Review Article

An Overview on Buccoadhesive Drug Delivery System – A Promising Option for Topical and systemic Drug Application

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ABSTRACT

Oral drug administration is the traditional and most common method of drug administration but the drugs bioavailability is reduced as it is subjected to extensive pre-systemic degradation in the gut wall (or) liver. Parenteral route of administration is the only established route that overcomes all the drawbacks associated with these orally less/inefficient drugs. But, these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Administration of the drug via the mucosal layer is a novel method that can make treatment more effective and safe, not only for the topical diseases but also for systemic one. This review covers buccal buccoadhesive drug delivery system, mechanism of adhesion and literature about buccal adhesive formulations.

Keywords: Buccoadhesive, Mucoadhesive, mucoadhesive polymers, stages of Mucoadhesion.

INTRODUCTIONS

"Bioadhesion" is the state in which two materials at least one of which is biological in nature are held together for an extended period of time by interfacial forces. The term bioadhesion implies attachment of drug-carrier system to specific biological location. This biological surface can be epithelial tissue or the mucous coat on the surface of tissue. If adhesive attachment is to mucous coat then phenomenon is referred as "Mucoadhesion" is defined as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion can also be explained as the ability of synthetic or biological macromolecules to adhere to mucosal tissues.

In recent years, there has been increasing interest on the use of bioadhesive drug delivery system. These bioadhesive systems are useful for the administration of drugs, which are susceptible to extensive gastrointestinal degradation, first pass metabolism and drug having high dosing frequency. Buccal bioadhesive system appears to be attractive because it avoids significant limitations of traditional routes and first pass metabolism. Administration of the drug via the mucosal layer is a novel method that can render treatment more effective and safe, not only for the local diseases but also for systemic ones.[1-2]

Mucoadhesive controlled release devices can improve the effectiveness of the drug concentration between minimum effective concentration and maximum safe concentration. Also they inhibit the dilution of drug in the body fluids and allow targeting and localization of a drug at specific site. Mucoadhesive also increases the intimacy and duration of contact between a drug containing polymer and mucous surface. The combined effect of the direct drug absorption and decrease in excretion rate (due to prolonged residence time) causes an increased bioavailability of the drug with smaller doses and less frequent administration. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the blood stream so that these drugs are prevented from enzymatic degradation in the GIT.[2]

Oral mucosal drug delivery is classified into three categories.[3]

1. Sublingual delivery
Administration of drug via membranes of the floor of the mouth for the systemic circulation.

2. Buccal delivery
Administration of drug through the mucus membrane lining the cheeks (buccal mucosa).

3. Local delivery
Drug delivered in oral cavity..
Buccal delivery has the advantage over sublingual drug delivery in many ways. In sublingual route, part of drug gets dissolved in saliva and lost by swallowing. The unpleasant taste and odor is felt by the patient. Such effects are not observed in buccoadhesive route.

Advantages of Buccal Drug Delivery Systems [4, 5]

1. Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
2. Termination of therapy is possible.
3. A significant reduction in dose can be achieved there by reducing dose related side effects.
4. Maximum utilization of drug enabling reduction in total amount of drug administered.
5. Ease of administration and better patient compliance.
6. Permits localization of drug to the oral cavity for extended period of time**.**
7. A relative rapid onset of action can be achieved.
8. Avoids first pass metabolism.
9. Drugs which are unstable in acidic environment of stomach or destroyed by the alkaline environment of intestine can be given by this route.
10. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Limitation of Buccal Drug Delivery Systems [5, 6]

1. Drugs which irritate oral mucosa or have bitter taste, or cause allergic reactions, discoloration of teeth cannot be formulated.
2. Delayed release system is not possible in this type of drug delivery as eating and drinking has to be restricted till the complete absorption has taken place.
3. Drug which is impermeable to oral mucosa cannot be used.
4. Continuous dilution of suspended or dissolved drug occurs and involuntary swallowing also may takes place.
5. Not suitable for bitter, irritable drugs.

A) Overview of Buccal Mucosa [7, 8]
The oral mucosa is anatomically divided into 3 parts –

1) Epithelium
2) Basement membrane and Connective tissues.
3) Vascular system of the oral mucosa.

1. Epithelium
The epithelium is mechanical barrier that protects underline tissue, the epithelium of the buccal mucosa is about 40-50 cell layers thick. The epithelial cells increase in size and become flatter as they travel from the basal layer to the superficial layers. The turnover time for the buccal epithelium has been estimated to be 5-6 days. The oral mucosal thickness varies depending on the site. The buccal mucosa measures at 500-8000 μm.[7]

2. Basement membrane and connective tissues
The basement membrane is a continuous layer of extra cellular material, forming the boundary between the basal layer of the epithelium and the connective tissues of the lamina propria and submucosa. It forms a barrier to the passage of cells and some large molecular compounds across the mucosa. Below the basement membrane lies the lamina propria, a continuous sheet of connective tissue containing collagen, elastic fibers and cellular components in a hydrated ground substance. It also carries blood capillaries and nerve fibers that serve the mucosa.[9]

3. Vascular system of the oral mucosa

The mucosal membranes of the buccal cavity are highly vascular nature and blood flow (2.40 mL/min/100 cm^2) and drugs diffusing across membrane have easy access to the systemic circulation via the internal jugular vein. The blood supply to the mouth is delivered principally via the external carotid artery. As shown in Fig.1

The surface of the mucosa membrane is constantly washed by a stream of about 0.5 to 2 mL of saliva daily produced in the salivary glands. The chief secretion is supplied by three pairs of glands, namely, the paranoid, the sub maxillary, the sublingual glands. Minor salivary glands are situated in the buccal, palatal and retromolar regions of the oral cavity.[10]

Permeability of the oral mucosa

A primary function of the oral mucosa is to provide a barrier. At the same time, it also maintains a moist surface of the oral mucosa. As far permeability is concerned, is the both strength and a weakness, since component of saliva may contribute to the barrier function while the accompanying hydration may increase permeability. The permeability of the oral mucosa in general is probably intermediate between that of the epidermis and that of the intestinal mucosa. It is estimated that the permeability of buccal mucosa to be 4-4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in the order: sublingual > buccal > palatal. It is based on the relative thickness and degree of keratinization of this tissues.[11]

Routes of drug transport [8]

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa.

a) Trans cellular (intracellular, passing through the cell)
b) Para cellular (intercellular, passing around the cell)

Permeates can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compound would have low solubility in this environment. The cell membrane however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to low partition coefficient. Therefore the intercellular spaces pose the major barrier to permeation of lipophilic compounds and the cell membrane act as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. Fig.2 shows rout of drug transport.

B) Buccal dosage form types [12]

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry. Fig.3 showed design of buccal mucoadhesive dosage form.

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

Type II devices, 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 of the dosage form into the oral cavity.

Type III is a unidirectional 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. Buccal dosage forms can also be classified as either a reservoir or matrix type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network.

Buccal mucoadhesive dosage forms include tablets, patches, films, and semisolids gels and ointments forms have

been investigated; only a few products are commercially available.

1) Buccal tablet[13]

Buccal tablets are generally flat, elliptical or capsule-shaped held between the gum and cheek Buccoadhesive tablet may be monolithic or bilaminated system. Monolithic is multidirectional release. Bilayered containing core layer & backing layer. Backing layer may be of water insoluble material like Ethyl cellulose or may be polymeric coating layer. Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. Table 1 containing list of some commercially available buccal tablets.[13]

2) Buccal Patches and Films[14]

These dosage forms are usually prepared by casting a solution of the polymer, drug and any excipients (such as a plasticiser) on to a surface and allowing it to dry. Patches can be made 10-15 cm^2 in size but are more usually 1-3 c m^2 with perhaps an ellipsoid shape to fit comfortably into the centre of the buccal mucosa. The buccal films are usually manufactured by a solvent casting method, in which the polymeric material, with or without plasticizer, is dissolved in a solvent or solvents mixture and into which the active constituent is dissolved or dispersed. This solution is then cast onto a suitable substrate and the solvent is allowed to evaporate, leaving a solid polymeric film containing the drug. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. These drawbacks can be overcome by other techniques such as direct compression and hot-melt extrusion. Examples of investigated buccoadhesive film /patches were shown in Table .2 [14-17]

3) Buccal Semisolids (ointments and gels)[13]

Semisolid dosage forms have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. In comparison to solutions, gels can significantly prolong residence time and hence improve bioavailability. Hydro gels can also be used in semi-solids for drug delivery to the oral cavity. These are formed from polymers and can be hydrated in an aqueous environment without dissolution, acting as drug delivery systems by physically entrapping molecules, which are then slowly released by diffusion or erosion after gel hydration.

Mucoadhesion and its Theories

The process of Mucoadhesion is occurs in two stages shown in Fig. 4. The first stage of the Mucoadhesion is the contact stage and is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. The second stage is the consolidation step in which the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bond. [18]

Theories of Mucoadhesion

Several theories have been developed in the formation of bioadhesive bonds and are based on the formation of mechanical bonds, while others focus on chemical interactions. They are as follows: The electronic, adsorption, wetting, diffusion and fracture theory.

The Electronic Theory

The theory based on assumption that bioadhesive material and the target biological membranes have different electronic structures. Formation of a charged double layer at the interface of the mucus and the polymer due to the electron transfer results in attraction in the interface region and contributes to the inter diffusion of the two surfaces.[19]

The Adsorption Theory

This is the most widely accepted theory of bioadhesion. Based on this theory, the bioadhesive bonds formed between an adhesive substrate and tissue is due to various surface interactions (primary and

secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. The formation of secondary chemical bonds greatly depends on properties of the polymer.[20]

The Wetting Theory

The wetting theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the ‘‘spreadability” of the API delivery system across the biological substrate describes the ability of bioadhesive polymer to spread over biological surfaces to develop intimate contact with the corresponding substrate for bond formation. This theory is used predominantly in liquid adhesives.[21]

The Diffusion Theory

The formation of semi permanent adhesive bonds due to the interpenetration and entanglement of bioadhesive polymer chains and mucus polymer chain is supported by diffusion theory. Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. The depth of penetration of polymer chains increase with the bond strength. This penetration is depends upon the concentration gradient and the diffusion coefficients. The bioadhesive polymers and mucus should have similar chemical structures for the formation of strongest bioadhesive bond. For the diffusion to occur, it is important to have good solubility of one component in the other.[22]

The Fracture Theory

States that, the force required for the detachment of polymers from the mucus depends on the strength of the adhesive bond. It measure the maximum tensile stress produced during detachment. The maximum tensile stress produced during detachment is the ratio of maximum force of detachment and the total surface area involved in the adhesive interaction.[23]

None of these mechanisms or theories alone can explain the mucoadhesion which occurs in an array of different situations. However, the understanding of these mechanisms in each instance can help toward the development of new mucoadhesive products.

Factors Affecting Mucoadhesion in the oral cavity

The various factor including both polymer related and environmental related factors are affect the mucoadhesive properties of polymers.

Polymer-related factor

1. Molecular weight

Low-molecular-weight polymers penetrate the mucus layer better. High molecular weight promotes physical entangling. The bioadhesion increases with increase in molecular weight up to 100,000.Beyond this there is no significant gain.[24]

2. Polymer chain flexibility

Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. The interpenetration of the polymer within the mucus network is promoted by flexibility of polymer chain.[25]

3. Degree of Cross-linking

It influences chain mobility and resistance to dissolution. 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, which reduces mucoadhesive strength.[26]

4. Charge and degree of ionization

Nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers.[27] It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or

slightly alkaline medium. The attachment of EDTA an anionic group increased the mucoadshesive strength significantly .The mucoadhesive strength can be attributed as anion>cation>non-ionic.[28]

5. Concentration

An optimum concentration is required to promote the mucoadhesive strength. 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.[27] However, for each polymer, there is a critical concentration, above which the polymer produces an "unperturbed" state due to a significantly coiled structure. For solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi solid dosage forms an optimum concentration is essential beyond which the adhesive strength decreases.[29]

6. Hydration (swelling)

Hydration is required for a mucoadhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Excessive hydration leads to decreased mucoadhesive strength.[23]

Environmental factors includes

1. pH

pH influences the charge of the surface of both mucus and the polymers. Mucus will have a different charged density, changes in pH lead to differences in the extent of dissociation of functional groups in carbohydrate sequences or polypeptide amino acid sequences, as well as in the polymer. Mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration.[30]

2. Applied Strength

To place a solid bioadhesive system it is necessary to apply defined strength, whatever the polymer, 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 side can affects the depth of diffusion.[26]

3. Duration of initial contact

The initial contact time between the mucoadhesive and mucus layer determines the extent of swelling and the inter penetration of polymer chains. The mucoadhesive strength increase as the initial contact time increases.[31]

4. Presence of metal ions

Metal ions interact with charged groups of polymers and/or mucus can decrease the number of interaction sites and the tightness of mucoadhesive bonding.

- **Formulation design**[31]
- To fulfill the therapeutic requirements, buccal administration should contain the following functional agents:
- **Mucoadhesive polymers**
- To maintain an intimate and prolonged contact of the formulation with the absorption site.
- **Penetration enhancers**
- To improve drug permeation across mucosa or into deepest layers of the epithelium (mucosal delivery).
- **Enzyme inhibitors**
- To eventually protect the drug from the degradation by means of mucosal enzymes.

Mucoadhesive Polymers [32]

Most of the mucoadhesive materials are either synthetic or natural hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of presence of carboxyl, sulphate or hydroxyl functional groups.

Mucoadhesive polymers are mainly divided in to 3 different categories according to their charges

a) Anionic polymers, b) Cationic polymers, c) Non-ionic polymers

a) Anionic polymers

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Such polymers are characterised by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include poly (- acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC).[33]

b) Cationic polymers

Chitosan is a cationic polymer (polysaccharide), it is produced by the deacetylation of chitin. Chitosan is a popular polymer to use due to its biocompatibility, biodegradability and favourable toxicological properties. Chitosan has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus. The major benefit of using chitosan within pharmaceutical applications has been the ease with which various chemical groups may be added, in particular to the C-2 position allowing for the formation of novel polymers with added functionality.[34]

c) Non-ionic polymers

They are includes as Hydroxyethyl starch, Hydroxy Propyl Cellulose, poly (ethylene oxide), Poly Vinyl Alcohol, Poly Vinyl Pyrrolidone.

Newer second generation polymers [34]

They have the more site specific hence called cytoadhesives and are least effected by mucus turnover rates. They includes,

Lectins

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis., they hence allow a method for site specific and controlled drug delivery.[35]

Thiolated polymers

These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum.The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from delivery system due to increased rigidity and cross linking. e.g. Chitosan iminothiolane.[36]

Bioadhesion property of some mucoadhesive polymers was shown in Table 3.[37]

Penetration Enhancers

Substances that facilitate the permeation through buccal mucosa are referred as penetration enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients. Examples of common penetration enhancer were given in Table 4.[31]

Enzyme inhibitors

The co-administration of a drug with enzyme inhibitors is another strategy for improving the buccal absorption of drugs, particularly peptides. Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including affecting the activities of the enzymes, altering the conformation of the peptides or proteins and/or rendering the drug less accessible to enzymatic degradation.[37]

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, low enzymatic activity, economy and high patient compliance. An adhesion of buccal drug delivery devise to mucosal membrane not only improves

drug concentration at site of application (local) but also improves systemic concentration too. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Thus Buccoadesive drug delivery is one of the very fast and novel approaches for topical and systemic administration of drugs.

Table 1: Commercially available buccal tablets[13]

Brand name	Polymer	Company
Suscard	HPMC	Forest
Aphtach	Hydroxypropyl cellulose Polyacrylic acid	Tejin Ltd
Buccastem buccal	Xanthan gum	Reckitt
Striant SR	Carbomer 974 P	Columbia Laboratories (UK) Ltd.

Table 2: List of some investigated buccoadhesive film /patches[14-17]

Drug	Polymers	Techniques	Dosage Form
Lidocaine HCl	EC, HPC	Solvent casting	Film
Acyclovir	Chitosan HCl, PAA	Solvent casting	Film
Cetylpyridinum chloride	PVA, HEC, chitosan	Solvent casting	patch
Clotrimazole	HPC, PEO	Hot melt extrusion	Film

(EC-ethyl cellulose, HPC-hydroxypropyl cellulose, HEC-hydroxyethyl cellulose, PVA-polyvinyl alcohol, PAA-polyacrylic acid and PEO- polyethylene oxide.)

Table 3: Bioadhesion property of some mucoadhesive polymers[37]

No.	Polymer	Bioadhesive property
1	Carboxy methyl cellulose	+ + +
2	Carbopol 934 P	+ + +
3	Polycarbophil	+ + +
4	Tragacanth	+ + +
5	Poly (acrylic acid/ divinyl benzene)	+ + +
6	Sodium alginate	+ + +
7	Hydroxy ethyl cellulose	+ + +
8	Hydroxy propyl methyl cellulose	+ + +
9	Poly vinyl alcohol	+ + +
10	Gaur gum	+ +
11	Thermally modified starch	+
12	Pectin	+
13	Hydroxy ethyl methacrylate	+
14	Polyvinyl pyrrolidine	+
15	Acacia	+
16	Polyethylene glycol	+
17	Psyllium	+
18	Amberlite- 200 resin	+
19	Hydroxy propyl cellulose	+
20	Chitosan	+

(+++Excellent, ++ Fair, + Poor)

Table 4: Examples of penetration enhancer with their mechanism[31]

Category	Examples	Mechanism(s)
Surfactants and Bile Salts	Sodium glycodeoxycholate Sodium dodecyl sulphate Sodium lauryl sulphate Polysorbate 8	Acting on the components at tight junctions; Increasing the fluidity of lipid bilayer membrane.
Fatty Acids	Capric acid, Lauric acid. Cod liver oil, Oleic acid	Increasing the fluidity of lipid bilayer membrane.
Cyclodextrins	α, β, γ,-cyclodextrin, methylated β - cyclodextrins	Inclusion of membrane compounds
Polymers and Polymer Derivatives	Chitosan, Trimethyl chitosan.	Ionic interaction with negative charge on the mucosal surface.
Others	Ethanol, Azone®, Octisalate, Padimate Menthol.	Acting on the components at tight junctions, Increasing the fluidity of lipid bilayer membrane.

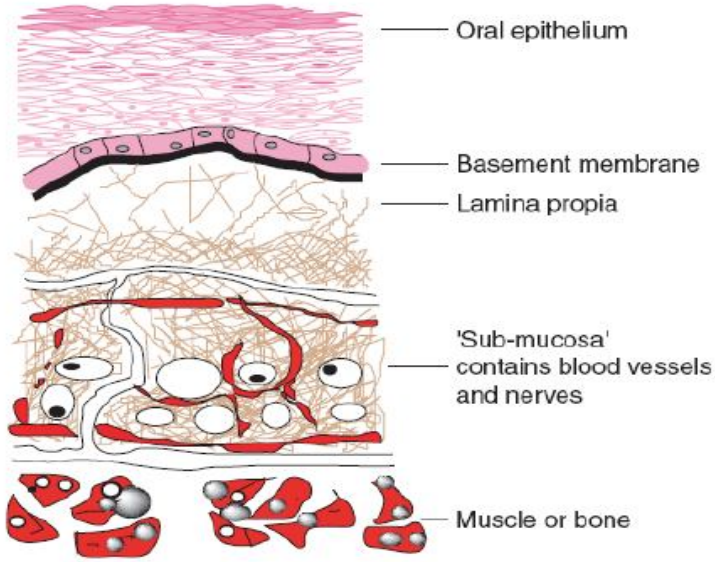
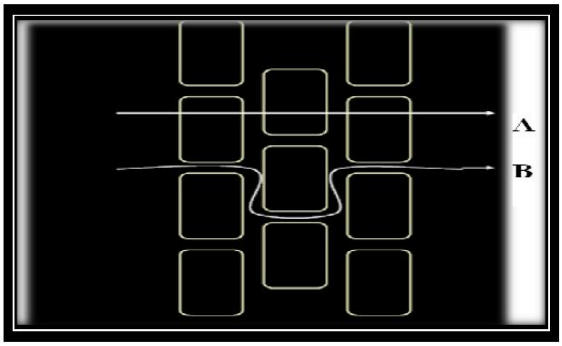


Fig. 1: Cross section of Oral Mucosa



A= Trans cellular B= Para cellular

Fig. 2: Rout of drug transport

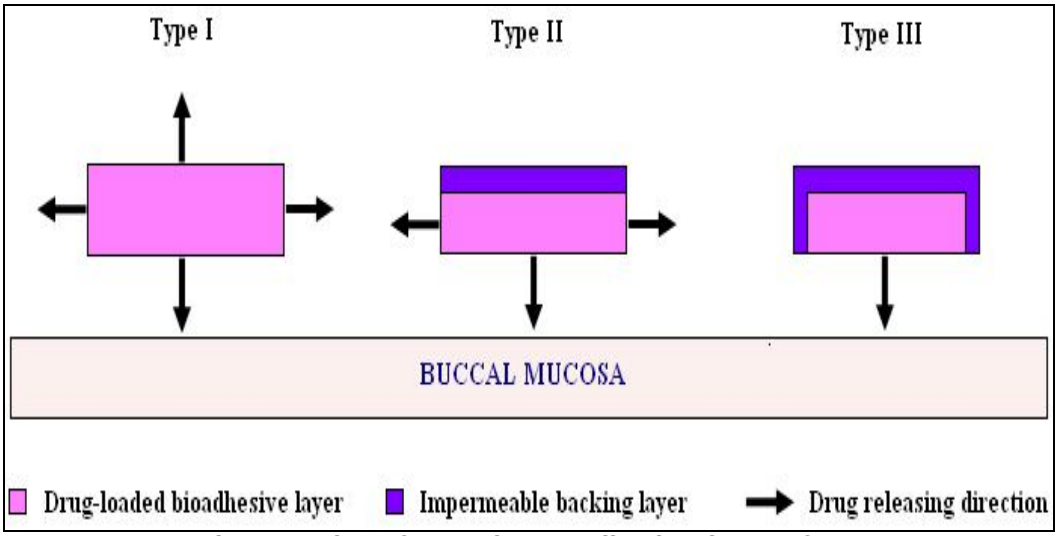


Fig. 3: Design of Buccal Mucoadhesive dosage form

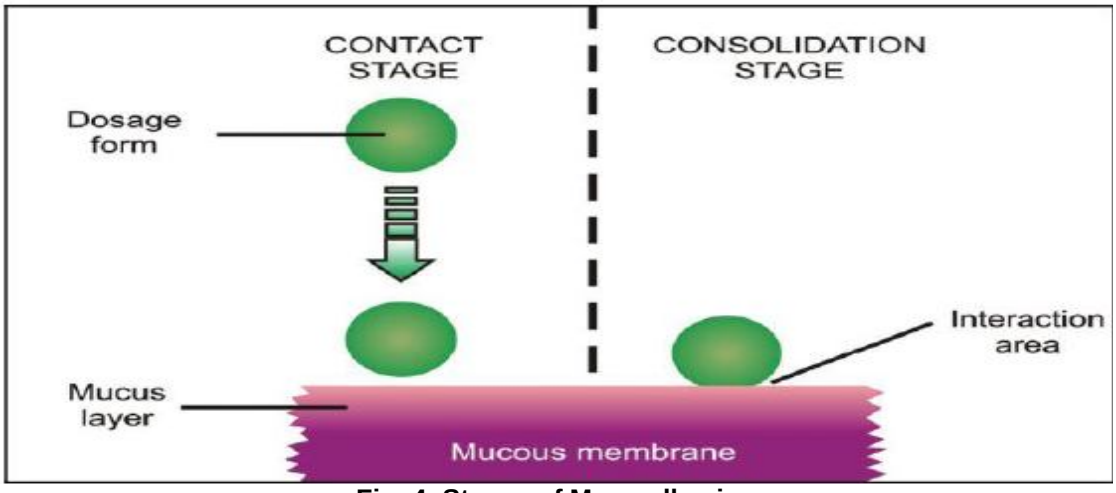


Fig. 4: Stages of Mucoadhesion

REFERENCES

1. Jain NK. Controlled and Novel Drug Delivery, 1st edition, CBS publishers, New Delhi, 1997:353-376.
2. Khanna R, Agarwal SP and Ahuja A. Mucoadhesive buccal drug delivery: A potential alternative to conventional therapy. Indian J Pharm Sci. 1998;60:1-11.
3. Senel S, Kremer M, Nagy K and Christopher S. Delivery of BioactivePeptides and Proteins across Oral (Buccal) Mucosa, Current Pharmaceutical Biotechnology. 2001;2:175-186
4. Vyas SP and Khar RK. Controlled drug delivery-concepts and advances. Vallabh Prakashan, first edition, New Delhi, 2002.
5. Verma Surender, Kaul Mahima, Rawat Aruna and Saini Sapna. An overview on buccal drug delivery system. Int. J Pharma Sci and research. 2011;2(6):1303-1321
6. Miller NS.The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005; 57:1666-1691.
7. Harris D and Robinson JR. Drug delivery via the mucous membranes of the oral cavity. Pharm Sci. 1992;81:1-10.
8. Gandhi Pankil A, Patel MR and Patel KR. A Review Article on Mucoadhesive Buccal Drug Delivery System. IJPRD. 2011;3(5) :159-173.

9. Gandhi RB and Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Deliv Rev.1994;13:43-74.
10. Vyas and Khar. Controlled drug delivery; Concept and Advances, Vallabh Prakashan; Delhi. 2002;314-527
11. Squier CA and Wertz PW. Structure and function of the oral mucosa and implications for drug delivery, in: M. J. Rathbone (Ed.), Oral Mucosal Drug Delivery, Vol. 74, Marcel Dekker, Inc., New York, 1996;1-26.
12. Bhalodia Ravi, Basu Biswajit, Kevin Garala, Joshi Bhavik and Mehta Kuldeep. Buccoadhesive drug delivery systems: a review, International Journal of Pharma and Bio Sciences. 2010; 2:1-32.
13. Puratchikody A and Prasanth VV. Buccal drug delivery: past, present and future – a review. Int J Drug Delivery. 2011;3:171-184
14. Kohda Y. Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion. Int J Pharm.1997;147-155
15. Rossi S, Sandri G, Ferrari F, Bonferoni MC and Caramella C. Buccal delivery of acyclovir from films based on chitosan and polyacrylic acid. Pharm Dev Tech. 2003;8: 199-208.
16. Nafee NA. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm.2003;199-212.
17. Repka MA, Prodduturi S and Stodghill SP. Production and characterization of hot-melt extruded films containing clotrimazole. Drug Dev Ind Pharm. 2003;29:757-765.
18. Smart JD. The basics and underlying mechanisms of Mucoadhesion. Adv Drug Del Rev. 2005**;** 57(11):1556- 1568.
19. Derjaguin BV, Toporov YP, Muller VM and Aleinkova IN. On the relationship between the molecular component of the adhesion of elastic particles to a solid surface. J Colloid Interface Sci.1966;58:528-533.
20. Nazila Salamat-Miller, Montakaran Chittchang and Thomas P. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Del Rev. 2005;57:1666-1691.
21. Pranshu Tangri and Satheesh Madhav NV. Oral mucoadhesive drug delivery systems: a review. Int J Biopharm. 2011;2(1):36-46.
22. Mikos AG and Peppas NA. Systems for controlled release of drugs. V. Bioadhesive systems. STP Pharmacol.1986;2:705-716.
23. Mathiowitz E, Chickering DE III and Lehr CM. Bioadhesive Drug Delivery Systems, Fundamentals, Novel Approaches, and Development. Marcel Dekker, Inc. New York, 2010;4-8.
24. Huang Y, Leobandung W, Foss A and Peppas NA. Molecular aspects of mucoadhesion and bioadhesion: tethered structures and site specific surfaces. J Control Release.2000; 65:63-71.
25. Imam ME, Hornof M, Valenta Reznicek G and Bernkop-Schnurch A. Evidence for the interpretation of mucoadhesive polymers into the mucus gel layer. STP Pharma Sci. 2003; 13:171-176.
26. Sudhakar Y, Knotsu K and Bandopadhyay AK. Bio adhesive drug delivery – A promising option for orally less efficient drugs. J Control Rel. 2006;114:15-40.
27. Peppas NA and Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J ControlRelease.1985; 2:257-275.
28. Lehr CM, Bouwstra JA and Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm.1992;78:43-48.
29. Solomonidou D, Cremer K, Krumme M and Kreuter J. Effect of carbomer concentrationand degree of neutralization on

themucoadhesive properties of polymer films. J. Biomater Sci Polym. Ed 2001;12:1191-1205.
30. Rathbone M.J, Drummond BK and Tucker IG. The oral cavity as a site for systemicdrug delivery. Adv Drug Deliv Rev. 1994; 13:1-22.
31. Silvia Rossi, Giuseppina Sandri and Carla M Caramella. Buccal drug delivery -A challenge already won. Drug Spring. 2005; 2:59-65.
32. Punitha S and Girish Y. Polymers in mucoadhesive buccal drug delivery system – A review. Int J Res Pharm Sci. 2010;1(2):170-186.
33. Andrews GP, Thomas P, Laverty TP, David S and Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009;71:505-518.
34. Senel S.Enhancing effect of chitosan on peptide drug delivery across buccal mucosa. Biomat. 2001;21: 2067–2071.
35. Smart JD. Lectin-mediated drug delivery in the oral cavity. Adv Drug Del Rev.2004;56: 481–489
36. Berkop-Schnurch A., Thiomers: a new generation of mucoadhesive polymers. Adv Drug deliv *Rev.* 2005;57:1569- 1582
37. Yadav Vimal Kumar, Gupta AB, Raj Kumar, Jaideep S Yadav and Brajesh Kumar. Mucoadhesive Polymers: Means of Improving the Mucoadhesive Properties of Drug Delivery System. J Chem Pharm Res. 2010;2(5):418-43.