

Different Variable and Recent Development in Noval Buccal Drug Delivery System

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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. 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.

KEYWORDS: Bioadhesion, Barriers, Pathway, Transmucosal Dosage Form, first-pass effect

INTRODUCTION

Buccal drug delivery is a favorable route compare to parenteral, injectable and adds a several advantages over other routes¹. The parenteral route offers excellent bioavailability, similarly having poor patient compliance, anaphylaxis, and some other infections. Per-oral route possess some inconvenience to patients. Hence for the immediate release of medication and for instant release at desire location in which the drug is absorbed distributor and easily metabolized. This limitation leads to the development of alternative routes of administration. Buccal mucosa has absorptive function and offers many benefits like avoidance of first pass effect, which is a noninvasive route, increase in bioavailability, a rapid action is possible and reduce side effects.¹⁻²

Buccal, sublingual, palatal and gingiva regions shows effective drug delivery in oral cavity. Buccal and sublingual route of drug delivery are most widely in which local and systemic effects are treated. The permeability of oral mucosa

denotes the physical nature of the tissues. The permeable part is sublingual mucosa and buccal mucosa is thinner part and in which there is a high blood flow and surface area; it is a feasible site when a rapid onset of action is desired. For the treatment of acute disorders sublingual route is a preferred one; however, its surface washed with saliva which makes formulations in the oral cavity hard in nature.³⁻⁴

Buccal drug delivery system is well accepted because it is having several advantages. Buccal areas offer a control release system which is having immobile surface. The buccal layer is tolerate to potential allergens and has capability of preventing damage compare to other mucosal tissues. In treatment of the local or systemic therapies, buccal mucosa favors a useful measure by overcoming drawbacks and as convenient route for the administration. This type of route is well vascularized draining to the heart unswervingly via the internal jugular vein. In chronic systemic therapies, buccal drug delivery acts as potential site and chemical

modification due to salivary production and its composition. There is a chance of drug loss at site of absorption in case of the oral route and for some dosage form salivary scavenging is constant within oral cavity which make difficult for retaining to an extensive duration at the site to enhance the absorption. Bioadhesive polymers have prolonged contact time with the tissues and can notably maintain the performance of several drugs. The controlled drug delivery products have high patient compliance and a low cost with enhanced bioavailability.⁵⁻⁶

Advantages:-

1. It is richly vascularised and additional reachable for administration and removal of formulations.
2. Patient accessibility is high.
3. Retentive dosage forms are suitable for administration.
4. Improves bioavailability by eliminating first pass metabolism.
5. Surface of buccal mucosa achieves a fast cellular recovery.
6. Low enzyme activity.
7. Non-invasive method of drug administration.
8. Ability to incorporate permeation enhancer in the formulation

Disadvantages:-

1. Buccal membrane has low permeability
2. Small surface area (170 cm²).

3. Continuous secretion of saliva results in following dilution of the drug.
4. Inconvenience route of drug administration when the patient is swallowing or taking.
5. Relatively small absorption area.

Anatomy of oral mucosa

Buccal cavity is a component of mouth in which lips and cheeks are anteriorly bounded and teeth, gums bounded posteriorly and medially. The buccal glands are positioned between the mucous membrane and buccinators muscle. The thickness of buccal mucosa is having uneven texture and about 500-800µm and buccal epithelium return time at 5-6 days. The non-keratinised stratified squamous epithelium lines the buccal mucosa and having 500-600µ and surface area of about 50.2 cm²

Structure

The oral mucosa consists of three distinctive layers. They are epithelium, basement membrane and connective tissues. Buccal cavity is lined with epithelium; supported by basement membrane which intern supported by connective tissues. In underlying tissues, protective layer is epithelium which is divided into

- A. Surface which is non-keratinised lining of soft palate, tongue surface, lips and vestibule.
- B. Hard palate and other non flexible regions keratinized epithelium present in oral cavity.

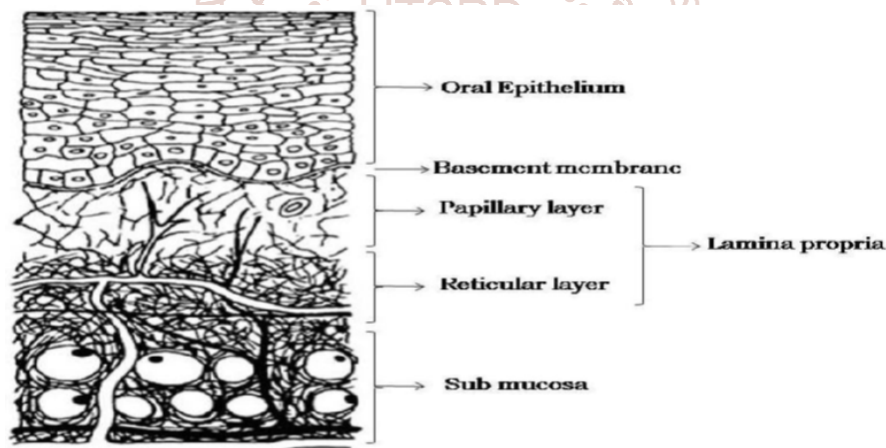


Fig: 1.1. Cross-section of buccal mucosa

The epithelial cells originating from the basal cells mature, change their shape, and increase in size while moving towards the surface. The basement membrane acts as mechanical support for the epithelium and forms a distinctive layer between the connective tissues and the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. The non-keratinized tissue is a part of buccal epithelium which is penetrated by connective tissues that are tall and conical in form. These tissues, which are also referred to as the lamina propria, consisting collagen fibers, smooth muscles, blood vessels and an underneath film of connective tissues. Lamina propria is followed by the sub mucosa (Fig 1).The external carotid artery supplies to the oral mucosa. The main sources of blood supply to the lining of the cheek in the buccal cavity are derived from the buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infra orbital artery.⁸⁻⁹

Permeability

The oral mucosal epithelium is somewhat leaky and intermediate between that of the epidermis and intestinal mucosa. Buccal mucosal having 4-4000 times greater permeability than skin and different regions having difference in permeability of oral cavity because of its diverse structures and functions of the oral mucosa. The relative thickness and degree of keratinization of the tissues precedes the ranking. Both the sublingual mucosa and buccal mucosa are non-keratinized, however they differ in thickness. The buccal mucosa is thicker than the sublingual mucosa and the palatal. mucosa is intermediate in thickness but keratinized. The permeability of the oral mucosa is in the decreasing order sublingual > buccal > palatal.¹⁰⁻¹¹

Barriers to penetration across buccal mucosa

About quarter to one-third of the epithelium consists of barrier which is mainly useful for penetration. The barriers which retard the rate and extent of drug absorption through the buccal mucosa are

- Membrane coating granules
- Basement membrane
- Mucus
- Saliva

Membrane coating granules:- Membrane coating granules are which extrudes into the intercellular region of both keratinized and non-keratinized oral epithelium and are responsible for preventing the transmucosal penetration. The component of the membrane coating granules is different in keratinized and non-keratinized epithelia.¹²

Basement membrane:- The superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior; the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. 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. The molecular weight of the permeant molecule and its reactivity with the barrier as well as the structural and functional factors of the barrier influences the barrier function of basal lamina.¹³

Mucus:- Mucus is having mainly of water where mucins and inorganic salts are present. Mucin chiefly includes glycosylated proteins having oligosaccharide chains. These are responsible for gel like character of mucus. The composition of mucin is 70–80% carbohydrate, 12–25% protein and 5% ester sulphate. The sugar coating layer responsible for withstanding of water and acting against proteolysis, this is very essential for the barrier properties of mucosa.¹⁴

Saliva:- The mucosal surface has a salivary coating estimated to be 70 µm thick, which act as unstirred layer. Saliva consists of high molecular weight mucin named MG1 which maintains hydration, provides lubrication, concentrate protective molecules such as secretory immunoglobulin's and limit the attachment of microorganisms by binding to the surface of oral cavity³⁰. The constant flow of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption at this site. The intercellular spaces act as a major source for permeation of hydrophilic compounds, and major transport barrier for lipophilic compounds is the cell membrane which is lipophilic in nature. Due to a low partition coefficient it is difficult to permeate through the cell membrane.¹⁵

Drug transport mechanisms

The main mechanisms involved for the penetration of various substances include simple diffusion (paracellular and transcellular), carrier mediated transport and endocytosis³³. The convey of drugs across the buccal mucosa follows the mechanism involved in passive diffusion; although it has been reported that carrier mediated transport plays a small role upto some extent. Depending on the physicochemical properties of the molecule and the type of tissue being traversed rate of penetration may vary and leads to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption which depends on the physicochemical properties of the diffusant, but one route is predominant over the other.¹⁶⁻¹⁷

1. Passive diffusion

- A. Transcellular or intracellular route
 - B. Paracellular or intercellular route
2. Carrier mediated transport
 3. Endocytosis

The transport of drugs across buccal epithelium may follow different pathways but their selection depends upon the nature of the permeant, i.e. the overall molecular geometry, lipophilicity and charge. Most of the compounds diffuse through the buccal mucosa by passive diffusion or simple Fickian diffusion.¹⁷

Enhancement of buccal transport

The buccal mucosa exhibits insufficient permeability depending on physicochemical characters of the drug and represents a major limitation in the development of a transmucosal drug delivery system⁴¹. Also, the limited absorptive area and the short exposure time, due to the washing effect of saliva can decrease absorption efficiency even more. 'Permeation enhancers' are used to permeate the drugs across epithelial barriers. However, proper penetration enhancers are used to improve the drug permeability.¹⁸

➤ Ideal permeation enhancers should have the following properties

- Safest and non-toxic nature
- Pharmacologically and chemically inert and non irritant.
- Should be non-allergenic

Classification of permeation enhancers

- Chelators:- sodium salicylate, methoxy salicylates, EDTA, citric acid.
- Surfactants:- SLS, Polyoxyethylene-9-laurylether, cetyltrimethyl ammonium bromide, Benzalkonium chloride.
- Bile salts:- sodium glycocholate, sodium taurocholate, sodium deoxycholate, sodium taurodeoxycholate.
- Fatty acids:- phosphatidylcholine, oleic acid, propylene glycol, methyloleate.
- Inclusion complexes:- cyclodextrins.
- Thiolated polymers: chitosan-4-thiobutylamide, chitosan-cysteine, Na CMC
- Others:- Polysorbate 80, sulfoxides, aprotinin, azone, cyclodextrin, dextran sulfate, menthol and various alkyl glycosides.

Approaches of buccal drug delivery system

- Non-attached drug delivery systems
This includes Fast dissolving tablet dosage forms, Chewing gum formulations and Micro-porous hollow fibers.
- Bio-adhesive drug delivery systems
 - A. Solid buccal adhesive dosage forms.
 - B. Semi solid buccal adhesive dosage forms.
 - C. Liquid buccal adhesive dosage forms.
- Liposome
- Delivery of proteins and peptides

Non-attached drug delivery systems

The local physiological environment greatly affects the non-attached drug delivery system, e.g. the presence of saliva and the intake of foods and liquids

Bio-adhesive drug delivery systems

A. Solid buccal adhesive dosage forms

Dry formulations achieve bio-adhesion via dehydration of the local mucosal surface

Buccal tablets

Buccal tablets are small, flat and oval in shape with a diameter of approximately 5–8 mm. The direct compression technique is most widely used for preparation of buccal tablets; other techniques like wet granulation can also be employed. These tablets stick to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectional, targeting buccal mucosa or multidirectional in to the saliva.

Microspheres, microcapsules, micro particles

The local irritation caused by microspheres or microcapsules or micro particles at the site of adhesion is less and provide comfortable sensation of a foreign object within the oral cavity.

Wafers

Wafer is a drug delivery system with surface layers possessing adhesive properties.¹⁸

Lozenges

Bioadhesive lozenge offers prolonged drug release with improved patient compliance compared to Conventional lozenges, thus avoiding multiple daily dose.

B. Semi-solid buccal adhesive dosage forms.**Gels**

Bioadhesive polymers forming gels which form cross linked polyacrylic acid used in which mucosal surfaces are fixed to provide the release in control manner for extensive period of time and drug at the absorption site. Bioadhesive polymers forming gels are of limited use for drugs with narrow therapeutic window due to their inability to deliver a measured dose of drug to the site.

Buccal patches

Patches are laminates consists of drug-containing reservoir layer and an impermeable backing layer. Drug is released in a controlled manner from the drug-containing reservoir layer, and a bioadhesive surface for mucosal attachment. Buccal adhesive Patches can be prepared by two methods. Solvent casting technique and Direct milling method. In solvent casting technique, the solvent is evaporated by casting the solution of the drug and polymer onto a backing layer sheet and the patches were punched in intermediate sheet. In method like direct milling in which the constituents of formulation forms desired thickness by proper mixing, by which the desired shapes are cut and punched out in case of patches. Backing layer acts as protective layer which is impermeable and is applied to control the prevention of drug loss and direction of drug release during the administration.

Buccal films

These are the most recently developed dosage form which meant for buccal administration. Buccal films have more flexibility and comfort when compared with adhesive tablets. So, buccal films are preferred instead of adhesive tablets. In addition to these, they have saliva which removes and wash easy and short residence time on mucosa of oral gels. The wound surface is protected mainly by films, when the drugs are administered orally for local delivery and treat the disease more effectively by reducing the pain. An ideal film should be soft, elastic, flexible and possess adequate strength to withstand breakage due to stress from mouth movements. It should retain in the mouth to produce desired action with good bioadhesive strength. Swelling of film

should not be too extensive in order to prevent discomfort. Solvent casting method is widely used for the preparation of buccal films. In solvent mixture, drug and polymer(s) are dissolved. The solution made in to film and dried, a liner or a backing layer are used to finally laminate. The salivary diffusion in to drug layer is avoided by the backing layer; there is a reduction in the drug loss and by enhancing adhesion time in oral cavity. The main disadvantage with solvent casting technique is time consuming, long processing and some concerns with the environment by the usage of different type of solvents. Hot-melt extrusion method is used to overcome the drawbacks.

C. Liquid buccal adhesive dosage forms

Liquids used to coat buccal surface are viscous and serve as either protective agents or as drug vehicles for delivery of drug on to the mucosal surface. Recently, pharmaceutically acceptable polymers were used to improve the viscosity of products to aid their maintenance in the oral cavity. Lubrication can be provided by treating dry mouth with artificial saliva solutions and to retain the drug on mucosal surfaces. This solution consists of SCMC as bioadhesive polymer.

Liposomes

Drugs which are encapsulated in liposome formulations have been investigated for buccal administration. Applications of liposome formulation in buccal delivery resulted in a decrease of systemic and an increase of local, drug concentration. Peptides can be entrapped within the liposome. The transport of hydrophilic substances to the layer of the epithelium through liposome formulations can be limited. Poly methyl methacrylate is a hydrophilic polymer and found to be the most appropriate mucoadhesive ointment for local application in the oral cavity since the liposomes were shown to be more stable in this polymer. The performance of less effective liposome peptide delivery systems can be improved by incorporation of protease inhibitors.

Delivery of proteins and peptides

The buccal drug delivery systems avoids pre systemic (or) hepatic first-pass metabolism, acidity and protease activity come across in the gastrointestinal tract hence provide as potential important site for controlled delivery of macromolecular therapeutic agents, such as peptides and protein drugs. Another attractive advantage is its tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers

Factors effecting buccal mucosal drug delivery system designs

Many factors affect the successful delivery of a drug molecule into the systemic circulation via buccal mucosa. In general, the approach taken in the development of oral mucosal drug delivery systems is to identify suitable drug candidate based on both their physicochemical properties and ability to penetrate the buccal mucosa and to optimize their delivery through rational drug delivery system design the factors affecting the buccal mucosal drug delivery system are given below:

Drug factors

- Taste
- Discoloration of teeth
- Solubility

- Partition coefficient
- pka
- Biological half life
- Rate of absorption
- Irritation potential
- Allergenicity
- Diffusion coefficient in the epithelium
- Drug stability

Biological factors

- Area
- Thickness
- Composition of buccal mucosa
- Composition of Saliva
- Structure of buccal mucosa
- pH of environment
- Saliva flow rates

Drug Delivery system factors

- Excipients selection taste, odour
- Release characteristics
- Protection from saliva
- Size, shape and texture
- Retentive properties
- Mobility of backing layer of delivery system
- Irritation and allergy potential

Factors to be considered in buccal formulation design

A. Drug characteristics

The penetration of drugs or other chemicals into or through the buccal mucosa depends on a number of factors. These include the physicochemical properties of the drug and the condition of buccal mucosa, the composition and thickness of the buccal mucosa, the presence of other chemicals (E.g.: penetration enhancers) and external conditions impelled by the oral fluids such as pH amongst others. The physicochemical properties of the drug influence the rates of diffusion and partitioning with in the delivery system and buccal mucosa by affecting the,²⁰

- Drug's physical state in the dosage form. Eg: Dissolved or Suspended
- Release rate of the drug from the delivery system
- Concentration of released drug in the saliva film
- Percentage of absorbable non-ionized species at the site of absorption
- Drug's ability to partition into the superficial layers of epithelium
- Concentration of drug in the superficial layers of epithelium
- Diffusion rate through the membrane

B. Drug release from the formulation

When designing a buccal mucosal drug delivery systems there are two options available for the formulation scientist. Firstly, the design of delivery system is slower than the rate of transport though the buccal mucosa. In such a case the drug plasma profiles would be controlled by the release characteristics of the delivery systems. Second, the design of delivery system whose rate of release from the formulation into the salivary film is faster than drug transport across the epithelial layer. In such a case the drug plasma profiles would be controlled by the penetration rate of drug through the buccal mucosa. In either case the rate of release from a formulation would be dependent upon the drug (its physicochemical properties) and the delivery system (its ingredient and formulation).

C. Drug dissolution in the salivary film

The driving force for transport across buccal mucosa is the chemical potential gradient. To create this gradient with in the buccal mucosa, released drug becomes dissolved in saliva and establishes a certain concentration of drug in the outer surface of the buccal epithelium. This occurs because the drug has an affinity for both the saliva and the buccal epithelium. Thus, if the delivery system is designed such that release of drug does not control blood levels, i.e. passage of drug through the membrane is the determinant of drug plasma profiles, to ensure maximal absorption rates the drug should exist in the salivary film at its solubility limit.

D. Partitioning in to the superficial layers of the epithelium

The partition coefficient is usually assumed to be concentration independent, and can be determined from knowledge of the concentrations of the drug at equilibrium in each phase. Clearly, such a value is difficult to determine experimentally and often the partition coefficient of the drug between a suitable buffered aqueous solution (which mimics the saliva) and an organic solvents such as octonol (which mimics the lipid properties of the epithelium) is used.

E. Ionization

An inherent assumption of partition coefficient is that the same drug species exist in both the aqueous and organic phases. In other words the drug must exist in the non-ionized form in both phases. The degree of ionization of a drug is a function of both its pka and pH of the aqueous phase. Changes in pH can significantly alter the apparent partition coefficient of the drug and its rate of absorption. It has been shown using the buccal absorption test technique that for most of the weak acids and bases studied to date, only the non-ionized form of the compound is absorbed across human buccal mucosa, Becket et al.,1968. Absorption is observed to be highest when pH values dictate that the drug is present predominantly in the non-ionized form, and as the degree of ionization increases with a change in solution pH, the absorption decreases in a characteristics sigmoidal fashion. These observations are explained by considering that the non-ionized form of the drug possesses a high degree of lipid solubility and therefore an affinity for the oral cavity membrane. In contrast the ionized drug species are poorly lipid soluble and remain confine to the aqueous environment of the saliva in the oral cavity.

F. Diffusion across the epithelial layer

Once the drug has partitioned into the outer epithelial layer lipids, it will setup a concentration gradient and diffuse along that gradient according to Fick's Law of diffusion. Due to the barrier properties of the epithelium it is assumed that passage across the epithelium is the slowest, and therefore rate controlling step in the process of drug absorption across buccal mucosa. In this case, the rate of transport from the saliva into and across the buccal mucosa can be described by the following approximation of Fick's First Law of diffusion:

$$J = D KP \Delta C_e / h$$

Where J is the flux of drug across the epithelium (gm/cm² /sec.), D is diffusivity of the drug in the epithelial layer (cm² /sec.), ΔC_e is the difference in drug concentration between one side of the epithelium and the other (gm/cm³), KP is the membrane: saliva partition coefficient and h is the effective diffusional path length of the epithelium (cm). In above

equation both the diffusivity and the concentration difference are closely tied to properties of the drug and components of the epithelium.

G. Dependence of diffusivity on molecular size and weight

Molecular size and weight influence the diffusivity of the drug through the epithelial layer. Diffusivity can be viewed as a rough measure of the ease with which a molecule can move above with in a medium (in this case, the epithelial layer). As a general rule, the larger the molecule the more difficult it is to move about and the lower the diffusivity. For large molecules in non homogenous media (such as the epithelium), the dependence of diffusivity on molecular weight would be evident because of physical hindrance of movement as the molecular size of the drug approaches the dimensions of the pathways available for diffusion. It is likely that for hydrophilic drugs, the rate of absorption would be related to its molecular size. Indeed, small molecules (<75-100 Dalton) appeared, however permeability fall off rapidly as molecular size increase.

H. Partitioning into and transport away by the blood

The partitioning into and transport away by the blood is considered to the rapid and does not contribute any barrier to the whole permeation process. Thus far we have considered the physicochemical properties of the drug that effect its selection as a drug candidate to penetrate the buccal mucosa. Other factors include organoleptic properties of the drug and excipients, texture of delivery system, irritation or allergenic properties, discoloration or erosion of the teeth, the potential to alter the natural micro flora. Any of these properties may limit the drug candidate list for this route.

I. Organoleptic properties

The organoleptic properties of a drug or the delivery system may result in poor patient compliance or acceptance of the product. The detection of a bad taste would be detrimental to the success of the delivery system. This can be overcome through the formulation of a unidirectional delivery system which will prevent the release of the drug in to the oral cavity. The texture of the delivery system may also affect patient compliance or acceptability.

J. Toxicity to buccal mucosa

If a pharmacologically active material is to be presented to the mucosa over an extended period, there is the potential for an irritant or allergic response to the drug. It should be noted that the sensitization should not only be limited to the drug but also to the components of the delivery system which are also in intimate contact with the buccal mucosa. Again the toxic effects of excipients e.g.: penetration enhancers would be enhanced by the occlusive nature of the system and by extended contact times of the system in contact with the mucosa

K. Daily dose size

The buccal epithelium being an efficient barrier to drug penetration allows only small quantities of drug for penetration even over a period of a day. This means that an upper limit exists on daily delivery of drug. For example, realistically an unidirectional buccal drug delivery system would not cover an area of buccal mucosa larger than 2cm² and would be unlikely to be retained on the buccal mucosa for longer than 24 hours. The total amount of drug that could

be systematically delivered across buccal mucosa from a 2cm² system in one day has been estimated to be 20-50 mg (Robinson et al., 1987). Therefore, buccal drug delivery is suitable only for drugs whose daily dose is on the order of few mg. clearly the resultant plasma concentration of the drug will depend upon the clearance. It should be also noted that the physical size of the delivery system itself will also defined the amount of drug that can be incorporated into such a system.

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