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A VIEW ON BUCCAL DRUG DELIVERY

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ABSTRACT

Oral cavity is the one of the easiest sites for the delivery of the drugs. By the oral drug delivery system, it is possible to gain more information about the mucosal and transmucosal drug delivery. The main aim is to achieve site specific drug delivery. To overcome this mucoadhesive, enzyme inhibitors and penetration enhancers are employed. Here, a brief description of advantages and limitation of buccal drug delivery, mechanism of drug permeation are presented.

KEYWORDS: Buccal drug delivery, mucoadhesion, permeation enhancers, transmucosal membrane.

INTRODUCTION

In the past pharmaceutical dosage forms like tablets, pills, capsules, ointments and liquids were used for the treatments of acute or chronic diseases. But nowadays these conventional dosage forms are replaced by controlled release pharmaceutical products. They have been used to achieve controlled release of drug over a prolonged period of time. This helps us to reduce adverse drug reaction which leads to increase

in bioavailability of the product. Novel drug delivery is a combination of innovative development, novel methodology formulations, and new technology for the release of drug into the body. Nowadays, Novel drug delivery widely contributes to the development of pharmaceutical industries. They aim at delivering the therapeutic drug at the appropriate site of the body thereby maintaining plasma drug concentration of drug. It results in the improved patient compliance as frequent dosing is not required and due to minimum drug toxicity. Some carriers are used for incorporate the drug for targeted drug delivery. These carriers protect the drugs from physical and chemical degradation during its administration. These positive features of novel drug delivery increase its demand.

Buccal drug delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity.[1] One of the most commonly used routes of administration is oral route because by the biochemical and physiological aspects of absorption and metabolism, most of the drugs cannot be administered through conventional oral route since after administration, drugs are exposed to pre systemic clearance this leads to lack of absorption and bioavailability.[2] Various limitations in the parenteral delivery and oral availability encouraged the use of alternative routes of drug delivery.[3] In comparison various transmucosal routes, buccal mucosa has an easy access due to smooth muscles and immobile mucosa. It is suitable for the administration of controlled release dosage form. Accidental ingestion through oral route can cause choking, especially in children, the elderly and patients with dysphagia, while swallowing of saliva may impair the biological activity of medication.

The protective buccal epithelial membrane consisting of flexible non keratinized mucosal surface lining the soft palate, ventral surface of the tongue, sublingual mucosa, floor of oral cavity, inner lips, buccal pouch, keratinized mucosa. Due to poor absorption hydrophilic and enzyme susceptible proteins and peptides cannot be administered through oral route[3]. So an alternative buccal route is preferred. Straight approach to the systemic circulation through the internal jugular vein avoids acid hydrolysis in the GIT and bypasses the drug from hepatic first pass metabolism leading to high bioavailability. In addition to this fast cellular recovery of the buccal mucosa is another benefit of this route.[4] The total area of membrane available for drug absorption is 170 cm. Rapid dilution of drug takes place due to spontaneous secretion of saliva. The amount of drug administered is absorbed into systemic circulation in its unchanged form from its site of administration called systemic availability.[5]

The main reasons for poor availability are.

- Destruction of drug by gastric acid
- Modification of drug by metabolic enzyme before entering into systemic circulation.
- Organs involved in degradation of drug are gut wall, liver, and lungs. This is known as first pass metabolism.
- The drugs that undergo first pass metabolism are propranolol, verapamil, methyldopa, imipramine.
- Liver is responsible for such metabolism as blood drawn from gut via the portal vein and passes through liver before its entry into systemic circulation.
- As the drugs into systemic circulation, it is distribution into other organs.
- Liver receives approximately 20 % of cardiac output which protect the drug from metabolizing organ.
- Pre -systemic elimination can be achieved by choosing the alternative route of administration.
- As the blood drains from the oral cavity enters into the systemic circulation through internal jugular vein, oral administration by buccal route helps to improve the bioavailability.

Anatomy and Physiology of Buccal Cavity

According to different areas of the epithelium, oral cavity, light microscopy shows a number of diverse patterns of maturation in the epithelium of the human oral mucosa. The masticatory mucosa, mucous secretory region and specialized mucosa are three distinctly different layers that make up the oral mucosa. The epithelium that lines the mouth cavity is supported by connective tissues, and beneath it is the supporting basement membrane. The buccal mucosa is shown the various cell layers. The soft palate mucosa, ventral surface of the tongue, floor of the mouth, alveolar mucosa, vestibule, lips and cheeks all have non-keratinized surfaces. The epithelium serves as protective covering for the tissues beneath. The non-flexible areas of the oral cavity and the hard palate both include keratinized epithelium. The basal cells give rise to the epithelial cells, which develop, change into different shapes, and grow larger as they move towards the surface. It is recognized that the buccal epithelium is a non-keratinized tissue. It has been discovered that the buccal epithelium in humans, dogs and rabbits has a thickness of roughly 500800µ. The term ‘buccal’ indicates the upper and lower lip linings, which together make up one third of the entire oral mucosal surface. Differentiation, followed by migration and desquamation of the surface cells, are necessary

for tissue homeostasis. Low molecular weight cytokeratin and lipids are accumulated by the prickle cells but not filamentous lipids. In contrast to the intestinal and nasal mucosae, which have tight junctions, desmosomes and hemidesmosomes which are loose intercellular connections. When it comes to permeability, it is mainly due to the presence of 'membrane coating granule' (MCG) which are intercellular components, are primarily responsible for the oral mucosa's permeability barrier feature. The MCG moves to cell's apical surface, where their membranes fusion with the cell membranes causes lipid content to be ejected into the extracellular space.[5, 6]

The buccal mucosa includes mucosal surface of cheek and lips from the line of contact of the opposing lips. This extends to the line of attachment of mucosa of the upper and lower alveolar ridge superiorly and inferiorly. The muscles of cheek are the buccinator muscle. The buccal fat pad is superficial to the fascia covering the buccinator muscle. Branches of maxillary and mandibular nerve provide sensory innervation to the mucous membrane lines. The desired drug to be delivered is placed between the upper gingivae and cheek.[6]

Advantages

- Low dose is needed
- Continued release of drugs
- Avoid first pass metabolism
- Avoid hostile gastric environment
- In case of any toxic or adverse reactions the action can be halted

Disadvantages

- Inconvenient
- Unpalatable and bitter taste
- Irritation of oral mucosa
- Large quantities cannot be administered
- Few drugs are absorbed

Mucoadhesion

The unique features of the oral cavity adopt its potential for the site-specific drug delivery. The continuous production of saliva leads to rapid removal of released drugs. This indicates that the oral cavity restricted only to shortly circulating systemic drugs. The thin mucin film on the oral mucosal surface helps to retain drug delivery system for prolonged periods with

mucosa with the help of mucoadhesive compounds in formulation which allows a strong affinity with absorbing membrane, thus optimizing the drug concentration gradient across biological membrane. Compared to the oral mucosa the buccal membrane has easily accessible smooth surface providing an opportunity for localizing drug delivery system for sustained drug delivery. Since the buccal area has smaller flow of saliva the duration of adhesion of drug delivery system would be longer at these areas. Special anatomical structure of buccal mucosa makes different from GIT and it's morphologically similar to skin. Oral mucosa lacks the good permeability shown by the intestine, for the maximum permeability of drug substance to the buccal mucosa are can use mucoadhesive.[7]

Need of Mucoadhesive

- For prolonged release of drug
- For targeted and localized drug delivery
- To minimize the drug degradation by avoiding first pass metabolizing
- For prolonged therapeutic effect
- For the high and rapid kinetic movement of drug through the absorbing tissue
- To minimize the variability of steady state plasma level

Theories of Mucoadhesion

1) Wetting Theory: The ability of the adhesive to spread on the mucin to influence the intimate contact between the mucoadhesive and mucin and to increase the mucoadhesive strength.
2) Electronic Theory: The mucoadhesive and biological material having opposite charges come into contact with each other, they transfer electrons which end up in formation of double electronic layer at the interface.
3) Diffusion Theory: The polymer chain and mucous mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucous depends on the diffusion coefficient and the time of contact.
4) Fracture Theory: It relates the difficulty of separation of two surfaces after adhesion.
5) Adsorption Theory: This involves the formation of chemical bonds such as the Van Der Waals force, hydrogen force and electrostatic attraction for the formation of the attachment of adhesive to the biological membrane.[8]

Mucoadhesion works to deliver the drug by forming bonds based on the molecular interactions. This interaction is composed of attraction and repulsion. Repulsion takes place by electrostatic and steric repulsions. Their mechanism occurs by.

Stage 1: Wetting and swelling of polymer to allow intimate contact.

Stage 2: Interpenetration of bioadhesive polymer chains and entrapment of polymer chains and mucin chains.

Stage 3: Formation of chemical bond between entrapped chains.

For the mucoadhesive formulation various types of bioadhesive polymers are used.

Properties of Bioadhesive Polymers

- Water soluble, linear and random polymer.
- Water insoluble polymer that are swellable networks joined by cross linking agents.

Polymer with hydrophilic functional group like carboxyl, amide, hydroxyl and sulphate groups are favorable in formulating. Hydration is necessary for the proper working of polymers. Sufficient water is required to properly hydrating the polymer. Expand the gel to create pores of proper size is mandatory for interpenetration. Chain length also plays important role in Bioadhesion. By minimizing the chain length of polymer increase the potential to diffuse and interpenetration through mucosal surface. As the concentration of cross linking agent increases the mucoadhesion strength.[9]

Drug Permeability through Buccal Mucosa

The squamous stratified epithelial layer of oral mucosa has both lipophilic and hydrophilic regions. It allows drug absorption through two possible routes.

- Transcellular (Intracellular, passing through the cell).
- Paracellular (Intercellular, passing around the cell).

Since Paracellular route possessing hydrophilic area, this preferred for transport of hydrophilic drugs with molecular weight less than 500 Daltons. That is proteins or peptides rapidly aqueous fluid found in intracellular spaces by adopting passive diffusion. The transcellular route is specifically used for lipophilic drugs.[10] One of the reasons for transport of lipophilic drug is due to the larger surface area.

Factors Affecting Adhesion

Polymer Related Factors

- Molecular Weight

According to various studies there is a certain molecular weight at which molecular adhesion is maximum. Interpenetration of polymers is favorable for low molecular weight molecules. Intensity of bio adhesive strength of the polymer depends on optimum molecular size. The polymer in water determines the interpenetration of polymer molecules within the mucous. For polymer chain interpenetration, it should have adequate length and its size configuration is also important factors.

- **Flexibility of Polymer Chain**

The presence of cross-linking causes decreases the mobility of individual polymer in water soluble polymers. With the increase in the cross-linking density, the effective chain length that can penetrate the mucous layer decreases and thereby the mucoadhesive strength is reduced.

- **Spatial Confirmation**

Along with the molecular weight or chain length the spatial confirmation significantly affect the mucoadhesion.

Environmental Related Factors

- **pH**

The charge present on mucus as well as polymers is influenced by pH.

- **Applied Strength**

Definite strength must be needed for effective solid bioadhesive system. As the applied strength increases adhesion strength increases and duration of its application. The depth of interpenetration is affected by pressure initially applied to the mucoadhesive tissue contact site. The interaction of polymer with low affinity to the mucin can be increased by subjecting to the high pressure for the longer period of time.

- **Initial Contact Time**

The extent of swelling and interpenetration of polymer chains are determined by initial contact time between polymer and mucus membrane. As the initial contact time increases the mucoadhesive strength also increases.

Physiological Related Factors

- **Mucin Turnover**

Mucin turnover confines the residence time of mucoadhesive on mucus layer. Small amount of soluble mucin molecule will cooperate with muco-adhesives before they cooperate with the mucus layer due to mucin turnover.

- **Diseased State**

Physiochemical properties of mucus alter during diseased condition; it will affect the mucoadhesive property.[11]

Buccal Routes of Drug Administration

- **Drug Delivery through Buccal Mucosa**

The administration of drug through the buccal mucosa into the systemic circulation is known as buccal delivery. Buccal mucosa is less permeable than sublingual mucosa and it is not able to provide rapid drug absorption and good bioavailability. It is one of the most desired sites for sustained release delivery. It acts as a physical barrier against toxins and microorganisms. Due to accessibility of cheek lining the buccal drug delivery is having high patient compliance. In case of any adverse drug reaction, the administration of drug can be stopped but one of the main limitations of buccal drug delivery system is its enzymatic degradation and first pass metabolism.[12, 13]

- **Drug Delivery through Sublingual Mucosa**

Sublingual delivery consists of systemic administration of drug through membranes of mouth floor or ventral surface of tongue. Due to the thin membrane and large veins sublingual mucosa permeates rapid absorption and bioavailability of many drugs in a convenient way in easily accessible location. Besides that, the sublingual mucosa is a smooth surface and free of mucosa and undigested food.[14]

- **Local Delivery to Mouth**

Local delivery to mouth consists of any system that is applicable to the oral mucus membrane to treat several mouth diseases such as periodontal disease, gingivitis, oral candidiasis other chronic lesions or topical fungal infection. Chewing gum, mouth washes, ointments and gels are used in indigenous methods of delivery to the diseased site. Relatively short residence time that may leads to failure in maintaining therapeutical concentrations long enough to affect the bacterial population are the main limitation that these suffers. Besides that, due to

frequent drug administration often leads to low patient compliance and loss of drug in the saliva by swallowing. By using sustained release drug delivery system and also bio adhesive systems current research is attempting to overcome the disadvantages by prolonging the residence time and increasing the patient compliance.[15]

Barriers of Buccal Drug Administration

Buccal drug delivery system has many advantages such as easy application, wide drug distribution and high patient compliance. But its efficacy is limited due to various barrier which results in low permeability and drug degradation.[7,16]

- **Anatomical Factors**

Oral cavity is covered by oral mucosa having good permeability and absorption of drugs but it is having limited surface area and enzymatic composition. Stomach shows strong acidic environment with pH of 1.0- 2.5 which is one of the barriers to drug absorption. The stomach posses' extrinsic epithelial cells and mucin-bicarbonate barrier. The tight junction below the intrinsic barrier limits drug absorption. The presence of villi and microvilli in the intestinal lumen makes the surface area of small intestine huge. Chemical microenvironment, pancreatic enzyme, bile salt, and mucosal layer decrease the bioavailability. The gut micro flora metabolizes the drugs which affect the release characteristic of drugs.

- **Biochemical Factors**

The main biochemical barrier for buccal drug delivery is digestive enzymes and different pH environment. The pH of the GIT raise from stomach to colon rises from 1-8. This variation affects the activity of drugs and its bioavailability. The presence of hydrolytic and reductive metabolizing enzyme in the gut can catalyze the metabolism of xenobiotics and other biomolecule. Since most of the drugs are susceptible to colonic enzyme it leads to the biotransformation of drugs.

- **Physiological Factors**

The low permeability of GIT to bloodstream and extraneous substance decreases the bioavailability and absorption of drugs. The main physiological barrier is the epithelium cellular barrier and mucus barrier. The GI epithelium is a phospholipid bilayer which allows the penetration and absorption of lipophilic macromolecules whereas its absorption is limited to hydrophilic macromolecule. Mucous is a lubricant for ingested food. Also, it is a barrier for entrapping for foreign particle.

Enhancement of Absorption of Buccal Dosage Forms

For enhancing the drug absorption over buccal mucosa, various formulations are used. They are.

- **Permeation Enhancers**

Selection of enhancer and its efficacy based on physicochemical properties of drugs, nature of solvent and excipient profile. It should be non-toxic, safe, chemically and pharmacologically inert, non-irritant and non-allergic.[17]

Mechanism of permeation enhancers

1) Changing Mucus Rheology: Mucus forms thick layer that hinders the drug absorption most of permeation enhancers minimizes its thickness and saliva overcomes this barrier.

2) Increase in the Fluidity of Lipid Bilayer Membrane: Some of the enhancers react with either the lipid or protein component it leads to altering the intracellular lipid packing.

3) Action on the Tight Junction: Acts by interacting with desmosomes components.

4) Overcoming the Enzymatic Barrier: By interacting with the peptidases and proteases in buccal cavity and overcome the enzymatic barriers.

5) Increasing the Thermodynamic Properties of Drugs: Increasing the thermodynamic activity by altering partition coefficient there by increasing the solubility.

- **Enzyme Inhibitor**

Enzyme inhibitors like Bestatin, aprotinin, puromycin helps in drug absorption by changes in enzymatic activity, altering the peptide conformation or making the drug less accessible to enzymatic degradation. Besides, chitosan undergoes modification and form chitosan – EDTA complex with EDTA it has great potential to inhibit the metallopeptidases.

Dosage Forms for Buccal Drug Delivery

The ability of delivery system to achieve and maintain plasma drug concentration for define period of time causes the clinical success of oral drug delivery. An oral mucosal drug delivery should be focused on delivering of adequate amount of drug based upon desired absorption profile.[18] The formulation factor of delivery system determines amount of drug.

Types of Buccal Dosage Forms

Based on the geometry of buccal mucosa, adhesive dosage form can be categorized into three types;

Type 1: It is single layer dosage form having multidirectional drug release. One of the main disadvantages of this type of dosage form is that it suffers from the significant loss of drug due to swallowing.

Type 2: In this type, an impermeable backing layer is superimposed on top of the drug loaded bio adhesive layer, creating a double layered device and preventing drug loss from the top surface of the dosage form in to the oral cavity.

Type 3: It is a unidirectional drug release device from which the drug loss is minimal, since drug is release only from the side that attaches to the buccal mucosa. This can be achieved by covering every phase of dosage form, expect that is contact with buccal mucosa.

Dosage Forms for Buccal Administration

Buccal Mucoadhesive Tablets

Tablets are small, flat and oval with diameter of approximately 5-8 mm. Bio adhesive tablets are immobilized drug delivery systems. They can be monolithic, partially coated or multilayered matrixes. In contrast to conventional tablets the mucoadhesive tablets enable for speaking and drinking without any significant discomfort. They are placed directly on the mucosal surface for local or systemic drug delivery. These become soften, adhere to the mucosa and held in position until the complete dissolution or release. They can be applied to different sites in the oral cavity. Specialized tablets with two layers have been developed in order to prevent drug loss from top surface of the dosage form. They contain drug loaded bio adhesive layer and an impermeable backing layer to promote unidirectional drug release and minimize the drug loss from the dosage form.[19, 20]

Limitations for Buccal Tablets

1) Small contact surface with mucosa.

2) They are rigid.

3) High release rates for some drugs are difficult to achieve.

4) Chances of irritation.

Buccal Patches

The buccal patches are laminates consists of an impermeable backing layer, a drug containing reservoir which releases the drug in a controlled manner and a mucoadhesive surface for mucosal attachment.[21] They have more patient compliance mainly due to the ease of

application, thinness and elasticity that make it less discomfort to the patient. It is a safe and convenient mode of administration because the drug absorption can be terminated if any undesirable effects occur. The drug is delivered in a unidirectional or bidirectional way either into the sub mucosal layers, oral cavity or both[4]. The use of an impermeable backing layer helps in maximize the drug concentration gradient and prolong the adhesion since this system is protected from saliva. Examples are represented in **Table 1**.

Table 1: Different Types of Polymers Used as Backing Membrane.

Types	Polymer Constituents
Controlled Release	Carbopol, Hydroxyl propyl methyl cellulose
Sustained Release	Sodium alginate, Hydroxy propyl methyl cellulose, Sodium carboxymethyl cellulose and Carbopol
Modified Release	Xanthan gum, Polyvinyl alcohol
Immediate Release	Hydroxy propyl methylcellulose, Polyvinyl alcohol

A combination of fast dissolving unit and a bio adhesive part was incorporated to this delivery system in order to overcome the certain absorption problems in this buccal drug delivery.

Buccal Films

Mucoadhesive film offers the strong adhesion with mucosal membrane, it helps to get greater surface area, increase the total absorption and are intended for local and systemic therapy. They have more patient acceptance compared to bio adhesive tablets due to it propose easy administration and improved bioadhesion. Besides that, film helps to protect the wound by reduces the pain and helps to treat the condition in case of local delivery for oral disease. A typical film should be flexible, elastic and soft but enough strong to withstand the breakage due to stress results from mouth movement.[22] Some of the examples were given in the following **Table 2**.

Table 2: **Different Types of Polymers Used in the Preparation of Buccal Films.**

Therapeutic Classification	Polymers	Active Ingredients
Antihypertensive	Chitosan, Polyvinylpyrrolidone, Polyvinyl alcohol, Gelatin, Propylene Glycol	Propranolol
Antifungal	Dextran, Hydroxy propyl, Methyl cellulose and Glycerol	Amphotericin B
Antiprotozoal	Hydroxy propyl methyl cellulose, Polyvinyl alcohol, Chitosan	Ornidazole
Antiepileptic	Hydroxy propyl methyl cellulose	Diazepam
Anesthetic	Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose	Lidocaine HCL

Anti-inflammatory	Hydroxy propyl methylcellulose, Ethyl cellulose, Chitosan	Fluticasone Propionate

Ointments and Gels

In response to several limitations of different semisolid dosage like gels and ointments formulations have been developed with effective advantage of being easy dispersion throughout the oral mucosa. But the drug dosing from this formulation may be not accurate as tablets, patches or films. This type of formulation may cause poor retention of gels at site of application. For the development of this type of formulation different polymers are used including cellulose derivatives like methylcellulose, sodium carboxy methylcellulose, natural gums like xanthan gum and Carbopol which submitted to phase change from liquid to semisolid. This may result in increased viscosity further results in sustained and controlled release of drug.[23]

Evaluations of Buccal Formulations

Evaluation of Buccal Patches

- Initial Bioadhesion: The peeling strength of various polymers like Carbopol (polyacrylic acid, PAA), chitosan, acacia patches which has been made in combination with poly isobutylene and poly isoprene has been evaluated. This evaluation shows that PAA have 0.021 Kg/mm peeling strength than HPMC. From the evaluation it has been concluded that PAA is the second strongest Bioadhesive materials used.
- Duration of Adhesion: It is necessary to determine the duration of adhesive force of the polymer that we have chosen as these bioadhesive material are affected by water and it may dissolve in oral cavity. The instrument commonly used for the determination of duration of adhesion is Instron instrument. Adhesion is expressed in the form of peeling strength or load. The patches retained approximately 50 % of its bioadhesive strength after 72 h of contact.
- Patch Hydration: Patch has been covered with aqueous medium and its weight has been plotted against time for the evaluation of uptake of water by patches. From this, swelling ratio and swelling rate are calculated. Phosphate buffer having pH 7 which is near to pH of saliva and pH 2.6 has been used. After 10 hours, the extend of hydration was around 200 % with pH 2.6 and around 1000 % with pH 7.
- Drug Release: Mainly two methods has been used for the determination of drug release from the patches they are;

1) Simple dissolution using modified paddle apparatus.

2) By using diffusion cell.

In simple dissolution method appropriate medium, stirring speed, time of sampling and method of analysis has been used. In diffusion cell one face of the patch is contacted in medium which mimics the moist surface of buccal cavity. Protective backing has been given to the patch and applied to a hydrated hydrogel film. The medium has been absorbed by these patches through hydrogels and release of drug take place through these hydrogels into the receptor medium.[7, 22]

Evaluation of Buccal Tablets

Swelling and Erosion Studies of Buccal Tablets: Phosphate buffer at pH 6.6 can be used for swelling and erosion studies of tablets gravimetrically. The tablets were adhered to pre weighed glass medium using cyanoacrylate adhesive sealant. This glass was dipped into the phosphate buffer at 37°C. At regular intervals these glass plates were taken from the buffer for determining wet weight after it is blotted with tissue paper. Then it is dried at 40°C. And the swelling index and erosion were determined by following equation.[7, 20]

Swelling index= W_s-W_d/W_d

W_d and W_s are the weights of swollen device.

Applications of Buccal Drug Delivery System

- **Cardiovascular Diseases**

For the treatment of hypertension and stable angina pectoris, a non-selective beta-adrenergic antagonist carvedilol has been used. Polymers like hydroxyl propyl methyl cellulose have been used. From studies we have come to know that using hydrophilic polymers in formulations helps in the controlled release of drugs. Mostly buccal tablets are two layered tablets which make them to release the drugs in zero order. These bilayered tablets on ex vivo evaluation on human saliva show no appreciable change in color and shape, maintaining the integrity of the device. This bilayered tablet bypasses first pass metabolism and improves the bioavailability of the tablets.

- **Antimicrobial Therapy**

The use conventional dosage forms like gels, ointments, suspensions and mouthwashes remain ineffective in the treatment of oral candidiasis as they are quickly removed from the oral cavity. To overcome this problem multilayered mucoadhesive tablets using nystatin has been designed. These tablets release nystatin quickly from the lactose layer but in a sustained

way during approximately 6 h from the polymeric layer. Buccal discs and films of fluconazole for tropical treatment of oral candidiasis ensure controlled release of drugs from the formulations. This reduces the adverse drug reactions and possible drug interactions during the systemic therapy of fluconazole. Major concern during the usage of antibiotics is that it may develop resistance. Antibiotic combinations may develop synergetic effect during the treatment of infections. The formulations exhibit good activities against the species like *Pseudomonas aeruginosa* which indicate a synergistic action between tetracycline and carvacrol since both of them were separately ineffective.

- **Anti- inflammatory Therapy**

One of the major reasons for the oral diseases is inflammation. This is managed by the topical administration of various non-steroidal, anti-inflammatory drugs like flurbiprofen, ibuprofen etc. Their main advantage is the reduction in the dose and controlled release of drugs. The optimized formulation loaded with 20 mg of drug produces good anti-inflammatory sustained release in the buccal cavity for 12 h which reduces the daily dose. The conversion of crystalline drugs to amorphous drugs during film formation and the film matrix maintain the two model drugs in a stable form. Freeze dried wafers and solvent cast films prepared from sodium alginate and sodium carboxy methyl cellulose using paracetamol as a model soluble drug. The rate of release of drugs from the films depends upon the physical structure and the amount of the polymer present in the formulations.

- **Muscle Relaxants**

Tizanidine hydrochloride is an imidazole derivative which acts as agonist on centrally located alpha receptors which leads to myotonolytic effect on skeletal muscle. Bioadhesive buccal tablets of tizanidine have been prepared by using polymers like 11PMC K4M, SCMC alone or their combinations. These polymers avoid first pass metabolism and provide prolonged release of the drug. With increase in the concentrations of SCMC the degree of swelling also get increases which leads to increased bio adhesion strength. With improved entanglement between the polymer chain and the mucus layer leads to higher degree of swelling within short period of time. The rate of swelling is directly proportional to SCMC content and inversely proportional to the HPMC K4M content.

- **Antiemetics**

A 5HT3 serotonin antagonist Ondansetron hydrochloride is used in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. The delivery of ondansetron to systemic circulation increases the bioavailability. The polymers used are Cp 934, sodium alginate, SCMC and HPMC which provide mucoadhesion and ethyl cellulose which act as an impermeable backing layer. The stability was tested in human saliva for 6 h. Both drug and device were found to be stable in the human saliva. Maximum swelling was observed in drugs having carbapol than PVP as a mucoadhesive polymer.[24, 25]

CONCLUSION

As the drug administered through oral mucosa, especially through buccal and sublingual mucosa provides several benefits like accessibility, administration, withdrawal, low enzymatic activity and high patient compliance has achieved acceptance status in recent years. This motivated many scholars to conduct researches concerning with permeation through oral mucosa and it light up tremendous growth and advances in the past few decades. Buccal drug delivery system assures that systemic delivery of orally inefficient drugs. The future prospects of buccal dosage forms are lies in the vaccine formulations and delivery of proteins or peptides. It provides great promises that buccal dosage form at affordable rate will be appear in future market as replacement of conventional dosage forms.

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