Indo-Global Journal of Pharmaceutical Sciences, 2011, Vol 1., Issue 3: Page No. 223-233

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

A Review on Buccal Mucoadhesive Drug Delivery Systems

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Abstract: Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. In this review article the advantages and limitations related to the buccal drug delivery has also been discussed. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. Various bioadhesive dosages form such as Chewing gum, tablets, Patches, Hydrogel, Thiolated tablets are discussed in this review article. Lastly the absorption/permeation study and different dissolution testing methods for bioadhesive dosages forms have also been discussed.

Keywords: Buccal; Anatomy of Oral Mucosa; Mucoadhesive Polymer; Permeation; Dissolution.

INTRODUCTION

Adhesion [1] as a process, simply defined as the ‘‘fixing” of two surfaces to one another. There are many different terminological subsets of adhesion de-pending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed ‘‘bioadhesion”, Bioadhesion may be defined as the state in which two meterials,at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces. For drug delivery purposes, bioadhesion term implies the attachment of a drug carrier systems to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If the adhesive attachment is to a mucous coat, then the phenomenon is knows as mucoadhesion. Mucosal layer represents potential sites for the attachment of any bioadhesive systems because mucosal layer lines number of the body including the gastro intestinal tract, the urogenital tract, vaginal tract,the eye,ear,nose. The recent advances in the various mucoadhesive drug delivery systems oral transmucosal drug delivery gaining important than other mucoadhesive delivery systems like vaginal delivery, rectal delivery,nasal delivery, ocular delivery. The nasal cavity is a good site for systemic drug delivery. However, the potential irritation and the irreversible damage to the ciliary of the nasal cavity was found by continuous application of nasal dosages form, as well as the large intra and inter subject variability in mucous secretion in the nasal mucosa, could significantly affect drug absorption from this site. He Even though the rectal, vaginal. and ocular mucosa all offer poor patients acceptability associated with these sites renders them reserved foe local applications rather than systemic drug administration. On other hand oral cavity [2, 3] are highly acceptable because the mucosa is relatively permeable with a reach blood supply. Furthermore it’s also bypasses first pass effect and avoids pre systemic elimination in the GI tract.

The delivery of drug into oral mucosal cavity is classified into three categories:-

- Sublingual delivery- which is systemic delivery of drug through the mucosal membranes lining the floor of the mouth.
- Buccal delivery- which is drug administration through the mucosal membranes lining the cheeks.
- Local delivery- which is drug delivery into the oral cavity.

Structure and function of oral mucosal membrane:-

The oral mucosa is composed of an outermost layer called stratified squamous epithelium (fig 1) and below a basement membrane; a lamina propria followed by the sabmucosa as the inner most layer. . It also contains many sensory receptors including the taste receptors of the tongue. The blood epithelium is classified as nonkeratinized [4] tissues .It is penetrated by tall and conical shaped connective tissues .These tissues which are refferd to as lamina propria ,consist of colagen fibers a supporting layer of connective tissues ,blood vessel and smooth muscles.The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface [5]**.** Specialized glands producing components of the mucous layer may also be located beneath the epithelium. The moist surface of the tissue results from the mucus – a viscous, gelatinous secretion whose composition includes glycoproteins, lipids, inorganic salts, and up to 95% water. Mucus may be secreted either constantly or intermittently. The volume of secretion changes under the influence of external and internal factors. Mucin(Glycoprotines) are the most important components of mucus and it is also very responsible for gelatinous structure, cohesion, and antiadhesive properties .Mucin consist of three dimensional network with large number of loops.The main functions of the mucus are to protect and lubricate the supporting epithelial layer. In the gastrointestinal tract, the mucus facilitates the movement of food boluses along the digestive canal and protects the epithelium from harmful influences due to intrinsic peristaltic movements and proteolytic enzymes. The components of the mucus secreted onto the surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells, protecting the epithelium from damage and facilitating the movement of the eyelids.

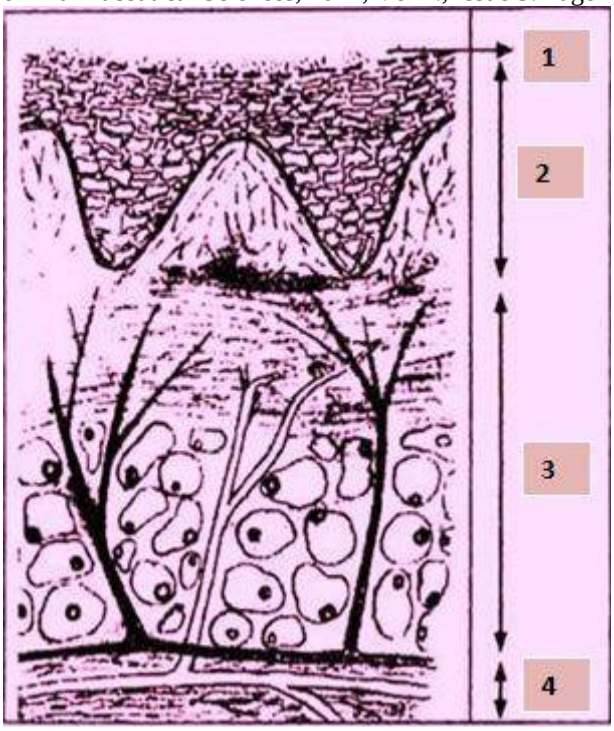

Figure 1 Structure of the mucosa of the Oral Cavity [2]: (1) Mucus layer; (2) Epithelium; (3) Connective tissue(lamina propria); (4) Smooth muscles layer(kharenko et al,2009)

Permeability:-

It is estimated that the permeability of the buccal mucosa is 4-4000 times grater than the skin [6]. There are considerable differences in permeability between different region of the oral cavity because of diverse structures and functions of the different oral mucosa. . In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal [7]**.** This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.The permeability barrier property of the oral mucosa is predominantly due to intracellular materials derived from the so called – "membrane coating granules"(MCGS). Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, carrier mediated transport has been reported to have a small role.In buccal mucosa two routes of passive transport are found one involves the transport of compounds through the intercellular space between the cells(paracellular) and other involves passage into and across the cells(transcellular). Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Some proteolytic enzyme has been found in the buccal epithelium.

Environment:-

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Role of Saliva [8]

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

Role of Mucus

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

Buccal Drug Delivery and Mucoadhesivity [9]:-

For the development of these Buccal drug delivery systems, mucoadhesion of the device is a key element. For proper and good mucoadhesion mucoadhesive polymer have been utilized in many different dosages form such as tablets, patches, tapes, films, semisolids and powders. Many studies showed that addition of various polymers to drug delivery systems such as gums, increased the duration of attachment of the formulations to the mucous surface and and also increased the efficacy. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as –

- Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impuri-ties.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should possess peel, tensile and shear strengths at the bioadhesive range.

Classification of some mucoadhesive polymers [10] are listed in **Table no- I.**

Table 1 Classification of mucoadhesive polymers [10]

Types	Example
Natural and modified natural polymers	Agarose, Chitosan, Gelatin, Pectin, Sodium alginate, CMC, Na CMC, HPC, HPMC, Methyl cellulose.
Synthetic	Carbopol,Polycarbpphil, Polyacrilic acid, Polyacrylates.
Cationic and anionic	Aminodextran, Chitosan, Chitosan –EDTA, Dimethylaminoethyldextran.

There are some Novel Mucoadhesive Polymers under development **,** these include Copolymer of PAA and PEG monoethylether monomethacrylate, PAA complexed with PEGylated drug conjugate, Hydrophilic pressure-sensitive adhesives (PSAs), AB block copolymer of oligo(methyl methacrylate) and PAA , Polymers with thiol groups (cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator.

Factors affecting buccal drug delivery [11]:

The permeability of drug decreases with increase the molecular size. Generally small molecule show rapid transport across the mucosa. For hydrophilic macromolecules such as peptides, absorption enhancers 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. Drug in no ionized form can easily cross -lipoidal membranes in significant amounts. The more lipids soluble a compound is, the higher its permeability. The permeabilities for these compounds are direct functions of their oil-water partition coefficients. For determine the absorption potential of a drug partition coefficients is a very important tool. In addition of hydroxyl, carboxyl, or amino groups in a drug it will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. The partition coefficient also related with the pH of the drug absorption site. With increasing pH, the partition coefficient of acidic drugs decreases, while that of basic drugs increases.

In short it can say that the lipid solubility of drugs is an important factor in Transmucosal Drug Delivery system. Along with the drugs which are selected for Transmucosal Drug Delivery system the lipid solubility of the drug is very important physiochemical properties, including size and pKa that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentrations. The drug must resist, or be protected by salivary and tissue enzymes that could cause inactivation. Additionally, the drug and adhesive materials must not damage the teeth, oral cavity, or surrounding tissues (e.g. by keratinolysis, discoloration, and irritation).

Methods to increase drug delivery via buccal route:-

- **Absorption enhancer [12]:**

The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

Mechanism [13]:

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

• 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.

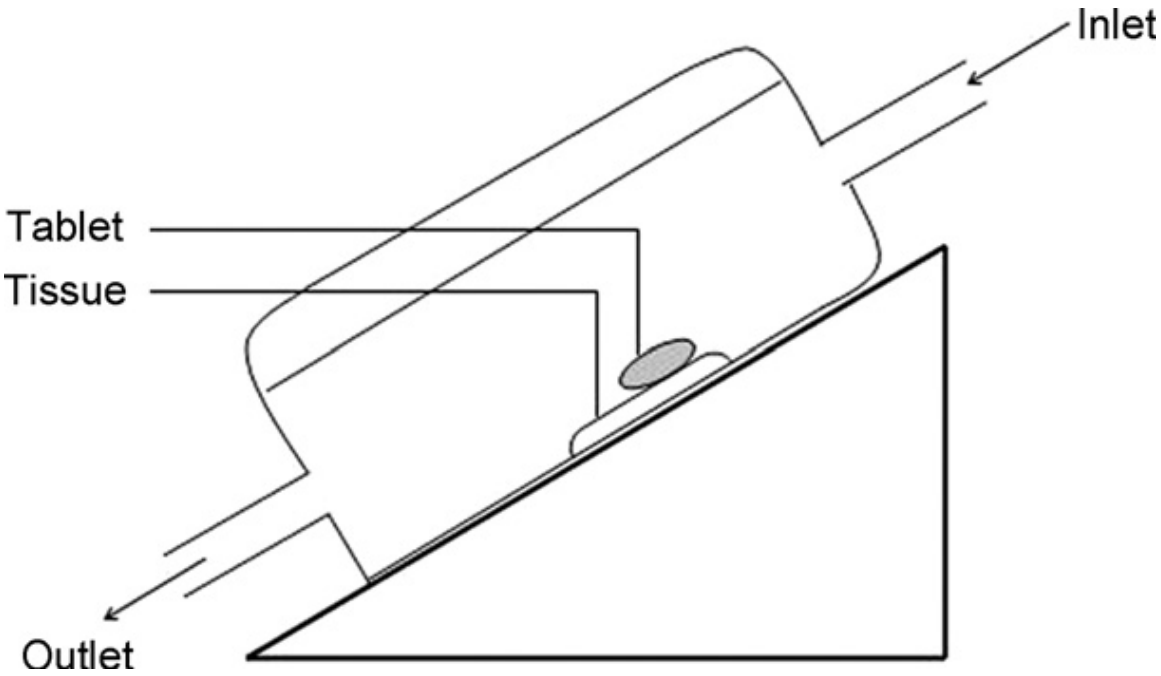

Figure 2 Schematic drawing of the dissolution apparatus used by Mumtaz and Ch'ng (1995) for studying the dissolution of buccal tablets.

• 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.

• Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

• 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.

• Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption.

Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favorable properties such as biodegradability, biocompatibility and antifungal/antimicrobial properties in addition to its potential bioadhesion and absorption enhancer.

List of some permeation enhancer [14] are listed in **Table no-II.**

Table 2 List of Permeation Enhancers [14]

Sr. no	Permeation Enhancers	Sr. no	Permeation Enhancers
1	2,3-Lauryl ether	12	Phosphatidylcholine
2	Aprotinin	13	Polyoxyethylene
3	Azone	14	Polysorbate 80
4	Benzalkonium chloride	15	Polyoxyethylene
5	Cetylpyridinium chloride	16	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	17	Sodium EDTA
7	Cyclodextrin	18	Sodium glycocholate
8	Dextran sulfate	19	Sodium glycodeoxycholate
9	Glycol	20	Sodium lauryl sulfate
10	Lauric acid	21	Sodium salicylate
11	Lauric acid/Propylene	22	Sodium taurocholate

Prodrug:-[11]

Hussain et al administrated nalbuphine and naloxone bitter drugs to dogs via buccal mucosa then it is caused excess salivation and swallowing.As a result ,the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds.

pH:-[11]

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

Patch design [11]

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

Different bioadhesive dosages form:-

- **Buccal chewing gum:-**

Some commercial products of buccal chewing gum are available in the market [15] like 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.

- **Bioadhesive hydrogel tablets:-**

Bioadhesive hydrogel tablets [16] are similar to conventional tablets and the bioadhesive tablet easily can adhere to the buccal mucosa and are prepared by wet granulation, dry granulation, or direct compression processes. Drug is released upon the hydration and adhesion of the device. Buccal tablets should be fabricated and optimized for swelling behavior and drug release to ensure a prolonged period of bioadhesion and sustained or controlled release. Generally, the tablets are formulated with flat punches with dimensions less than 10 mm in diameter and 2 mm thick to aid in establishing intimate contact with buccal mucosa and reduce their interference with normal activities. The excipients which is used for preparation of bioadhesive tablets are water soluble such as high molecular weight polyethylene glycols and manitol because the tablets contain some mucoadhesive component.A single-layer buccal tablet of triamcinolone acetonide, Aftac, is used in the treatment of aphthous ulcers [17].

- **Bilayer buccoadhesive tablets:-**

Specialized tablet formulations with two layers buccoadhesive tablets are being designed to achive biphasic drug release and minimize drug leakage into buccal cavity, Iga and Ogawa formulated a slowly disintegrating gingival tablet for sustained release of isosorbide dinitrate and nitroglycerin. Flatfaced tablets 8 mm in diameter were prepared using lactose and hydroxypropyl cellulose. In order to control the deformation of the tablet caused by softening and mouth movements, they were covered with a bioadhesive containing polyethylene film with a 5 mm hole in the center of the top surface. When evaluated in dogs, these tablets remained in position for about 10 hours, whereas plain tablets disintegrated within 3–6 hours. Constant blood drug levels were maintained for about 10 hours from covered tablets. It has been shown that the rate of tablet disintegration, which in turn refers the buccal residence and the drug blood levels, can be controlled by changing the size of hole. A size larger than 50% of the top surface of tablets is suggested to obtain a constant disintegration rate.

- **Biobadhesive Spray:**

Buccoadhesive sprays are gaining important over other dosage forms because of flexibility, comfort, high surface area and availability of drug in solution form.The first FDA-approved (1996) formulation was developed by fentanyl Oralet ™ to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children. In 2002, the FDA approved Subutex (buprenorphine) for initiating treatment of opioid dependence (addiction to opioid drugs, including heroin and opioid analgesics) and Suboxone (buprenorphine and naloxone) for continuing treatment of addicts. In 2005, Oral-lyn buccal spray was approved for commercial marketing and sales in Ecuador .

- **Thiolated tablet:**

Thiolated tablet formulated with thiolated polymers which is also called as a thiomers.These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric back bone. These polymers are capable to forming disulphide bonds with cystine rich subdomains of mucous glycoprotein covering mucosal membrane[18]. The bridging structure is most commonly used in biological systems to utilize the binding of drug on the mucosal membrane. Thiomers are capable of forming intra- and inter chain disulphide bonds within the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix tablets. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhe-sive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process. They also exhibit permeation enhancing effects for the paracellular uptake of drugs based on a glutathione-mediated opening process of the tight junctions. So for those features matrix-tablets based on thiolated polymer epresent a promising type of buccal drug delivery systems.

Evaluation of novel buccal drug delivery systems:-

1. Permeation studies:-

Buccal permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. in vitro and/or in vivo both methods are involved to determine the buccal permeation profile and absorption kinetics of the drug.

A. In vitro methods:-

For examine drug transport the in vitro studies are carried out with animal buccal tissues. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments. Buccal cell cultures have also been suggested as useful in vitro models for buccal drug permeation and metabolism[19]. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled [20].

B. In vivo Methods:-

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled (. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs[21]. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa). For study the permeation characteristics of buccal drug delivery systems special attention is require to choice of experimental animal species for such experiments. Many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue but it is hard to

isolate the desired non-keratinized region due to sudden transition to keratinized tissue at the mucosal margins. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys,dogs , and pigs which are having non-keratinized tissue.

2. Dissolution and drug release test:-

Drug release studies for buccal tablets are normally performed using **USP apparatus** How ever some authors are develop special apparatus or methods for drug release study of buccal tablets.

Ikinci et al. used an alternative method to study the release of nicotine from buccal tablets. They used modified Franz diffusion cells for this purpose. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH 7.4) 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 which was placed on top of a bovine buccal mucosa as membrane [22].

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- II. 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" [23]

Limitations of Buccal Drug Administration (3):-

Drug administration via the buccal mucosa has certain limitations -

- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be adminis-tered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and loses the ad-vantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slip-pery surface and structural integrity of the formu-lation may get disrupted by the swelling and hy-dration of the bioadhesive polymers.

CONCLUSION

Buccal region provides a convenient route of administration for both local and systemic drug actions. Buccal adhesive systems offer innumerable advantages in term of accessibility, administration and withdrawal, retentivity, low enzyme activity, economy and high patients compliance. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Currently solid dosage forms, liquids, spray 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.

ACKNOWLEDGEMENT

The authors are express sincere thanks to honorable Chairman and worthy MD Madam of Sri Sai College of Pharmacy for providing every facility for literature review and other needs for this article.

The authors are also thankful to Principal and all the teaching and non teaching staff of Sri Sai College of Pharmacy for their valuable suggestion, assistance and encouragement.

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