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An overview on buccoadhesive drug delivery system: tool to enhance bioavailability

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ABSTRACT
Oral cavity is the foremost part of digestive system of human body due to its excellent accessibility and reasonable patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and systemic therapy. The purpose of the buccal tablet is absorption of the drug through the lining of the mouth. Buccal tablets can be most easily held between the gum and cheek. Various drugs have been investigated for their delivery through the buccal mucosa in a mucoadhesive buccal tablet form.

Key words: Mucoadhesive, Buccoadhesive, Drug delivery.

INTRODUCTION
In recent years the interest in novel route of drug administration occurs from their ability to enhance the bioavailabilty of drugs. Drug delivery via buccal route,using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as carriers. Amongst various routes of drug delivery oral route is perhaps the most preferred to the patient and the clinician alike. However this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug in some cases can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs[1] . In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route[2]. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration[3].

BUCCAL DRUG DELIVERY SYSTEM

ORAL MUCOSAL SITES

Within the oral mucosal cavity, delivery of drugs is classified into three categories

SUBLINGUAL DELIVERY is the administration of the drug via the sublingual mucosa to the systemic circulation.

BUCCAL DELIVERY is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.

LOCAL DELIVERY for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease.

DRUG DELIVERY VIA BUCCAL ROUTE

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY

Drug administration via the oral mucosa offers several advantages.

1. Flexibility in physical state, shape, size and surface.
2. Easy of administration and termination of therapy in emergency.
3. Permits localization of the drug for a prolonged period of time.
4. Administered to unconscious and trauma patients.
5. Offers an excellent route for the systemic delivery of drugs which bypasses first pass metabolism, there by offering a greater bioavailability.
6. Significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
7. Drugs, which are unstable in acidic environment of stomach and/or are destroyed by the enzymatic or alkaline environment of the intestine can be administered.
8. It offers passive diffusion for drug absorption.
9. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response.
10. Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.
11. Drugs with shorter half life can be administrered by this route (2-8 hrs) E.g: Nitroglycerin (2hrs), Isosorbide dinitrate (2-5 hrs)
12. Improved patient compliance.

DISADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

Drug administration via buccal mucosa has certain limitations,

1. Drugs which irritate the oral mucosa have a bitter or unpleasant taste or odour cannot be administered by this route.
2. Drugs, which are unstable at buccal pH, cannot be administered by this route.
3. Only drugs with small dose requirements can be administered.
4. Drugs may get swallowed with saliva and loses the advantages of buccal route.
5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
6. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.
7. Surface area available for absorption is less[4].

ANATOMY AND NATURE OF ORAL CAVITY

ORAL CAVITY

Oral cavity is the foremost part of digestive system of human body due to its excellent accessibility and reasonable patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and systemic therapy.

OVERVIEW OF ORAL CAVITY

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

1. Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingiva (gums).
2. Oral cavity proper, which extends from teeth and gums back to the faces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity[5,]

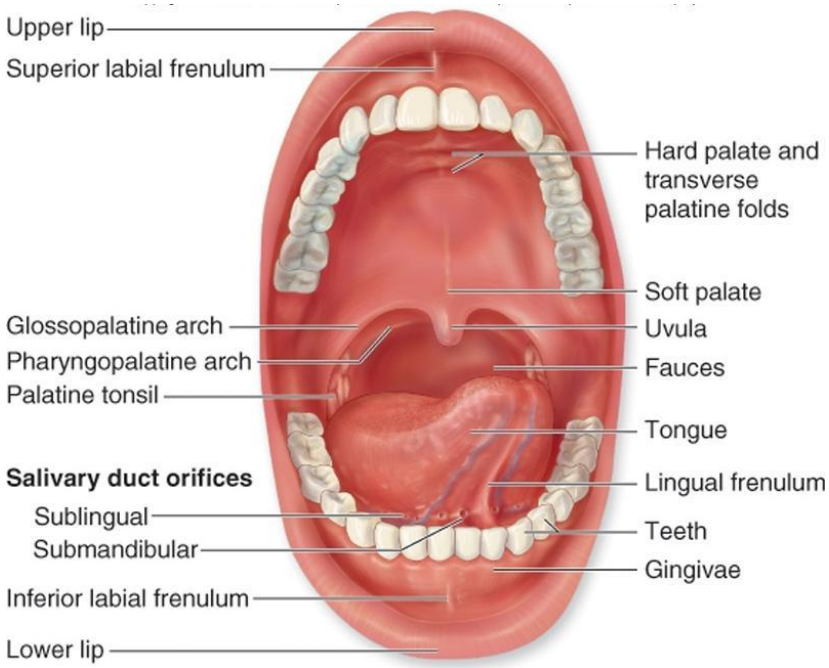

Figure 1: Structure of buccal cavity

The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein. The secretion in the oral cavity includes saliva, crevicular fluid and mucus. From that, Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity[7]. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time, glands had been stimulated, the age and sex of the individual and by their state of health. The average resting flow rate for whole saliva is 0.3 ml/ min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7 ml/min (range 1.1 to 3.0 ml/min). Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)]. Second was the crevicular fluid it s a fluid secreted from the gingival glands of oral cavity. The third type was the mucus, it is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoprotein, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of salivary glands in oral cavity to produce whole saliva[7,8]. The two main glycoproteins found in buccal mucus or mucin is MG1 and MG2. The mucin glycoprotein, MG1 consists of several disulphide-linked subunits containing a protein core with 4-16 oligosaccharide side-chain units. Its molecular size is over 1000 KDa. A small mucin glycoprotein, MG2 has a molecular weight of 200-250 KDa and consists of a single peptide chain with 2-7 oligosaccharide side-chain units. The glycoprotein of mucus has amphoteric properties and is therefore capable of buffering small amounts of either acids or alkalies. The mucus however acts as a potential barrier to the drug penetration. There are some physiological aspects and functions of oral cavity which are explained as, the oral cavity is accountable for the following primary functions such as it is a portal for intake of food material and water, to.bring chewing, mastication and mixing of food stuff, then for lubrication of food material and formation of bolus, for the identification of ingested material by taste buds of tongue, to carry out

initiation of carbohydrate and fat metabolism and absorption of catabolic products thereafter metabolism and lastly it has s light antisepsis of ingested material and within oral cavity by saliva[5,6,9].

ORAL MUCOSA

ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA

The mucosa that lines the oral cavity may be divided into three types, classified according to their function as;

1. Masticatory mucosa: Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.
2. Lining mucosa: Which covers the lips, cheeks, fornix, base of the oral cavity,lower part of tongue, buccal mucosa and the soft palate and these regions have non-keratinized epithelium.
3. Specialized mucosa: covering the dorsum of the tongue with highly keratinization[10].

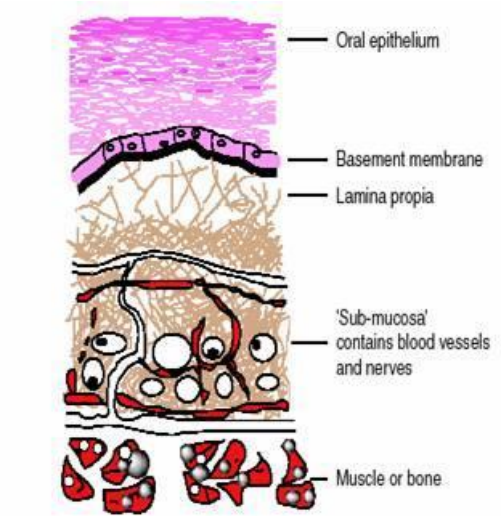

Figure 2: Structure of buccal mucosa.

Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is in turn supported by connective tissues (Fig. 2). The epithelial cells originating from the basal cells mature change their shape and increase in size while moving towards the surface. The thickness of buccal epithelium in humans, dogs and rabbits has been determined to be approximately 500–800 μm. The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the .required adherence between the epithelium and the underlying connective tissues and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa[7].

BIOCHEMISTRY OF ORAL MUCOSA

All the layers of the oral mucosal membranes contain a large amount of protein in the form of tona filaments, consisting at least seven proteins called „keratins" with molecular sizes of 40-70 Kda. Both keratinized and non-keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissues occupy about 50% and 30% respectively of the total surface area of the mouth. The difference between keratinized and non-keratinized epithelia is merely the difference in the molecular size of existing keratins. Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular weight keratins. The lipid content of the cells varies between tissues[4,7].

Table 1: Composition and state of keratinization of oral mucosa

Tissue	State of Keratinization	Composition
Buccal mucosa	Non-keratinized	Few neutral, but mainly polar lipids, particularly cholesterol sulphate and glucosylceramides
Sublingual mucosa	Non-keratinized	
Gingiva mucosa	Keratinized	Neutral lipids i.e., ceramides
Palatal mucosa	Keratinized	

MECHANISMS INVOLVED IN DRUG ABSORPTION ACROSS THE ORAL MUCOSA

The mechanisms by which drugs cross biological lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Small water-soluble molecules may pass through, small water filled pores. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of high concentration in the mouth to a region of low concentration within the buccal tissues[11]. Further diffusion then takes place into the venous capillary system, with the drug eventually reaching the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for this diffusion process. The permeability barrier property of the oral mucosa is predominantly due to intercellular materials derived from the so-called „membrane coating granules"(MCGs). MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. These organelles have also been referred to as small spherically shaped granules "corpusula", small dense granules, small lamellated bodies, lamellated dense bodies, keratinosomes, transitory dense bodies and cementsomes[12]. MCGs are found near the upper, distal or superficial border of the cells and a few occur near the opposite border. Several hypotheses have been suggested to describe the functions of MCGs including a membrane thickening effect, cell adhesion, production of a cell surface coat, cell desquamation and permeability barrier[13,14]. They discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers and this discharge forms a barrier to the permeability of various compounds. Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Saliva contains no proteases but does contain moderate levels of esterase, carbohydrates and phosphatases. However, several proteolytic enzymes have been found in the buccal epithelium[15]. Walker et al. reported that endopeptidases and carboxy peptidases were not present on the surface of porcine buccal mucosa, whereas amino peptid -ases appeared to be the major enzymatic barrier to the buccal delivery of peptide drugs[8].

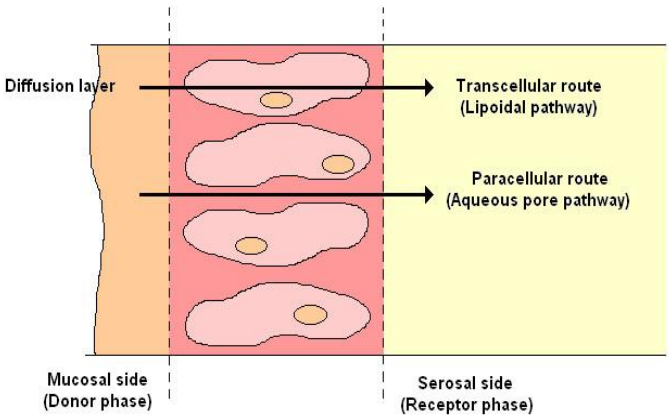

Figure 3: Drug absorption pathways across buccal mucosa

TYPES OF BUCCAL DRUG DELIVERY SYSTEM

For delivery of drug through buccal region several mucoadhesive dosage forms have been reported because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage forms the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a mucoadhesive system. The various types of buccal drug delivery system are explained as follows.

BUCCAL PATCHES/FILMS

Patches are laminates consisting of an impermeable backing layer a drug-containing reservoir layer from which the drug is released in a controlled manner and a bioadhesive surface for mucosal attachment. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymers onto a backing layer sheet and subsequently allowing the solvents to evaporate. In the direct milling method formulation constituents are homogenously mixed and compressed to the desired thickness and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss and minimize deformation and disintegration of the device during the application period[16].

BUCCAL GELS AND OINTMENTS

Such semisolid dosage forms have the advantage of easy dispersion throughout the oral mucosa. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations. Certain bioadhesive polymers undergo a phase change from a liquid to a semisolid; this change enhances the viscosity which results in sustained and controlled release of drugs. Hydrogels are also promising dosage forms which are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. These dosage forms provide an extended retention time, adequate drug penetration as well as high efficacy and patient acceptability[17, 18, 19,20,21,22].

BUCCAL TABLETS

Buccal tablets are small, flat, and oval shaped dosage form. Unlike conventional tablets buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They so often adhere to the mucosa and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity including the palate the mucosa lining the cheek as well as between the lip and the gum. These tablets are usually prepared by direct compression but wet granulation techniques can also be used. Multilayered tablet may be prepared by sequentially adding and compressing the ingredients layer by layer. Some newer approaches use tablets that melt at body temperature[23]

ADVANCES IN BUCCAL DRUG DELIVERY DOSAGE FORMS

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry.

TYPE I

It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

TYPE II

It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer creating a double- layered device and preventing drug loss from the top surface into the oral cavity.

TYPE III

It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa[23].

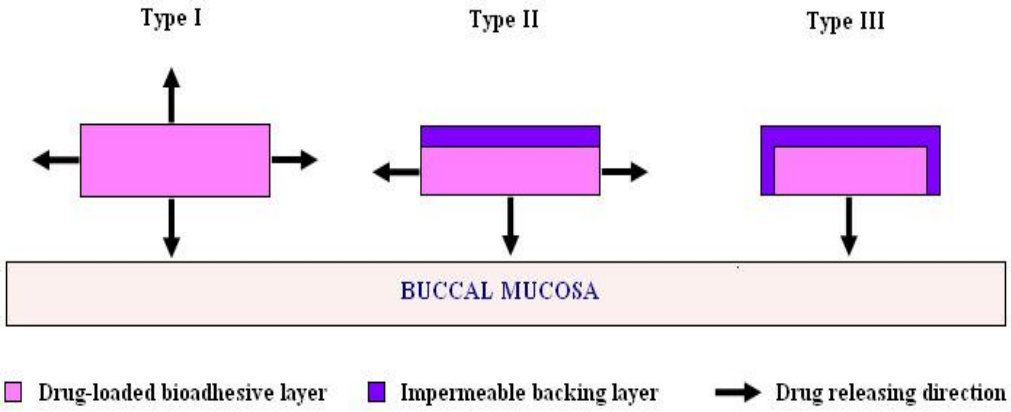

Figure 4: Design of buccal mucoadhesive dosage forms.

CONVENTIONAL DOSAGE FORM

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges.(pastilles or cough drops) are usually made with the drug incorporated in a flavoured, hard-candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy – moulding process. Troches, on the other hand, are manufactured by compression as are other tablets. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps minute or less[24].

MUCOADHESIVE BUCCAL TABLETS

The purpose of the buccal tablet is absorption of the drug through the lining of the mouth. Buccal tablets can be most easily held between the gum and cheek. Various drugs have been investigated for their delivery through the buccal mucosa in a mucoadhesive buccal tablet form.

Table 2: List of drugs investigated for mucoadhesive buccal tablet[25,26,27,28,29]

S.NO	DRUG NAME	S.NO	DRUG NAME
1	Carbamazepine	**6**	Omeprazole
2	Metronidazole	**7**	Morphine sulfate
3	Chlorhexidine	**8**	Diltiazem hydrochloride
4	Miconazole nitrate	**9**	Nicotine
5	Diclofenac Sodium	**10**	Ergotamine tartrate

FACTORS AFFECTING MUCOADHESION IN THE ORAL CAVITY

POLYMER-RELATED FACTORS

MOLECULAR WEIGHT

For successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular eight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The fact that bio adhesiveness improves with increasing molecular weight for linear polymers imply two things:

1. Interpretation is more critical for lower molecular weight polymers to be a good bioadhesive.
2. Entanglement is important for higher molecular weight polymers.

CONCENTRATION OF ACTIVE POLYMERS

There is an optimum concentration of a bio adhesive polymer to produce maximum bioadhesion. In highly

concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

FLEXIBILITY OF POLYMER CHAINS

It is critical for interpenetration and entanglement. As water-soluble polymers become cross linked, mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength

SPATIAL CONFORMATION

Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.

HYDROGEN BONDING CAPACITY

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity.

CROSS-LINKING DENSITY

With increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. Flory has reported this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer.

CHARGE

Nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

CONCENTRATION

When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an unperturbed state due to a significantly coiled structure. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish muco-adhesive properties.

HYDRATION (SWELLING)

Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bio-adhesion occurs.

ENVIRONMENT RELATED FACTORS

APPLIED STRENGTH

Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

PH

Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of cross linked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then hydration decreases as the alkalinity increases.

INITIAL CONTACT TIME

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive

strength increases as the initial contact time increases.

PHYSIOLOGICAL VARIABLES

A) MUCIN TURNOVER

Mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. Mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to interact with the mucus layer.

B) DISEASE STATES

The physiochemical properties of mucus are known to Change during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, and cystic fibrosis, bacterial and fungal infections of the female reproductive tract[36.]

CHARACTERIZATION OF BUCCAL TABLETS[37,38]

THICKNESS

The thickness of the tablets was measured by Vernier calipers. It is expressed in **mm**.

HARDNESS

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in **Kg/cm^2**.

WEIGHT VARIATION TEST

Ten tablets were selected at randomly from the lot and weighed individually to check for weight variation.

FRIABILITY

It was performed in Roche friabilator where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre weighted samples of 20 tablets were placed in the Friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loose less than 0.5 to 1 % of their weight are generally considered acceptable.

% Friability= (initial weight-final weight/initial weight) x100

DETERMINATION OF DRUG CONTENT

Twenty tablets were taken and triturated well. The quantity equivalent to 50mg of Labetalol was dissolved in 100ml of phosphate buffer pH 6.8 solution on rotary shaker overnight. The solution was centrifuged and supernatant was collected. The absorbance was measured using UV-Visible spectrophotometer at 302nm.

MICROENVIRONMENT PH STUDY

The microenvironment pH of the tablets was determined by the method proposed by Bottenberg, et al, 1991[39]. The tablets were allowed to swell for 2 hours in 2ml of pH 6.8 phosphate buffer (pH 6.8±0.05) in specially fabricated glass tubes and microenvironment pH was measured by placing the pH electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.[39]

SWELLING STUDY

The swelling properties of the tablets were evaluated by determination of percent of swelling. Each tablet was weighed (W1) and placed in petri dish with 5ml of PB P^{H}6.8 and incubated at 37^{0}c for predetermined times. After placing the formulation for specified time, the tablets were wiped off to remove excess of surface water by using filter paper and weighed (W2)

$$\%Swelling\ Index = \frac{(W2) - (W1)}{W1} \times 100$$

Where, W 1=Initial weight of the tablet. W2= Weight of tablet after swelling time interval.

DETERMINATION OF THE EX VIVO RESIDENCE TIME

The ex vivo residence time was found using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8 phosphate buffer maintained at 37°C. The sheep buccal tissue was tied with thread to the central stand. The buccal tablet was hydrated with 0.5ml of pH

6.8 phosphate buffer and then the hydrated surface was brought in contact with the mucosal membrane. The tissue was allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from

the mucosal surface was noted.

IN VITRO DRUG RELEASE STUDY

In vitro drug release study of mucoadhesive tablets were performed using standard USP dissolution apparatus type II. The bowls of the dissolution apparatus was filled with 500ml of phosphate buffer pH 6.8 and maintained at a temperature of 37 ± 0.5^0C[52]. The protocol of the dissolution apparatus was settled for automatic 5ml sample withdrawal and replacement of fresh media at predetermined time interval the dissolution apparatus was covered with the black colour polythene cover to protect the solution from light. The collected samples were filtered through the 0.45µm 59millipore filter. The samples were analyzed for drug release using double beam UV spectrophotometer at 302nm.[40]

REFERENCES

[1]. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers & Distribu tors; 1997: 52-81.
[2]. Patel VM, Prajapati BG, Patel MM. Formulation, evaluation and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS Pharm Sci Tech. 2007; 8(1): 1-8.
[3]. Miller NS, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005; 57: 1666- 1691.
[4]. Vyas SP, Khar RK. Controlled drug delivery-concepts and advances. 1st ed. New Delhi: Vallabh Prakashan; 2002.
[5]. Shojaei HA. Buccal mucosa as a route for systemic drug delivery: A Review. J Pharm Sci. 1998; 1(1): 15-30.
[6]. David Haris, Robinson JR. Buccal drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992; 81(1): 1-9.
[7]. Tor-Tora Gorahowski. Principles of anatomy and physiology. 7th ed. Edited by Gerad J. Tor Tora and Sandro Reynolds Gorahowski: Harpet Collins College Publishers; 1992: 770-774.
[8]. Ross & Wilson. Anatomy & physiology in health and illness. 9th ed. Edited by Anne Waugh and Allison Goraw: Churchill Livingstone Edinburgh Publishers; 2001: 289-293.
[9]. Chatterjee CC. Human physiology. 10th ed. Calcutta: Medical Allied Agency; 1985: 427-434.
[10]. Pramod KTM, Shivakumar HG and Desai KG. Oral transmucosal drug delivery systems. Indian Drugs. 2004; 41(2): 63-67.
[11]. Chen YS, Squier CA. The ultra-structure of the oral epithelium. In: J. Meyer, CA. Squier, SJ. Gerson (eds.), the structure and function of oral mucosa, Pergamon Press, Oxford. 1984: 7-30.
[12]. Swarbrick James. Bioadhesive drug delivery systems. 1st ed. New York: Marcel Dekker Inc; 1999: 541-562.
[13]. Hayward AF. Membrane-coating granules. Int Rev Cyt. 1979; 59: 97-127.
[14]. Squier CA, Eady RA, Hopps RM. The permeability of epidermis lacking normal membrane-coating granules: an ultra-structural tracer study of Kyrle-Flegel disease. J Invest Dermatol. 1978; 70: 361-364.
[15]. Robinson JR, Yang X. Absorption enhancers. In: J. Swarbrick, JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker Inc; 2001; 18: 1-27.
[16]. Walker GF, N. Langoth, A. Bernkop- Schnürch. Peptidase activity on the surface of the porcine buccal mucosa. Int J Pharm. 2002; 233: 141-147.
[17]. Miller SC, Donovan MD. Effect of poloxamer 407 gel on the meiotic activity of pilocarpine nitrate in rabbits. Int J Pharm. 1982; 12: 147-152.
[18]. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm. 1999; 178: 11-22.
[19]. Kumar S, Haglund BO, Himmelstein KJ. In situ- forming gels for ophthalmic drug delivery. J Ocul Pharmacol. 1994; 10: 47-56.
[20]. Gurny R, Ryser JE, Tabatabay C, Martenet M, Edman P, Camber O. Precorneal residence time in humans of sodium hyaluronate as measured by gamma scintigraphy. Graefe Arch Clin Exp Ophthalmol 1990; 228: 510-512.
[21]. Meseguer G, Gurny R, Buri P. Gamma scintigraphic evaluation of precorneal clearance in human volunteers and in rabbits. Eur J Drug Meta Pharma. 1993; 18: 190-194.
[22]. Martin L, Wilson CG, Koosha F, Uchegbu IF. Sustained buccal delivery of the hydrophobic drug denbufylline using

physically cross- linked palmitoyl glycol chitosan hydrogels. Eur J Pharm Biopharm. 2003; 55: 35-45.

[23]. Rudnic EM, Schwartz JD. Oral solid dosage forms. In: Gennaro AR (editor). Remington: the science and practice of pharmacy. 20th ed. Lippincott Williams & Wilkins, Baltimore; 2000: 858-859.

[24]. Hannan Butchelov. Novel bioadhesive formulation in drug delivery an oral presentation at the British pharmaceutical conference. The drug delivery companies pharmaventures Ltd. 2004: 22-26.

[25]. Dkinci G, Çapan Y, Senel S, Alaaddinogu E, Dalkara T, Hıncal AA. In vitro/in vivo studies on a buccal bioadhesive tablet formulation of carbamazepine. Pharmazie. 2000; 55: 762-765.

[26]. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug- loaded chitosan microspheres. Eur J Pharm Biopharm. 2002; 53: 233-239.

[27]. Cassidy J, Berner B, Chan K, John V, Toon S, Holt B, Rowland M. Human transbuccal absorption of diclofenac sodium from a prototype hydrogel delivery device. Pharm Res. 1993; 10: 126-129.

[28]. Ahuja A, Dogra M, Agarwal SP. Development of buccal tablets of diltiazem hydrochloride. Ind J Pharm Sci. 1995; 57: 26-30.

[29]. Tsutsumi K, Obata Y, Nagai T, Loftsson T, Takayama K. Buccal absorption of ergotamine tartrate using the bioadhesive tablet system in guinea-pigs. Int J Pharm. 2002; 238: 161-170.

[30]. Bhaskara Jasti et al;Recent Advances in mucoadhesive Drug delivery system,*Business Briefing:Pharmatech*,2004,194-196.

[31]. Navneet verma et al;Polymeric platform for Mucoadhesive Buccal Drug Delivery System:A Review; *International Journal of Current PharmaceuticalResearch,* 3(3), 2011,3-8.

[32]. Anay R.Patel et al;Mucoadhesive Buccal Drug Delivery system, *International Journal of Pharmacy and Life sciences*,2(6),2011,848-856.

[33]. Ravi Bhalodia, Biswajit Basu, Kevin Garala, Bhavik Joshi and Kuldeep Mehta. Buccoadhesive drug delivery systems: a Review. International Journal of Pharma and Bio Sciences 1(2),2010.

[34]. Deepak Sharma, Mankaran Singh, Dinesh Kumar and Gurmeet Singh Novel Paradigms In Mucoadhesive Drug Delivery System. IJPSR, 2012; Vol. 3(8): 2455-2471.

[35]. Alexander Amit, Sharma Sharad, Ajazuddin, Khan Mohammed Junaid, Swarna. Theories And Factors Affecting Mucoadhesive Drug Delivery Systems: A Review. *IJRAP* 2011, 2 (4) 1155-1161.

[36]. S. Roy, K. Pal, A. Anis, K. Pramanik and B.Prabhakar. Polymers in Mucoadhesive Drug Delivery System: A Brief Note. Designed monomers and polymers 12(2009), pages 483-495.