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BUCCAL BIOADHESIVE DRUG DELIVERY –A PROMISING OPTION FOR CONVENTIONAL THERAPY

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ABSTRACT
Since, the last four decades, the concept of mucoadhesion has achieved a much valuable interest in the various fields of pharmaceutics. There are many advantages of mucoadhesive buccal drug delivery system that made this a novel drug delivery system for the local as well as systemic delivery of various drugs. The main advantage of this drug delivery system is that it prolongs the residence time of the dosage form at the site of application. Due to the high blood supply and relatively high permeability of the buccal mucosa, the buccal cavity is the best option for both local as well as systemic delivery of various drugs. This review concludes that the mucoadhesive drug delivery system was found to be a better alternative to the conventional oral route. It is a unique alternative to conventional drugs by virtue of its ability in overcoming hepatic metabolism, reduction in dose, frequencies and enhancing bioavailability. This delivery system will shows a controlled release of drug; ease of application and the formulation and evaluation of such systems does not have any complication. So we can expect that the mucoadhesive system may be one of the important dosage form in the future pharmaceutical and health care sector.

KEYWORDS: Mucoadhesion; Permeation enhancers; Bioadhesive polymer.

INTRODUCTION[1]
Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first-pass effect. The stratified squamous epithelium supported by a connective tissue lamina propria, which is present in buccal mucosa, was targeted as a site for drug delivery several years ago. Problems accompanied with oral route of administration such as extensive metabolism by liver, drug degradation in gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route. The buccal route appears to offer a number of advantages, like good accessibility, robustness of the epithelium, usage of the dosage form in accordance with need, and comparatively less susceptibility to enzymatic activity. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets adhesive gels and adhesive patches. The permeation of hydrophilic drug through membrane is one of the major limiting factors for the development of bioadhesive buccal delivery devices.[2] The epithelium that lines the buccal mucosa is a main barrier for the absorption of drugs. In order to improve buccal absorption, several approaches have been introduced. Increased permeation of the drug through the buccal membrane and prevention of the drug degradation by enzymes was achieved by changing the physicochemical properties of the drug. Alternatively, improving the bioadhesion and release characteristics of buccal delivery devices increases the amount of drug available for absorption. The incorporation of absorption enhancers to the buccal formulation is one interesting approach. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Different types of potential permeation enhancers have been studied for buccal route to increase the penetration of drugs. The complexation of steroidal hormones with cyclodextrins was not effective in increasing the permeation through buccal route, whereas condensation products of cyclodextrin with propylene oxide or epichlorohydrins were able to form complexes with estradiol, testosterone, and progesterone, thereby enhancing absorption through the buccal membrane in humans. The delivery of hydrophilic macromolecular drugs via buccal membrane was made possible by incorporation of absorption or permeation enhancers, which could reduce barrier properties of the buccal epithelium.[3,4]

Advantages[5]
- Buccal drug delivery system has following advantages over conventional drug delivery systems.
- Persists the residence time of the dosage form at the absorption site, hence rises the bioavailability.

- Outstanding availability, rapid onset of action possible.
- Fast absorption because of huge blood supply and good perfusion rates.
- An alternative to oral route, whereby the drug is secure from degradation in the acidic environment of the GIT.
- Preferable patient acquiescence.[6]
- Likewise, rapid cellular recuperating and healing of the local site.
- In this, there is reduced dosing frequency.
- It required shorter treatment period.
- Developed safety margin of high strength drugs due to better control of plasma levels.
- Extreme utilization of drug facilitating reduction in total amount of drug administered.

ANATOMY OF ORAL MUCOSA[6]

1) *Structure:* The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer can be seen in figure. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides.

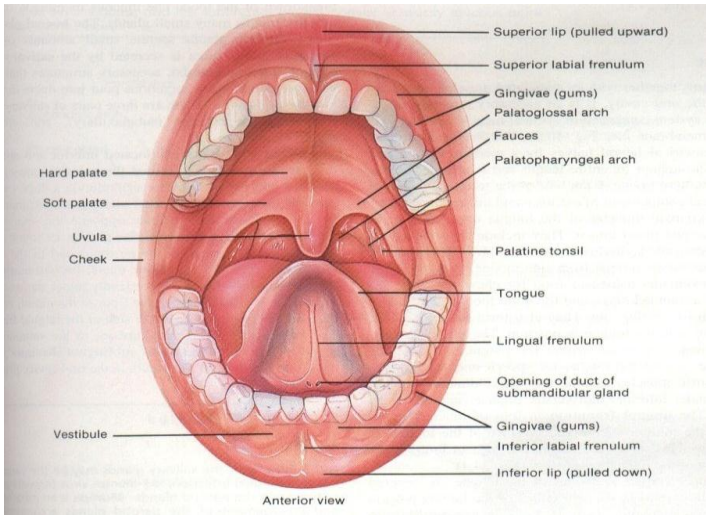

Fig no. 1: Structure of oral cavity.

DRUG TRANSPORT MECHANISM

The main mechanisms involved for the penetration of various substances include simple diffusion (paracellular and transcellular), carrier mediated transport and endocytosis. 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.[9]

i. Passive diffusion

a. Transcellular or intracellular route

b. Paracellular or intercellular route

ii. Carrier mediated transport

iii. 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.

The basic drug transport mechanism for the oral epithelium is the same as for other epithelia in the body. There are two major routes involved: the transcellular route (directly through the cells, or intracellularly) and the paracellular route (through the spaces between the cells, or intercellularly). These routes are illustrated in Figure in general, for many drugs, permeation across the buccal epithelium is thought to be through the

paracellular route by passive diffusion. This pathway is favored especially by hydrophilic drugs such as peptides/proteins which dissolve more readily in the aqueous fluids filling the intercellular spaces.

The transcellular pathway, in contrast, involves drugs permeating the cell membrane and going through the cell to then penetrate the opposite cell membrane and into the next cell, and so on, as shown in Figure. An example of a drug known to penetrate via the transcellular pathway is fentanyl. It is feasible that some drugs may penetrate via both pathways and this may occur with drugs that have approximately balanced hydrophobic and hydrophilic properties, with a slight predominance of hydrophobicity. Such drugs will usually penetrate the fastest. Most often, however, one pathway predominates.

For the paracellular pathway, the drug moves in a tortuous fashion around the cells, thus this is a longer pathway. It is important to make the following distinction: while the shortest pathway that the drug may take around the cells is longer than the transcellular pathway, there is also a greater tendency, in paracellular permeation, for the drug to diffuse laterally over a wider area of the mucosa. This may help to explain the longer lead time (the time until steady-state absorption occurs) often observed with drugs that are known to be absorbed by the paracellular pathway. Caffeine is an example of a drug absorbed via the paracellular route and it is used as a marker of paracellular absorption. While the transcellular route is more direct, the drug has to traverse the lipophilic cell membrane, then the hydrophilic interior of the cell before passing through two cell membranes to reach the cytoplasm of the next cell. Therefore, the predominantly hydrophobic drug should have some hydrophilicity if absorption into the systemic circulation is required. If the drug is extremely hydrophobic, there would be a tendency for it to be retained in the more hydrophobic components of the mucosal tissue, such as the cell membranes of the superficial epithelial layers, and not reach the blood circulation in significant amounts. This, of course, would be a desirable feature for a topical effect (e.g., anti-inflammatory action) but not if a systemic effect is desired.[11]

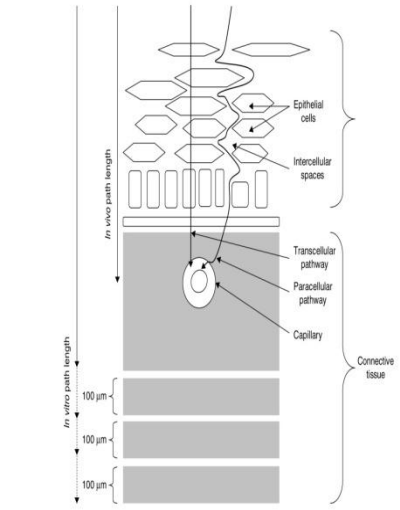

Figure Diagrammatic representation of pathways for drug delivery through the oral cavity mucosa showing the direct transcellular and tortuous paracellular pathways; and the *in vivo*, and longer *in vitro*, path lengths.

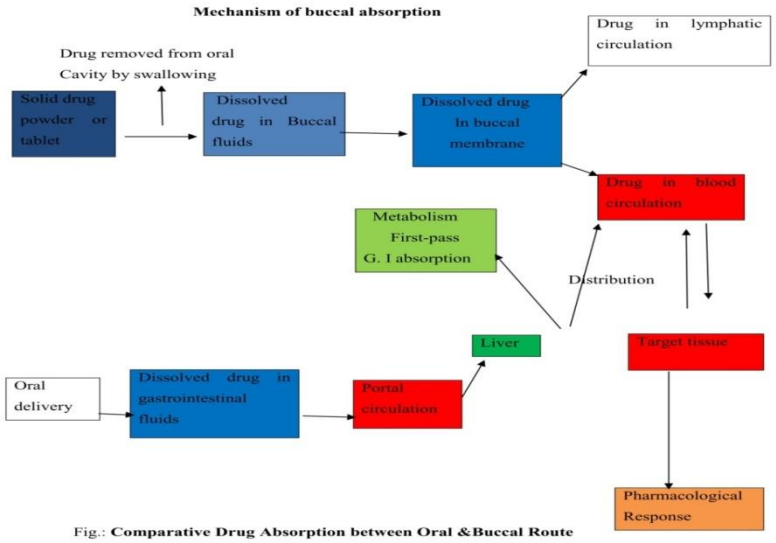

Fig.: **Comparative Drug Absorption between Oral &Buccal Route**

Bioadhesion

'Bioadhesive' is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for persistent period of time. Bioadhesive are classified into three categories.

- Bioadhesion among biological layers without involvement of artificial materials. e.g. Cell diffusion and cell aggregation
- Bioadhesion can be showed by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.
- Adhesion of artificial substances to biological substrate such as adhesion of polymer to soft tissue or skin.[12]

Mechanism of bioadhesion

For bio-adhesion to occur, three steps take place:

- A close contact among a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.
- Penetration of the bio-adhesive into the tissue takes place.
- Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle.

The bonding between the mucus and the biological substance occurs mainly through both physical and chemical interactions results from expansion of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

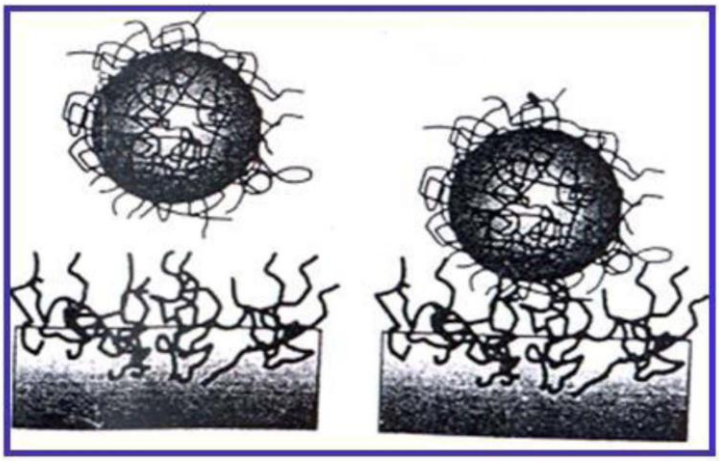

Figure no 4: Inter penetration of bioadhesive and mucus polymer chain.

Bioadhesive Polymers

The first step in the development of buccal dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in

matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs. Bioadhesive polymers are by far the most diverse class and they have considerable benefits upon patient health care and treatment. The drug is released into the mucous membrane by means of rate controlling layer or core layer. A Bioadhesive polymer which adheres to the mucin/epithelial surface is effective and lead to significant improvement in the oral drug delivery.

An ideal polymer for buccoadhesive drug delivery systems should have following characteristics.

- It should be inert and compatible with the environment.
- The polymer and its degradation products should benon-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.
- It should allow easy incorporation of drug in to the formulation.

Table no 1: Mucoadhesive Polymers used in the oral cavity.

Criteria	Categories	Examples
Source	Semi natural/ Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar gum, xanthan, gellan, carrageenan, pectin and sodium alginate).
	Synthetic	Cellulose derivatives: [CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC,MC.]
		Poly (acrylic acid)-based polymers: [CP, PC, PAA, polyacrylates, poly (methyl vinyl ether-co-methacrylic acid), poly (2- hydroxy ethyl methacrylate), poly (acrylic acidco-ethyl hexyl acrylate), poly (methacrylate), poly (isobutyl-cyanoacrylate), copolymer of acrylic acid and PEG].
		Others: polyoxyethylene, PVA, PVP, thiolated Polymers.
Aqueous solubility	Water soluble	CP, HEC, HPC, HPMC (cold water), PAA, NaCMC, sodium alginate.
	Water insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Aminodextran, Chitosan, (DEAE)- dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, xanthan gum.
	Non-ionic	Hydroxy ethyl starch, HPC, poly(ethylene oxide), PVA,
Potential	Covalent	PVP, scleroglucan
	Hydrogen bond	Cyanoacrylate
Bioadhesive forces	Electrostatic interaction	Acrylates [hydroxylatedmethacrylate,poly(methacrylic acid)], CP, PC, PVA, Chitosan

Backing Membrane

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.

Penetration Enhancers

Penetration enhancer's are used in buccal formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are Sodium lauryl sulphate, CPC, Polysorbate 80, Laureth 9, Sodium Fusidate, Sodium glycocholate, Dimethyl formamide etc.

Table no. 2: Examples of permeation enhancers with mechanism.

Category	Examples	Mechanism
Surfactants and Bile Salts	Surfactants and Bile Salts Sodium dodecyl sulphate Sodium lauryl sulphate Polysorbate 80	Acting on the components at tight junctions Increasing the fluidity of lipid bilayer membrane;
Fatty Acids	Oleic acid, Cod liver oil, Capric acid, Lauric acid	Increasing the fluidity of lipid bilayer membrane.
Polymers and Polymer Derivatives	ChitosanTrimethyl chitosanChitosan-4-thiobutylamide	Increasing the fluidity of lipid bilayer membrane; Increased retention of drug at mucosal surface.
Others	Ethanol, Azone, Octisalate, Padimate, Menthol	Acting on the components at tight junctions; Increasing the fluidity of lipid bilayer membrane

APPROACHES OF BUCCAL DRUG DELIVERY SYSTEM

1) Non-attached drug delivery systems

This includes Fast dissolving tablet dosage forms, Chewing gum formulations and Micro-porous hollow fibers.

2) Bio-adhesive drug delivery systems

a) Solid buccal adhesive dosage forms.
b) Semi solid buccal adhesive dosage forms.
c) Liquid buccal adhesive dosage forms.

3) Liposome

4) Delivery of proteins and peptides

1) Non-attached drug delivery systems

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

2) Bio-adhesive drug delivery systems

a) Solid buccal adhesive dosage forms

- **Buccal tablet:** 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.[16]
- **Microspheres, microcapsules, micro particles:** The local irritation caused by microspheres 54, 55 or microcapsules 56 or micro particles57 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.
- **Lozenges:** Bioadhesive lozenge offers prolonged drug release with improved patient compliance compared to Conventional lozenges, thus avoiding multiple daily doses.

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.[17]
- **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 desire 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 posses 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.[18]

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.

3) 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.

4) 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.

Table: Commercially available oral mucosal drug delivery systems.

Drug	Mucosal site	Dosage form	Product name	Manufacturer
Fentanyl citrate	Buccal	Lozenge	Actiq	Cephalon
	Buccal	Tablet	Fentora	Cephalon
Buprenorphine hydrochloride	Buccal	Tablet	Subutex	Reckitt Benckiser
Buprenorphine hydrochloride-naloxone HCl	Buccal	Tablet	Suboxane	Reckitt Benckiser
Proclorperazine	Buccal	Tablet	Buccastem	Reckitt Benckiser
Triamcinalone	Buccal	Tablet	Aphtac	Teijin Ltd
Testosterone buccal	Buccal	Tablet	Striant SR	Columbia Pharmaceuticals
Nitroglycerine	Sublingual/ Buccal	Tablet, Spray	Nitrostat	W Lambert-P Davis-Pfizer Pharmaceuticals
Glyceryl trinitrate	Buccal	Spray	Nitromist	NovaDel
	Buccal	Tablet	Suscard	Forest Laboratories
Nicotine	Buccal	Chewing gum	Nicorette	GSK Consumer Health
	Buccal	Lozenge	Nicotinelle	Novartis Consumer Health
Miconazole		Tablet	Loramyc	BioAlliance Pharma SA
Cannabis-derived		Spray	Sativex	GW Pharmaceuticals, PLC

Rationalist approach of MBDDS towards different diseases

Cardio vascular disease

Hypertension, one of the major cardiovascular diseases, needs a lifelong therapy to remain under control. Most of the antihypertensive drugs like carvedilol, metoprolol, propranolol, isosorbide mononitrate etc. have low oral bioavailability and smaller half-life. Two main reasons for low bioavailability are poor aqueous solubility and high first pass metabolism. The buccal mucoadhesive route of drug delivery provides direct access to the systemic circulation through the internal jugular vein by passing the first pass metabolism, leading to high bioavailability. The dose of carvedilol, a model antihypertensive drug, is 25 mg twice a day; however, a lower effective dose is reported to be approximately 3.125 mg. Thus, by increasing the contact time and avoiding the first pass metabolism, a lower amount of drug can effectively produce the normal dose effect. Again, by sustaining the drug release, the frequent administration of drug can be avoided, thereby increasing the patient compliance.[30]

Fungal/microbial infections

Oral candidiasis is an opportunistic fungal infection caused by Candida albicans. These yeast infections are usually treated locally by application of gels or suspensions. Release of drugs from these preparations involves an initial burst of activity whose level rapidly declines to sub therapeutic concentrations. Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis. The oral dose of fluconazole for the treatment of oral candidiasis (100 mg/day for 1 or 2 weeks) results in notable side effects varying from headache, nausea to liver dysfunction, and hepatic failure. Furthermore, oral fluconazole is reported to interact with a number of medications, including oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. The pathogenic yeasts in oral candidiasis are usually detected in the superficial layers of the oral mucosa. Thus, the effectiveness of the systemic fluconazole may be partially topical through its concentration in oral fluids. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of MBDDS containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a long time.[24]

Migraine

Migraines are thought to occur when certain blood vessels in the brain become swollen (dilated). Drugs used for the treatment include the “triptan” group, comprising

of sumatriptan, zolmitriptan, and rizatriptan. These drugs work by helping blood vessels in the brain to return to normal size. It may also block pain signals in the brain. The model drug, sumatriptan is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously as two 6-mg doses over 24 hours. Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution and inability of self-administration for injectables, respectively.[29]

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.

Nausea and vomiting

Ondansetron HCl, chosen as a model drug for treating postoperative nausea and vomiting associated with emetogenic cancer chemotherapy, possesses certain characteristics that a drug should have to get absorbed through buccal mucosa viz., biphasic solubility and low molecular weight. Moreover, the primary route of ondansetron clearance is by hepatic phase I metabolism, so its bioavailability may be improved when delivered through the buccal mucosal route. Patients may have frequent vomiting following chemotherapy and they may be unable to swallow a tablet to prevent vomiting. It justifies the need to develop a buccal patch/film of ondansetron hydrochloride, which increases patient compliance. Its bioavailability when administered by oral route is only 50% to 60% and its dose is low i.e., 4-8 mg; hence, it can be conveniently loaded onto a patch.[28]

Cardio vascular diseases

Carvedilol is a non-selective beta-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. Yamsani et al. proposed the utilization of carvedilol mucoadhesive tablets for the treatment of hypertension. In this hydrophilic polymer formulation, hydroxypropyl methylcellulose (HPMC K4M and K15M) and Carbopol 934 (CP 934) were used to obtain controlled and zero order release. Studies revealed that increasing the concentration of the polymer in the formulations showed a sustained effect on carvedilol release. The rapidly hydrating polymer dominated in controlling the release of carvedilol from the buccal tablets. Buccoadhesive patch of PRO-HCl was developed by the same workers using the hydrophobic polymer Eudragit L-100 as the base matrix. A stability study of optimized Eudragit patches was done in natural human saliva; it was found that both drug and buccal patches were stable in human saliva.[27]

Antimicrobial therapy

The clinical treatment of oral candidosis (a common pathological condition of the oral cavity) using conventional pharmaceutical dosage forms-such as solutions, gels, suspensions, and mouthwashes-is usually not very effective, mainly because drugs are quickly removed from the oral cavity. These tablets released nystatin quickly from the lactose layer and then in a sustained way, during approximately 6 hours, from the polymeric layer. Chlorhexidine diacetate was used by Giunchedi et al. to formulate buccal tablets based on chitosan microspheres.

Anti-inflammatory therapy

Inflammatory processes are one of the major reasons for oral cavity diseases. This problem is managed with topical administration of various nonsteroidal, anti inflammatory drugs, like flurbiprofen, flufenamic acid, ibuprofen etc. Designed sustained-release mucoadhesive bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for topical administration of flurbiprofen in the oral cavity. The optimized formulation, loaded with 20 mg of the drug, showed the best results, producing good anti-inflammatory sustained release in the buccal cavity for 12 hours and thus a reduction in daily drug dosage (40 mg /vs. 70 mg). This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.[26]

Antiemetics

Ondansetron hydrochloride is a 5HT3 serotonin antagonist used in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. As administering drug by buccal route avoids hepatic first-pass metabolism, delivery of ondansetron to the systemic circulation via the buccal route would improve its bioavailability. The stability of drug in the optimized adhesive tablet was tested for 6 h in natural human saliva; both the drug and device were found to be stable in natural human saliva.

Muscle relaxants

Tizanidine hydrochloride is an imidazoline derivative which acts as agonist on centrally located α2 receptors and this leads to myotonolytic effects on skeletal muscle. Shanker et al. formulated and evaluated bioadhesive buccal tablets of tizanidine using bioadhesive polymers such as HPMC K4M, SCMC alone, and a combination of these two polymers, in an attempt to avoid first-pass effect and provide for prolonged release of the drug The degree of swelling indicated that the rate of swelling is directly proportional to SCMC content and inversely proportional to HPMC K4M content.

Protein and hormone delivery

The delivery of peptide drugs across the buccal mucosa is more convenient and safer than other delivery approaches. It is shown that the buccal administration of drugs has some advantages, such as low enzymatic activity compared with the gastro intestinal track, and tolerance to potential sensitizers. Insulin was used by Cui

et al. as a model protein and its release behavior from bilaminated films was evaluated. The insulin loaded bilaminated film showed a pronounced hypoglycemic effect following buccal administration to healthy rats, achieving a 17% pharmacological availability compared.[25]

FUTURE CHALLENGES AND OPPORTUNITIES

Novel drug delivery systems are becoming one of the most important fields in the modern pharmaceutical formulation technology. Several techniques are employed to design the sustained or controlled drug delivery systems. Studies on mucoadhesive systems have focused on a broad array of aspects. It is a growth area whose goal is the development of new devices and more "intelligent" polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals. The main advantages of the buccal route of administration over the traditional per oral route are that drug degradation in the stomach is avoided, first-pass metabolism is avoided, and therapeutic drug levels of drug can be achieved rapidly. Clearly these advantages are presently clinically relevant for only a limited number of drugs. However, with the recent developments of new formulation types, such as mucoadhesive preparations and the use of peptides as drugs, this number may increase in the future. Mucoadhesive drug delivery systems available in the market include attach tablet (Triamcinolone acetonide), suradrin tablet (Nitroglycerin), Buccostem tablet (prochlormperazine maleate). Salcoat powder sprays (Beclomethazone dipropionate). Rhinocort powder spray (Beclomethazone Dipropionate) and sucralfate (Aluminum hydroxide). Though there are only a few mucoadhesive formulations available currently, it can be concluded that drug delivery using mucoadhesive formulations offers a great potential both for systemic and local use in the near future.[21]

Mucoadhesive drug delivery systems, are gaining popularity day by day in the global pharma industry and a burning area of further research and development. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion.[22]

The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery system (CDDS). There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the everevolving drug delivery arena.

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Novel buccal delivery such as soluble thin films, mucoadhesive films and rapid mist spray offers newer route of delivery for the generics that has lesser patient's compliances. This report will provide detailed analysis on buccal delivery systems in broader pharma market in finding companies and technologies and complexities involved in developing this unique high potential delivery system.[23]

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. 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. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

This review concludes that the mucoadhesive drug delivery system was found to be a better alternative to the conventional oral route. It is a unique alternative to conventional drugs by virtue of its ability in overcoming hepatic metabolism, reduction in dose, frequencies and enhancing bioavailability. This delivery system will shows a controlled release of drug; ease of application and the formulation and evaluation of such systems does not have any complication. So we can expect that the mucoadhesive system may be one of the important dosage form in the future pharmaceutical and health care sector.

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