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BIOADHESION DRUG DELIVERY SYSTEM

Pranita P. Zodape*, Sanskruti B. Gudadhe, Prof. Vishnudas K. Lokhnade, Dr. Rahul.S Bijwar and Dr. Laxmikant N. Barde

Jagadambha Institute of Pharmacy & Research, Kalamb.

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***Corresponding Author**
Pranita P. Zodape
Jagadambha Institute of Pharmacy & Research, Kalamb.

ABSTRACT

Since the early 1980 the concept of bioadhesion has gained considerable intrest in pharmaceutical technology. This article focuses on defining the principles of bioadhesive drug delivery system based on hydrogels to biological surfaces that are covered by mucus. It is ideal for the buccal distribution of drugs that have a short biological half-life, a low molecular weight, poor water solubility, an unstable pH, a low dose, and a high first-pass metabolism. There are many routes of mucoadhesive drug delivery system, oral route is the most ancient as well as preferred by patient being convenient to take. The buccal mucosa is very suitable for a bioadhesion system because of a smooth and relatively immobile surface and accessibility. Attention is given to latest breackthroughs such as new polymers, and also adherence to therapy in patients. The bioadhesive polymers can exert control over the rate and extend of drug release and are selected in the formulation of mucoadhesive drug delivery systems.

KEYWORDS: Global adhesion, histoarchitectural features, translucent, cyclodextrin, keshary chie cell, buccostem.

1. INTRODUCTION

In any pharmaceutical formulations, an excipient is one of the ingreadients or inactive substances that help in designing the dosage form and improving physiochemical properties such as solubility, absorption and bioavailability of the dosage form.[1] It has been reported that the chemical modification of polysaccharides improves the functional properties of native gums in different literatures.[2] During the past 20 years, advances in drug formulation have been made.[3] The administration of drugs by transdermal or transmucosal routes offers

the advantage of being relatively painless.[4] Selecting a suitable route of drug delivery within the oral cavity is mainly based on anatomical and permeability differences that exist across the various oral mucosal routes.[5] The buccal mucosa offers an easily accessible and generally well-accepted site for delivering systemically acting drugs for the treatment of chronic diseases.[6] The traditional oral method of medicine administration is not always effective, according to our present knowledge of the biochemical and physiological variables impacting absorption and metabolism. It is often seen that there is a strong lack of correlation between membrane permeability, absorption, and bioavailability.[7]

This is mostly due to the medications' substantial pre-systemic clearance after delivery.[8] Even though rectal, vaginal, and ocular mucosae all have all their advantages, the unwillingness of patients to utilize them restrict than systemic medication delivery.[9-11] Increasing the release of the drug at a long term and achieving mucoadhesive drug delivery system may have the lowdose and multi-route administration through nasal, oral, vaginal, rectal and buccal delivery.[12] The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora.[13] The polymers used for delivery of drugs through rectal and vaginal routes are gelatin, mucin, poloxamer and polycarbophil. Various rectal and vaginal formulations include creams, ointment, in-situ gels, emulgels, tablets.[14] In case of polymer attached to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used.[15] The aim of strategy is to avoid this reduction of drugs by enzymes of liver and synthesize in the gut by the first-pass hepatic metabolism.[16]

BASED ON SOURCE

Synthetic polymers	Natural polymers
• cellulose derivatives • poly (acrylic acid) • poly (hydroxyethyl methyl acrylate) • poly (ethylene oxide) • poly (vinyl alcohol) • thiolated polymer	• tragacanth • sodium alginate • agarose • pectin • chitosan • gelatin[17]

BASED ON SOLUBILITY

Water soluble polymers	Water insoluble polymers
• hydroxy ethyl cellulose • hydroxy propyl cellulose • poly (acrylic acid) PAA	• Chitosan • Ethyl cellulose • polycarbofil

• sodium CMC • HPMC	

BASED ON CHARGE

Cationic polymers	Anionic polymers	Non anionic polymers
• chitosan • dimethyl amino ethyl dextran • amino dextran	• chitosanEDTA • CMC • CP (Carrageenan) • Pectin • PPC (Polyvinyl carboxylic acid) • PPA	• hydroxyethyl starch • PVA • HPC • Scleroguca n

BASED ON POTENTIAL

Bioadhesive forces	Covalent bond	Hydrogen bond
• Cynoacrylates	• HPC	• CP (carrageenan) • PVA • PC • Acrylates

BASED ON GENERATION

First generation	Second generation
• Aminodextran • Chitosan • CMC • Scleroglucan • Pectin • Xantham gum • PAA (Polyacrylic acid)	• Lectins • Thiolated polymers[18]

2. Theory of mucoadhesion

1. Wetting theory
2. Electronic theory
3. Fracture theory
4. Adsorption theory
5. Diffusion theory
6. Mechanical theory

1. Wetting theory

The ability of bioadhesive or mucus to spread and develop intimate contact with its corresponding substrate is an important factor in bond formation.[19] The wetting theory was developed predominantly in regard to liquid adhesive, uses interfacial tensions to predict spreading and in turn adhesion.[20-21] The study of surface energy of polymers and tissues to

predict mucoadhesive performance has been given considerable attention.[22-23] According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion[24]. The general rule status that the lower the contact angle should be equal or close to zero to provide adequate spreadability.[25]

It involves the ability of a liquid to spread spontaneously on to a surface as a prerequisite for the development of the adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle of the liquid on the surface, with the general rule being that the lower contact angle, the greater the affinity of a liquid to the solid.[26]

2. Electronic theory

The hypothesis of the electronic theory relies on the assumption that the bioadhesive material and the target biological material have different electronic structure.[27] On this assumption, electron transfer occurs upon contact of an adhesive polymer wit the mucus glycoprotein network because of differences in their electronic structure.[28] This results in the formation of an electrical double layer at the interface of the mucus and the polymer, which results in forces of attraction in the region and interdiffusion of the two surfaces.[29]

3. Fracture theory

This is by-far the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum tensile stress (S_m) produced during detachments.[30]

$$\mathbf{S_f=F_m/A_0}$$

Where F_m and A_0 represent the maximum force of detachment and the total surface area respectively. In a uniform single-component system, fracture strength (S_f), which is equal to stress of detachment (S_m),is proportional to the fracture energy(g_c), Youngs modulus of elasticity (E) and the critical crack length (c) of the fracture site.[31]

$$\mathbf{Sf=(gcE/c)1/2}$$

Fracture energy can be obtained by the sum of the reversible work adhesion, W_r(work done to produce new fracture surface) and the irreversible work of adhesion, W_i (work of plastic deformation).[32-33]

$$gc=Wr+Wi$$

4. Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der waals and hydrogen bonds, elrctrostatic attraction or hydrophobic interaction.[34] for example, hydrogen bonds are prevalent interfacial forces in polymers containing carboxyl groups.[35-36] Such forces have been considered the most important in adhesive interaction phenomenon.[37-38] Because, although they are individually weak, a great number of interactions can result in an global adhesion.[39]

5. Diffusion theory

The basic of the diffusion theory is chain entanglement between glycoproteins of the mucus and the mucoadhesive polymer chains.[40] The production of semipermanent adhesive bond is supported by diffusion theory.[41] Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymer, similar chemical structure, and the diffusion coefficient of the bioadhesive polymer are among the factors that influence the inter-diffusion of the macromolecule of network. Therefore, the strongest bioadhesive bonds should form between biomaterials whose solubility parameter are similar to those of the target mucus glycoproteins.[42]

6. Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surfaces by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.[43]

3. Factors affecting mucoadhesion[44]

The mucoadhesion of a drug carrier system to the mucus membrane depends on the below mentioned factors.

- Polymer based factors
- Hydrophilicity[45-47]
- Molecular weight of the polymer[48]
- Concentration of polymer chains[42]
- Swelling factors[49-51]
- Stereochemistry of polymers[52-58]

➢ Physical factors

- pH at polymer substrate interface[59]
- Applied strength[60]
- Contact time[61]

➢ Physiological factors

- Mucin turnover rate[62]
- Diseased state[63]

4. Methods of analyzing mucoadhesion

No technology has still been developed specifically to analyze mucoadhesion**.** Most of the tests available were adapted from other preexisting techniques but are useful and necessary for selecting the promising candidates as mucoadhesives as well as elucidating their mechanism of action.

In vitro tests/exvivo[64]

- methods determining tensile strength
- methods determiningshear stress
- adhesion weight method
- fluorescent probe method
- flow channel method
- thumb method
- adhesion number
- electrical conductance
- swelling properties
- in vitro drug release studies ✓ mucoretentability studies

In vivo methods[65]

- use of radioisotops
- use of gamma scientigraphy
- use of pharmacoscientigraphy
- use of electron paramagnetic resomamce (EPR) oximetry
- X ray studies
- Isolated loop technique

5. ROUTES OF MUCOADHESION DRUG DELIVERY SYSTEM

5.1. BUCCAL DRUG DELIVERY SYSTEM:- The buccal mucosa, which is the inner cheek inner lining, is a prime area for drug delivery. These oral forms are developed specifically for placement between the gums and the cheek on the upper side of the mouth, thus allowing delivery of the drug to systemic as well as local condition. This means can provide a viable alternative especially for substances that may have challenges with traditional delivery methods. In this regard, buccal delivery route is more suitable for submits characterized by large size, hydrophilic, and probable unstable properties such as proteins, oligonucleotides, and polysaccharides. On the other hand, the administration of even the conventional small drug molecules can take place intradermal way. The oral mucosa enables beneficial substances to be absorbed directly into the bloodstream skipping the intestinal tract and paralleling degradation in the stomach due to the acidic environment. The oral cavity itself is an area that has unanimously been identified as an ideal site for drugs to be locally delivered together with improved bioavailability and therapeutic efficiency due to its accessibility. The buccal mode of drug administration provides the highest degree of convenience and patient-friendliness for many medications.[66] The oral mucosa is a quite sophisticated structure made up of three distinct layers – epithelium, basement membrane and connective tissues.

Permeability barrier property: The oral mucosa functions as a diffusion barrier through the channels which are constructed from the materials obtained from the cellular membranes of the glycocalyx. The epithelial layer integrity is compromised by these materials, thus, they become the passage through the mucosa. Buccal Mucosa: The oral mucosa, representing a third part of the oral cavity's total surface area of 100 cm^2, also presents itself as an alternate route of drug delivery. However, a patient's preference often goes for oral route, which poses certain hurdles that prevent using oral form for peptides and protein drugs such as hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract (GI). Transmucosal drug administration occurs across mucosa linings, for example the nasal, rectal, vaginal and ocular mucosa, which provides advantages relative to oral administration. Transmucosal routes have advantage of bypassing first-pass metabolism, avoiding pre-systemic elimination in gastrointestinal tract and exerting action against favourable enzymatic flora in the intestines for absorption. Even though nasal, rectal, vaginal, or ocular mucosa have several advantages, their poor patient acceptability limits their use in systemic drug transport. Only the local applications are thought to be worth their use.[67]

The oral cavity which has a surface area of 100 cm^2 containing the buccal or cheek surface covered with a 0.5 mm thick epithelium. The main role of the oral mucosa is to cover the underlying structures. The epithelial tissue is able to retain liquids due to the lipid-based permeability barriers which protect it from fluid loss and environmental agents such as toxins and antigens, carcinogens, and enzymes. Oral epithelium undergoes mitosis in 5-6 days. The oral cavity encompasses two regions: the outer oral vestibule, bordered on the outside by cheeks, lips, teeth, and gums, and the oral cavity proper, stretching from teeth and gums to throat points leading to the pharynx. The roof is the hard and soft palate, and the tongue is the projection from the floor of the cavity. The buccal mucosa, with its unique properties, is a potential site for drug delivery, as this has a joint preference on the part of the patient and systemic drug absorption advantages.[68]

5.2. ORAL DRUG DELIVERY SYSTEM

Oral mucosa: In the oral mucosal cavity, the buccal region appears to be a much more attractive pathway to administer drug delivery on a system level. The mucosa has a very rich blood supply and is a type of barrier that is comparatively permeable.

Oral histology: This epithelium being notably thicker, in the buccal mucosa contains about 50 cell layers. On the contrary, the sublingual epithelium has less layers than the root epithelial tissue. The transitional process involves the epithelial cells undergoing variations in the shape as they advance from the deepest layer to the outermost layer. These histoarchitectural features subsequently affect the movement and function of oral mucosa, particularly in areas like buccal cavity where oral drug delivery relies predominantly on the systemic delivery system.[69]

The drug delivery systems are aimed at the disease periodontitis that is manifested by inflammatory tissue destruction of the supporting tissues of teeth. Treatment usually involves the combo of mechanical interventions and administration of chemotherapeutic agents into the intraperiodontal pockets. Last but not the least, the oral cavity accommodates both local and systemic administration of drugs, the availability of various formulations makes treatment of the patients reasonably comfortable and compliant.[70]

Recent Application in Oral Mucoadhesive Drug Delivery: Recent Application in Oral Mucoadhesive

Drug Delivery: The oral mucoadhesive system of drug delivery has such a therapeutic goal to take into account all drugs that easily undergo rapid degradation and display poor bioavailability after administering the drug orally. These mucoadhesion properties, by extension, offer drugs with a longer residence time in the oral cavity and lead to better absorption and bioavailability, specially for the drugs that are confronted with difficulties in the gut or other parts of the body.[71]

5.3. VAGINAL DRUG DELIVERY SYSTEM

Vagina serves as the main avenue of administration of the different pharmaceutical products such as contraceptives, anti-fungal drugs and antibiotics among others. This option can be used for realizing local effects or to absorb persistent, thus making it mobile among the drug delivery means. Vagina and its vasculature network specifically incline to drug absorption and its systemic use. Agents and formulations administered vaginally are often developed in order "dual prophylaxis" which means addressing both contraception and microbial infections such as sexually transmitted infections (STDS), HIV among other that cause AIDS. The ability of this route to deliver drugs to the walls of the vagina allows for the effective treatment of both women's health problems and reproductive issues as well.[72]

5.4. NASAL DRUG DELIVERY SYSTEM:

The nasal cavity has a significant role as a therapeutic site for certain local diseases such as sinusitis and nasal block. Nevertheless, the last few years had been witnessing a tremendous upsurge in the nasal drug delivery as the promising hurdle to reach systemic therapy. This specific attitude has to do with the anatomical and physiological characteristics of the nasal cavity, which contains a high-surface area, greatly vascularized epithelium, permeable endothelial membrane and the bypass of first-pass metabolism. Additionally, at the nasal mucosa, the large surface area for absorption, reduced proteolytic activity accompanied by a possibility of higher patient compliance as well as lower cost of production compared to the parenteral products make it a potential site for vaccine delivery.[73]

This cavity is lined with three types of epithelia: basal, respiratory, and olfactory cells as well.Anterior part of the nose shows a flattened mucosa without cilia, which is followed by a respiratory epithelium in the anterior nostrils. The olfactory epithelium is located in the posterior nasal cavity; its ciliated cells drive a unidirectional mucus movement from the nose down to the pharynx.[74]

5.5. RECTAL DRUG DELIVERY SYSTEM

The rectum serves as the final segment of the large intestine, extending from the end of the sigmoid colon to the anal canal.

The drug when given via the rectal route offers the benefit of resistance to enzymatic breakdown could be the insulin, avoids first-pass metabolism when the suppository is appropriately placed, and protects the mucosa from the gastric pain inducer drugs, including the NSAIDs.[75]

Rectal Anatomy and Physiology: The rectum acts the last part of the large intestine beginning at end of the sigmoid colon up until the anal canal. Its main objective is to act as a channel for a temporary detour or storage site process and is of low importance in the way of water and electrolytes uptake of its contents. The abdomen of children has a lesser size as compared to that of adults' when it comes to anatomy. The rectum is a sidewalk in adults, measuring 15-20 signage. It has a surface area of 3-4 handsized pieces of scaffolding. The reason why children growth-wise show variance in size is that their guts keep growing to be more of a man.Mark another instance of the rectum, which at 1 month after birth will have a length of approximately 3cm and a surface area of about 18 cm2, but it will grow in length to around 12 cm and a surface area of 230 cm2 at aged 10. Routinely a rectum is filled with 1-3ml of fluid, pH balance 7-8 and doesn’t have any abilities to buffer.[76]

- Liquid Formulations: These formulations represent quick drug degradation and solubilization within the rectal fluid. Liquids are featured with the excellent spreading capability, not only contributing to the local and systemic effects of a drug.

- Solid Formulations: Rectal solid dosage forms are subjected to a process that involves disintegration, liquefaction, and dissolution which enable the drug to be absorbed through the epithelium. Among the reasons is that the beginning of the therapeutic impact of the solid formulations is usually slower than for the liquids.

- Semi-Solid Dosage Forms: Employed to treat local conditions like ano-rectal pruritus, swelling, and hemorrhoid-specific pain, the semi-solid rectal forms of dosage have enhanced retention time in rectum. It leads to improved patient compliance, reduced discomfort, and accelerated drug release efficacy.[77]

6. Mechanism

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism[78],

1. Intimate contact between a bioadhesive and a membrane[79] (wetting or swelling phenomenon).
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane.[79] (interpenetration).[80] Residence time for most mucosal routes is less than an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption.[81] Many of the ortho-linked oligosaccharides side chains are often terminated in salicylic acid, sulfonic acid, L-fructose.[82]

7. Limitations

Drug administration via this route has certain limitations

1. Drugs that are unstable at buccal pH cannot be administered.
2. Only drugs with a small dose requirement can be administered
3. Eating and drinking may become restricted.
4. There is a possibility of the patient swallowing the tablet.[83-85]
5. Surface area available for adsorption is less.
6. Sometimes, the degradation of moisture sensitive drugs may take place by saliva.[86]

8. Overview of the oral mucosa

Antomy and structure of the oral cavity:- the oral cavity is lined by a relatively thick, dense, and multilayered mucous membrane of a highly vascularized nature. The epithelium of the oral cavity is in principal similar to that of the skin, interesting difference regarding keratinization and the protective and the lubricant mucus across its surface.

The oral cavity can be divided into three functional zones:

1. The mucus-secreting regions consisting of the soft palate, the floor of the mouth, the underside of .the tongue, and the labial and buccal mucosa, which have a normally nonkeratinized epithelium.
2. The hard palate and the gingival are the regions of the masticatory mucosa and have a normally keratinized epidermis.

3. Specialized zone consisting of the tongue with its highly selective keratinization.[87-88]

9. Composition of mucus layer

mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450um in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cell acini. The exact composition of the mucus layer varies substancially, depending on the species, the anatomical location and the pathological state. However, it has the following general composition.[89]

1. Water	95%
2. glycoproteins and lipids	0.5 to 5%
3. mineral salts	1%
4. free proteins	0.5 to 1%

Mucus glycoproteins are high molecular proteins possessing attached oligopolysaccharide units. They are

a) L-fructose
b) D-galactose
c) N-acetyl –D-glucosamine
d) N-acetyl-D-galactosamine
e) Salicylic acid

10. Advantage of the mucoadhesive buccal drug delivery system

drug administration via the oral mucosa offers several advantages[83-85]:

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for a long time.
4. Can be administered to unconscious patient.
5. Because its accessibility it prmits localization of controlled drug delivery system and allows opportunity to locally modify tissue permeability, inhibit protease activity, or decrease immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins, and ionized species can be achieved.[87]
6. Therapeutic serum concentration of the drug can be achieved more rapidly.[90]
7. Drug is protected from degradation in the acidic environment in the GIT.[91]

11. Disadvantages of the mucoadhesive buccal drug delivery system

1. low permeability of the buccal membrane, specifically when compared tp the sublingual membrane.
2. The continuous secretion of saliva (0.5-21/day) leads to subsequent dilution of drug.
3. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately the involuntary removal of the dosage form.[92]
4. Patient acceptability in terms to taste and irritancy.
5. One of the major limitations in the development of oral mucosal delivery is the lack of good model for in vitro screening to identify drugs suitable for such administration.
6. Eating and drinking is prohibited.[93]

12. Buccal mucoadhesive dosage forms

An ideal drug delivery system should possess the two main properties given below:

a) Spatial placement (for targeting drug to specific organ/tissue)
b) Temporal delivery (for controlling the rate of drug delivery)

Today, it is very difficult to formulate an ideal drug delivery. This led to development of sustained/controlled release delivery systems. Still, sustain or controlled delivery system lacks in preventing drugs loss by either hepatic first pass metabolism or presynaptic elimination like grastic, intestinal, or colonic degradation. So, several approaches have been tried to form a suitable dosage form for the above said conditions. Oral mucosal drug delivery, one of the physiological approaches, was reported to be a method to formulate these drugs into suitable dosage form with good therapeutic effects.[94]

13. General consideration in designing dosage forms

13.1. Physiological aspects: Due to the constant flow of saliva and regular movement of tissues present in the oral cavity is the most challenging aspects. Due to this, the residence time of drugs for this routes is very short[95]. The bioadhesive polymers are been use for improving the residence time in the buccal mucosa, and hence increase the absorption of drugs, side effects are also being reduced as compare to in case of systemic delivery.[96]

13.2. Pathological aspects: The barrier property of buccal mucosa is mainly due to presence of epithelial tissue. The thickness of epithelial tissue can be affected by many diseases that may change the barrier property of epithelial tissue. Some disease or treatment may cause the alteration in rate of mucus secretion. These changes at the mucosal surface due to various pathological conditions may affect the residence time buccal delivery device.[97-99]

13.3. Pharmacological aspects: the design and formulation of a buccal delivery dosage form depends upon the nature of delivery (local or systemic), drugs targeting site and mucosal site to be treated. The buccal delivery is generally preferred for systemic delivery as compared to the local delivery of drugs.[100]

13.4. Pharmaceutical aspects: The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstly the water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increase in buccal mucosa.[101] There are some polymer such as carbopol, polycabophil that can inhibit certain proteolytic enzymes.[102]

14. Classification of Buccal Adhesive Dosage Forms

14.1. Solid dosage form

Buccal tablet: The bioadhesive tablets are most preferable mucoadhesive device in order to I improve bioavailability of drugs. Mucoadhesive tablet can be prepared by methods such as wet granulation and direct compression. In case of buccal drug delivery, the tablets are placed in buccal pouch below the muscles of teeth. Mechanism of drug release is erosion.

Advantages: The buccal tablet can developed for verity of drug including insoluble to soluble, low dose to high dose, hydrophilic to lipophilic. As compared to conventional tablet, buccal tablet are flats mall and retained at site until release and/or dissolution is complete.

Disadvantages: They provide little bit of discomfort to the buccal cavity because of their solid nature.[103]

1. Bioadhesive microsphere: Microsphere is an important part in case of novel drug delivery system. This mucoadhesive microsphere is mainly used for purpose of targeting of specific body cavity.

Advantages: They provide high absorption and enhanced bioavailability of drug due to their surface-to-volume ratio that provide highest contact of microspheres with mucus membrane.

2. Bioadhesive wafers: It is a newer dosage form for bioadhesive buccal delivery. It is used at the periodontal region for the treatment of infections related with periodontitis.[104]

3. **Bioadhesive lozenges**: Bioadhesive lozenges are generally used for delivery of drugs that are antimicrobials, corticosteroids, local anesthetics, antibiotics and anti-fungals and are used topically in the buccal cavity.

Advantages: Better patient compliance and easy to swallow. Disadvantages: The lozenge produce a high release rate of drug at initial stage and rapidly reaches the sub-therapeutic level.[104]

14.2. Semisolid dosage form

1. Bioadhesive patch/film: Patches or film are preferred over tablet because of their comfort and flexibility. they are formulated such that it can provide contact between bioadhesive formulation and mucosa. Thickness of patch is a constraint which cannot provide control release of drug for longer period of time. In case of drug containing reservoir layer type; drug is released in controlled manner. Patches and film are mostly preferred for local action to treat oral diseases. There are many methods used for formulation of patch or films such as solvent casting method, hot melt extrusion technique, direct milling, semisolid casting, solid dispersion extrusion etc. Among that solvent casting is most popular method and widely used.[105]

2. **Buccal gel and ointment**: As the advantage of dispersion gel and ointment has come in focus. They do not have accurate dosing as unit dosage form like tablet, patches or films hence they are mostly preferred for local action where dose accuracy is less or not concern.

Advantages: local application of steroidal gel for treatment of mucosal ulceration in order to decrease the side effects of steroids.

Disadvantages: It has less patient acceptability than other mucoadhesive formulation.[106]

3. **Medicated chewing gum**: Medicated chewing gum contains drug which after chewed, offer high amount of drug to prove local action in mouth. It can also shows absorption through systemic circulation. The medicated chewing gum for nicotine replacement therapy is available. Likewise caffeine chewing gums are also available.[107]

14.3. Liquid dosage form

These are available in form of solution or suspension of drug in suitable vehicle. There are many liquid dosage forms that are available in market such as mouthwashes, mouth

freshener, and are generally used for local delivery of drugs. Wide varieties of polymers are use from that chitosan has greatest binding capacity than other. Viscous liquid formulations are preferred to coat buccal cavity either as vehicle or as protectant.[108]

15. Evaluation of Buccal Mucoadhesive Dosage Forms

15.1. Experimental methodologies for buccal absorption/ permeability study

1. **In-vitro and ex-vivo methods of evaluation**: the in-vitro studies are used to determine the release, solubility and dissolution of dosage forms. The ex-vivo studies conducted on the animal tissues and membranes by preparing animal models. The tissues are taken from the freshly died animals and are been used within 2 hrs aier their separation. The membranes are then placed and stored in ice-cold (4°C) Kreb's buffer up to the time before they are mounted between diffusion cell for the ex-vivo permeation experiments.[109]

2. **In-vivo methods**: It is also called as buccal absorption test. For kinetic drug absorption measurement this method can be used. the procedure involves the swirling of a 25 ml sample of the test solution for up to 15 min by human volunteers in their buccal cavity. after 15 min the solution expelled out. In order to calculate the amount of drug absorbed, the amount of drug present in expelled volume can be calculated. The main disadvantages including salivary dilution of drug and accidental swallowing of sample solution may arise.

3. **Experimental animal species**: Choice of animal for the experimental study is very important factor. To perform in-vivo study researchers can prefer the animals depending on test to be perform. Most of animals having the keratinized buccal mucosa, but the rabbit and pig are the only animals which having non-keratinized mucosa as like humans. To study permeation of drug monkey, dog, pig animals are mostly used. In-vitro release study:

For simulating in-vivo conditions, researchers have developed different apparatus like:

- Beaker method
- Dissolution apparatus
- Interface diffusion system
- Modified Keshary Chien cell

16. Permeability

The oral mucosa in general are somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported

value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. In general, the permeability of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal.[110] This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and nonkeratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG).[111] This barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase.[112] and lanthanum nitrate.[113] When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.

17. Penetration enhancer

The permeability barrier is one major obstacle to utilizing the oral mucosa for drug delivery. Researchers have looked at permeability enhancers as a possible remedy for this issue. Permeability enhancers are also necessary when an Active Pharmaceutical Ingredient (API) demands to reach the systemic circulation across the buccal mucosa to begin functioning. Enhancers contain various surfactants, one of which is bile salts. For bile salts to function, the membrane must be free of lipids or proteins, fluidized, reverse micellization initiated, and aqueous channels created. Azone produces a fluid area in intercellular lipids, fatty acids disrupt the intercellular lipid packing, and alcohols rearrange lipid domains and alter the conformation of proteins. The following are some elements that influence permeation enhancer selection and effectiveness:

- site of administration
- Physicochemical properties of the drug
- Nature of the vehicle

- Other excipients

Combining penetration enhancers usually yields a more noticeable result than using each enhancer separately. The efficiency of a penetration enhancer varies at different sites due to variations in structural and functional features, such as membrane thickness, lipid composition, cellular morphology, enzymatic activity, and potential protein interactions. Increasing buccal membrane penetration can take different forms depending on the medication.[114]

18. Evaluation of mucoadhesive buccal drug delivery systems

Buccal adhesive drug delivery devices are subjected to the routine evaluation tests such as weight variation, thickness variation, friability, hardness, content uniformity, in vitro dissolution of tablets; tensile strength, film endurance, hygroscopicity, etc. for gels and ointments. They should also to be evaluated specifically for their bioadhesive strengths and permeabilities.[115]

19. Previous Work Done on Buccal Mucoadhesive Drug Delivery System

In 2007, Ramana et al. designed and evaluated the buccal mucoadhesive drug delivery systems of Metoprolol Tartrate using the mucoadhesive polymers i.e., Carbopol-934, hydroxy methyl propyl cellulose, hydroxyl ethyl cellulose and sodium carboxy methyl cellulose. The best mucoadhesive performance and in-vitro drug release profile were exhibited by tablets containing hydroxyethyl cellulose and Carbopol-934 in 1:2.[116]

In 2008, Kolli et al. developed the buccal mucoadhesive patch of Prochlorperazine using various concentrations of HPMC E15 and Polyester backing membrane. They concluded that the formulation containing 2500 mg of HPMC E15 and 375 µl of Propylene glycol was the optimized formulation aier evaluating it in-vitro as well as ex-vivo studies.[117]

In 2010, Chaudhary et al. developed the mucoadhesive buccal patches of Methotrexate. They used the backing membrane prepared by ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The mucoadhesive polymers used were Sodium Alginate, carbopol-934, sodium carboxy methyl cellulose and polyvinyl pyrrolidine. The cumulative drug release of the formulation containing sodium alginate with a secondary polymer was found in order of Sodium alginate >carbopol-934 >Sodium Carboxy methyl cellulose >polyvinyl pyrroliidine at the end of 8 hours. The

formulation containing Sodium Alginate (800 mg), Carbopol-934 (200 mg), glycerol (10%) and water (30 ml) waste optimized formulation.[118]

In 2010, another study was also conducted by Velmurugan et al. They formulated the buccal tablets of Piroxicam using HPMC K4M and Carbopol-934 in different ratios. In this study H3 formulation comprising of piroxicam and HPMC K4M (1:3) show edoptimum drug release and satisfactory bioadhesive properties.[119]

In 2011, Naga Raju et al. formulated the buccal tablets of Metoprolol Tartrate using different Mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. Th prepared tablets were evaluated for bioadhesive strength and in-vitro drug release. In-vitro bioadhesive strength and in-vitro release studies showed that formulation containing 1:1.25 ratio of drug and polymer (Carbopol-934 and HPMC K4M) combination showed optimum bioadhesive and exhibited optimum drug release (77.33 ± 0.23).[120]

In 2011, the further study was conducted by Deshmukh et al. they formulated Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive agent obtained from the Fruits of Ficuscarica L. the formulation F1, F3, F4 and F5 showed Fickian diffusion formulation F2 showed Anomalous (non-Fickian) di ٍusion.[121]

In 2012, Mishra et al. formulated the buccal patches of Simvastatin. He buccal patchs were prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC. The formulation containing eudragit-RS100 and PVP(1:1) showed the maximum and faster release.[122]

In 2013, Sandhya et al. formulated buccal films of Ketorolac Tromethamine. Hese films were prepared by polymers like HPMC K 100M, HPMC E15, HPMC E50, Eudragit RLPO and developed by solvent casting method. Formulation F5 (HPMC E15-Polysorbate - Eudragit RLPO) exhibited best mucoadhesive performance and matrix controlled release. Swelling behaviour and duration of mucoadhesion are critical factors in the selection of satisfactory formulation.[123]

In 2013, the further study was conducted on Formulation and invitro evaluation of Losartan Potassium mucoadhesive buccal tablets by Velmurugan et al. They used mucoadhesive polymers such as Carbopol -940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination as release retarding agent to

prolong the drug release and to avoid first pass metabolism. Ex-vivo mucoadhesive strength, ex vivo residence time and in-vitro release studies showed that formulation F10 (sodium alginate and HPMC K100M) containing 1:1.25 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release.[124]

In 2014, Ganaie et al. formulated the mucoadhesive buccal film of Methyldopa using Hydroxy propyl methyl cellulose K-47 (HPMCK-47), poly vinyl pyrrolidine K-30 (PVP K30), sodium CMC and ethyl cellulose. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation F5 (HPMC K-47 and PVP K-30). The correlation coefficient value (r) indicates the kinetic of drug release was zero order.[125]

In 2015, Madhuri et al. designed the solid dosage form for buccal drug delivery of Diltiazem Hydrochloride using various polymers i.e., Carbopol971P (CP) and secondary polymers such as Hydroxy propyl methyl cellulose (HPMCK4M) and Psyllium husk in Six formulations. They concluded that the formulation B3 containing Carbopol971P and HPMC K4M in the ratio of 1:5 showed good mucoadhesive strength (51.34 gm) and maximum drug release of 94.72% in 8 hrs. Swelling of tablets increased with increase in concentration of HPMC K4M.[126]

In 2016, Nagarani et al. formulated the Esomeprazole mucoadhesive buccal tablets using mucoadhesive polymers like hydroxy propyl methyl cellulose K 100 M, Carbopol 934, HPMC K 15 M. Drug: polymer ratio for F5 is 1:1, this F5 (guar gum and carbopol -971P) formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug in desired period of 6 hrs and showed good swelling index properties.[127]

In 2016, the further study was conducted by Marimutho et al. On formulation and evaluation of Zidovudine mucoadhesive buccal patches using polymers i.e., HPMC E15, Sodium Alginate and gelatine. They concluded that the release of Zidovudine from the formulated patches followed zero order kinetics so that the drug release mechanism was controlled release.[128]

20. RECENT APPLICATIONS IN ORAL MUCOADHESIVE DRUG DELIVERY

Oral mucoadhesive drug delivery has widespread applications for many drugs which on oral administration result in poor bioavailability and are rapidly degraded by the oral

mucoadhesive drug delivery provides advantages of high accessibility and low enzymatic activity. Earlier the hydrophilic polymers like SCMC, HPC and polycarbophil were used for the treatment of periodontal diseases, but now the trend is shifting towards the effective utilization of these systems to the delivery of peptides, proteins and polysaccharides.[78]

The buccal cavity has additional advantages of high patient compliance. Orabase, a first generation mucoadhesive paste has been used as barrier system for mouth ulcers. Semisolids offer more ease in administration, but tablets have also been formulated. Tablets include matrix devices or multilayered systems containing a mucoadhesive agent. The tablet is kept under the upper lip to avoid clearance mechanism of the salivary gland. Buccostem, an adhesive antiemetic tablet containing prochlorperazine is usually administered in this manner.[129]

Buccal mucoadhesive dosage forms may be classified into three types,

- A single layer device with multidirectional drug release. - A dosage form with impermeable backing layer which is superimposed on top of and drug loaded bioadhesive layer, creating a double layered device and preventing loss from the top surface of the dosage form into the oral cavity.
- Unidirectional release device, the drug is releasesd only from the side adjacent to the buccal mucosa.

21. CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. The factors which are determinant in the overall success of the mucoadhesive drug delivery are the polymer physicochemical properties and the in-vivo factors such as the mucin turnover rate, mucin flow. A number of both in-vitro and in-vivo techniques have been developed for the evaluation of the mucoadhesive drug delivery systems. Mucoadhesive dosage forms extend from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The most widely studied and accepted polymers for mucoadhesion have been the hydrophilic, high molecular weight, anionic molecules like carbomers. Recently the focus has been on the novel second generation polymers like the thiolated polymers, lectins and lecithins. Despite the huge amount of work

been done on this drug dekivery platform, the focus has been primarily on the formulation of gastroretentive dosage forms, hence, work must be done to exploit this drug delivery system for various other approaches like drug targeting and site specific drug delivery systems.

22. REFERENCES

1. Kulkarni Vishakha S, Butte Kishor D, Rathod Sudha S. Natural polymers–A comprehensive review. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012; 3(4): 1597-1613.
2. Shankar B. Kalbhare,Vivek Kumar Redasani, Mandar J. Bhandwalkar, Rohit K. Pawar, Avinash M. Bhagwat. Role of Aminated derivatives of Natural Gum in Release Modulating Matrix Systems of Losartan Potassium: Optimization of Formulation using Box-Behnken Design. Asian Journal of Pharmaceutical Research, 2021; 11(2): 73-74.
3. Robinson, D. H.; Mauger, J. W. Drug delivery systems. Am. J. Hosp. Pharm., 1991; 48: S14 – S23.
4. Ullyot, S. C. Paediatric premedication. Can. J. Anaesth., 1992; 39: 533–536.
5. Bandyopadhyay, A. K.; Sudhakar, Y. Advances in buccal adhesive drug delivery. Drug Delivery Technology, 2006; 6(6): 51–55.
6. Giannola, L. I.; De Caro, V.; Giandalia, G.; Siragusa, M. G.; Campisi, G. Current status in buccal drug delivery. Wolff Pharmaceutical Technology Europe, May 1, 2008.
7. Harris, D. and Robinson, J.R., Drug delivery via the mucous membranes of the oral cavity. Journal of pharmaceutical sciences, 1992; 81(1): 1-10.
8. Janga, K.Y., Tatke, A., Dudhipala, N., Balguri, S.P., Ibrahim, M.M., Maria, D.N., Jablonski, M.M. and Majumdar, S., Gellan gum based sol-togel transforming system of natamycin transfersomes improves topical ocular delivery. Journal of Pharmacology and Experimental Therapeutics, 2019; 370(3): 814-822.
9. Donthi, M.R., Dudhipala, N.R., Komalla, D.R., Suram, D. and Banala, N., Preparation and evaluation of fixed combination of ketoprofen enteric coated and famotidine floating mini tablets by single unit encapsulation system. Journal of Bioequivalence & Bioavailability, 2015; 7(6): 279.
10. Mamatha, Y., Selvi, A., Prasanth, V.V., Sipai, M.A.B. and Yadav, V., Buccal drug delivery: a technical approach. Journal of Drug Delivery and Therapeutics, 2012; 2(2).
11. Reddy, P.C., Chaitanya, K.S.C. and Rao, Y.M., A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences, 2011; 19(6): 385.

12. Dhutwalia Pooja, KanwarKapil, Anju, Amrit, Ankush, CT Institute of Pharmaceutical Sciences, Shahpur, Jalandhar, "Review On Mucoadhesive Drug Delivery System" International Journal of Pharmaceutical, Chemical and Biological Sciences, Published in, 2014; 278-280.
13. Shaikh R, Raghurai ST, James GM, David WA, Donnelly R Mucoadhesive drug delivery systems. J of Pharm and Bioallied Sci., 2011; 3: 89-100.
14. Kumar K, Dhawan N et al. Bioadhesive polymers: Novel tool for drug delivery. $rtificial Cells. Nanomed. Biotech 42: 274-283 4. Miller NS, Johnston TP (2005) He use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews, 2014; 57: 1666-1691.
15. Gandhi S., Pandya P., Umbarkar R., Tambawala T., Shah M., Mucoadhesive Drug Delivery System- An Unusual Maneuver for Site Specific Drug Delivery System, Int J of Pharm Sci., 2011; 2: 132- 152.
16. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci., 2011 Jan; 3(1): 89-100. doi: 10.4103/09757406.76478. PMID: 21430958; PMCID: PMC3053525.
17. Priya Mahajan, Amanpreet Kaur, Geeta Aggarwal, S.L. Harikumar, Mucoadhesive Drug Delivery System: A Review, 2013; 16.
18. Gite Shital Shridhar*, Dattatraya Manohar, Saudagar Ravindra Bhanudas, *Department of Pharmaceutics, KCT'S RGS College of Pharmacy, Anjaneri, Nashik, 422 213. Maharashtra, India. 1Department of Pharmaceutical Chemistry, KCT'S RGS College of Pharmacy, Anjaneri, Nashik, 422 213. Maharashtra, India., "Mucoadhesive buccal drug delivery: An Overview", Journal of Advanced Pharmacy Education & Research Oct-Dec 2013; 3: 324.
19. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissue. J. Controlled Release, 1985; 2: 257-275.
20. Mikos AG, Peppas NA. Measurement of the surface tension of mucin solutions. Int J Pharm., 1989; 3: 1-5.
21. Baszkin A, Proust JE, Monsengo P, Boissonnade MM. Wettability of polymers by mucion aqueous solutions. Biorheology, 1990; 27: 503-514.
22. Kaelble DH, Moacanin J. A surface energy analysis of bioadhesion. Polymer., 1977; 18: 475-482.

23. Lehr CM, Bodde HE, Bowstra JA, Junginger HE. A surface energy analysis of mucoadhesion. II: Prediction of mucoadhesive performance by spreading coefficients. Eur J Pharm Sci., 1993; 1: 19-30.
24. Varma N, Chattopadyay P (2011) Polymeric Platform for Muco Adhesive Buccal Drug Delivery System: a Review. Int Journal of Current Pharmaceutical Research.
25. Mathiowitz, E.; Chickering, D. E.; Lehr, C. M. (Eds.). Bioadhesive drug delivery systems: fundamentals, novel approaches, and development. Drugs and the Pharmaceutical Sciences. New York: Marcel Dekker, 1999; 696.
26. Smart J.D., The basics and underlying mechanisms of mucoadhesion, Adv. Drug Deliv. Rev., 2005; 57: 1556-1568.
27. Bhowmik D, Niladry C Mucoadhesive Buccal Drug Delivery System- An over view. J of Advance Pharm Edu And Res., 2013; 3: 319-331.
28. Dodou, P.; Breedveld, P.; Wieringa, P. A. Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications. Eur. J. Pharm. Biopharm., 2005; 60(1): 1–16.
29. Derjaguin, B. V.; Smilga, V. P. The electronic theory of adhesion. In: Adhesion: Fundamentals and Practice; University of Notingham, England andGordon & Breach: New York, 1996.
30. Mathiowitz E, Chickering DE III, Lehr CM. Bioadhesive Drug Delivery Systems, Fundamentals, Novel Approaches, and Development. Marcel Dekker, Inc. New York, 2010.
31. Gupta, A.; Garg, S.; Khar, R. K: Mucoadhesive buccal drug delivery systems: a review. Indian Drugs, 1992; 29(13): 586 –593.
32. Khar, K.; Ahuja, A.; Javed, A. Mucoadhesive Drug Delivery. In Controlled and Novel Drug Delivery, 1st ed.; Jain, N. K., Ed.; CBS Publishers and Distributors, New Delhi, 1997.
33. Good RJ. Surface energy of solids and liquids. Thermodynamics, molecular forces, and structure. J Colloid Interface Sci., 1977; 59: 398-419.
34. Tabor D. surface forces and surface interactions. J Colloid Interface Sci., 1977; 58: 2-13.
35. Hägerström, H.; Edsman, K.; Strømme, M. Lowfrequency Dielectric Spectroscopy As A Tool For Studying The Compatibility Between Pharmaceutical Gels And Mucus Tissue. J. Pharm. Sci., 2003; 92(9): 1869-1881.
36. Hassan, E. E.; Gallo, J. M. A simple rheological method for the in vitro assessment of mucin-polymer bioadhesive bond strength. Pharm. Res., 1990; 7(5): 491-495.

37. Huang, y.; leobandung, w.; foss, a.; peppas, N. A. Molecular aspects of muco- and bioadhesion: Tetheres structures and site-specific surfaces. J. Control. Release, 2000; 65(1): 63-71.
38. Kockisch, s.; rees, g. D.; young, s. A; tsibouklis, j.; smart, J. D. A direct-staining method to evaluate the mucoadhesion of polymers from aqueous dispersion. J. Control. Release, 2001; 77(1): 1-6.
39. Smart, J. D. The basics and underlying mechanisms of mucoadhesion. Adv.Drug Del. Rev., 2005; 57(11): 1556- 1568.
40. Mikos AG, Peppas NA. Systems for controlled release of drugs. V. Bioadhesive systems. STP Pharmacol., 1986; 2: 705- 716.
41. Andrews, G. P.; Laverty, T. P.; Jones, D. S. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm., 2009; 71(3): 505–518.
42. Lee, J. W.; Park, J. H.; Robinson, J. R. Bioadhesive-based dosage forms: the next generation. J. Pharm. Sci., 2000; 89(7): 850 – 866.
43. Peppas, N. A.; Sahlin, J. J. Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials, 1996; 17(11): 1553-1561.
44. Ch'ng HS, Park H Kelly P, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. II: Synthesis and evaluation of some swelling water insoluble bioadhesive polymers. J. Pharm. Sci., 1985; 74: 399-405.
45. Jimenez-Castellanos, M. R.; Zia, H.; Rhodes, C. T. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm., 1993; 19(1–2): 143–194.
46. Ahuja, A.; Khar, R. K.; Ali, J. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm., 1997; 23(5): 489 –515.
47. Peppas, N. A.; Little, M. D.; Huang, Y. Bioadhesive ControlledRelease Systems. In Handbook of Pharmaceutical Controlled Release Technology; Wise, D. L., Ed.; Marcel Dekker: New York, 2000; 255–269.
48. Tiwari, D.; Goldman, D.; Sause, R.; Madan, P. L. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS PharmSci., 1999; 1(3): 50 – 57.
49. Hagerstrom, H.; Paulsson, M.; Edsman, K. Evaluation of mucoadhesion for two polyelectrolyte gels in simulated physiological conditions using a rheological method. Eur. J. Pharm. Sci., 2000; 9(3): 301–309.
50. Sigurdsson, H.; Loftsson, T.; Lehr, C. Assessment of mucoadhesion by a resonant mirror biosensor. Int. J. Pharm., 2006; 325(1–2): 75– 81.

51. Mortazavi, S. A.; Smart, J. An investigation into the role of water movement and mucus gel dehydration in mucoadhesion. J. Controlled Release, 1993; 25(3): 197–203.
52. Huang, Y.; Leobandung, W.; Foss, A.; Peppas, N. A. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. J. Controlled Release, 2000; 65(1–2): 63– 71.
53. Park, K.; Robinson, J. R. Mechanisms of mucoadhesion of poly(acrylic acid) hydrogels. Pharm Res., 1987; 4(6): 457– 464.
54. Flory, P. J. Principlse of Polymer Chemistry; Cornell University Press: Ithaca, New York, 1953; 541–556.
55. Park, K.; Robinson, J. R. Bioadhesive polymers as platforms for oral controlled drug delivery: method to study bioadhesion. Int J. Pharm., 1984; 19(2): 107–127.
56. Park, K.; Ch'ng, H. S.; Robinson, J. R. Alternative approaches to oral-controlled drug delivery: bioadhesive and in situ systems. In Recent Advances in Drug Delivery Systems; Anderson, J. M., Kim, S. W., Eds.; Plenum Press: New York, 1984; 163.
57. Ch'ng, H. S.; Park, K.; Kelly, P.; Robinson, J. R. Bioadhesive polymers as platform for oral controlled drug delivery. II. Synthesis and evaluation of some swelling, waterinsoluble bioadhesive polymers. J. Pharm Sci., 1985; 74(4): 399 – 404.
58. Park, H.; Amiji, M.; Park, K. Mucoadhesive hydrogels effective at neutral pH. Proc. Int. Symp. Control. Release Bioact. Mater., 1989; 16: 217–218.
59. Asane, G. S.; Nirmal, S. A.; Rasal, K. B.; Naik, A. A.; Mahadik, M. S.; Rao, Y. R. Polymers for mucoadhesive drug delivery system: acurrent status. Drug Dev. Ind. Pharm., 2008; 34(11): 1246 –1266.
60. Salamat-Miller, N.; Chittchang M.; Johnston, T. P. The use of mucoadhesive polymers in buccal drug delivery. Adv. Drug. Del. Rev., 2005; 57(11): 1666 –1691.
61. Kamath, K. R.; Park, K. Mucosal Adhesive Preparations. In Encyclopedia of Pharmaceutical Technology; Swarbrick, J., Boylan, J. C., Eds.; Marcel Dekker: New York, 1994; 133–138.
62. Lehr, C. M.; Poelma, F. C. G.; Junginger, H. E.; Tukker, J. J. An estimate of turnover time of intestinal mucus gel layer in the rats, in situ loop. Int. J. Pharm., 1991; 70(1): 235–240.
63. Ugwoke, M. I.; Agu, R. U.; Verbeke, N.; Kinget, R. Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Adv. Drug Del. Rev., 2005; 57(11): 1640 – 1665.
64. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strenghs of mucoadhesive buccal tablets: Design of in-vitro assembly. Indian Drugs, 1992; 30(4): 152-155.

65. Cafaggi S, Leardi R, Parodi B, Caviglioli G, Russo E, Bignardi G. Preparation and evaluation of a chitosan salt-poloxamer 407 based matrix for buccal drug delivery. J. Control. Release, 2005; 102: 159-169.
66. Monali sonawane, dattatrey shinkar, ravindrasaudagar, mucoadhesive buccal drug delivery system: review article, 2017; 9.
67. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci., 2011.
68. Monali Sonawane, Dattatrey Shinkar, Ravindrasaudagar, Mucoadhesive Buccal Drug Delivery System: Review Article, 2017; 9(1).
69. Pranshu Tangri, N.V.Satheesh Madhav, recent advances in oral mucoadhesive drug delivery systems: a review, 2011; 3(153).
70. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci., 2011.
71. Dr Satpute K.L. , Jadhav Madhav , Panchal Ashitosh, Oral Mucoadhesive Drug Delivery Systems: A Review, 2020; 7: 132.
72. Chinmaya Keshari Sahoo , Prakash Kumar Nayak , Deepak Kumar Sarangi , Tanmaya Keshari Sahoo, Intra Vaginal Drug Delivery System: An Overview, 2013.
73. N G N Swamya,, Zaheer Abbas, Mucoadhesive in situ gels as nasal drug delivery systems: an overview, 2012; 168.
74. Chaturvedi M, Kumar M, Pathak K. A review on mucoadhesive polymer used in nasal drug delivery system. J Adv Pharm Technol Res., 2011; 216.
75. Trusha J Purohit, Sara M Hanning & Zimei Wu, Advances in Rectal Drug Delivery Systems, 2018.
76. Susan Hua, Physiological and Pharmaceutical Considerations for Rectal Drug Formulations, 2019.
77. Rathi R, Sanshita, Kumar A, Vishvakarma V, Huanbutta K, Singh I, Sangnim T. Advancements in Rectal Drug Delivery Systems: Clinical Trials, and Patents Perspective. Pharmaceutics. 2022.
78. Andrews GP, Thomas P, Laverty TP, David S, Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm., 2009; 71: 505-518.
79. Chowdary KPR, Srinivas L. Mucoadhesive drug delivery systems: A review of current status. Indian Drugs, 2000; 37(9): 400-406.
80. Gandhi RB, Robinson JR. Bioadhesion in drug delivery. Ind. J. Pharm. Sci., 1988; 50(3): 145-152.

81. Yang X, Robinson JR. In: Okano T, ed. Biorelated functional polymers and gels : controlled release and applications in biomedical engineering, San Diego, Academic Press, 1998; 135.
82. Shojaei, A. H. Buccal mucosa as a route for systemic drug delivery: a review. J. Pharm. Pharm. Sci., 1998; 1(1): 15–30.
83. Khanna, R.; Agarwal, S. P.; Alka, A. Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Indian J. Pharm. Sci., 1998; 60(l): 1–11.
84. Miller, N. S.; Chittchang, M.; Johnston, T. P. The use of mucoadhesive polymers in buccal drug delivery. Adv. Drug Deliv. Rev., 2005; 57(1): 1666 –1691.
85. Vyas, S. P.; Khar, R. K. Controlled Drug Delivery—Concepts and Advances, 1st ed.; Vallabh Prakashan: New Delhi, 2002.
86. Patel PS, Parmar AM Buccal Drug Delivery System: A Review. Int J Drug Dev Res., 2013; 5: 35-48.
87. Alka, G.; Sanjay, G.; Khar, R. K. Mucoadhesive buccal drug delivery systems: a review. Indian Drugs, 1992; 13(29): 586 –593.
88. Khanna, R.; Agarwal, S. P.; Alka, A. Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Indian J. Pharm Sci., 1998; 60(l): 1–11.
89. Lehr, C. M. Lectin-mediated drug delivery: the second generation of bioadhesives. J. Controlled Release, 2000; 65(1–2): 19 –29.
90. Veillard, M. M.; Longer, M.; Martens, T. W.; Robinson, J. R. Preliminary studies of oral mucosal delivery of peptide drugs. J. Controlled Release, 1987; 6(1): 123–131.
91. Gandhi RE. Robinson JR. Bioadhesion in drug delivery. Ind. J. Pharm. Sci., 1988; 50: 145152.
92. Janet AJ, Hoogstraate, Philip W Drug delivery via the buccal mucosal. Wertz PSTT, 1998; 1: 306-316.
93. Tangri P., Khurana S., Madhav N.V.S. Mucoadhesive Drug Delivery System: Material and Method, Int. J. Of Pham. Bio. Sci., 2011; 2(1): 34-46.
94. Bruschi ML, de Freitas O Oral bioadhesive drug delivery systems. Drug Dev Ind Pharm, 2005; 31: 293-310.
95. Miller NS, Chittchang M, Johnston TP He Use of Mucoadhesive Polymers in Buccal Drug Delivery, Adv. Drug Deliv Rev., 2005; 57: 1666-1691.
96. Lee JW, Park JH, Robinson RJ Bioadhesive - based dosage forms: the next generation. J Pharm Sci., 2000; 89: 850-866.

97. Gandhi RB, Robinson JR Oral cavity as a site for bioadhesive drug delivery, Adv. Drug Deliv Rev., 1994; 13: 43-74.
98. Sigurdsson H, Loisson T Assessment of mucoadhesion by a resonant mirror biosensor. Int J Pharm., 2006; 325: 75-81.
99. Khanvilkar K, Donovan MD Drug transfer through mucus. Adv. Drug Deliv Rev., 2001; 48: 173-193.
100. Jain AC, Aungst BJ, Christianah MA Development and in-vivo evaluation of buccal tablets prepared using danazol sulfobutylether 7_cyclodextrin (SBE 7) complexes. J Pharm Sci., 2002; 91: 1659-1668.
101. Veuillez F, Kalia YN Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm., 2001; 51: 93-109.
102. de Vries ME, Bodde HE Developments in buccal drug delivery Crit. Rev. Her Drug Carr Syst., 1991; 8: 271-303.
103. Parthasarathy G, Bhaskar K, Jayaveera KN, Prasanth V Buccal Mucosa: a *iied Choice for Systemic Drug Delivery. Int J of Drug Deli., 2011; 3: 586-596.
104. Narasimha RR, Sindhu RK Formulation and evaluation of rapidly dissolving buccal patches. Int J Pharm Bio Sci., 2011; 1: 145-159.
105. Shridhar GS, Manohar SD, Bhanudas RS Mucoadhesive buccal drug delivery: An Overview. J of Adv Pharm Edu & Res., 2013; 3: 319–332.
106. Kamimori GH, Karyekar CS He rate of absorption and relative bioavailability of caٞeine administered in chewing gum versus Capsules to normal healthy volunteers. Int J Pharm., 2002; 234: 159-67.
107. Lee J, Kellaway IW Buccal permeation of (D-Ala2, DLeu5) enkephalin from liquid crystal-line phases of glyceryl monooleate. Int J Pharm, 2000; 195: 35–38.
108. Shinkar DM, Dhake AS, Shetty CM Drug delivery from oral cavity: A focus on mucoadhesive buccal drug delivery system. PDA J of P'ceutical Sci and Tech., 2012; 66: 466-500.
109. Muraleedhara KK, Senthil Kumar SK, Parthiban S Mucoadhesive vaginal drug delivery system: A review on advance status. Int J of Pharm Res and Analysis, 2013; 3: 33-46.
110. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sci., 1992; 81: 1-10.
111. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv. Drug Del. Rev., 1994; 13: 43-7.

112. Squier CA, Hall BK. The permeability of mammalian non-keratinized oral epithelia to horseraddish peroxidase applied in vivo and in vitro, Arch. Oral Biol., 1984; 29: 45-50.
113. Hill MW, Squier CA. The permeability of oral palatal mucosa maintained in organ culture, J. Anat., 1979; 128: 169-178.
114. Steward, A., Bayley, D.L. and Howes, C., The effect of enhancers on the buccal absorption of hybrid (BDBB) α-interferon. International journal of pharmaceutics, 1994; 104(2): 145-149.
115. Jug, M.; Becirevic-Lacan, M. Influence of hydroxypropyl-B-cyclodextrin complexation on piroxicam release from buccoadhesive tablets. Eur. J. Pharm. Sci., 2004; 21: 251–260.
116. Patel VF, Liu F, Brown MB Modeling the oral cavity: In-vitro and in-vivo evaluations of buccal drug delivery systems. J of Controlled Rel., 2012; 161: 746–756.
117. Ramana MV, Nagdaand C, Himaja M Design and Evaluation of Mucoadhesive Buccal Drug Delivery Systems containing Metoprolol Tartrate. Ind J of P'ceutical Sci., 2007; 69: 515-518.
118. Kolli CS, Gannu R, Yamsani VV, Kishan V, Yamsani MR Development of Mucoadhesive Patches for Buccal Adminstration of Prochlorperazine: Evaluation of in– vitro Release and Mechanical Properties. Int J of P'eutical Sci and Nanotech, 2008; 1: 64-70.
119. Chaudhary R, Shamim Q, Patel J, Panigrahi UP, Giri IC Formulation, Development and In-Vitro Evaluation of Muco-adhesive Buccal Patches of Methotrexate. Int J of Pharma Sci and Res., 2010; 1: 357-365.
120. Velmurugan S, Deepika B, Nagaraju K, Vinushitha S Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam. Int J of Pharm Tech Res., 2010; 2: 1958-1968.
121. Naga Raju K, Velmurugan S, Deepika B, Vinushitha S Formulation and invitro Evaluation of Buccal Tablets of Metoprolol Tartrate. Int J of Pharm and P'ceutical Sci., 2011; 3: 239–246.
122. Deshmukh GJ, Varma MM, Manjunath YS Development and evaluation of Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive Agent obtained from the Fruits of Ficus carica L. Indo American Journal of Pharmaceutical Research, 2011; 1: 69-79.
123. Mishra S, Kumar G, Kothiyal P Formulation and Evaluation of Buccal Patches of Simvastatin by Using Di ؤerent Polymers. He Pharma Innovation, 2012; 1: 87-92.
124. Sandhya P, Tazyeen N, Sunitha M, Sirisha M, Sunil M Formulation and Evaluation of Buccal Films of Ketorolac Tromethamine. J of Global Trends in P'ceutical Sci., 2013; 4: 1184-1192.

125. Velmurugan S, Srinivas P Formulation and in- vitro Evaluation of Losartan Potassium Mucoadhesive Buccal Tablets. Asian J Pharm Clin. Res., 2013; 125-130.
126. Mehraj Ud Din G, Mohan G, Sharma S, MohiUdDin S, Shukla TP, et al. Formulation development and Evaluation of Mucoadhesive Buccal Film of Methyldopa. J of Global Trends in P'ceutical Sci., 2014; 1893–1904.
127. Madhuri C, Mahendra K Design of Solid Dosage Form for Buccal Drug Delivery of Diltiazem Hydrochloride. Int J of Pharm. and P'ceutical Res., 2015; 4: 30-44.
128. Nagarani K, Krishnaveni J, Kommera H, Sinha LK, Prakash Rao AH formulation and evaluation of Esomeprazole Mucoadhesive buccal tablets. EurJ of P'ceutical and Med Res., 2016; 3: 365-377.