ejpmr, 2018,5(03), 81-103

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

IN-DEPTH RECENT ADVANCES IN BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM.

Riad K. El Qidra*

Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Al-Azhar University- Gaza, Gaza Strip, Palestine.

***Corresponding Author: Dr. Riad K. El Qidra**

Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Al-Azhar University- Gaza, Gaza Strip, Palestine.

Article Received on 05/01/2018 **Article Revised on 26/01/2018** **Article Accepted on 16/02/2018**

ABSTRACT

Since the early 1947s the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. This technology has emerged as an advanced alternative to the other conventional types of drug delivery systems. The unique physiological features make the buccal mucosa as an ideal route for mucoadhesive drug delivery system. Buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The various advantages associated with these systems made buccal drug delivery as a novel route of drug administration. These advantages include a rich blood supply and it is relatively permeable. In buccal drug delivery systems, mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. Thebuccal drug delivery system prolong the residence time of dosage form at the site and thus contribute to improved and/or better therapeutic performance of the drug. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation with improved bioavailability. In addition, buccal drug system is the most acceptable and palatable dosage form due to its small size, small dose and thickness of the film. Moreover, it does not require swallowing of the drug, which is most suitable for pediatric as well as geriatric patients.In this paper main focus is done on various issues like oral mucosa pathway, barriers to penetration of drug, benefits of buccal drug delivery, manufacturing methods, the theories of mucoadhesion, factors affectingmucoadhesion, different polymes utilized through buccal drug delivery, different dosage forms, evaluation parameters.

KEYWORD: Buccal Mucosa**,** Mucoadhesion, Mucoadhesive drug delivery system, Bioadhesive polymers, permeation enhancers, evaluation.

INTRODUCTION

Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs.[1] Buccal drug delivery is a favorable route compare toparenteral, injectable and adds a several advantages over otherroutes.[1] The parenteral route offers excellent bioavailability, similarlyhaving poor patient compliance, anaphylaxis, and some otherinfections. Peroral route possess some inconvenience to patients. Hencefor the immediate release of medication and for instant release atdesire location in which the drug is absorbed distributer and easilymetabolized. This limitation leads to the development of alternative routes of administration. Buccal mucosa has absorptive function andoffers many benefits like avoidance of first pass effect, which is a non-invasive route, increase in bioavailability, a rapid action is possibleand reduce side effects.[2]

In addition to low cost, ease of administration and high level of patient compliance the oral route is perhaps the most preferred to the patient and clinician alike. However administration of drugs has short termlimitations like first pass metabolism, which leads to a lack significant correlation between Membrane Permeability, Absorption, Bioavailability and Drug degradation within the gastro intestinal (GI) tract that forbid oral administration of certain classes of drugs eg. proteins and peptides.[3]

Transmucosal routes (mucosal lining of nasal, rectal, vaginal, ocular and oral cavity) offers some distinct advantages such as possible bypass of the first pass effect, avoidance of pre systemic elimination within the GIT and better enzymatic flora for drug absorption.[4-5] Buccal, sublingual, palatal and gingival regions shows effectivedrug delivery in oral cavity. Buccal and sublingual route of drug delivery are most widely in which local and systemic effects aretreated. The permeability of oral mucosa denotes the physical natureof the tissues. The permeable part is sublingual mucosa and buccal mucosa is thinner part and in which

there is a high blood flow andsurface area; it is a feasible site when a rapid onset of action isdesired. For the treatment of acute disorders sublingual route is apreferred one; however its surface washed with saliva which makes formulations in the oral cavity hard in nature.[6]

Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug.

Oral mucosa[7-9]

The total area of the oral cavity is 100cm^2. One third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions. Outer oral vestibule which is bounded by cheeks, lips, teeth and gingival (gums). Oral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and softpalate. The tongue projects from the floor of the cavity, figure (1).

FUNCTIONS OF ORAL CAVITY[10]

- It helps in chewing, mastication and mixing of food stuff.
- It is Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water.
- To aid in speech and breathing process.

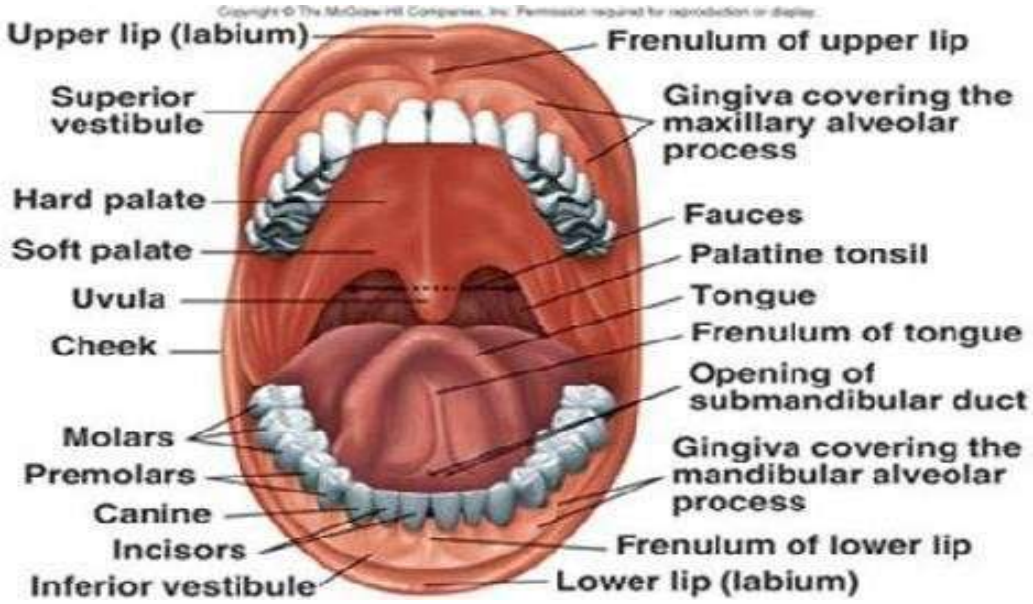


Figure 1: Structure of oral cavity.

Mucous membranes are the moist linings of the orifices and internal parts of the body that are in continuity with the external surface. They cover, protect, and provide secretory and absorptive functions in the channels and extended pockets of the outside world that are incorporated in the body. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 µm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states.[11] They secrete a viscous fluid known as mucus, which acts as a protective barrier and also lubricates the mucosal membrane. Mucosal membranes of human organism are relatively permeable and allow fast drug absorption They are characterized by an epithelial layer whose surface is covered by mucus[12] The primary constituent of mucus is a glycoprotein known as mucin as well as water and inorganic salts.[13] However, it has general composition table (1).

Table (1): Composition of Mucous Membrane.

NO.	COMPOSITION	%AMOUNT
1	WATER	95
2	GLYCOPROTEINS & LIPIDS	0.5-5.0
3	MINERAL SALTS	1
4	FREE PROTEINS	0.5-1.0

EXAMPLES OF MUCOSA[14]

1. Buccal mucosa.
2. Oesophageal mucosa.
3. Gastric mucosa.

4. Intestinal mucosa.
5. Nasal mucosa.
6. Olfactory mucosa.
7. Oral mucosa.
8. Bronchial mucosa.
9. Uterine mucosa.
10. Endometrium (mucosa of the uterus).
11. Penile mucosa.

Oral (Buccal) Mucosa[15]

The oral mucosa is composed of an outermost layer ofstratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized contain only small amounts of ceramides figure(2).

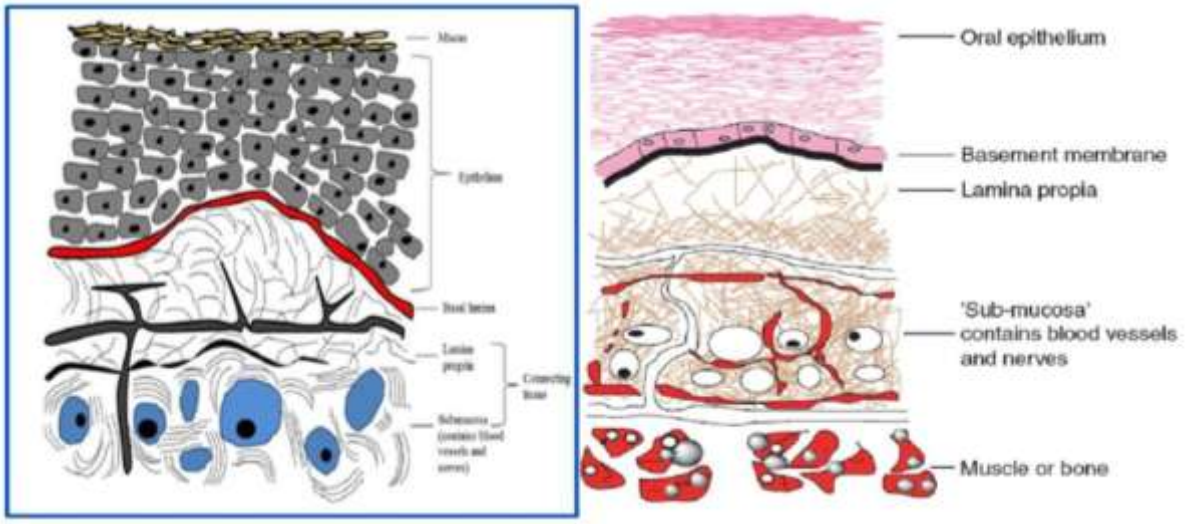


Figure (2): Structure of buccal mucosa.

FUNCTIONS OF MUCOUS LAYER

The mucous layer, which covers the epithelial surface, has various roles.[16,17]

1. PROTECTIVE ROLE

The Protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface.

2. BARRIER ROLE

The role of mucus layer as barrier in tissue absorption of drugs and othersubstances is well known as its influence the bioavailibity of the drugs. The mucus constitutes diffusionbarrier for molecules and especially against drug absorption diffusion through mucus layer depends onmolecule charge, hydration radius, ability to form hydrogen bonds and molecular weight.

3. ADHESION ROLE

Mucus has strong cohesive properties and firmly binds the epithelial cellssurface as a continuous gel layer.

4. LUBRICATION ROLE

An important role of the mucus layer is to keep the membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of themucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules.

5. MUCOADHESION ROLE

One of the most important factors for bioadhesion is tissue surfaceroughness.[18], Adhesive joints may fail at relatively low applied stresses if cracks, airbubbles, voids, inclusions or other surface defects are present. Viscosity and wetting power are the mostimportant factors for satisfactory bioadhesion. At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bioadhesion.

MUCOADHESIVE DRUG DELIVERY SYSTEM DEFINITIONS

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface.[20-21] The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both.[21] When the adhesion involves mucus or mucus membrane it is termed as mucoadhesion.[22]

Bioadhesion is used to describe the bonding or adhesion between a synthetic or natural polymer and soft tissues biological substrate such as epithelial cells, which allows

the polymer to adhere to the biological surface for an extended period of time figure (3).

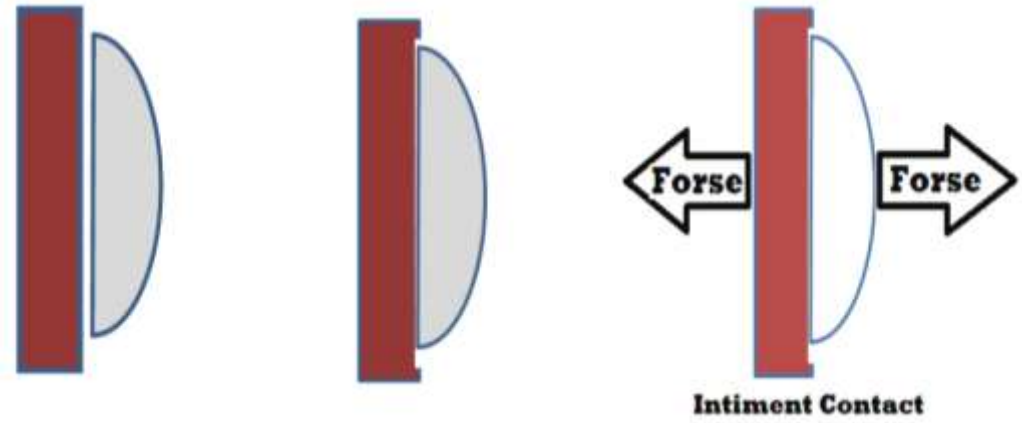


Figure (3): Bioadhesion Structure.

CONCEPTS

In biological systems, four types of bioadhesion can be distinguished as follows.

1. Adhesion of a normal cell on another normal cell.
2. Adhesion of a cell with a foreign substance.
3. Adhesion of a normal cell to a pathological cell.
4. Adhesion of an adhesive to a biological substance[23,24] figure.[4]

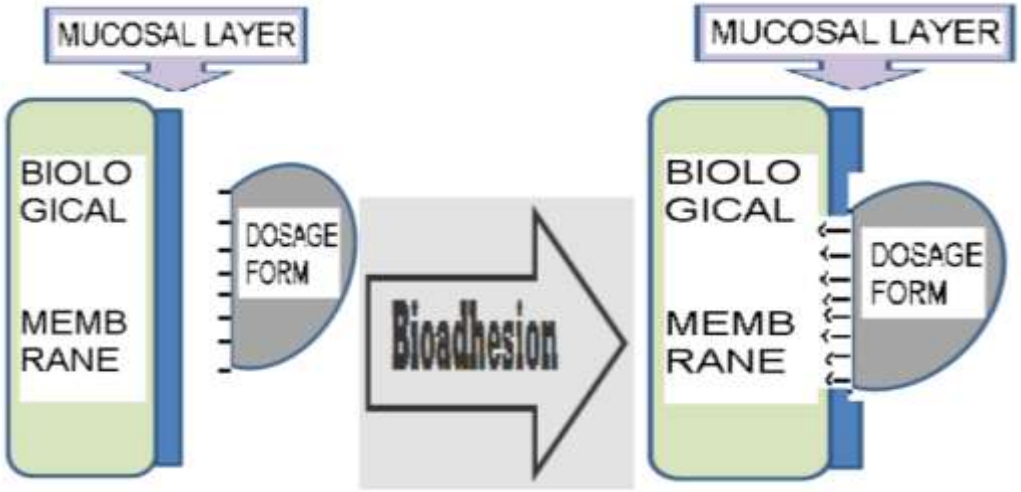


Figure (4): Adhesion of an adhesive to a biological substance.

NEED OF MUCOADHESIVE DELIVERY

i. Controlled release.
ii. Target & localized drug delivery.
iii. By pass first pass metabolism.
iv. Avoidance of drug degradation.
v. Prolonged effect.
vi. High drug flux through the absorbing tissue.
vii. Reduction in fluctuation of steady state plasma level.[25]
viii. Mucoadhesive formulations use polymers as the adhesive component. These polymers are water soluble. When polymers are used in a dry form, they attract water from themucosal surface and leads to a strong interaction which increases the retention time over the mucosal surfaces.[26]

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma andmaintains constant for entire duration of treatment. This is possible through administration of aconventional dosage form in a particular dose and at particular frequency. In most cases, the dosingintervals much shorter than the half-life of the drug resulting in a number of.

limitations associated with such a conventional dosage form are as follows.

ix. Poor patient compliance; increased chances of missing the dose of a drug with short half-life for whichfrequent administration is necessary.
x. A typical peak plasma concentration time profile is obtained which makes attainment of steady statecondition difficult.

xi. The unavoidable fluctuation in the drug concentration may lead to under medication or over medication asthe steady state concentration values fall or rise beyond in the therapeutic range.
xii. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with smalltherapeutic index whenever overmedication occurs.[27]

ADVANTAGES OF MUCOADHESIVES[28,29]

- A prolonged residence time at the site of drug action or absorption.
- A localization of drug action of the delivery system at a given target site.
- An increase in the drug concentration gradient due to the intense contact of particleswith the mucosal.
- A direct contact with mucalcells that is the first step before particle absorption.
- Ease of administration.
- Termination of therapy is easy.{except gastrointestinal}
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients. except gastrointestinal}
- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, therebyoffering a greater bioavailability.
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environmentof intestine can be administered by this route. Eg. Buccal sublingual, vaginal.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case ofrectal and transdermal routes.
- Systemic absorption is rapid.
- This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
- Less dosing frequency.
- Shorter treatment period.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.
- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced
- intensity of local or systemic side effects.
- Despite the several advantages associated with oral controlled drug delivery systems, there are somany disadvantages, which are as follows.
- Basic assumption is drug should absorbed throughout GI tract
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level.

LIMITATIONS[29]

- Drug administration via the buccal mucosa has certain limitations
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

Mucoadhesive drug delivery system in oral cavity.[30,31]

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

1. Buccal Delivery

Drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.

2. Sublingual Delivery

Drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.

3. Local Delivery

Drugs are delivered into the oral cavity.

BUCCAL DRUG DELIVERY

Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Substantial efforts have recently been focused on placing a drug or drug delivery system in a particular region of the body for extended periods of time. The mucosal layer lines a number of regions of the body including the oral cavity, gastro intestinal tract, the urogenital tract, the airways,

the ear, nose and eye. Hence the mucoadhesive drug delivery system can be classified according to its potential site of applications.[32]

The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.[33]

Based on current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. Direct access to the systemic circulation through the external jugular vein by pass the drugs from the hepatic first pass metabolism which may lead to higher bio availability. Further these dosage forms are self-administrable, cheap and have superior patient compliance. Unlike oral drug delivery which presents a hostile environment for drugs especially proteins and peptides due to acid hydrolysis enzymatic degradation, hepatic first pass effect the mucosal lining of buccal tissues provides a much milder environment for drug absorption. In the case of both mucosal and transmucosal administration, conventional dosage forms are not able to assure therapeutic drug levels on the mucosa and in the circulation. This is because of the physiological removal mechanisms of the oral cavity (washing effect of saliva and mechanical stress), which take the formulation away from the mucosa, resulting in a too short exposure time and unpredictable distribution of the drug on the site of action/absorption.[34]

Advantages of Buccal Drug Delivery Systems[35,36]

Drug administration via buccal mucosa offers several distinct advantages,

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of drug to the buccal cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route, for the systemic delivery of drugs which undergo extensive first pass metabolism or degradation in harsh gastrointestinal environment.
- A significant reduction in dose can be achieved thereby reducing dose related side effects.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.
- Systemic absorption is rapid as buccal mucosa is thin and highly perfused with blood.
- Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascularagents etc.
- It allows the local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response. Thus, delivery of therapeutic agents like peptides, proteins and ionized species can be done easily.

Disadvantages of Buccal drug delivery system[37,38]

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Drugs, which irritate the oral mucosa, have abitter or unpleasant taste or odour; cannot be administered by this route.
- Drugs, which are unstable at buccal pH, cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may get swallowed with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Surface area available for absorption is less.
- The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

C LASIFICATION OF BUCCAL BIOADHESIVE DOSAGE FORM[39,40]

1. Buccal Bioadhesive Tablets

Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. These tablets are solid dosage forms that are prepared by the direct compression of powderand can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form.

They can deliver drug multi- directionally into the oral cavity or to the mucosal Surface figure(5)

Figure 5: Mucoadhesive Buccal Tablets.

2. BuccalBioadhesivc Semisolid Dosage Forms

Buccal bioadhesive semisolid dosage forms consist of finally powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution. Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms and most of the dosage forms are used only for localized drug therapy within the oral cavity.

One of the original oral mucoadhesive delivery systems consists of finely ground pectin, gelatin and NaCMC dispersed in a poly (ethylene) and a mineral oil gel base, which can bemaintained at its site of application for 15-150 mins.

Example: Orabase.

3. Buccal Bioadhesive Patches and Films

Buccal bioadhesive patches consists of two laminates or multilayered thin film that are round or oval in shape, consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer figure 6.

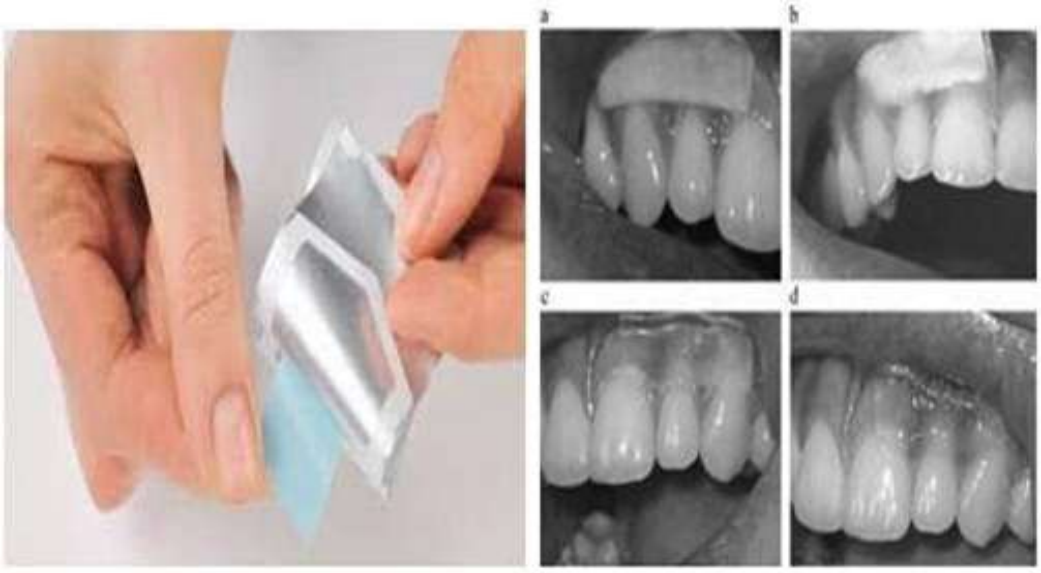


Figure (6): Mucoadhesive Buccal Films.

Composition of buccal patches[41]

A. Active ingredient.

B. Polymers (adhesive layer): HEC, HPC, polyvinyl pyrrolidone(PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluents for its high aqueous solubility, its flavoring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. other example : microcrystallinestarch and starch.

D. Sweetening agents: Sucralose, aspartame, Mannitol, etc.

E. Flavoring agents: Menthol, vanillin, clove oil, etc.

F. Backing layer: EC etc.

G. Penetration enhancer: Cyano acrylate, etc

H. Plasticizers: PEG-100, 400, propylene glycol, etc.

4. Buccal Bioadhesive Powder Dosage Forms

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto thebuccal mucosa, the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine.

Another example, HPC and beclomethasone in powder formwhen sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccalmucosa for over 4 hrs.[42]

5. Buccal chewing gum

Some commercial products of buccal chewing gum are available in the market like Caffeine chewing gum.

Stay Alert, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability wascomparable to that in capsule formulation. Such as (Nicotine chewing gums).

Example:(Nicorette and Nicotinell) have been marketed for smoking cessation. The permeability of nicotine across the buccal mucosa is faster than across the skin.

6. Bioadhesive spray

Buccoadhesive sprays are gaining important over other dosage forms because of.

- Flexibility
- Comfort
- High surface area
- Availability of drug in solution form.

The first FDA-approved (1996) formulation: was developed by fentanyl Oralet ™ to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children.

In 2002, the FDA approved Subutex (buprenorphine):for initiating treatment of opioid dependence (addiction to opioid drugs, including heroin and opioid analgesics). And **Suboxone** (buprenorphine and naloxone) for continuing treatment of addicts.

In 2005, Oral-lynbuccal spray: was approved for commercial marketing and sales in Ecuador.

✓ **Commercially available buccal adhesive drug delivery systems**

Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%. Some of the commercially available buccal adhesive formulations are listed in table (2).

Table 2: Commercially available buccal adhesive formulations.[43]

No.	Brand Name	Bioadhesive Polymer	Company	Dosage forms
1	Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckiser	BuccalTablet
2	Suscard	HPMC	Forest	Tablet
3	Gaviscon Liquid	Sodium alginate	Rickitt Benckiser	Oral liquid
4	Orabase	Pectin,gelatin	Orabase Batesham	Pectin, gelatin paste
5	Corcodyl gel	HPMC	Glaxosmi- thkline	Oromucosal Gel
6	Corlan pellets	Acacia	Celltech	Oromucosal Pellets
7	Fentanyl Oralet™		Lexicomp	Lozenge
8	MiconaczoleLauriad	-	Bioalliance	Tablet
9	Emezine™	-	BDSI's	-
10	Zidoval®	Carbomer	3-M	Vaginal gel

PHYSIOLOGICAL FACTORS AFFECTING BUCALL BIOAVAILABILITY[44,45]

1. Inherent permeability of the epithelium

The permeability of the oral mucosal epithelium is intermediate between that of the skin epithelium, which is highly specialized for barrier function and the gut, which is highly specialized for an adsorptive function. Within the oral cavity, the buccal mucosa is less permeable that the sublingual mucosa.

2. Thickness of epithelium

The thickness of the oral epithelium varies considerably between sites in the oral cavity. The buccal mucosa measures approximately 500- 800μm in thickness.

3. Blood supply

A rich blood supply and lymphatic network in the lamina propria serve the oral cavity, thus drug moieties which traverse the oral epithelium are readily absorbed into the systemic circulation. The blood flow in the buccal mucosa is 2.4ml.

4. Metabolic activity

Drug moieties adsorbed via the oral epithelium are delivered directly into the blood, avoiding first pass metabolism effect of the liver and gut wall. Thus oral mucosal delivery may be particularly attractive for the delivery of enzymatically labile drugs such as therapeutic peptides and proteins.

5. Saliva and mucous

The activity of the salivary gland means that the oral mucosal surfaces are constantly washed by a stream of saliva, approximately 0.5-2L per day. Thesublingual area in particular, is exposed to a lot of saliva which can enhance drug dissolution and therefore increase bioavailability.

6. Ability to retain delivery system

The buccal mucosa comprises an expense of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.

7. Species differences

Rodents contain a highly keratinized epithelium and thus are not very suitable as animal models when studying buccal drug delivery.

8. Transport routes and mechanism

Drug permeation across the epithelium barrier is viatwo main routes: a- The paracellular route: between adjacent epithelial cells.

b- The transcelluar route: across the epithelial cells, which can occur by any of the following mechanism: passive diffusion, carrier mediated transport and via endocytic processes.

9. Sites for mucoadhesive drug delivery systems[46]

The common sites of application where mucoadhesive drug delivery systems have the ability to 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 abovementioned delivery sites. The buccal cavity has a very limited surface area of around 50 cm2 but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliverpharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery. Like buccal cavity, nasal cavity also provides apotential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer has a surface area of around 150-200 cm2. 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. Ophthalmic mucoadhesives also is another area of interest. Due to the continuous formation of tearsand blinking of eye lids there is a rapid removal ofthe active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering thedrugs 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.

POLYMERS[47,48]

Polymers are substances whose molecules have high molar masses and compressed of a large number of repeating units. Polymers can form particles of solid dosage form and also can change the flow property of liquid dosage form. Polymers are the backbone of pharmaceutical drug delivery systems. Polymers have been used as an important tool to control the drug release rate from the formulation. They are also mostly used as stabilizer, taste-making agent, and proactive agent. Modern advances in drug delivery are now predicated upon the rational design of polymers tailored specific cargo and engineered to exert distinct biological functions.

The classified polymers for the drug delivery system are on the following characteristics

1. ***Origin:*** The polymers can be natural or synthetic, or a combination ofboth.
2. ***Chemical nature:*** It can protein based, polyester, cellulose derivatives,etc.
3. ***Backbone Stability:*** The polymers can be degradable or non-biodegradable.
4. ***Solubility:*** The polymer can hydrophilic or hydrophobic in nature.[49]

Polymers act as inert carriers to which a particular drug can be conjugated. There are numerous advantages of polymer acting as an inert carrier, for example, the polymer enhances the pharmacodynamic and pharmacokinetic properties of biopharmaceuticals though several sources, such as, increases the plasma ½life, decreases the immunogenicity, boost stability of biopharmaceuticals, improves solubility of low molecular weight drugs, and has potential for targeted drug delivery.[50]

Some drugs have a limited concentration range by which utmost benefit can be delivered. The concentrations above or below can causetoxic effects or show no therapeutic effect. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growingneed for a multidisciplinary approach to deliver the therapeutic to targets in the tissue. Through these new innovations in pharmacodynamic, pharmacokinetic, nonspecific

toxicity, immunogenicity, bio recognition and efficacy of the drug were generated. These new strategies were often called as drug delivery systems(DDS).

In order for controlled drug delivery formulation, the polymers must be[51]

- Chemically inert
- Free from impurities with appropriate physical structure,
- Minimal undesired aging,
- Readily processable.

Role of Polymer in Drug Delivery

1. Immediate drug release dosage form tablets

Polymers including polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose (HPMC) are found to be a good binder which increases the formation of granules that improves the flow and compaction properties of tablet formulations prior to tableting.

2. Capsules

Many of the polymeric excipients used to "bulk out" capsules fills are the same as those used in intermediate release tablets. For hard and soft shell gelatin has most often used.[52] By recent advances HPMC has been accepted as alternative material for hard and soft capsules.

3. Modified drug release dosage forms

To achieve gastro retention mucoadhesive and low density, polymers have been evaluated, with little success so far their ability to extend gastric residence time by bonding to the mucus lining of the stomach and floating on top of the gastric contents respectively.[53]

4. Extended release dosage forms

Extended and sustained release dosage forms prolong the time that' systemic drug levels are within the therapeutic range and thus reduce the number of doses. The patient must take to maintain a therapeutic effect there by increasing compliance. The most commonly used water insoluble polymers for extended release applications are the ammonium ethacrylate copolymers cellulose derivatives ethyl cellulose andcellulose acetate and polyvinyl derivative, polyvinylacetate.[54,55]

6. Gastro retentive Dosage forms

Gastro retentive dosage forms offer an alternative strategy for achieving extended release profile, in which the formulation will remain in the stomach for prolonged periods, releasing the drug in situ, which will then dissolve in the liquid contents and slowly pass into the small intestine.

TYPES OF POLYMERS IN PHARMACEUTICAL DRUG DELIVERY

1. Polymers used as colon targeted drug delivery

Polymers plays a very important role in the colon targeted drug delivery system. It protects the drug from degradation or release in the stomach and small intestine. It also ensures abrupt or controlled release of the drug in the proximal colon.[56]

2. Polymers in the mucoadhesive drug delivery system

The new generation mucoadhesive polymers for buccal drug delivery with advantages such as increasein the residence time of the polymer, penetration enhancement, site specific adhesion and enzymatic inhibiton, site specific mucoadhesive polymers will undoubtedly be uitilized for the buccal delivery of awide variety of therapeutic compounds. The class ofpolymers has enormous for the delivery of therapeutic macromolecules.[57]

3. Polymers for sustained release

Polymers used in the sustain by preparing biodegradable microspheres containing a new potent osteogenic compound.[58]

4. Polymers as floating drug delivery system

Polymers are generally employed in floating drug delivery systems so as to target the delivery of drug to aspecific region in the gastrointestinal tract i.e. stomach.Natural polymers which have been explored for their promising potential in stomach specific drug delivery include chitosan, pectin, xanthan gum, guar gum, gellan gum, karkaya gum, psyllium, starch, husk, starch, alginates etc.

5. Polymers in tissue engineering

A wide range of natural origin polymers with special focus on proteins and polysaccharides might be potentially useful as carriers systems for active biomolecules or as cell carriers with application in thet issue engineering field targeting several biological tissues.[59]

MUCOADHESIVE POLYMERS[60]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the mucin epithelial surface can be conveniently divided into three broad classes.

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self-surface.

Classification of mucoadhesive polymers[61]

✓ Natural and modified natural polymers.

Agarose, Chitosan, Gelatin, Pectin, Sodium alginate, CMC, NaCMC, HPC, HPMC, Methyl cellulose.

✓ Synthetic polymers.

Carbopol, Polycarbpphil, Polyacrilic acid, Polyacrylates.

Cationic and anionic.

Aminodextran, Chitosan, Chitosan –EDTA, Dimethy lamino ethyl dextran**,** table (3).

Table (3): Example of polymers used in mucoadhesive drug delivery system[62]

No.	Name of polymer	Molecular weight(Da)	Description	Application
1	Polyvinyl pyrolidine	2500-3,000,000	White,odourlessAnd hygroscopicpowder	Good emulsifying agent,thickening agent, bindingagent
2	Carbopol	7×10^5 to 4×10^9	White, fluffy, acidic, hygroscopic powder with slightcharacteristics odour	Excellent thickening,emulsifying, gelling, bindingagent, possess goodbioadhesive strength
3	Sodium carboxy methyl cellulose	90,000-70,000	White to fainty yellow, odourless, hygroscopic powder	As emulsifying, gelling, and binding agent, possess good bioadhesive strength
4	Methyl cellulose	10,000-220,000 Da	White, fibrouspowder or granules. It is odorless and tasteless	It is used in oral and topicalpharmaceutical formulationand used in disintegrant
5	Hydroxy propyl cellulose	60,000-1,000,000	White to slightly yellowish,odourless powder.	It is used as a thickening agent, emulision stabilizer, and suspending agent inoral.
6	Chitosan	10,000-1,000,000	Odorless, white or creamy-white powder or flakes	It is used in cosmetics andpharmaceuticalformulations and used as acompoment ofmucoadhesive dosage form,flims, gels, tablet and beads
7	Eudragit analogue	47,000	Transparent or pale Yellowishcolour, odourless	Good Emulsifying agent, binding agent
8	Sodiun alginate	220,000	Odorless andtasteless, white to yellowish-brown colored powder	It is used as a stabilizer inemulsions, as a suspending agent, tablet disintegrant and tablet binder
9	Tragacanth	84,000 Da	Flattened,lamellated,frequentl y curved fragmentsand white toyellowish in color,odourless.	Emulsifying and suspendingagent in a Varity of pharmaceuticalformulations. It is used increams and gels.
10	Gelatin	20,000-200,000	Light-amber tofaintly yellow colored, vitreous,brittle solid	It is used as oraladministration hard andsoft gelatin capsules
11	Xanthum gum	1,000,000	Cream or whitecolored,odourless,free flowing, fine powder	It is used in oral and topicalPharmaceuticalformulation, cosmetics andfood as a suspending agent, thickening agent andemulsifiying agent

Characteristics of ideal mucoadhesive polymer[63]

- Polymer and its degradation products should be non-toxic, non-irritant and non- absorbable in the gastrointestine tract.
- The polymer should have good properties like wetting, swelling, solubility and biodegradability properties.
- The polymer should show sufficient mechanical strength by adhere quickly to the buccal mucosa.
- The polymer should show sufficient tensile and shear strengths at the bioadhesive range.
- Polymer should not be of high cost and must be easily available.
- The polymer must have bioadhesive properties in both dry and liquid state.
- The polymer should have properties like penetration enhancement and local enzymatic inhibition.
- The polymer does not decompose during the shelf-life of dosage form and during storage.
- Should have narrow distribution and optimum molecular weight.
- The polymer should not have degree of suppression of bond forming group but should have sufficient cross-linkage.
- Should not produce the secondary infection in the dental caries.

The BAISIC COMPONENTS OF BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEMS ARE[64]

a. Drug substance
b. Bioadhesive polymers
c. Backing membrane
d. Penetration enhancers

a. Drug substance

The drug substances are decided on the basis of, does drug used for rapid release/prolonged release and for local/systemic effect? Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended. The drug should have following characteristics.

i. The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
ii. The conventional single dose of the drug should be small.
iii. The drug absorption should be passive when given orally.
iv. Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
v. Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

b. Bioadhesive polymers

The second step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation." Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs an ideal polymer for buccoadhesive drug delivery systems should have following Characteristics.

i. It should be inert and compatible with the environment
ii. The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
iii. It should adhere quickly to moist tissue surface and should possess some site specificity.
iv. The polymer must not decompose on storage or during the shelf life of the dosage form.
v. The polymer should be easily available in the market and economical.

c. Backing membrane

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc. The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers.

d. Penetration enhancers

To increases the permeation rate of the membrane of co-administrated drug they are added in the pharmaceutical formulation. Without causing toxicity and damaging the membrane they improve the bioavailability of drugs that have poormembrane penetration. The capability to enhance the penetration is depend upon they are used in combination or alone, nature of vehicle, table (4).

Table (4): Different permeation enhancers used in buccal drug delivery andmechanisms of action.

No	Class of permeation enhancers	Examples	Mechanism
1-	Thiolated polymers	Chitosan-4-thiobutylamide, chitosan- 4thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophilcysteine, polycarbophil- cysteine/GSH, chitosan-4thioethylamide/GSH, chitosan-4-thioglycholic acid	Ionic interaction with negative charge on the mucosal membrane surface.
2-	Surfactants	Sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-lauryl ether, Polyoxythylene20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide	Perturbation of intercellular lipids, protein domain integrity.
3-	Chelators	EDTA, citric acid, sodium salicylate, methoxy salicylates.	Interface with Capolyacrylate
4-	Non-surfactants	Unsaturated cyclic ureas	
5-	Fatty acids	Oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine	Increase fluidity of phospholipid domains.
6-	Inclusion complexes	Cyclodextrins	Inclusion of membrane compounds
7-	Bile salts	Sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate	Perturbation of intercellular lipids, protein domain integrity
8-	Others	Aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.	Inclusion of membrane compounds

MECHANISMS OF MUCOADHESION[65]

The mechanism of mucoadhesion is generally divided in two steps.

A. Contact stage and
B. Consolidation stage.

The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the oesophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier.[66] In the consolidation step, figure (7), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizers the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions. For example, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spread spread throughout the mucus layer, can present mucoadhesive properties.[67] According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated forms figure (8).

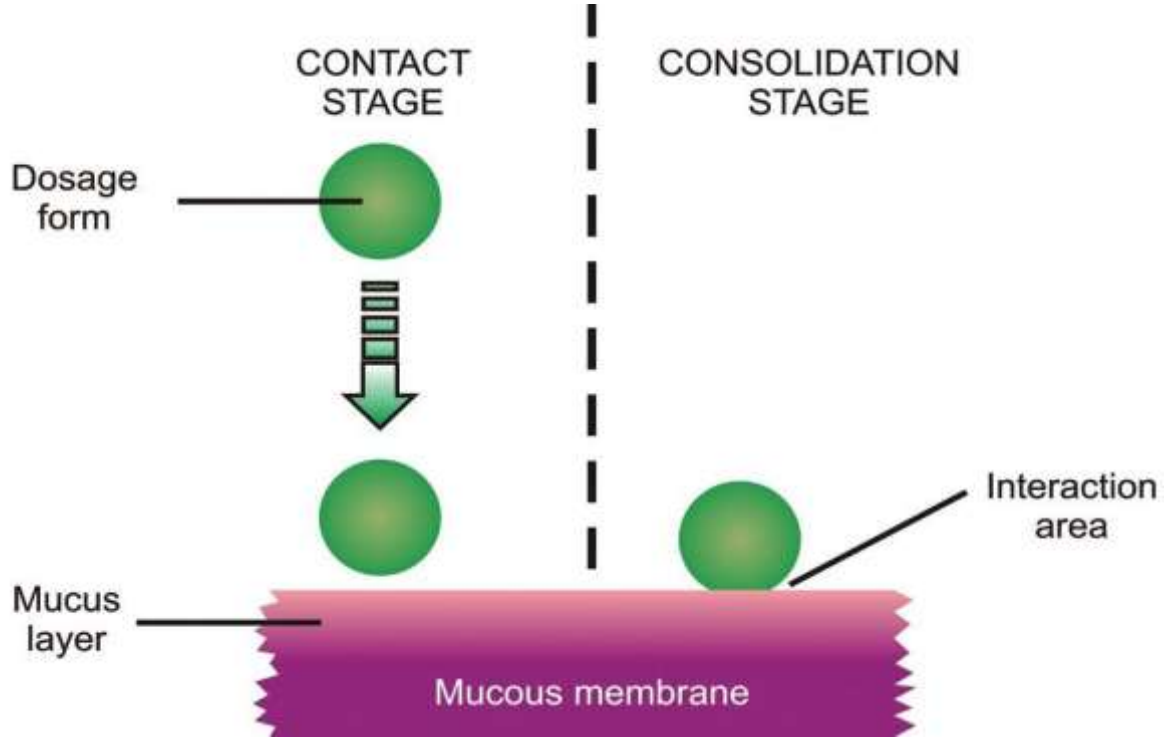


Figure (7): The two steps of the mucoadhesion process.

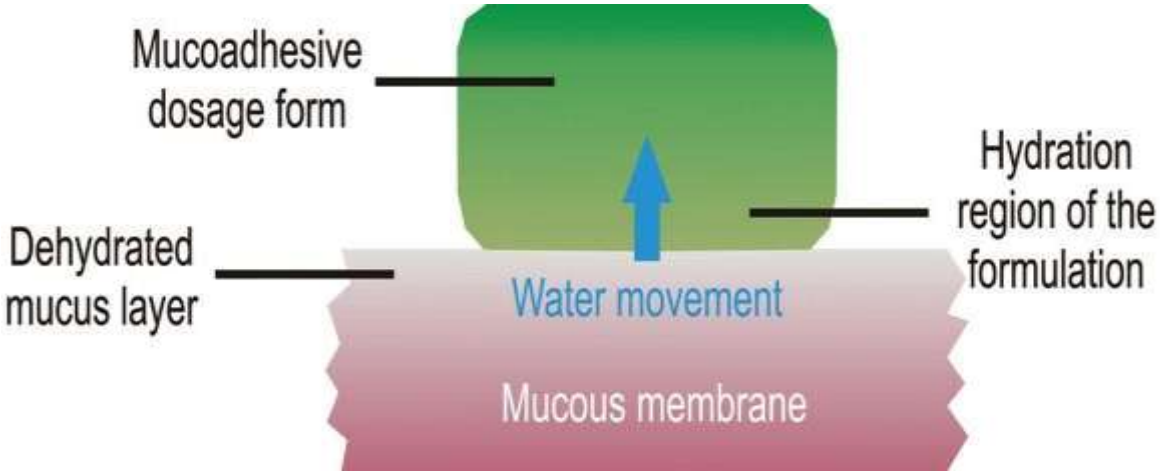


Figure (8): Dehydration theory of mucoadhesion.

Mucoadhesion Theories

There are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

1- Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.[68]

2- 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, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl groups. Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion[69] figure(9).

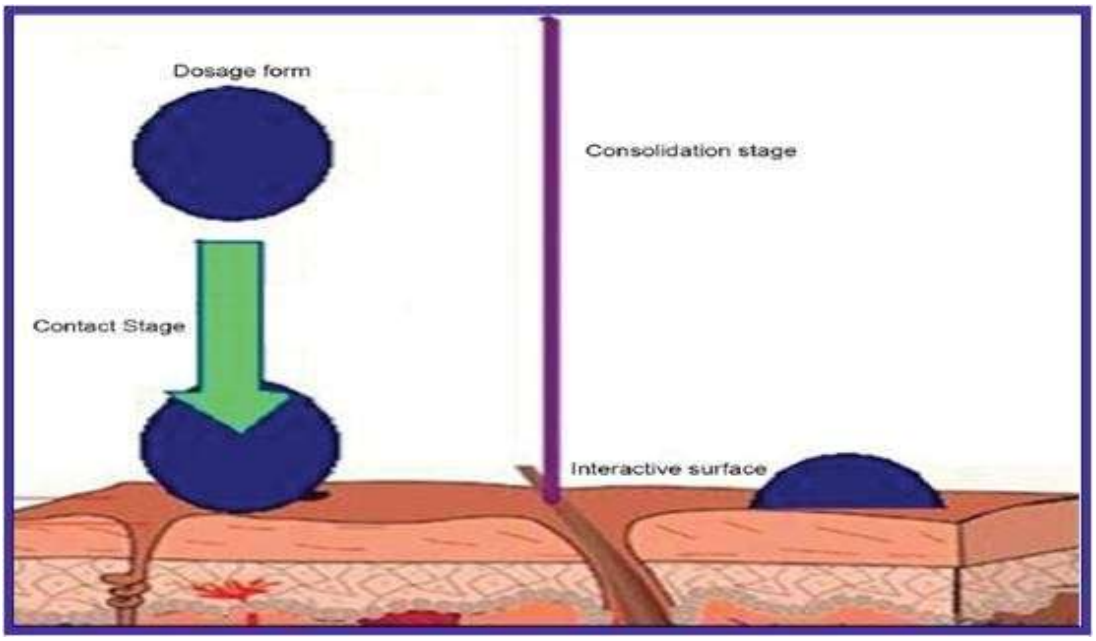
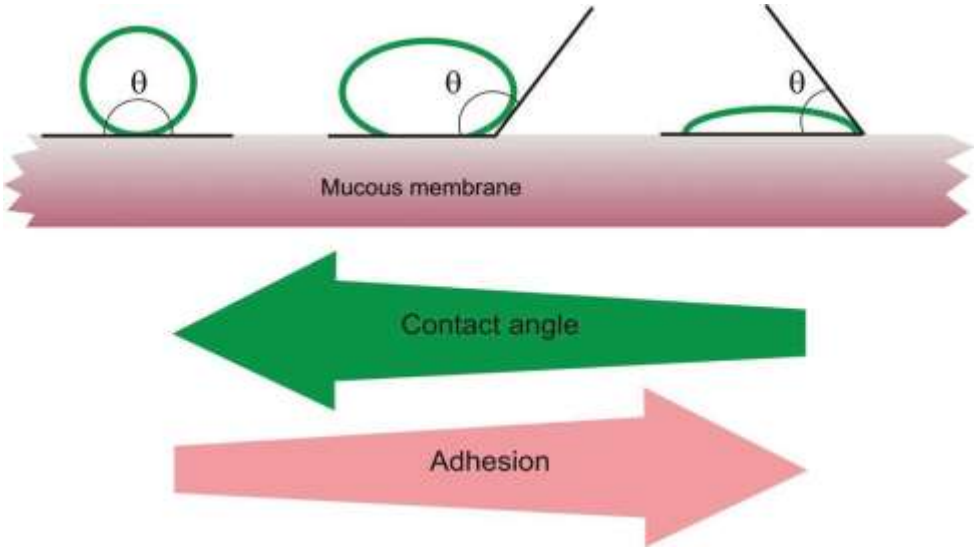


Figure 9: The process of consolidation.

3- Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity, figure (10). The contact angle should be equal or close to zero to provide adequate spreadability.



Figure(10): Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion.

Some important characteristic for liquidbioadhesive materials include.

i. A zero or near zero contact angle.
ii. A relatively low viscosity and.
iii. An intimate contact that exclude air entrapment.

The specific work of adhesion between bioadhesivecontrolled release system and the tissue is equal to the sum of the two surface tensions and less than the interfacial tension.

4- Diffusion theory

Diffusion theory describes the interpenetration ofboth polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond, figure (11). It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time.[70] The diffusion mechanism is the intimate contact of two polymers or two pieces of the same polymer. During chain interpenetration the molecules of the polymer and the dangling chains of the glycoproteinicnetwork are brought in intimate contact.

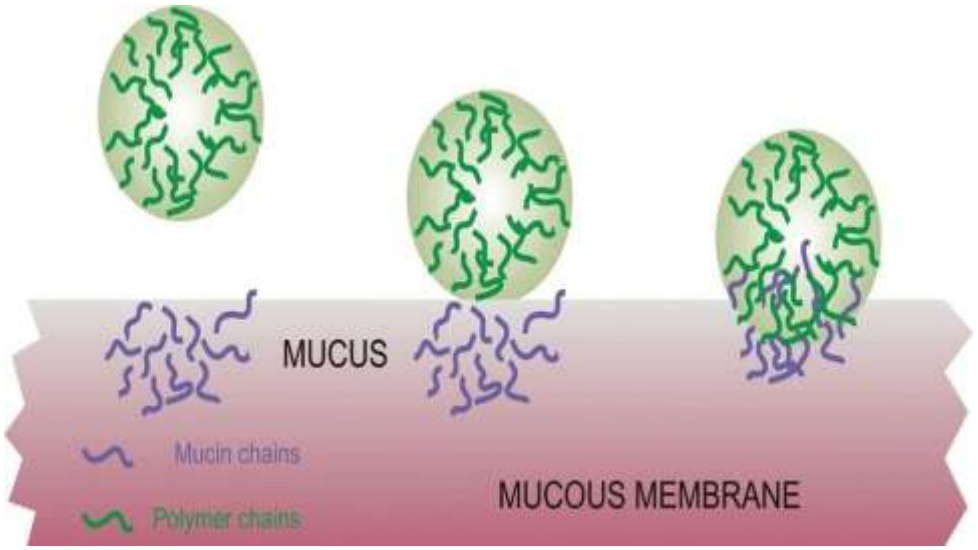


Figure (11): Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus

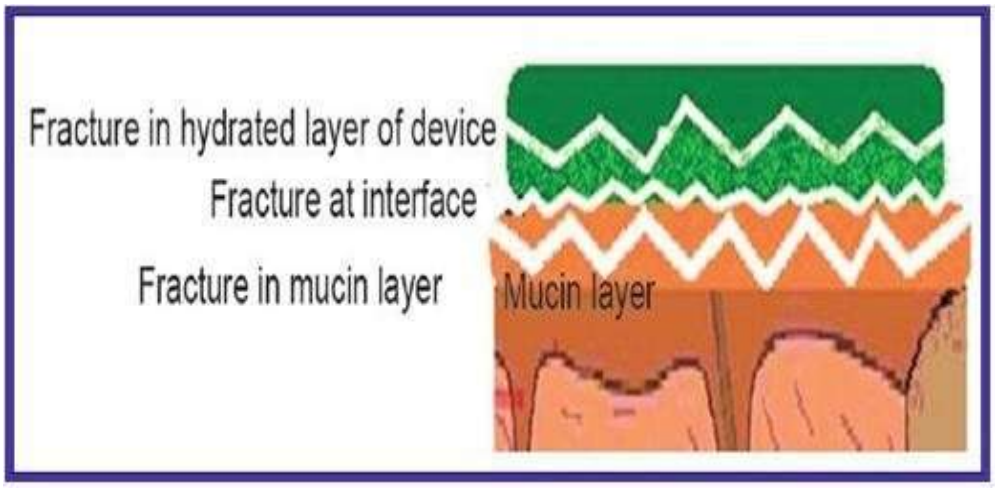
5- Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface 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.[71] It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables.

6- Fracture Theory

According to Fracture theory ofadhesion is related to separation of two surfaces after adhesion figure(12). The fracture strength is equivalent to adhesive strength as given by, **G = (Eε. /L) ½.**

Where: **E**= Young's module of elasticity.
ε = Fracture energy.
L= Critical crack length when two surfaces are separated.



Figure(12): Fractures occurring for Mucoadhesion.

FACTORS AFFECTING BIOADHESION[72]

Structural and physicochemical properties of a potential bioadhesion material influence bioadhesion.

A. Polymer related factors

a. Molecular weight

- The bioadhesive force rises with molecular weight of polymer upto 10,000 and beyond this level there is no much effect.
- To allow chain interpenetration, the polymer molecule must have an adequate length.

b. Concentration of active polymers

- There is an ideal concentration of polymer resultant to the best bioadhesion.
- In extremely concentrated systems, the adhesive strength drops considerably.
- In concentrated solutions, the coiled molecules become solvent poor and the chains presented for interpenetration are not abundant.

c. Flexibility of polymer chain

Flexibility is necessary part for interpenetration and enlargement.

When water soluble polymers become cross linked, the mobility of individual polymer chain declines.

- As the cross linking density increases, the effective length of the chain which can penetrate into the mucus layer drops further and mucoadhesive strength is reduced.

d. Spatial conformation

- Beside molecular weight or chain length, spatial conformation of a molecule is also important.
- Despite a high molecular weight of 19,500,000 for dextrans, they have same adhesive strength to that of polyethylene glycol with a molecular weight of 200,000.
- The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, different PEG polymers which have a linear conformation.

B. Environment related factors

a. pH

The pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH Because of change in dissociation of functional groups on the Carbohydrate moiety and amino acids of the polypeptide back bone. b. Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. c. Initial contact time: As soon as the mucoadhesive strength increases, the initial contact time is also increases. d. Selection of the model substrate surface: The viability of biological substrate should be confirmed by examining properties such as permeability, Electrophysiology of histology. e. Swelling: Swelling depends on both polymers concentration and on presence of water. When swelling is too great a decrease in bioadhesion occurs.

MANUFACTURING METHODS OF BUCCAL PATCHES /FILMS

Manufacturing processes involved in making mucoadhesivebuccal patches/films, namely[73]

1. Solvent casting,
2. Hot melt extrusion and
3. Direct milling.

1. Solvent casting

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a

sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

2. Direct milling

In this, patches are manufacturedwithout the use of solvents. Drug and excipients aremechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After themixing process, the resultant material is rolled on a releaseliner until the desired thickness is achieved. The backingmaterial is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associatedsolvent-related health issues.[74]

3. Hot melt extrusion of films

In hot melt extrusion blend of pharmaceutical ingredients is molten and then forcedthrough an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlledrelease matrix tablets, pellets and granules, as well as oral disintegrating films. However, only a hand full articleshave reported the use of hot melt extrusion for manufacturing mucoadhesivebuccal films. Table (5)givessuitable polymers and drugs for buccal delivery.

Table 5: List of Investigated Bio Adhesive Polymers.

No.	Bioadhesive Polymer(s) Studied	Investigation Objectives
1	HPC and CP	Preferred mucoadhesive strength on CP,HPC, and HPC-CP combination. Measured Bioadhesive property using mouse peritoneal Membrane Studied inter polymer complexation and its effects onbioadhesive strength.
2	CP, HPC, PVP, CMC	Studied inter polymer complexation and its effects on bioadhesive strength.
3	Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs.
4	Poly(acrylicacid) Poly(methacrylic acid)	Synthesized and evaluated cross-linked polymers differing in charge densities and hydrophobicity.
5	Number of Polymers including HPC, HPMC, CP, CMC	Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion.
6	Poly(acrylicacid-coacrylamide)	Adhesion strength to the gastric mucus layer as a function of cross-linking agent, degree of swelling, and carboxyl group density
7	Poly(acrylic acid)	Effects of PAA molecular weight andcross-linking concentration on swelling and drug release characteristics.
8	HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer.
9	HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base.
10	CP, PIP, and PIB	Used a two roll milling method to prepare a new bioadhesive patch formulation.
11	Xanthan gum and Locust bean gum, Chitosan, HPC, CMC, Pectin, Xanthan gum, and Polycarbophil.	Hydrogel formation by combination of natural gums. Evaluate mucoadhesiveproperties by routinely measuring the detachment force form pig intestinal mucosa.
12	Formulation consisting of PVP, CP, and cetylpyridinium chloride (as stabilizer)	Device for oramucosal delivery of LHRH - device containing a fast release and a slow release layer.
13	CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride	Mucoadhesive gels for intraoral delivery.

EVALUATIONS OF BUCCAL PATCH

1. Surface pH

Buccal patches are left to swell for 2 hrs on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollenpatch.[75]

2. Thickness measurements

The thickness of each film ismeasured at five different locations (centre and four corners) using an electronic digital micrometer.[76]

3. Swelling study

Buccal patches are weighed individually(designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1- hr time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper.[77] The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using thefollowing formula.

$$SI = \frac{(W2-W1)}{W1} \times 100$$

4. Folding endurance

The folding endurance of patches isdetermined by repeatedly folding 1 patch at the times without breaking.[78]

5. Thermal analysis study

Thermal analysis study isperformed using differential scanning calorimeter (DSC).

6. Morphological characterization

Morphologicalcharacters are studied by using scanning electron microscope (SEM).

7. Water absorption capacity test

Circular Patches, witha surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na_2HPO_4, 0.19 gKH_2PO_4, and 8 g NaCl per litter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.

Water uptake (%)= (Ww – Wi)/Wf x 100

Where,
Ww= is the wet weight and
Wf=is the final weight.

The swelling of each film is measured.[79]

8. Ex-vivo bioadhesion test

The fresh sheep mouthseparated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of thebalance are balanced with a 5g weight. The 5g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 min of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface.[80] Theweight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesivestrength, figure(13).

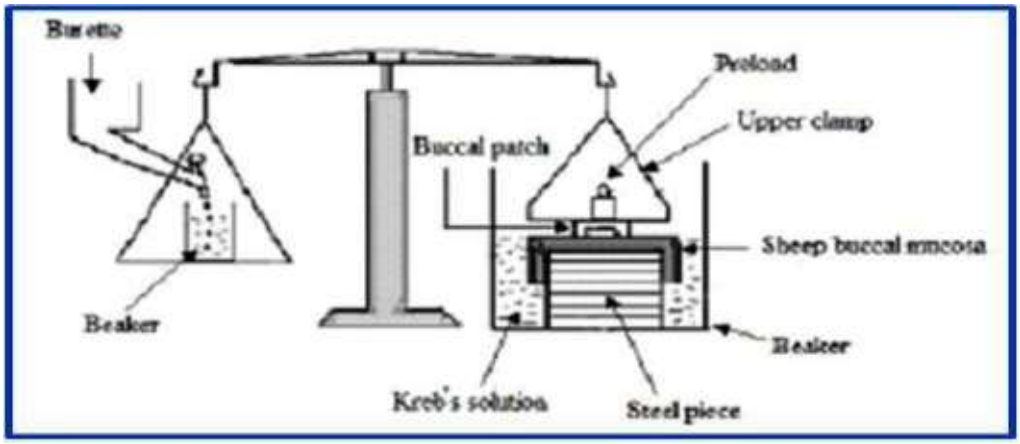


Figure (13): Ex-vivo bioadhesion test.

9. In vitro drug release

The United States Pharmacopeia(USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution. The in-vitro buccalpermeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien /Franz type glass diffusioncell at 37°C ± 0.2°C. Fresh

buccal mucosa is mountedbetween the donor and receptor compartments. The buccalpatch is placed with the core facing the mucosa and the compartments clamped together.[81]

10. Permeation study of buccal patch

Buccal permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. in vitro and/or in vivo both methods are involved to determine the buccal permeation profile and absorption kinetics of the drug. The receptorcompartment is filled with phosphate buffer pH 6.8, and thehydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.[82]

11. Ex-vivo mucoadhesion time

The ex-vivomucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 secs. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hrs. The time for changes in color, shape, collapsing of the patch, and drug content is noted.[83]

12. Measurement of mechanical properties

Mechanicalproperties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by theupper clamp moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula, figure (14).

T = m x g/ b x t Kg/mm2

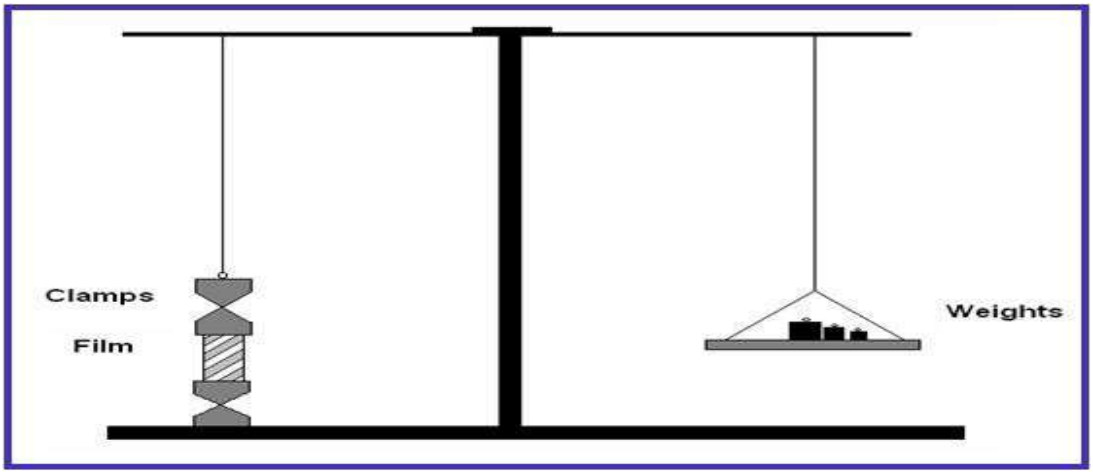
Where,

M =is the mass in gm, g - is the acceleration due to gravity 980 cm/sec 2,

B=is the breadth of the specimen in cm,

T =is the thickness of specimen in cm

Tensile strength (kg/mm2)= is the force at break (kg) per initial cross- sectional area of the specimen (mm2).



Figure(14): Modified tensile strength tester.

It measures the strength of patches as diametric tension ortearing force. It is measured in g or N/m2. It shows the strength of patches to various stresses and can be measured by using simple calibrated vertical spring balance.

13. Stability study in human saliva[84]

The stabilitystudy of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hrs), the dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosaland transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and

therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dose required and minimize side effects that may be due to systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Currently solid dosage forms, liquids and gels applied to oral cavity arecommercially successful. The future direction of buccaladhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptide.

14. In vivo Methods[85]

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa). For study the permeation characteristics of buccal drug delivery systems special attention is require to choice of experimental animal species for such experiments. Many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue but it is hard to isolate the desired non-keratinized region due to sudden transition to keratinized tissue at the mucosal margins. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys, dogs, and pigs which are having non-keratinized tissue.

Future Challenges And Opportunities

The future challenge of pharmaceutical scientists will not only be polypeptide cloning and synthesis, but also to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation.

Buccal permeation can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators and cyclodextrins.

Researchers are now looking beyond traditional polymer networks to find other innovative drugtransport systems. Much of the development of novel materials in controlled release buccal adhesive drug delivery is focusing on the preparation and use of responsive polymeric system using copolymer with desirable hydrophilic/hydrophobic interaction, block or graft copolymers, complexation networks responding via hydrogen or ionic bonding and new biodegradable polymers especially from natural edible sources. Scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies like inclusion of pH modifiers, enzyme inhibitors, permeation enhances etc. Novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

CONCLUSION

Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body. In addition, its prove to be a unique alternative to conventional drugs by virtue of its ability in overcoming hepatic metabolism, reduction in dose frequencies and enhancing bioavailability. Buccal region provides a convenient route of administration for topical, local and systemic drug actions. Buccal adhesive systems offerinnumerable advantages in term of accessibility, administration and withdrawal, retentively, low enzyme activity, economy and highpatients compliance. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orallyinefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Currently solid dosage forms, liquids, spray and gels applied to oral cavity are commercially successful. The future direction of buccaldhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Current use of mucoadhesive

polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. The general properties of these polymers for purpose of sustained release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal.

REFERANCES

1. Radha Madhavi B, Varanasi SN Murthy, Prameela Rani A and Dileep Kumar Gattu.(2013) Buccal Film Drug Delivery System-An Innovative and Emerging Technology. J. Mol Pharm Org Process Res, 1(3): 1-6.
2. Shrutika M. Gawas, AsishDev, Ganesh Deshmukh, S. Rathod, (2016) Current approaches in buccal drug delivery system. Pharmaceutical and Biological Evaluations, 3(2): 165-177.
3. Mamatha Y, Prasanth VV, Selvi AK, Sipai A. Yadav MV.(2012) Review Article on Buccal Drug Delivery A Technical Approach. Journal of Drug Delivery & Therapeutics, 2(2).
4. Doijad RC, Yedurkar P, Manvi FV. (2003) Formulation and evaluation of Transdermal Drug Delivery System containing Nimesulide. International Congress of Indian Pharmacy Graduates, 22: 120-5.
5. Doijad RC, Kapoor D, Kore S, Manvi FV. (2002) Improvement in dissolution rate, absorption and efficiency of Albendazole by solid dispersion. International Congress of Indian Pharmacy Graduate, Chidambaram, Annamalai University, Tamil Nadu.
6. Shojaei A. H.,(1998) Buccal Mucosa As A Route For Systemic Drug Delivery: A Review, J Pharm Pharmaceut Sci, 1(1): 15-30.
7. Suhel khan, Nayyar P, Pramod K. Sh, MdAftabAlam, and Musarrat H.W.(2016) Novel Aproaches-MucoadhesiveBuccal Drug Delivery System. Int. J. Res. Dev. Pharm. L. Sci, 5(4): 2201-2208.
8. Hooda, R., Tripathi, M., and Kapoor, K., 2012. A Review an oral mucosal drug delivery system. The Pharma innovation, 1(1): 14-21.
9. Siddaqui, M.D.N, Garg, G., and Sharma, P.K., (2011). A short Review on "A novel approach in oral fast dissolving drug delivery system and their patents". Advances in biological research, 5(6): 291-303.
10. Shidhaye SS et al.(2009). Mucoadhesive bilayered patches for administration of sumatriptan, AAPS pharm, sci. tech, 9(3).
11. Flávia Chiva Carvalho, et al.(2010) Mucoadhesive drug delivery systems. Brazilian Journal of Pharmaceutical Sciences, 46(1): 1-17.
12. Kuldeep Vyas et al.(2015) Buccal Patches: Novel Advancement In Mucoadhesive Drug Delivery System. Indo American Journal of Pharm Research, 5(02): 727-740.
13. Thulasiramaraju TV. et al. (2013)Asian Journal of Research in Biological and Pharmaceutical Sciences, 1(1): 28-46.
14. Amit Alexander et al,(2011) Mechanism Responsible For Mucoadhesion OfMucoadhesive Drug Delivery System: A review. IJACPT, 2(1): 434-445.
15. Shalini Mishra et al.(2012) A Review Article: Recent Approaches in Buccal Patches, THE PHARMA INNOVATION, (7): 78-86.
16. Rajput, G.C.; Dr. Majmudar, F.D.; Dr. Patel, J.K.; Patel, K.N.; Thakor, R.S.; Patel, B.P.; Rajgor, N.B., (2010), Stomach Specific Mucoadhesive Tablets as Controlled Drug Delivery System, International Journal on Pharmaceutical and Biological Research, 1: 30-41.
17. Jain, N.K., (1997), Controlled release and Novel Drug Delivery. 1st edition. CBS publishers and Distributors New Delhi, 353-370.
18. Asane, G.S., (2007), Mucoadhesive Gastro Intestinal Drug Delivery System, Pharmainfo.net, 5.
19. Chickering III D.E.; Mathiowitz E., (1999), Bioadhesive drug delivery systems. Fundamentals, novel approaches, and developments., In Mathiowitz E., Chickering III D.E.; Lehr C.M.; eds., Definitions mechanisms and theories of bioadhesion., New York, Marcel Dekker, 1-10.
20. Castellanos, M. Rosa Jimenez; Zia, Hussein; Rhodes, C. T., (1993), Mucoadhesive Drug Delivery Systems, Informa Health Care, 19: 143-194.
21. Ahuja A.; Khar R.K.; Ali J., (1997), Mucoadhesive drug delivery systems., Drug. Dev. Ind. Pharm, 23: 489-515.
22. Bhatt, J.H., (2009), Designing And Evaluation Of Mucoadhesive Microspheres Of Metronidazole for Oral Controlled Drug Delivery, Pharmainfo.net.
23. Ganga, S, (2007), Mucosal Drug Delivery, Pharmainfo.net, 5.
24. Ponchel, G; Touchard, F; Duchene, D; and Peppas, N.A., (1987), Bioadhesiveanalysis of controlled res. systems, I. fracture and interpenetration analysis in poly acrylic acid containing systems, J. Control. Res, 5: 129-141.
25. Abnawe, SumitAnand, (2009), Mucoahesive Drug Delivery System, Pharmainfo.net.
26. Tahsin Akhtarali Shaikh, et al. (2016) Review: Polymers Used in the Mucoadhesive Drug Delivery System International Journal of Pharma Res earch& Review, 5(5): 45-53.
27. Bramankar, M.; Jaiswal, S.B., (1995), Biopharmaceutics and Pharmacokinetics A treatise, 337-371.
28. Sachan Nikhil, K; Bhattacharya, A, (2009), Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems, International Journal of Pharmaceutical and Clinical Research, 1: 10-14.
29. Punitha, S; Girish, Y, (2010), Polymers in

mucoadhesivebuccal drug delivery system, International Journal of Research and Pharmaceutical Sciences, 1: 170-186.
30. Krupashree KG et al.,(2014)Approches To Mucoadhesive Drug Delivery System In Oral Cavity-A detailed Review. International Journal of Research in Pharmaceutical and Nano Sciences, 3(4): 257-265.
31. Jasvir Singh and Pawan Deep., (2013) Mucoadhesive buccal drug delivery system, IJPSR, 4(3): 916-927.
32. Jimenez MR, Castellanous, Zia H, Rhodes CT. (1993) Mucoadhesive Drug Delivery Systems. Drug Dev Ind Pharm, 19(1-2): 143-194.
33. Bomberag LE, Buxton DK, Friden PM.(2001) Novel periodontal drug delivery system for treatment of periodontitis. J.Control. Rel, 71: 251-259.
34. Salamat-Miller N, Chittchang M, Johnston TP. (2005)The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev, 57: 1666-1691.
35. Ravi Bhalodia, BiswajitBasu, Kevin Garala, Bhavik Joshi et al., (2010)Buccoadhesive drug delivery systems, Int J Pharm Bio Sci, 1(2): 1-32.
36. Nishan N Bobade, Sanreep C Atram, Vikrant P Wankhade, DrPande S D et al.,(2013) A Review Buccal drug delivery system, Int J Pharmacy Pharm Sci Res, 3(1): 35-40.
37. Pranshutangri, Shaffi Khurana, Sathesh Madhav.(2011) Mechanism and method of evaluation, Int J pharm Bio Sci, 2(1): 458-467.
38. Miller N S, Chittchang M, Johnston T P. (2005)The use of mucoadhesive polymers in buccal drug delivery, Adv Drug Deliv Rev, 5(7): 1666-1691.
39. Mujorruya R, Dhamande K, Wankhede U R and Dhamande K. (2011) A review on study of buccal drug delivery system, Innovative System Design and Engineering, 2(3): 1-14.
40. Birudaraj R, Mahalingam R.(2005) Advances in buccal drug delivery, Critical review in therapeutic drug carrier systems, 22(3): 295-330.
41. N.G.Raghavendra Rao et al.(2013) Overview on Buccal Drug Delivery Systems. J. Pharm. Sci. & Res, 5(4): 80–88.
42. Shojaei Amir H,(1998) Buccal Mucosa As A Route For Systemic Drug Delivery: A Review; J Pharm Pharmaceut Sci, (www.ualberta.ca/~csps), 1(1): 15-30.
43. Sudhakar Y, Knotsu K, Bandopadhyay AK. (2006) Bioadhesive drug delivery – A promising option for orally less efficient drugs. J Control Rel, 114: 15-40.
44. Jagadeeshwar Reddy R, Maimuna Anjum, Mohammed Asif Hussian.(2013) A comprehensive Review on Buccal drug delivery system, AJADD, 1(3): 300-312.
45. Gupta S K, Singhavi I J, Shirsat M, Karwani G,Agrawal A. (2011) A Review on Buccal adhesive drug delivery system, AJBPR, 2(1): 105-114.
46. Vinod K R, Rohit Reddy T, Sandhya S, David Banji et al. (2012) Critical Review on mucoadhesive drug delivery systems, Hygeia. J. D. Med, 4(1): 7-28.
47. VajraPriya et al., (2016) Polymers in Drug Delivery Technology, Types of Polymers and Applications Sch. Acad. J. Pharm, 5(7): 305-308.
48. Raizada A, Bandari A, Kumar B;(2010) Polymers in drug delivery:A Review. International Journal of pharma research and development, 2(8): 9-20.
49. Chandel P, Rajkumari, Kapoor A,(2013) Polymers–A Boon To Controlled Drug Delivery System, International research journal of pharmacy(IRJP), 4(4): 28-34.
50. Duncan R; (2003) The dawning era of polymertherapeutics. Nature Reviews Drug Discovery, 2: 347–360.
51. Harekrishna Roy, Sanjay Kumar Panda, Kirti Ranjan Parida, Asim Kumar Biswal. (2013) Formulation and In-vitro Evaluation of Matrix Controlled Lamivudine Tablets. International Journal of Pharma Research and Health Sciences, 1(1): 1-7.
52. Heller J.,(1984) Biodegradable polymers in controlleddrug delivery. Critical Reviews™ inTherapeutic Drug Carrier Systems, 1(1): 39-90.
53. Harekrishna Roy, Anup K Chakraborty, Bhabani Shankar Nayak, Satyabrata Bhanja, Sruti Ranjan Mishra, P. Ellaiah.(2010) Design and in vitro evaluation of sustained release matrix tablets of complexed Nicardipine Hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences, 2: 182-132.
54. Harekrishna Roy;(2015) Formulation of Sustained Release Matrix Tablets of Metformin hydrochloride by Polyacrylate Polymer. Int J Pharma Res Health Sci, 3(6): 900-906.
55. SatyabrataBhanja, Sudhakar M, Neelima V, Panigrahi BB, Harekrishna Roy. (2013) Developmentand Evaluation of Mucoadhesive Microspheresof Irbesartan. International Journal of Pharma Research and Health Sciences, 1(1): 8-17.
56. Nair Lakshmi S., Laurencin Cato T.,(2006) Polymersas Biomaterials for Tissue Engineering andControlled Drug Delivery. Tissue Engineering I Publisher: Springer Berlin / Heidelberg, 203-210.
57. Jones David.,(2004) Pharmaceutical Applications of Polymers for Drug Delivery. Chem Tec Publishing Inc, 300-301.
58. Sanghi DK, Borkar DS, Rakesh T;(2013) The Use of Novel Polymers In A Drug Delivery & Its Pharmaceutical Application. Asian Journal of Biochemical and Pharmaceutical Research, 2(3): 169-178.
59. Harekrishna Roy, P. VenkateswarRao, SanjayKumar Panda, Asim Kumar Biswal, Kirti Ranjan Parida, Jharana Dash.,(2014) Composite alginate hydrogel microparticulate delivery system of zidovudine hydrochloride based oncounter ion induced aggregation. Int J Applied Basic Med Res, 4(Sup 1): S31-36.
60. Vinod KR et al.,(2012) Critical Review on Mucoadhesive Drug Delivery Systems. Hygeia. J.D. Med, 4(1): 7-28.

61. Lehr CM.,(2000) Lectin-Mediated Drug Delivery:The Second Generation of Bioadhesives. J Control Release, 65: 19–29.
62. Nagpal et al., (2016) Mucoadhesion: A new Polymeric Approach Bulletin of Pharmaceutical Research, 6(3): 74-82.
63. Gandhi P A, Patel M R and Patel K R. (2011) A review article on mucoadhesivebuccal drug delivery system, Int J Pharm Res Deliv, 3(5): 159-173.
64. Venkatalakshmi R, Yajaman S, Chetty M., (2012) Buccal drug delivery using adhesive polymeric patch, Int J PharmaSci Res, 3(1): 35-41.
65. Khan et al. (2016)Mucoadhesive Drug Delivery System: A Review.W.J.P.P.S, 5(5): 392-405.
66. SMART, J. D.(2005) The basics and underlying mechanisms of mucoadhesion. Adv. Drug Del. Rev, 57(11): 1556-1568.
67. MATHIOWITZ, E.; CHICKERING, D. E.; LEHR, C. M. (Eds.).,(1999) Bioadhesive drug delivery systems: fundamentals, novel approaches and development. Drugs and the Pharmaceutical Sciences. New York: Marcel Dekker, 696.
68. HÄGERSTRÖM, H.,(2003) Polymer gels as pharmaceutical dosage forms: rheological performance and physicochemical interactions at the gel-mucus interface for formulations intended for mucosal drug delivery. Uppsala, 76 f. [Dissertation for the degree of Doctor of Philosophy in Pharmaceutics. Uppsala University].
69. SMART, J. D.,(2005) The basics and underlying mechanisms of mucoadhesion. Adv.Drug Del. Rev, 57(11): 1556-1568.
70. LEE, J. W.; PARK, J. H.; ROBINSON, J. R. (2000) Bioadhesive-based dosage forms: The next generation. J. Pharm. Sci, 89(7): 850-866.
71. PEPPAS, N. A.; SAHLIN, J. J.,(1996) Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials, 17(11): 1553-1561.
72. Mamatha Y, Prasanth VV, Selvi AK, Sipai A. Yadav MV.,(2012) Review Article on Buccal Drug Delivery A Technical Approach. Journal of Drug Delivery & Therapeutics, 2(2).
73. Sudhakar Y., Kuotsu K., et al. (2006). Buccal bioadhesive drug delivery-A promising option for orally less efficient drugs. Journal of Controlled Release, 114: 15-40.
74. Aungst BJ and Rogers NJ, (1988) Site Dependence of Absorption-Promoting Actions of Laureth, Na Salicylate, NaEDTA, and Aprotinin on Rectal, Nasal, and Buccal Insulin Delivery, Pharm. Res, 5(5): 305–308.
75. Kumar M et al, (2010) Design and in vitro evaluation of mucoadhesive buccal films containing Famotidine, International journal ofpharmacy and pharmaceutical sciences, 2, 3. 9.
76. Semalty M et al, (2008) Development of mucoadhesivebuccal films of Glipizide, International journal of pharmaceutical sciences and nanotechnology, 1(2).
77. Zhang.J et al, (1994) An In Vivo Dog Model for Studying RecoveryKinetics of the Buccal Mucosa Permeation Barrier after Exposure toPermeation Enhancers Apparent Evidence of Effective Enhancementwithout Tissue Damage, Int. J.Pharm, 10(1): 15–22.
78. Goudanavar PS et al,(2010)Formulation and In-vitro evaluation of mucoadhesive buccal films of Glibenclamide, Der pharmacialettre, 2(1): 382-387.
79. Choudhary A et al, (2010) Formulation and characterization of carvedilolbuccalmucoadhesive patches, www.ijrps.pharmascope.org, 1(4): 396- 401.
80. Kamel AH et al, (2007)Micromatricial metronidazole benzoate film as alocal mucoadhesive delivery system for treatment of periodontal diseases, AAPS pharm sci tech, 8(3): 75.
81. Giradkar KP et al, (2010) Design development and in vitro evaluation ofbioadhesive dosage form for buccal route, International journal ofpharma research & development, 2: 17.
82. Leung SS and J.R. Robinson,(1990) Polymer Structure Features Contributing to Mucoadhesion II, J. Contr. Rel, 12: 187–194.
83. Sanzgiri YD et al, (1994) Evaluation of Mucoadhesive Properties ofHyaluronic Acid Benzyl Esters, Int. J. Pharm, 107: 91–97.
84. Zhang. J et al, (1994) An In Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancementwithout Tissue Damage, Int. J. Pharm, 101: 15-22.
85. M. Jug, Becireviclacan,(2004) Influence of hydroxypropyl-betacyclodextrin complexation on piroxicam release from buccoadhesive tablets. Eur.J. Pharm. Sci, 21: 251-260.