Available online at www.ijpsdronline.com

International Journal of Pharmaceutical Sciences and Drug Research
2017; 9(6): 299-307

Review Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Modeling the Oral Cavity with Mucoadhesive Drug Delivery Systems - A Potential Alternative to Conventional Therapy

A. Deevan Paul*, P. Samatha, S. Manasa, R. Munemma, D. Supriya

SVU College of Pharmaceutical Sciences, SV University, Tirupati – 517502, Andhra Pradesh, India

ABSTRACT

Oral mucosal drug delivery system is widely applicable as novel site for administration of drug and controlled release action by preventing first pass metabolism and enzymatic degradation due to GI microbial flora. The oral cavity represents a challenging area to develop an effective drug delivery modelling. This arises due to the various inherent functions of the oral cavity (eating, swallowing, speaking, chewing), as well as the presence of the fluid that is involved in all these activities, saliva. This fluid is continually secreted into and then removed from the mouth. Oral Mucosa drug delivery system provides local and systemic action. The delivery of drugs through the buccal mucosa has attracted much research interest over the past two decades and numerous approaches, both conventional and complex, have been developed in an attempt to deliver a variety of pharmaceutical compounds via the buccal route. To outline the progress in the *in vitro* and in vivo modeling of Mucosal drug delivery and provide a critical review of currently used methods. The purpose of this review is to represent the modeling of oral cavity with Mucoadhesive drug delivery systems and clarify the potential alternative to conventional therapy.

Keywords: Mucoadhesion, Penetration enhancers, buccal epithelium, Vascularity absorption.

DOI: 10.25004/IJPSDR.2017.090603 **Int. J. Pharm. Sci. Drug Res. 2017; 9(6): 299-307**

***Corresponding author**: Mr. A. Deevan Paul
Address: SVU College of Pharmaceutical Sciences, SV University, Tirupati – 517502, Andhra Pradesh, India
E-mail ✉: deevan4@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 05 October, 2017; **Revised:** 17 October, 2017; **Accepted**: 25 October, 2017; **Published:** 20 November, 2017

INTRODUCTION

Hyperlipidemia is a major cause of atherosclerosis and the atherosclerosis-associated conditions, such as coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease. Although the incidence of the atherosclerosis related events has declined in the united states, these condition still accounts for the majority of morbidity and mortality among middle aged and older adults, the incidence and absolute number of annual events will increase over the next decade because of epidemic of obesity and ageing of the U. S. population. [1-2] Dyslipidemia, including hyperlipidemia and hypercholesterolemia and low level of high density of lipoproteins cholesterol HDL

are major cause of increased atherogenic risk; both genetic disorders and lifestyle diet high in calories, saturated fat, and cholesterol contribute to dyslipidemia seen in developed countries around the world. [3] Severe hypertriglyceridemia (i.e. Triglyceride level of >1000 mg/dl) requires therapy to prevent pancreatitis. [4] Moderately elevated triglyceride level 150 to 400 mg/dl also are concern because they often occur as part of the metabolic syndrome, which includes insulin resistance, obesity, hypertension, low HDL level and substantially increased CHD risk. [5-6] Medicinal plant based drug has now advantageous over modern drugs. As such are long history of use and better patient tolerance as well as public acceptance, renewable source cultivation and processing environmental friendly, local availability, plant may major source of lead generation. Several recent break through are gugulipid, taxol, artimesinin. [7] Medicinal plant contains so many chemical compounds which are the major source of therapeutic agents to cure human disease. [8] Mucoadhesion can be characterized as the state in which two materials adhere to each other for extended periods of time with the help of interfacial forces and when one of these materials is biological in nature, the phenomenon is known as Mucoadhesion. The term Mucoadhesion is the "attachment of an engineered or natural macromolecule to mucus and additionally epithelial surface. Mucoadhesion has turned into a zone of enthusiasm for the organization of different shaky bioactive including high atomic weight particles (proteins and oligonucleotides) through various courses of organization viz. ocular, nasal, vaginal and buccal. [1]

Mucoadhesion phenomenon has shown numerous path-breaking advantages including:

- Prolonged residence time enhances absorption, which results in an increase in the therapeutic efficacy of the drug.
- Enormous blood supply and good blood flow rates cause rapid absorption of the drug,
- prevention of first pass metabolism results in increasing the drug bioavailability,
- Avoidance of drug degradation due to acidic environment in gastrointestinal tract,
- Ease of drug administration therefore improved patient compliance, and
- Faster onset of action due to mucosal surface.

Researchers have reviewed applications of Mucoadhesive polymers in drug delivery. The potentials of natural Mucoadhesive biopolymers, silk and silk-like proteins, in controlled drug delivery and suggested that these biocompatible polymeric matrixes could have promising potential particularly in local controlled drug delivery including their role in the mitigation of immune response. At last, the researchers reasoned that these mucoadhesive frameworks could fill in as promising delivery systems. Mucoadhesive polymers are continuously being explored for various drug delivery applications. Mucoadhesive polymers have also been investigated in ocular, nasal and buccal delivery of bioactive agents along with polymers having special characteristics like thermo sensitive, pH sensitive, enzyme or chemical sensitive polymers. Mucoadhesive polymers are extensively being investigated for promising biomedical application which may soon be translated into potential clinical applications. [2]

REASONS FOR DEVELOPING ORAL MUCOSAL DRUG DELIVERY SYSTEMS

The oral cavity is an attractive site for the delivery of drugs either locally or directly into the systemic circulation. Ultimately, the decision to utilize the oral cavity as a site for drug delivery should be based on a comparison to other sites of delivery with regard to the following parameters the clinical objectives of the treatment, the inherent physicochemical properties of the drug, the relative advantages of the route, product differentiation opportunities, the patient population, the cost of production and R&D time. [3]

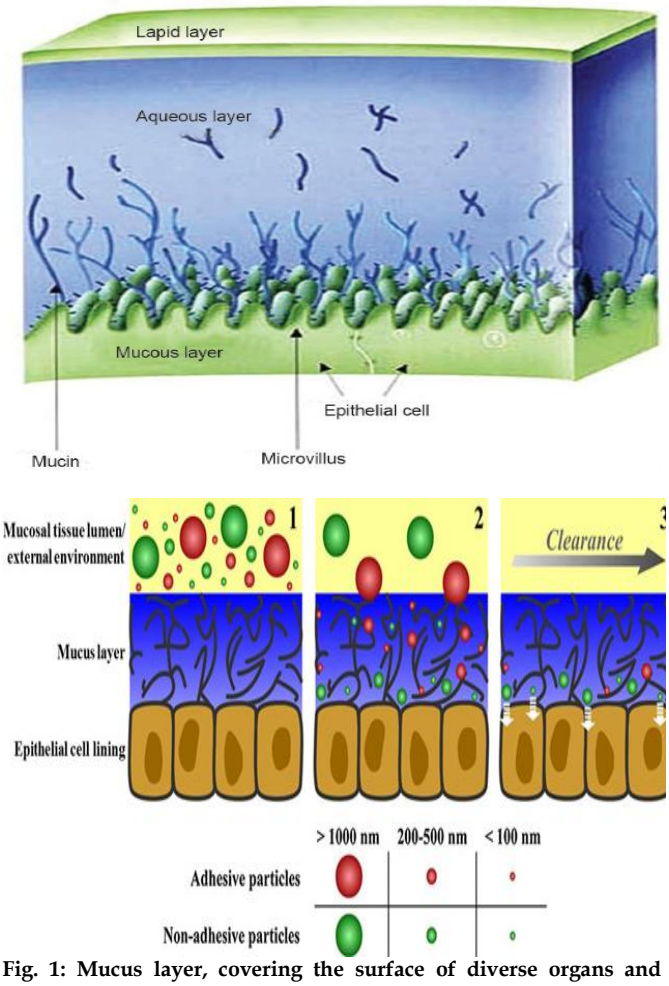

Fig. 1: Mucus layer, covering the surface of diverse organs and exploited the mucosal drug delivery systems

PHYSIOLOGY OF BUCCAL MUCOSA

Novel drug delivery systems are the new methods of entry of drugs into the body and Mucoadhesive drug delivery systems are one of them. Based on route of

administration they are classified as buccal, vaginal, rectal, ocular and gastro intestinal drug delivery systems. The oral route has various attractive advantages for the administration of drug. It includes avoidance of pain and discomfort related with injections. There are some barriers like proteins for the oral delivery of drugs to overcome the degradation of drug due to acidic environment of stomach, hydrolytic degradation, metabolism and easily cross the barriers. The oral cavity contains a large surface area of mucus for complete absorption of drugs. Oral drug delivery can be divided as sublingual, buccal and local. Sublingual mucosa has high permeability, shows rapid absorption and remarkable bioavailability of drugs even though it is not selected as delivery site because of high secretion of saliva which washes away the drug. Unlike sublingual mucosa, buccal site will not offer rapid absorption, superior bioavailability but still it is selected as favored site for retention of drug, controlled drug delivery. After this, the sub-mucosal part which contains the various blood vessels and nerves from CNS. The buccal -mucosal part provides the highest vascularity for the complete absorption of the drugs. [4-5]

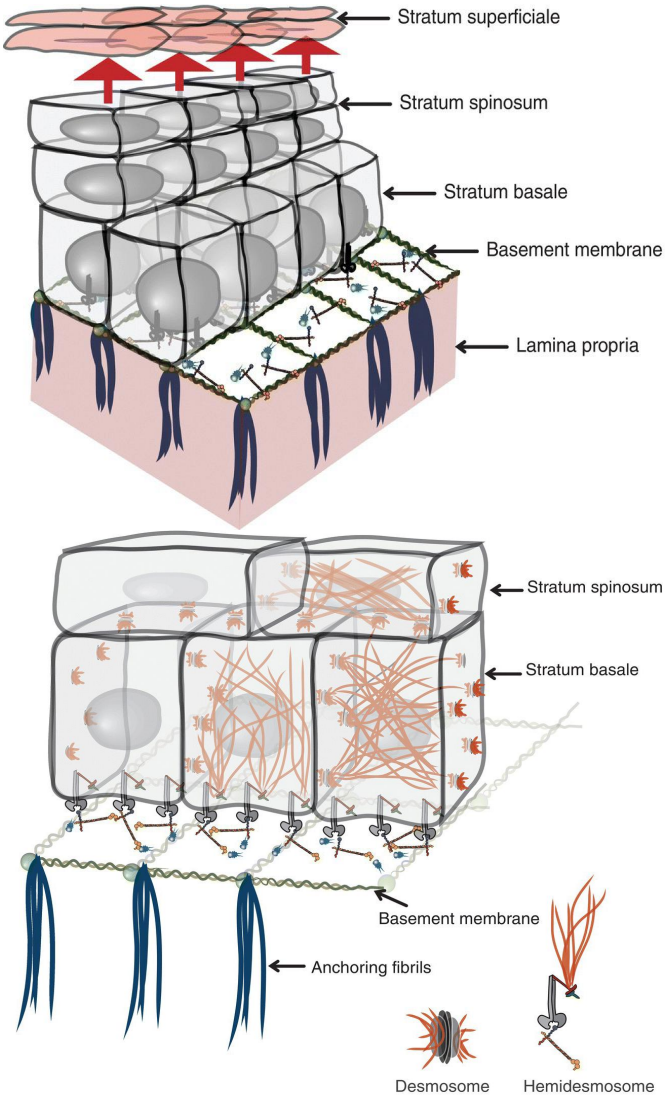

Fig. 2: Physiology of buccal mucosal and its highest vascularity absorption

The common sites of application where Mucoadhesive polymers can delivery pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current section of the review will give an overview of the above-mentioned delivery sites.

- The nasal mucosal layer has a surface area of around 150-200 cm^2. The residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter.
- Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches.
- The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location
- Gastrointestinal tract is also a potential site which has been explored since long for the development of Mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a location of the gastrointestinal system by using Mucoadhesive polymers has generated much interest among researchers around the world. [6-8]

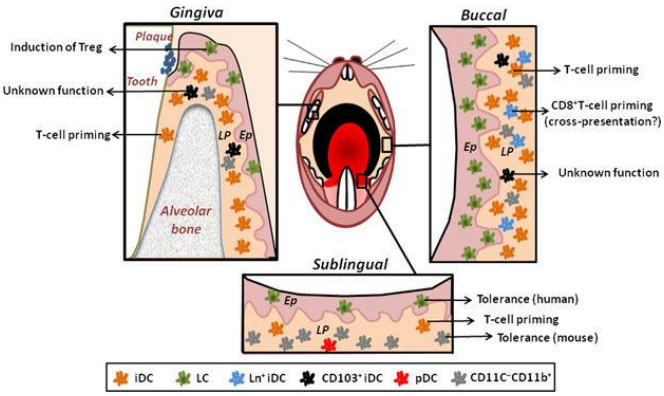

Fig. 3: Mechanism of the cell membrane, absorption enhancers

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL MUCOSA

Absorption enhancers: Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing

the fluidity of the cell membrane, extracting inters/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism. [9]

Prodrugs: The opioid agonists and antagonists in bitter less prodrug forms and found that the drug exhibited low bioavailability as prodrug.

pH: The permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single layered and multi-layered patches. [10]

First-Pass Effect

The first-pass effect, also known as first-pass metabolism or pre-systemic metabolism, takes place when a drug is metabolized between its site of administration and the site of sampling for drug concentration determination. This phenomenon affects both small molecules and biologics alike. The first-pass effect results in a net drug amount reduction prior to reaching systemic circulation. Proteins and peptides can be affected by hepatic first-pass metabolism, e.g., 43% of insulin has been found to be removed in the liver when administered by portal infusion. The intestine also contributes to the first-pass metabolism, and for some drugs, its effect is more important than hepatic and gastric metabolism. Avoiding the first-pass effect has become a goal in pharmaceutical innovation, replacing the traditional oral route for alternative delivery routes including the buccal epithelium. A well described attempt to decrease the first-pass effect can be found in a new drug delivery system developed. This potential carrier could be used in biologics but requires further investigation related to the drug molecular weight limit for encapsulation and formulation compatibility. [9, 11]

MUCO ADHESIVE FILMS AS BUCCAL DOSAGE FORMS

Mucoadhesive films are promising dosage forms for buccal administration essentially for their simplicity of administration, versatility reaching either local or systemic effect, Mucoadhesion providing enough time for absorption, and small size and flexibility improving patient compliance. The FDA identifies three different types of films related to pharmaceutical drug products.

- Film for a thin layer or coating,
- Film for extended release: a drug delivery system in the form of a film that releases the drug over an extended period in such a way as to maintain constant drug levels in blood or target tissue.
- Film for soluble: a thin layer or coating which is susceptible to being dissolved when in contact with liquid. These are also known as Orodispersable films, and other terms.

Mucoadhesive preparations are intended to be retained in the oral cavity by adhesion to the mucosal epithelium allowing systemic drug absorption. Films are very thin polymeric matrices intended to either be placed on the tongue, buccal, or sublingual mucosa, after which saliva hydrates and promotes dispersion/dissolution or swelling and adherence to the administration site. Depending on the formulation and intended effect, drug will be released for a local effect, gastrointestinal transit, or transmucosal absorption. Films can also be designed as mono or multilayer systems to further control or modify drug release. These dosage forms offer advantages to elderly people and children as they do not have to be swallowed for drug administration as opposed to tablets and capsules. Furthermore, Mucoadhesive films can allow for prolonged contact times with the epithelium resulting in higher bioavailability compared to solutions and suspensions. The limitations of films as buccal dosage forms can be identified in their potential hygroscopic, a rather small maximum dose (thus highly potent drugs will be preferred), and the need to consider sensorial requirements such as taste and texture. Currently, there are a number of pharmaceutical drug products formulated in films as dosage forms. Although validated for small-molecule drugs, no biologic drug product has been commercialized in films. [12-14]

KEY CONSIDERATIONS IN THE DESIGN AND DEVELOPMENT OF ORAL MUCOSAL DRUG DELIVERY SYSTEMS

Influence of Oral Cavity Anatomy and Physiology on Drug Delivery

The anatomy and physiology of the oral cavity have a direct influence on the design of oral mucosal drug delivery systems. The anatomy and physiology have been comprehensively dealt with in a separate chapter of this book. This section provides a summary of the positive and negative influences of the various physiological and anatomical features of the oral cavity that may influence oral mucosal drug delivery system design and evaluation.

Drug Absorption across the Oral Mucosa

Two major routes of absorption are involved in oral mucosal drug permeation: the transcellular or intracellular route (where drugs permeate directly through the cells) and the paracellular or intercellular route (where drugs permeate by passive diffusion through the spaces between the cells). The paracellular route is favored especially by hydrophilic drugs such as peptides/proteins which dissolve more readily in the aqueous fluids filling the intercellular spaces. An

example of a drug known to penetrate via the transcellular pathway is fentanyl, which is a highly lipophilic drug, whereas an example of a drug absorbed via the paracellular route is caffeine, which is a water-soluble drug. [15]

Table 1: Anatomical features of the oral cavity on drug delivery system and its aspects

ASPECT	ADVANTAGE	DISADVANTAGE
Saliva	Promotes dissolution of drug Wets dosage forms containing Mucoadhesive, thereby promoting adhesion to the oral mucosa Saliva continually bathes the surface of the oral mucosa and maintains a moist, stable environment Compared to the secretions of the gastrointestinal tract, saliva contains less mucin, limited enzymatic activity and virtually no proteases	Constant secretion and removal by swallowing can cause drug and delivery system to be removed from the intended site of absorption Saliva is a relatively mobile fluid
Flexible membrane	Some membranes are less flexible than others (e.g. gums, hard palate)	Can cause delivery systems to dislodge from the mucosa
pH	Saliva has a slightly acidic pH which is favourable for a wide range of drugs pH can by modified easily at the site of administration	
Keratinized mucosa	Usually located in regions of the mouth that do not flex (gum, palate)	Provides an additional barrier to drug absorption
Non-keratinized mucosa	More permeable than keratinized mucosa (buccal, sublingual	Tend to be in regions of the mouth that are flexible
Membrane thickness	Sublingual mucosa is relatively thin, therefore this region is good for the purpose of rapid drug Absorption	Buccal mucosa is relatively thick and absorption may be too slow to be useful for drug delivery
Surface area	Generally sufficient to allow for drug absorption of drugs with appropriate physicochemical properties	Relatively small compared to other absorption sites of the body

Influence of Drug Properties on Oral Mucosal Drug Delivery

The physicochemical properties of the drug play a crucial role in the design and formulation of an oral mucosal drug delivery system. The paramount importance of the physicochemical properties of the drug is characterized in order to allow for initial selection and subsequent into an oral mucosal drug delivery system. The physicochemical properties of the drug which was need to be known prior to its formulation into an oral mucosal drug delivery system. [16]

FACILITATION OF DRUG EFFECTIVENESS FROM AN ORAL MUCOSAL DRUG DELIVERY SYSTEM

Two factors influence the effectiveness of drug delivery from a delivery system designed for use in the oral cavity. The first is time of retention of the drug delivery system in contact with the oral mucosa; the second is the permeation rate of the drug across the oral mucosa. The ability to retain the drug delivery system in contact with the oral mucosa at a particular location can be achieved through the incorporation of carefully selected Mucoadhesive polymers into the formulation. This results in the delivery system having an intimate contact with the oral mucosa for a prolonged time. When Mucoadhesive polymers rapidly and securely interact with the mucin molecules, found on the surface of the oral mucosa, it results in intimate contact of the dosage form with the mucosa. The prolonged contact time allows for a longer duration for absorption of the drug. It also reduces the pathway for diffusion of released drug between the surface of the delivery system and the surface of the mucosa. Increasing the permeability of the drug through the oral mucosa is another approach used to assure therapeutic levels of a drug via the buccal route. This is commonly achieved through the use of a penetration enhancer in the formulation. Various chemicals have been used as permeation enhancers. [17-19]

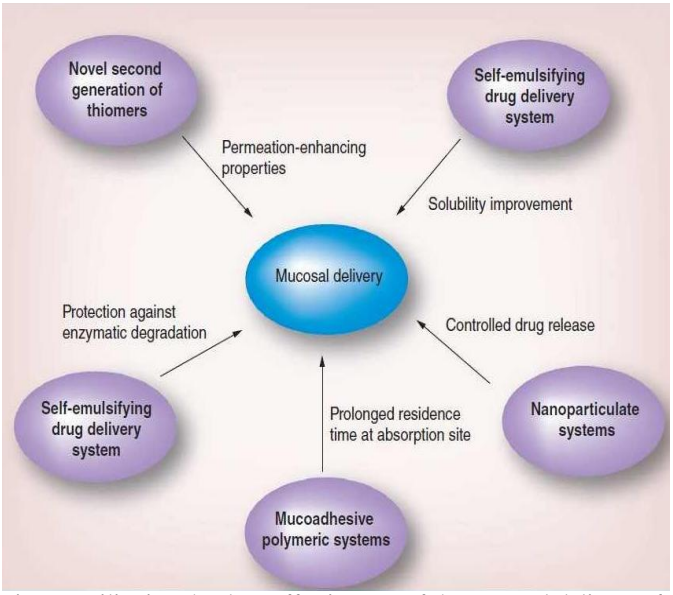

Fig. 4: Facilitating the drug effectiveness of the mucosal delivery of drug

IDEAL CHARACTERISTICS

- Safe and non-toxic, non-irritating and non-allergenic
- Pharmacologically and chemically inert
- They should have no pharmacological activity within the body
- The penetration enhancers should be compatible with both excipients and drugs

However, buccal drug delivery penetration route assessment is significant because it is deep-seated to

opt for the appropriate penetration enhancer to get better the drug permeability. [20]

Changing mucus rheology

Drug absorption mainly affect by the thickness of mucus viscoelastic layer. Additional, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' perform by diminishing the viscosity of the mucus and saliva overcomes this barrier.

Increasing the fluidity of lipid bilayer membrane

The preferential mechanism of buccal mucosa drug absorption is intracellular route. Some permeation enhancer perturbs the intracellular lipid packing by interaction with lipid or protein components.

Acting on the components at tight junctions

Some permeation enhancer's act on desmosomes, a foremost component at the tight junctions by this means enhances drug absorption.

By overcoming the enzymatic barrier

These permeation enhancers work by hinder the action of various peptidases and proteases present inside buccal mucosa, in this manner prevail over the enzymatic barrier. In addition, modification in membrane fluidity also alters the enzymatic activity indirectly.

Increase in the thermodynamic activity of drugs

Some permeation enhancers alter the partition coefficient of the API there by increase the solubility. This increase in the thermodynamic activity results better drug absorption.

Chemical penetration enhancers

A chemical penetration enhancer, or absorption promoter, is a substance added to a formulation in order to increase the buccal membrane permeation or absorption rate of a drug, without damaging the buccal membrane. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of drugs across the buccal mucosa. [21-25]

Enzyme inhibitors

The environment of the oral cavity and oral epithelium is highly enzymatic. This cause degradation of API before they are absorbed, therefore reducing bioavailability. In order to overcome this draw back research has begun into the use of enzyme inhibitors. Co-administration of a drug with enzyme inhibitors improves the buccal absorption of drugs, particularly peptides. [26]

***In vitro–in vivo* correlation for Mucoadhesive drug delivery systems**

The Correlations between *in vitro* and *in vivo* data (IVIVC) are often used during pharmaceutical development in order to optimize the formulation while reducing product development time and costs. A good correlation is a tool for predicting *in vivo* results based on *in vitro* data and it allows dosage form optimization with the fewest possible trials in man, fixes drug release acceptance criteria, and can be used as a surrogate for further bioequivalence studies. Very few attempts have been made so far to obtain *IVIVC* for buccal drug delivery systems and significant research effort is needed in this area. Some studies that involving the bioadhesion of miconazole nitrate buccal tablets, attempted to establish a correlation between *in vitro* and *in vivo* Mucoadhesion tests. The detachment force and work of adhesion was considered for the *in vitro* Mucoadhesion test and was compared against the *in vivo* adhesion time in human volunteers for different formulations. Changes in Mucoadhesive polymer systems in the formulation were well reflected in the *in vitro* Mucoadhesion test results, however these changes were not as obvious with the *in vivo* adhesion results; therefore, no good IVIVC was established and that *in vitro* Mucoadhesion test seems to provide information only on initial adhesion and not on the residence time of the tablet in the oral cavity. [27-29]

PHYSIOLOGICAL FACTORS

The physiological factors play a crucial role in governing the Mucoadhesive property of polymer matrix like texture, thickness of mucosa.

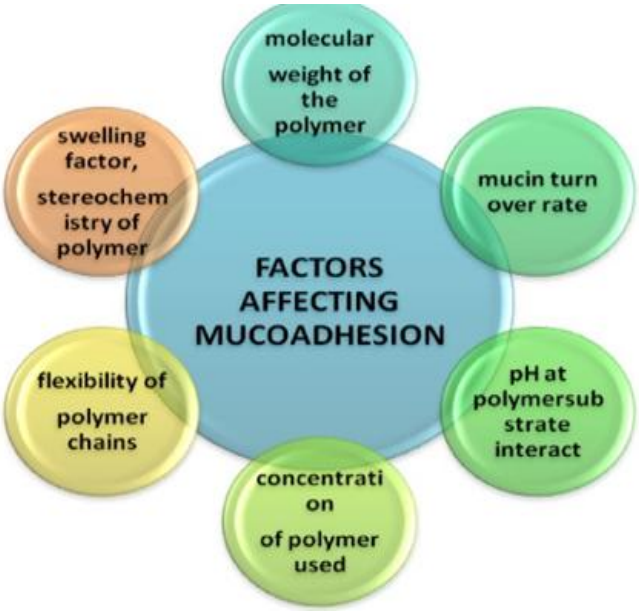

Fig. 5: Factors affecting the Mucoadhesion through various physiological factors

Mucin turnover

High mucin turnover is not beneficial for the Mucoadhesive property because of following reasons. The high mucin turnover limits the residence time of bio adhesive polymer as it detaches from the mucin layer, even though it has a good bio adhesive property. It may produce soluble mucin molecule, thus molecule interact with the polymer, before they interact with mucin layer. Hence there will not be sufficient Mucoadhesion.

Disease state

The physicochemical property of mucus may alter during some disease state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc. Thus alteration in the physiological state may affect the bioadhesive property.

Rate of renewal of mucosal cells

Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

Concomitant diseases

Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

Tissue movement

Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the Mucoadhesive system especially in case of gastro retentive dosage forms. [30-32]

MECHANISTIC APPROACHES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

There are a couple of general theories that can clear up Mucoadhesion, for instance, electronic speculation, adsorption theory, wetting speculation, scattering theory, part speculation and mechanical theory. A blend of all the possible hypotheses is together guides in clearing up a couple of frameworks about Mucoadhesion. The estimation outline needs to wind up discernibly swell and spread on the organic liquid, which clears up the wetting theory. Next, inside the organic liquid polymer interface as a result of electric charges flow (electronic theory), linkages might be made (adsorption speculation). Following that, the polymer and protein chains diffuse together (scattering theory) and capture together, forming further holding (electronic and adsorption theories) for longer connection. These frameworks so can be arranged into two, which are contact stage and union stage.

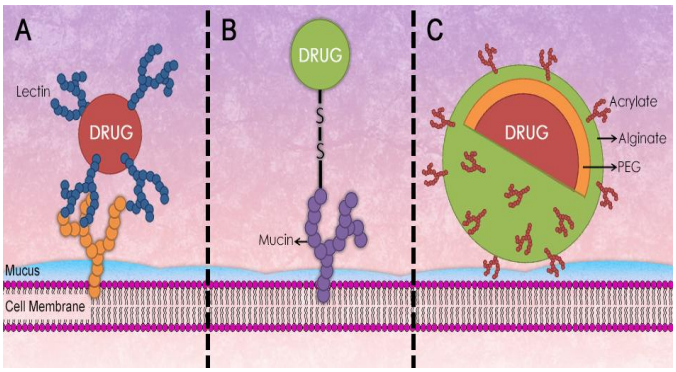

Fig. 6: Mechanistic approach in Mucoadhesive delivery system into the tissue/surface of the mucous membrane

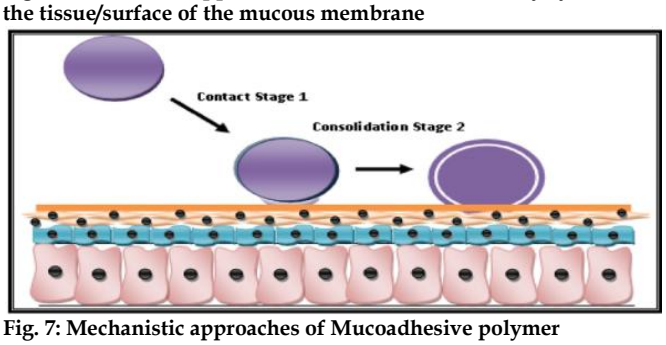

Fig. 7: Mechanistic approaches of Mucoadhesive polymer

Amid contact arrange, wetting will happen between measurements shape and bodily fluid surface. Amid solidification organize the plasticizing and attachment action of the polymers is actuated by the dampness that advances development of hydrogen bonds and van Der Waals drive. Dissemination hypothesis additionally clarifies the solidification stage where the glycoprotein of bodily fluid layer and the polymer particles between diffuses and frame optional bonds. This will fortify and draw out the attachment. One might say that bio bond or Mucoadhesion can't be clarified by a solitary hypothesis rather it is better clarified by joining all or a portion of the previously mentioned components.

A basic mechanistic approach of Mucoadhesion involves in two steps: (i) intimate contact between a Mucoadhesive and a membrane (wetting /swelling phenomenon) and (ii) penetration of Mucoadhesive into tissue or into mucus membrane. [6, 33-35]

ENVIRONMENTAL FACTORS

pH of polymer-substrate interface: pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

Applied strength

While placing a buccal Mucoadhesive agent, sufficient strength should be applied to provide a good bio-adhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient longtime make the polymer become bio-adhesive with mucus.

Initial contact time

Contact time between the bio-adhesive and mucus layer determines the extent of swelling and interpenetration of the bio-adhesive polymer chains. Moreover, bio-adhesive strength increases as the initial contact time increases.

Moistening

Moistening is required to allow the muco-adhesive polymer to spread over the surface and create a macromolecular network of sufficient size for the interpenetration of polymer and mucin molecules to increase the mobility of polymer chains. However, there is a critical level of hydration for muco-adhesive polymers characterized by optimum swelling and bio-adhesion.

Presence of metal ions

Interaction with charged groups of polymer and mucus can decrease the number of interaction sites and the tightness of muco-adhesive bonding. [36]

CHALLENGES AND FUTURE PROSPECTUS BY MUCOADHESIVES DRUG DELIVERY SYSTEM

Mucus layer otherwise called mucosal film and it makes difficulties to the medication drug delivery system and medication retention because of its

physiochemical nature and synthesis. Mucus is the unpredictable discharge of mucous layer which comprises of water and mucin. It outlines gel like layer which contains epithelial film of the oral pit. Artificially mucin is glycoprotein which is produced using single chain amino acids spines with extended oligosaccharide chain the advancement of fate of organic liquid is real characteristic factor. The organic liquid improvement rate in like manner encounters the patient assortment and disease conditions like peptic ulcers, ulcerative colitis, bacterial or parasitic et cetera along these lines, the blueprint MDDS for all patients and is truly testing. Low dissolvability is a noteworthy issue amid planning, cleansing, transportation, and capacity of protein and peptide pharmaceuticals. Keeping in mind the end goal to upgrade the dissolvability of ionizable biologics, the ionic condition can be controlled by salts. At low salt fixation, proteins are encompassed by an ionic situation with an abundance of oppositely charged particles. This phenomenon decreases the biologic electrostatic free energy, resulting also in a decrease of its activity and an increase in its solubility, so that the chemical potential of the protein in solid phase remains constant. In this manuscript, we provided a range of models surrogating mucosa but evidenced that the consideration of a mucus layer is often neglected. This observation is obviously variable depending on the route of administration and thus on the attempts to reproduce mucosae *in vitro*. The intestinal barrier has been studied for a long time and new promising techniques have been developed. However, their reproducibility and robustness are not yet completely defined. Other models mimicking the mucosa of the cervico-vaginal tract, the respiratory tract or the buccal mucosa are not exhaustive since their routes of administration are less used in practice. Thereby, the number of available cell lines, for instance, is lower and the development of cell-based model more tedious. [37]

The consideration of the mucus layer on *in vitro* mucosal barriers is not always the case whereas its consideration is crucial in order to develop new drug delivery Systems. Nano- or micro-particles are used to protect sensitive active molecules or to increase their permeability. Although a paradigm still exists between mucus penetrating particles (MPP) and muco-adhesive particles (MAP), they are currently one of the most attractive solutions to spread up the development of mucosal drug delivery. Moreover, the lack of well-characterized models-producing mucus and their reproducibility is still an issue. In order to demonstrate that a nanocarrier improves the permeability of an active molecule by increasing its mucus diffusion, a model with the presence and the right amount of mucus has to be used. The development of in vitro models which include all the components of the mucosal barrier and obviously the mucus layer will presumably help in developing new medicines. [38-40]

Over the last few decades, research in Mucoadhesive drug delivery becoming more popular because it does have significant advantages like avoidance of first pass metabolism, pre-systemic elimination in the gastrointestinal tract, low enzymatic activity and high patient compliance. Novel definitions need to consider the substance nature and physical structure of these materials to give satisfactory other options to medicate drug delivery systems. The mechanistic approach taken after by various polymeric frameworks to follow with the bodily fluid layer has appeared in the better approach to pick it for the novel definition to be planned and assessed. Significant work is still needed to develop models which are able to derive *in vitro* and *in vivo* correlations for such systems. Distinctive Mucoadhesion assessment strategies portrayed has been discovered helpful for the deliberate in vitro investigation of various Mucoadhesive plans. Assist the choice of best Mucoadhesive operator relies upon the helpful test which is to be tackled and as needs be a reasonable Mucoadhesive polymer or its subordinate could be chosen to build up a promising delivery system.

ACKNOWLEDGEMENT

The authors acknowledge the SVU College of Pharmaceutical Sciences, SV University, Tirupati.

REFERENCES

1. Mansuri S, Kesharwani P, Jain K, Tekade RK, Jain NK. Mucoadhesion: A promising approach in drug delivery system. Reactive and functional polymers. 2016; 100: 151-172
2. Shaikh TA, Shinkar DM, Saudagar RB. Review: Polymers used in the Mucoadhesion Drug Delivery System. International journal of pharma research & review. 2016; 5(5):45-53.
3. Khan AB, Mahamana R, Pal E. Review on Mucoadhesive Drug Delivery System: Novel approaches in modern era. RGUHS J Pharm Sci. 2014; 4(4): 128-141.
4. Chatterjee B, Amalina N, Sengupta P, Mandal UK. Mucoadhesive polymers and their mode of action: a recent update. Journal of applied pharmaceutical science. 2017; 7(05): 195-203.
5. Singh R, Sharma D, Garg R. Review on mucoadhesive drug delivery system with special emphasis on buccal route: An important tool in designing of novel controlled drug delivery system for the effective delivery of pharmaceuticals. J Dev Drugs. 2017; 6: 169.
6. Laffleur F. Mucoadhesive Polymers for Buccal Drug Delivery. Drug Dev Ind Pharm. 2014; 40(5):591-598.
7. Patel KV, Patel ND, Dodiya HD, Shelat PK. BuccalBioadhesive Drug Delivery System; An overview. International Journal of Pharmaceutical and Biological Archeives. 2011; 2(2):600-609.
8. Humphrey SP, Williamson RT. A review of saliva: normal composition, flow and function. J. Prosthet. Den. 2001; 85: 162-169.
9. Shojaei AH. Buccal Mucosa as A Route for Systemic Drug Delivery: A Review. J Pharm Pharm Sci. 1998; 1(1):15-30.
10. Hoogstraate JAJ, WWertz PW. Drug delivery via the buccal mucosa. Pharmaceutical Science & Technology Today. 1998; 1(7):309-316.
11. Onchel G. Formulation of oral mucosal drug delivery systems for systemic delivery of bioactive materials. Adved drug delivery systems. 1998; 13:75-87.

12. Galey WR, Lonsdale HK, Nacht S. The *in vitro* permeability of skin and buccal mucosa to selected drugs and tritiated water. J. Invest. Dermat 1976; 67:713-717.
13. Hoogstraate AJ, Cullander C, Nagelkerke JF, Senel S, Verhoef JC, Junginger HE, Bodde HE. Diffusion rates and transport pathways of fluorescein isothiocyanate (FITC)- labeled model compounds through buccal epithelium. Pharm. Res. 1994; 11: 83-89.
14. Magnusson BM, Walters KA, Roberts MS. Veterinary drug delivery: potential for skin penetration enhancement. Advanced Drug Delivery Reviews. 2001; 50: 205-227.
15. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Ross Kerr A, Lockhart PB, Patton LL, Porter S, Thornhill MA. A New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Advanced Drug Delivery Reviews. 2012; 64:16-28.
16. Nicolazzo JA, Reed BL, Finnin BC. Buccal penetration enhancers-How do they really work. Journal of Controlled Release. 2005; 105:1-15.
17. Steward A, Bayley DL, Howes C. The effect of enhancers on the buccal absorption of hybrid (BDBB) alpha-interferom. Int. J. Pharm. 1994; 104:145-149.
18. Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products. Expert Opin Drug Deliv. 2016; 13(4):493-506.
19. Parikh T, Gupta SS, Meena AK, Vitez I, Mahajan N, Serajuddin ATM. Application of film-casting technique to investigate drug-polymer miscibility in solid dispersion and hot-melt extrudate. J Pharm Sci. 2015; 104:2142–52.
20. Buanz ABM, Saunders MH, Basit AW, Gaisford S. Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. Pharm Res. 2011; 28:2386–92.
21. Londhe VY, Umalkar KB. Formulation development and evaluation of fast dissolving film of telmisartan. Indian J Pharm Sci. 2012; 74:122–6.
22. Lindén M. Hot-melt extrusion of modified release pellets influence of the formulation and extrusion process on extended-and enteric release profile. Master of Science Thesis in the Master Degree Programme, Biotechnology, Chalmers University of Technology, Gothenburg, Sweden, 2012.
23. Sahni J, Raj S, Ahmad FJ, Khar RK. Design and in vitro characterization of buccoadhesive drug delivery system of insulin. Indian J Pharm Sci. 2008; 70:61–5.
24. Park J-B, Prodduturi S, Morott J, Kulkarni VI, Jacob MR, Khan SI, et al. Development of an antifungal denture adhesive film for oral candidiasis utilizing hot melt extrusion technology. Expert Opin Drug Deliv. 2015; 12:1–13.
25. Scoutaris N, Alexander MR, Gellert PR, Roberts CJ. Inkjet printing as a novel medicine formulation technique. J Control Release. 2011; 156:179–85.
26. Repka MA, Munjal M, ElSohly MA, Ross SA. Temperature stability and bioadhesive properties of δ9-tetrahydrocannabinol incorporated hydroxypropylcellulose polymer matrix systems. Drug Dev Ind Pharm. 2006; 32:21-32.
27. Arrabito G, Pignataro B. Inkjet printing methodologies for drug screening. Anal Chem. 2010; 82:3104–7.
28. Krampe R, Visser JC, Frijlink HW, Breitkreutz J, Woerdenbag HJ, Preis M. Oromucosal film preparations: points to consider for patient centricity and manufacturing processes. Expert Opin Drug Deliv. 2015; 1–14.
29. Zhang Y, Cui L, Che X, Zhang H, Shi N, Li C, Chen Y, Kong W. Zein-based films and their usage for controlled delivery: origin, classes and current landscape. J Control Release. 2015; 206:206-19.
30. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: a focus on mucoadhesive buccal drug delivery systems. J Pharm Sci Technol. 2012; 66(5):466– 500.
31. Boddupalli B, Mohammed Z, Nath R, Banji D. Mucoadhesive drug delivery system: An overview. J Adv Pharm Technol Res. 2010; 1(4):381.
32. Dodou D, Breedveld P, Mucoadhesives in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm. 2005; 60(1):1–16.
33. Derjaguin B V, Toporov YP, Muller VM, Aleinikova IN. On the relationship between the electrostatic and the molecular component of the adhesion of elastic particles to a solid surface. J Colloid Interface Sci. 1977; 58(3):528–33.
34. Edsman K, Hägerström H. Pharmaceutical applications of mucoadhesion for the nonoral routes. J Pharm Pharmacol. 2005; 57(1):3–22.
35. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco- and bioadhesion: Tethered structures and site-specific surfaces. J Control Release. 2000; 65(1–2):63–71.
36. Good RJ. Surface free energy of solids and liquids: Thermodynamics, molecular forces, and structure. J Colloid Interface Sci. 1977; 59(3):398–419.
37. Kinloch AJ. The science of adhesion - Part 1 Surface and interfacial aspects. J Mater Sci. 1980; 15(9):2141–66.
38. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials: A review. Biomaterials. 1996; 17(16):1553–61.
39. Lee L-H. The chemistry and physics of solid adhesion. In: Fundamentals of Adhesion. New York: Plenum Press; 1991. pp. 454.
40. Ahagon A, Gent AN. Effect of interfacial bonding on the strength of adhesion. J Polym Sci Polym Phys Ed. 1975; 13(7):1285–300.

HOW TO CITE THIS ARTICLE: Deevan Paul A, Samatha P, Manasa S, Munemma R, Supriya D. Modeling the Oral Cavity with Mucoadhesive Drug Delivery Systems - A Potential Alternative to Conventional Therapy. Int. J. Pharm. Sci. Drug Res. 2017; 9(6): 299-307. **DOI: 10.25004/IJPSDR.2017.090603**