethyl ammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran sulfate	21	Sodium glycodeoxycholate
9	Glycol	22	Sodium lauryl sulfate
10	Lauric acid	23	Sodium salicylate

Formulation Factors

Several factors related to the formulation or delivery system can influence the bioavailability or therapeutic efficacy of a drug delivered via the oral mucosae; obviously, the rate, duration, and kinetics of drug release are critical in this respect. However, there are additional factors, not all of which are encountered in conventional drug delivery, which must be considered in oral mucosal drug delivery.Sublingual Delivery-As outlined earlier, the sublingual mucosa appears to be relatively permeable, capable of giving rapid and appreciable absorption of low- molecular-weight drugs. **To** the knowledge of the authors, the only delivery

systems evaluated clinically for sublingual delivery have been rapidly disintegrating tablets and liquid-fiIled **soft** gelatin capsules which are crushed open in the mouth.2~Jb.~,l2T6h ese systems are designed to give rapid drug release, leading to high local drug concentrations in the sublingual region. As a result of salivary flow, these concentrations are sustained for a relatively short period of time, probably in the order of only minutes. The sublingual area does not appear to have an expanse of smooth and relatively immobile mucosa that would be suitable for attachment of a retentive delivery system. For this reason, the main application of the sublingual **route** is likely to remain the delivery of small permeants for which short delivery times and infrequent delivery intervals are appropriate, or for which a rapid onset of action is desirable (e.g.,nitroglycerin). Buccal Delivery-The buccal site differs from the sublingual in a number of important respects. First, the buccal mucosa is less permeable than the sublingual and does not give the rapid onset of absorption seen with sublingual delivery. Second, the buccal mucosa appears to be better suited to the use of retentive systems, such as a mucoadhesive tablet or patch system, in that it has an expanse of smooth and relatively immobile surface for placement of such systems. These attributes make the buccal mucosa more suitable for sustained-delivery applications, delivery of less well permeating molecules, and perhaps peptide drugs. These applications place a number of additional constraints on the design of buccal delivery systems. First, it may be desirable to modify the local environment at the absorption site in order to optimize the buccal delivery of a drug. This may involve addition of a cosolvent or alteration of the pH at the mucosal surface in order to increase the local solubility of the drug or enhance its partitioning into the mucosal tissues. Alternatively, it may involve use of a penetration enhancer or enzyme inhibitor, as has been described earlier (see Penetration Enhancement). Obviously, these approaches require incorporation of one or more additional agents into the delivery system, which *can* greatly increase the complexity of the formulation and perhaps also the manufacturing process. Second, it may be necessary to confine the applied dose of a drug to a proscribed region of the mucosa, in order to maximize the residence time of the drug at the mucosal surface (i.e., the time available for absorption). Harris and Robinson127 demonstrated that the utility of mucosal delivery

routes, such as the buccal route, can be resolved into two issues: (1) whether therapeutic drug levels can be attained in the systemic circulation via this route (this is a function of, among other factors, the permeability of the delivery site to the drug), and **(2)** whether these therapeutic levels can besustained (this is a function of the clearance half-life of the drug and the residence time of the dose at the delivery site.

For drugs with half-lives of several hours and wide therapeutic indices, maintaining therapeutic levels is not a major problem. For drugs with short half-lives, however (and many peptide drugs, for example, have half-lives of minutes only), this issue becomes highly significant. In order to maintain therapeutic levels of such short half-life drugs, it is necessary to deliver these drugs virtually continuously, or at least at very frequent intervals. Obviously, retaining a delivery system at the oral mucosae for a period of several hours or more can be a major problem, due to such challenges as salivary flow, ingestion of food and beverages, mastication, and speech. The

same principles would also apply to the delivery of other constituents, such as penetration enhancers. In this case, it would be desirable to restrict the enhancer to the site of delivery not only to prevent a loss of enhancing effect at the absorption site, but also to prevent a generalized change in permeability of the membranes of the oral cavity. A third constraint of buccal delivery systems is that, since we are dealing with an unconventional delivery route, patient acceptance is likely to be an obstacle in many cases, particularlyfor retentive delivery systems. Success will therefore depend on the patient's motivation, and on the delivery system being convenient to use and unobtrusive once in place. When all of these factors are considered, it appears likely that resilient adhesive systems, such as patch systems30.34.44.66 or adhesive controlled-release tablets,1os3l366 have a greater potential for sustained delivery than, for example, gels or disintegrating tablets. As has been outlined, however, the critical factor will probably be the development of delivery systems that are able to provide delivery of active constituent(s) for periods of ***6*** to 12 h or thereabouts, while still being acceptable to patients. In addition to these sustained-delivery applications, the buccal route has also found clinical use in delivery over somewhat shorter time-spans, using more conventional tablet formulations as opposed to the retentive systems described above. Examples here include delivery of methyl testosterone prochlorperazine ,lZs rnorphine,129 and oxyto-Local Delivery-The simplest and probably the most widely used delivery systems for local delivery to the oral mucosae are conventional mouthwashes, oral suspensions, and lozenges.llJ30 These give high drug levels in the oral cavity **as** a whole, but only for a short time.131 Indeed, salivary flow is probably even more important an issue in the context of local delivery than in sublingual or buccal delivery. For these types of therapy to be effective, therefore, it is necessary either to select drugs which are rapidly absorbed and effective under conditions of discontinuous delivery, or to make use of frequent dosing intervals. The duration of action of a drug can be improved somewhat by the use of ointments or creams which can be applied to the oral mucosae. Buccal mucosa as a site for drug delivery [4]

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

Buccal Drug Delivery and Mucoadhesivity [7]

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

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

The polymers which have been tried and tested over the years include Carbopol, Polycarbophil, Poly(acrylicacid/ divinyl benzene), Sodium Alginate, Hydroxyethyl cellulose, Hydroxypropyl methylcellulose, Hyaluronic acid, Gelatin, Guar Gum, Thermally modified Starch, Pectin, Polyvinyl pyrrolidone, Acacia, Polyethylene glycol, Psyllium [8] Carboxymethyl cellulose.

CURRENT STATUS OF BUCCAL BIOADHESIVE DOSAGE FORM

Dosage forms such as mouthwashes, erodible/ chewable buccal tablets, and chewing gums allow only a short period of release, and reproducibility of drug absorption is poor. Application of bioadhesive semisolid gels creates considerable technical problems. Bioadhesive buccal films/patches and tablets are the less developed type of dosage forms. These bioadhesive buccal films/patches and tablets were usually fabricated in different geometry, as shown in Fig. A. Type I is a single-layer device, from which drug can be released multidirectionally. Type II device has a impermeable backing layer on top of the drug-loaded bioadhesive layer, and drug loss into oral cavity can be greatly decreased. Type III is a unidirectional release device, from which drug loss will be avoided and drug can penetrate only via the buccal mucosa.

Structure & Design of Buccal dosage form Structure and design Drug delivery designed for the buccal mucosa contains a polymeric adhesive component. When in contact with the saliva, the adhesive attaches to the mucosa causing immediate and rapid drug delivery. Transmucosal drug delivery systems can be unidirectional or bi-directional. Unidirectional patches release the drug only into the mucosa, while bi-directional patches release the drug in both the mucosa and the mouth. The buccal patch is designed in either a matrix configuration with drug, adhesive, and additives mixed together, or a reservoir system that contains a cavity for the drug and additives separate from the additives. 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.

Buccal dosage form for buccal delivery In the past decades, to till now, different drug delivery systems intended for buccal administration have been developed. The most common buccal dosage forms are tablets and patches. Such type of form must be of a small size and a suitable geometry so as to not interfere with physiological function of the mouth, even after their hydration in the oral cavity. One of the requirements is that they do not adhere too tightly because it is undesirable to exert too much force to remove the formulation/ dosage form after use, otherwise the mucosa could be injured. An alternative is the use of formulations that dissolve or disintegrate completely during the application period. Moreover, in the case of Transmucosal administration, Drug release should be unidirectional (towards the mucosa), and the release into the saliva should be avoided.

Matrix type:- The buccal patch designed in a matrix configuration contains drug, adhesive, and additive mixed together. Monolithic and two –layered matrix type have been designed for buccal delivery of drugs. In fig. 3, a schematic representation of several kinds of matrix tablets in given. Monolithic tablets consist of a mixture of drug with a swelling bioadhesive/ sustained release polymer (fig. 3a) 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 (Fig. 3b and c). Two layered tablets comprise an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bi-directional release but mainly a local action (Fig. 3d). 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

(Fig. 3e). 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 (Fig. 3f). Different drugs have been loaded in matrix tablets, such as propanolol, timolol, metronidazole, metoclopramide, morphine sulphate, nitroglycerin and codein . Peptides, such as insulin, calcitonin and glucagone-like peptide were also loaded in buccal mucoadhesive tablets.

Reservoir types 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.

Patches Patches are laminated and generally consist of an impermeable backing layer and a drug-containing layer that has mucoadhesive properties and from which the drug is released in a controlled manner. Moreover, buccal patches for systemic delivery of tyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin and leuenkephalinhave been studied.

Conclusions and future prospects

To date, only limited work has been completed on the retention of lectin-containing delivery systems within the oral cavity. Their possible uses includes retaining a delivery system in the oral cavity for extended periods, or targeting lesions (carcinomas, ulcers), inflamed tissues (gingivitis) or bacteria. Taking advantage of their multifunctional properties, targeting a lectin with a potential therapeutic action (cytotoxic, or stimulation of cell proliferation in wound repair) would provide interesting possibilities. However, the toxicity and cost of many lectins could restrict their use for all but the most severe disease states. The exploiting of endogenous lectins to act as „handles" for carbohydrate-containing delivery systems presents another opportunity for targeting within the oral cavity. Further work would need to consider J.D. Smart / Advanced Drug Delivery Reviews 56 (2004) 481–489 48. the strength of lectin binding relative to the size of a potential delivery system and its ability to resist the considerable challenges faced within the oral cavity. The need for research on drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of the current treatments may be improved if their delivery rates, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. From both a financial and global health care perspective, finding ways to administer injectable medications is costly and sometimes leads to serious hazardous effects. Hence, inexpensive multiple 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. Since the introduction of OrabaseR in 1947, when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa, the market share of bioadhesive drug delivery systems has increased. Mucosal (local) and transmucosal (systemic) delivery of drugs via the buccal route is still very challenging. The main obstacles arise from the limited absorption area and from the barrier properties of the mucosa, particularly in the case of drugs intended for a transmucosal delivery. Moreover, the effective physiological removal mechanisms of the oral cavity, which take the formulation away from the absorption site, are factors that have to be considered in the design of buccal drug delivery systems, notably in the case of local delivery.

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