



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1215051>Available online at: <http://www.iajps.com>

Review Article

**NOVEL APPROACHES ON BUCCAL MUCOADHESIVE DRUG  
DELIVERY SYSTEM**

Dibyalochan Mohanty\*, C. Gurulatha, Dr. Vasudha Bakshi, B. Mavya

Department of Pharmaceutics, School of Pharmacy, Anurag Group of Institutions, Hyderabad,  
Pin: 500088, India**Abstract:**

*Among novel drug delivery system, Buccal mucoadhesive systems have attracted great attention in recent years due to their ability to adhere and remain on the oral mucosa and to release their drug content gradually, bioadhesion refers to any bond formed between two biological surface or a bond between a biological and a systemic surface. Buccal mucosa is preferred for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. Buccal mucoadhesive films can improve the therapeutic effect of the drug by increasing the absorption of drug through oral mucosa which increases the drug bioavailability by reducing the hepatic first pass effect. In pharmaceutical field natural polymers have gained very much importance. Mucoadhesive polymers are used to improve drug delivery by increasing the dosage forms contact time and residence time with mucous membranes. This review article deals with the novel approaches use in the buccal drug delivery system.*

**Keywords:** Buccal delivery, Permeation enhancers, Mucoadhesive, Chitosan, Bioadhesive strength.

**Corresponding author:**

**Dibyalochan Mohanty,**  
Department of Pharmaceutics,  
School of Pharmacy,  
Anurag Group of Institutions,  
Medchal (D), 500088.  
Ph.no: 9014288184

QR code



Please cite this article in press Dibyalochan Mohanty et al., *Novel Approaches on Buccal Mucoadhesive Drug Delivery System*, Indo Am. J. P. Sci, 2018; 05(04).

## INTRODUCTION:

Oral route is most convenient and preferred route of administration amongst the various routes of administration. But solubility and first pass metabolism sensitivity of the drug are important characteristic to be accepted by this route. However it associated with some drawbacks like hepatic first pass metabolism and enzymatic degradation with in the GI tract [1].

Oral delivery systems have been developed to act as drug reservoir from which the active substances can be released over a period of time at a predetermined and controlled rate. In such cases buccal drug delivery is the promising approach because of its relatively immobile smooth muscle, abundant vascularization, After exposure to stress rapid recovery time. high molecular weight of drugs, poor penetrating drugs, and extensive first pass metabolism drugs need alternative routes. Muco adhesive route of administration is becoming popular and alternative for most of the drugs [2].

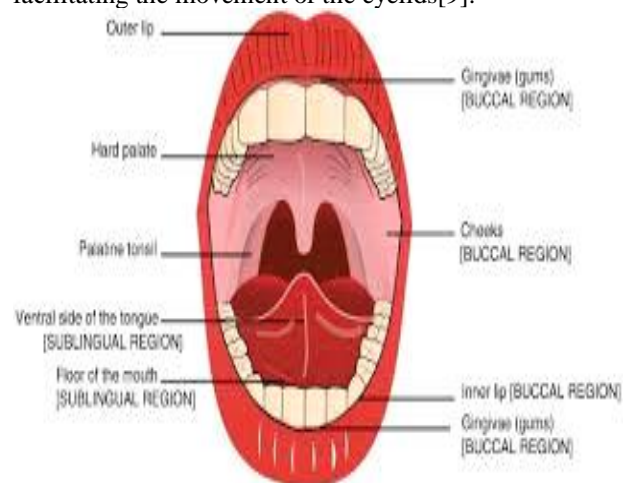
Buccal drug delivery is the one of the novel drug delivery systems .It is also a safer mode of drug delivery system. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drug from hepatic first pass metabolism. The buccal route administration provides a direct entry of drug molecule into systemic circulation[3].

Mucoadhesive drug delivery system interact with mucus layer covering the mucosal epithelial surface and mucin molecules and increase the resistance time of the dosage form at the site of absorption. Buccal patches are highly flexible and thus much more readily tolerated by the patients than tablets [4]. Mucoadhesive drug delivery is a part of controlled drug delivery system through buccal , sublingual, rectal and nasal mucosa can be faster and systemic mode of non invasive for most of the drugs. Faster delivery and enhanced bioavailability of drugs is observed through mucoadhesive administration.[2]

## ANATOMY OF ORAL CAVITY:

The oral mucosa is composed of an stratified squamous epithelium which is the outer most layer and it is below a basement membrane and the inner most layer sub mucosa which is followed by the lamina propria [5]. The blood epithelium is classified as the non keratinized tissues . lamina propria consists of collagen fibers a supportive layer of connective tissues blood vessel and smooth vessels [6]. The total area of the oral cavity is 100cm<sup>2</sup>. One third is the buccal surface which is lined with epithelium of about 0.5mm thickness. The upper layer contains goblet cells which secrete mucus components directly on to the epithelial surface[7].

These epithelium layer protect the lipid based permeability barriers in the tissues from fluid loss and also from the attack of the harmful environment agents like microbial toxins, antigens ,carcinogens ,enzymes etc . The oral cavity consists of two regions outer oral vestibule which is bounded by cheeks, lips, teeth and gingival (gums) this cavity extends from teeth and gums back to the faucets(which leads to pharynx) the tongue projects from the floor of the cavity. Oral epithelium proliferation time is 5-6days[8]. The secreted components on the mucus surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells protecting the epithelium from damage and facilitating the movement of the eyelids[9].



## BUCCAL MUCOSA:

- 1) Epithelium
- 2) Basement membrane
- 3) Connective tissue.

## Oral mucosa are divided into three types:

### MASTICATORY MUCOSA:

About 25percentage of the total oral mucosa covers the gingival and the hard palate.

### LINING MUCOSA:

It covers the oral mucosa of 60 percentage it covers the lips, cheeks ,soft palate, lower surface of the tongue and the floor of the oral cavity.

### SPECIALIZED MUCOSA:

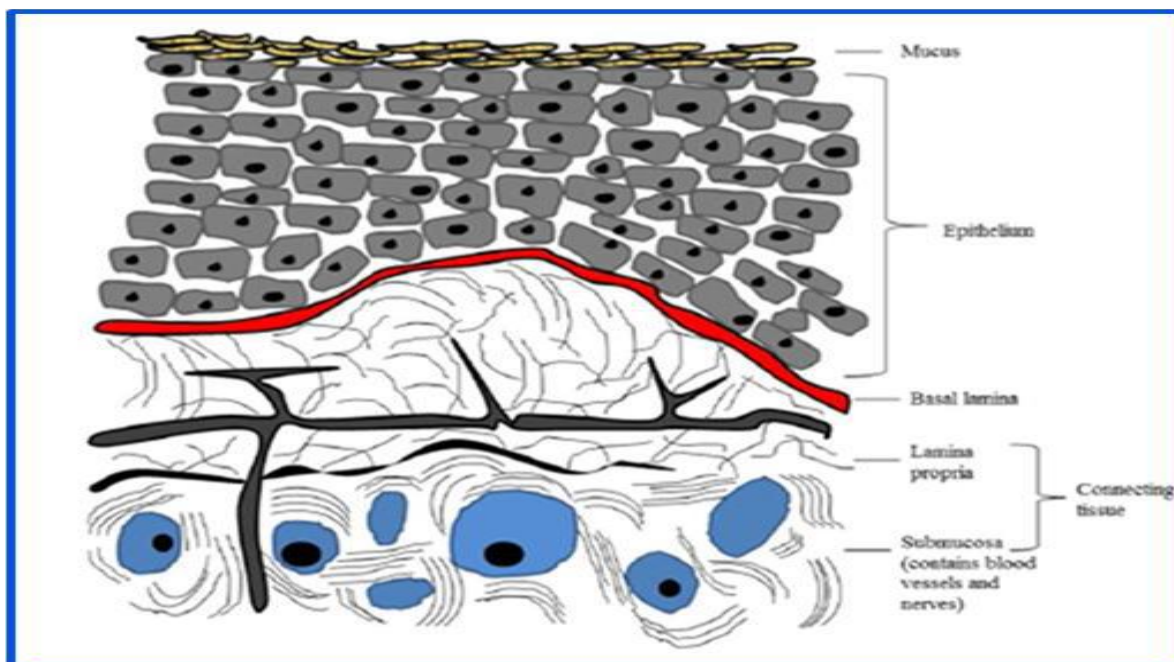
It covers 15 percentage of the total oral mucosa and it is found on the dorsum of the tongue.

**BUCCAL EPITHELIUM:**The Buccal epithelium is a non keratinized and composed of multiple layers of the cells which show different patterns of the maturation between the deepest cells and the surface .An intracellular lipid portion is packed in small organells called Membrane coating granules or lamellar granules.

### Mucus:

Mucus is a translucent and viscid secretion which forms a thin continuous gel adherent to mucosal epithelium surface made up of glycol proteins located various body cavities from respiratory and

gastrointestinal tract. This mucus layer of thickness of about 50-450um in humans actually creates adhesive interface for drugs.[10]



#### Composition of mucus layer :[11]

Sno.	Components	Amount(percentage)
1	Water	90-95
2	Glycoproteins and lipids	0.5-6.0
3	Mineral salts	1-1.5
4	Proteins	0.5-1.5

This mucus layer performs various functions:

**Protective:** It protects the epithelium surface from acid diffusion through lumen.

**Barrier:** It allows the selective absorption of the drugs.

**Adhesion:** Mucus layer with cohesive properties allows firm adhesion surface for molecules cell-cell adhesion.

**Lubrication:** Moisture presents in mucus provides lubrication to mucosal layer made up of proteins and carbohydrates.[12].

#### **SALIVA:**

The saliva with in the oral cavity makes it very difficult for the drugs to be retained for a significant amount of the time in oder to facilitate absorption in these site.[13]

#### **Role of saliva:**

Saliva continuous mineralization of the tooth enamel and the protective fluid for all tissuses of the oral

cavity. It hydrate the oral mucosa of the dosage forms.[14]

#### **FUNCTIONS OF THE ORAL CAVITY:[15]**

- 1) Oral cavity initiate the carbohydrate and fat metabolism
- 2) It helps in speech and breating process
- 3) It identifies the ingested material by taste buds of the tongue
- 4) To lubricate the food materials and bolus
- 5) It helps in chewing , mastication, and mixing of food stuff
- 6) As a portal for intake of food materials and water

#### **ADVANTAGES:[16]**

- 1) MDDS offer several advantages over other controlled oral controlled release systems by virtue of prolongation of residence of drug in GIT
- 2) High drug flux at the absorbing tissue
- 3) MDDS will serve both the purpose of Sustain release and presence of dosage form at the site of absorption

- 4) Low Enzymatic activity and avoid the first pass metabolism
- 5) Both hydrophilic and lipophilic drugs can be permeated
- 6) These dosage forms are readily localized in the region applied to improve and enhance bio-availability of drugs
- 7) Extent of perfusion is more therefore quick and effective
- 8) Some drugs are that are unstable in acidic environment of stomach can be administrated by buccal delivery
- 9) Drug administration can be terminated in case of emergency
- 10) Mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at absorbing tissue

#### DISADVANTAGES:[17,18].

- 1) Medications administered orally do not enter the blood stream immediately after passage through the buccal mucosa
- 2) The absorption of Muco adhesive drugs is adversely affected by the presence of food. One of the side effects of many antibiotics is the destruction of normal GI flora resulting in Diarrhea and overgrowth with dangerous organisms
- 3) Drugs which are un stable at buccal PH cannot be administrated
- 4) Drugs which have a bitter taste or unpleasant taste or an obnoxious odor, irritate the mucosa cannot be administrated by this route
- 5) Only the small dose is given by this drug delivery
- 6) If formulations contains Antimicrobial agents effect the natural Microbial flora of the mouth
- 7) Some patients suffers unpleasant feeling to swallow the tablets
- 8) Less surface area
- 9) Dilution or loss of the drug due to constant secretion of the saliva

#### FACTORS AFFECTING THE MUCOADHESIVE DRUG DELIVERY SYSTEM:[19,20,21]

##### 1) Polymer related factors:

- i) Concentration of active polymers
- ii) Flexibility of polymer chains
- iii) Molecular weight.

##### 2)Environment related factors:

- i) PH of the polymer-substrate interface
- ii) Initial contact time
- iii) Applied strength
- iv) Swelling.

##### 3) Physiological factors:

- i) Disease state
- ii) Mucin turnover
- iii) Rate of renewal of mucosal cells.

- iv) Tissue movement
- v) Concomitant diseases

#### TYPES OF MDDS:[22]

- 1) Buccal drug delivery system
- 2) Sub lingual drug delivery system
- 3) Vaginal DDS
- 4) Rectal system
- 5) Nasal DDS
- 6) Ocular DDS
- 7) Gastrointestinal DDS.

#### MECHANISM OF MUCOADHESION :[23]

Bio adhesion is an adhesion of a synthetic and natural material to biological surface while muco adhesion is adhesion of material to mucus and or an epithelial surface muco adhesion occurs in two stages depending on the nature of dosage form and its delivery .

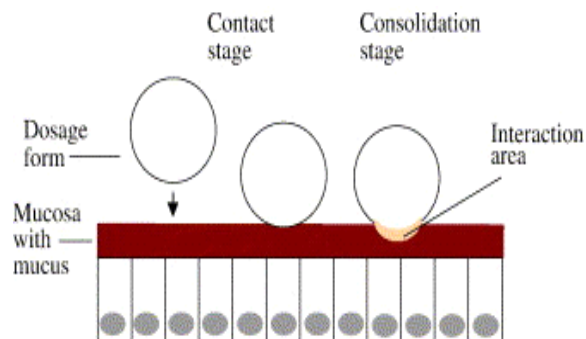
Contact between a pressure sensitive adhesive material and a surface is called as Adhesion which can be defined as the state in which two surfaces or attached together due to valence interfacial forces are interlocking action or both.[24]

##### Step 1) Contact stage:

The first stage is characterized by the contact between the muco adhesive and the mucus membrane with spreading and swelling of the formulation initiating its deep contact with the mucus layer . Sometimes additional forces like mechanical system in vaginal delivery aero dynamics in nasal delivery and peristaltic motions in the intestinal delivery of the dosage forms.[25]

##### Step2) Consolidation stage:

In consolidation step the mucoadhesive materials are activated by the presence of moisture plasticizers the system allowing the mucoadhesive molecules to break free and to link up by weak Vander walls and hydrogen bonds, electrostatic attractions, hydrophobic interactions for complete bioadhesion at attractive forces must overcome repulsive forces. consolidation step was explained by two theories:[26]



- 1) diffusion theory
  - 2) dehydration theory
- 1) **diffusion theory :**



Mucus glycol proteins interact with the mucoadhesive molecules by the interpenetrating their chains and forming the secondary bonds. This is a mechanical as well as chemical interactions.

## 2) dehydration theory:

After contact with mucus material undergoes dehydration until osmotic pressure balance and gelly mixture of mucus with material is obtained. solid or hydrated formulation does not work by this theory.[27]

## THEORIES OF MUCOADHESION.[28,29]

There are seven different theories which explain phenomenon of mucoadhesion :

- i) The Electronic theory
- ii) The Adsorption theory
- iii) Wetting theory
- iv) The Diffusion theory
- v) The Dehydration theory
- vi) Fracture theory
- vii) The Mechanical theory.

### i) The electronic theory :

In these both mucoadhesive and biological materials possess opposing electrical charges. when both materials come in contact, they transfer electrons leading to the building of a double electronic layer at the interface where the attractive forces within these electronic double layer determines the mucoadhesive strength.[30]

### ii) the adsorption theory:

In these mucoadhesive device adheres to the mucus by secondary chemicals interaction such as in Vander walls and hydrogen bonds ,electrostatic attraction or hydrophobic interactions.[31]

### iii) the wetting theory:

This applies to liquid system 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. lower the contact angle than the greater the affinity.[32]

### iv) The diffusion theory :

Interpenetration of both polymer and mucin chain create semipermeable adhesive bond.

Adhesion forces increases with increase in penetration it depends on diffusion coefficient 0.2-0.5micro meter.[33]

### v) The dehydration theory :

In dehydration theory materials that are able to readily jelly in an aqueous environment when placed in contact with the mucous 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 increases the contact time of formulation with the mucous membrane.

### vi) The fracture theory :

It analyses the force required to separate to surfaces after adhesion is established fraction theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains.

### vii) The mechanical theory :

It explains the diffusion of the liquid adhesive into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.

## TYPES OF MUCOADHESION FORMULATIONS :[34,35]

### 1) Solid mucoadhesive formulations:

Tablets, inserts , lozenges , matrix tablets , bioadhesive microparticles .

### 2) Semi solid mucoadhesive formulations:

Gels , films , patches , ointment .

### 3) Liquid mucoadhesion formulations:

Viscous liquids , gel forming liquid , suspensions .

## BASIC COMPONENTS OF BUCCAL DRUG DELIVERY SYSTEM:[36]

The basic components of buccal drug delivery system are

**1) Drug substance:** drug substance should be selected on the bases of pharmacokinetic properties. the drug should have the following characteristics:

The one time dose of the drug should be small (less than 25mg) the drug should be having short biological half life ranging from 2to8hours.

**2) Bioadhesive polymers:** The use of bioadhesion polymers determines the various parameters such as mucoadhesive strength, thickness, invitro release and the residence time of the drug delivery device. The polymers with high molecular weight are preferred because they show the effective release rate controlling polymers.

**3) Backing membrane:** Backing membrane should be used for formulations should be impermeable to drug as well as the mucus in order to prevent the unnecessary drug loss from all sides of the device.

**4) Plasticizers:** The plasticizer are used in order to improve the folding endurance of the delivery device .they provide enough flexibility to the dosage form for improving its patient acceptability and patient compliances.

**4) Permeation enhancers:** These are the chemicals or the liquids used to improve the permeation of the drug from device into mucus membrane. it works by the following mechanisms:

- i) By reducing the viscosity of the mucus
- ii) By increasing the fluidity of lipid bilayer membrane
- iii) By increasing the thermodynamic property of drug
- iv) By countering the enzymatic barrier.

EX: Benzalkoniumchloride, Dextransulfate, Fattyacid, SodiumEDTA etc.

## BUCCAL ROUTE

□ **Buccal administration** is where the dosage form is placed between gums and inner lining of the cheek (buccal pouch)

□ absorbed by buccal mucosa



### LIST OF PENETRATION ENHANCERS AND ITS MECHANISM OF ACTION:[37,38,39]

CLASSIFICATION	EXAMPLES	MODE OF TRANSPORT	MECHANISM OF ACTION
Fatty acids and derivatives	Oleic acid, caprylic acid, mono(di)glycerides lauric acid, linolic acid, S. caprate oleic acid.	Para cellular	Increase fluidity of phospholipids domains.
Bile salts and derivatives	Sodium deoxycholate sodium taurocholate sodium taurocholate, sodium glcocholate,,, sodium deoxycholate.	paracellular	Perturbation of intercellular lipids, protein domain integrity.
surfactants	l-lysine, chitosin, trimethyl chitosin, poly-arginine, polysorbates, tween80, SLS,	paracellular	Perturbation of intercellular lipids, protein domain integrity.
sulfoxides	Dimethyl sulfoxide, decylmethyl sulfoxide		Perturbation of intracellular lipid proteins.
Chelating agents	EDTA citric acid salicylates	paracellular	Perturbation of intracellular lipids integrity with C ions.
Monohydric alcohols	Ethanol isopropanol	paracellular	Disrupt arrangements of intercellular lipids.
polyols	Propylene glycol, polyethylene glycol, glycerol, propanediol.	paracellular	

**CHARACTERISTICS OF AN IDEAL MUCOADHESIVE SYSTEM:[40,41,42]**

- It should have good mechanical strength.
- Immediate adherence to the buccal mucosa.
- Optimum drug absorption
- Sufficient patient compliance without hampering normal functions such as talking eating and drinking.

**POLYMERS USED FOR MUCOADHESIVE DRUG DELIVERY SYSTEM**

Mucoadhesive polymers are two types:

**1) Natural polymers:[43]**

- lectin
- Soluble starch
- Xanthum gum
- Sodium alginate
- Karaya gum
- Tragacanth
- Soluble starch

**2) synthetic polymers:[44,45]**

- Poly (hydroxyl ethyl methyl acrylate)
- Poly (vinyl pyrrolidone)
- Poly (vinyl alcohol)
- Poly (ethylene oxide)
- Poly( acrylic acid )polymers(carbomers, polycarbophil)
- Cellulose derivatives (methyl cellulose, ethyl cellulose hydroxyl ethyl cellulose, hydroxyl propyl cellulose, sodium carboxy methyl cellulose)

Other polymers used in Bioadhesion are water soluble, water insoluble, charged and uncharged polymers.

**CLASSIFICATION BASED ON THE ELECTRIC CHARGES ARE :****Anionic polymers:**

Carboxy methyl cellulose, carbopol, polyacrylic acid , pectin polycarbophil, sodium alginate .

**Cationic polymers:**

Chitosin, aminodextrin, dimethylaminoethyl, dextran, trimethylated chitoson, polyysene.

**Neutral polymers:**

Hydoxyethyl starch, hydroxyl propyl cellulose, poly vinyl alcohol.

**LIST OF DRUGS DELIVERED Via BUCCAL ROUTE PENETRATION ENHANCERS:[47]**

DRUG	POLYMERS	PENETRATION ENHANCERS	TYPE	REFERANCE
Diltiazem	HPMC,Eudragit,Ethyl cellulose.	PVP	mucoashesive	29
Carvedilol	HPMC ,hydroxyl propyl methyl cellulose E 15,hydroxy propyl cellulose(HPC)	Propylene glycol	Mucoadhesive buccal patches	26
Cetylpyridinium	Poly vinyl alcohol (PVP)	Poly vinyl pyrrolidine	Mucoadhesive patches	27
Clotrimazole	Sodium carboxy methyl cellulose	glycerol	Buccal bioadhesive films	28

**Ideal characteristics of muco polymers:**

- 1) Polymer must have a high molecular weight upto 100,00 or more.
- 2) High viscosity.
- 3) Degree of cross linking.
- 4) Spatial conformation.
- 5) Flexibility of polymer chain.
- 6) Charge and degree of ionization.
- 7) Optimum hydration.
- 8) High applied strength and initial contact time.
- 9) It should be biocompatible,economic, non toxic,preferably biodegradable,
- 10) Strong ionic charges.
- 11) High molecular weights.
- 12) Sufficient chain flexibility.
- 13) Surface energy properties favoring spreading onto mucus.

**NOVEL POLYMERS:[46]**

- 1) Shajaei and li have designed and characterized a co polymer of PAA and PEG monoethylether monomethacrylate PAA co PEG for exhibiting optimal buccal adhesion.
- 2) Tomato lectin showed that it has binding selectivity to the small epithelium.
- 3) Laleetal investigated novel polymer of PAA complexed with PEGylated drug conjugate.
- 4) Bogataj et al., prepared and studied mucoadhesive microspheres for application in urinary bladder.
- 5) A new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by corium technologies .complex have been prepared by non covalent hydrogen bonding ,non covalent cross linking of a film forming hydrophilic polymers with a short chain plasticizer having reactive OH groups at end chains.
- 6) Alur et al. studied the transmucosal sustained delivery of chlorophenazine maleate in rabbits using noval natural mucoadhesive gum from hakea as an excipient in buccal tablets .
- 7) Langath N et al.investigated the benefit of thiolated polymers for the development of buccal drug delivery system.

**METHOD OF PREPARATION :[48]****1) Solvent casting method:[49]**

In this method all patch excipients including the drug co dispersed in an organic solvent and coated on to a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated on to a 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:[50,51]**

Drug excipients are mixed by kneading, usually without the presence of any liquid. After the mixing process materials are rolled on a release linear until a

desired thickness is achieved .The baking material is laminated as previously described while there are only minor or even no difference between patches fabricated by the two processes ,the solvent free processes is preferred because there is no possibility of residual solvents and associated solvent related health issues.

**3) Hot melt extrusion of films:**

In hot melt extraction blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogenous materials in different shapes such as granules, tablets are films.

**DRUGS ADMINSTRATED BY BUCCAL ROUTE:**

SNO	DRUG	DOSE
1	Morphine sulphate	-
2	Pantaprazole	40mg
3	Nicotin	15-30mg
4	Nifedipine	5-20mg
5	Omeprazole	20-40mg
6	Piroxicam	10-20mg
7	Acitretin	25-30mg

**SOME COMMERCIALY AVAILBLE ORAL MDDS:[52]**

DRUG	DOSAGEFORM	TYPE OF RELEASE	PRODUCT NAME	MANUFACTURE
Fentanyl citrate	Lozenge,films and tablets	Quick	Actiq,fentora,onsolis	Cephalon
Buprenorphine hcl and Naloxone	Tablet	Quicks	Subutex	Reckitt benckiser
Nicotine	lozenge	Quick	Nicotinelle	Novartis consumer
Zolpidem	Tablet,chewing gum	Quick	Suscard nicorette	Forest laboratiors,GSK consumer health
Prochlorperazine	Tablet	Controlled	Buccastem	Reckitt benckiser
Nitroglycerine	Spray	Quick	Nitrostate	Lambert davis
Glycerylnitrate	Spray	Quick	Nitromist	Nova del

**EVALUATION METHODS:**

- Water absorption capacity test
- Morphological characterization
- Folding endurance
- Thermal analysis study
- Swelling study
- Surface pH
- Thickness measurement
- Ex vivo bioadhesion test
- Permeation study of buccal patch
- In vitro drug release
- Ex vivo mucoadhesion time
- Mechanical properties measurement
- Animal model for permeability measurement
- Moisture absorption study
- Determination of tensile strength

- Colloidal gold staining method
- Direct staining method
- Shear stress method
- Detachment force measurements
- Stability study in human saliva.
- Weight variation
- Friability
- Hardness
- Content uniformity

**Water absorption capacity: [53]**

Circular patches with a surface area of 2.3cm<sup>2</sup> are allowed to swell on the surface of agar plates prepared in simulated saliva(2.38 g Na<sub>2</sub>HPO<sub>4</sub>,0.19g KH<sub>2</sub>PO<sub>4</sub> and 8g NaCL per liter of distilled water is adjusted with phosphoric acid is adjusted to ph 6.7),and kept in an incubator maturated at 37c +or- 0.5c .At various time intervals upto 4 hours . The



samples are weighed and then left to dry for seven days in an desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded. water uptake percentage is calculated.

**Morphological characterization:**[54]

They are determined by using Scanning Electron Microscope(SEM).

**Folding endurance:**

It can be done by folding the patches up to 200 times without breaking.

**Thermal analysis study:**

It was performed by using Differential Scanning Calorimeter(DSC).

**Swelling study:**

Weighed the Buccal patches individually and placed separately in 2percentage agar gel plates incubated at 37degree centigrade and examined for physical changes. At regular intervals until three hours patches are removed for gel patches and excess surface water was removed carefully using the filter paper. The swollen patches are then reweighed and swelling index were calculated.

**Surface pH:**

Buccal patches are left to swell for 2 hours on the surface of an agar plate .the surface pH is measured by means of a pH paper placed on the surface of the swollen patch.

**Thickness measurements :**

The thickness of each film is measured by five different locations using an Electron Digital Micrometer.

**Ex vivo bioadhesion test:**

A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer .this glass vial is tightly fitted into a glass beaker filled with phosphate buffer. So it is just touched to the mucosal surface.

**Invitro drug release study:**

The dissolution medium consisted of phosphate buffer PH 6.8 maintaining a temperature at 37degree c. with a rotation speed of 50rpm, the disk is allocated to the bottom of the dissolution vessel .Samples such as 5ml are withdrawn at predetermined time intervals and replaced with fresh medium . The samples filtered through the watsman filter paper and analyzed for drug content after appropriate dilution in a UV spectrophotometer .

**Ex-vivo mucoadhesion time:**

The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa.the fresh buccal mucosa is tied on the glass slide ,and a mucoadhesive patch is wetted with one drop of phosphate buffer PH6.8 and pasted to the buccal mucosa by applying a light force with a finger tip for 30 seconds.the glass slide is then put in

the beaker,which is filled with 200ml of phosphate buffer ph 6.8.after 2 minutes a 50rpm stirring rate is applied to simulate to the buccal cavity environment .

**Measurement of mechanical properties:**

Mechanical properties of the patch include tensile strength and elongation at break is evaluated using a tensile tester.film strip with the dimensions of 60\*10mm and without any visual defects cut and positioned between two clamps separated by a distance of 3cm.force and elongation of the film at the point when the strip break is recorded.

**Animal model for permeability measurement:**

The most commonly used animal models are dogs,rabbits, pigs.A general criterion for selecting an in vivo animal model is the resemblance for the animal mucosa to the oral mucosa of human beings in both ultra structure and enzyme activity which represents the physical and metabolic barrier of the oral mucosa.

**Moisture absorption studies:**

The moisture absorption studies for the buccal patch give an indication about the relative moisture absorption capacity of the polymers and an idea whether that the buccal patch maintain their integrity after absorption of the moisture.

**Determination of tensile strength:**

Tensile stress is also called as maximum stress or ultimate tensile strength.the resistance of a material to a force tending to tear it a part measured as the maximum tension the material can withstand without tearing .tensile strength can be defined as the strength of material expressed as the greatest longitudinal stress. It can bear without tearing apart.it is measured as newtons.

**Colloidal gold staining method:**

Park proposed the gold staining technique for the study bioadhesion .These technique employees red colloidal gold particles which were absorbed on the mucin gold conjugates which upon interaction with bio adhesive hydrogels develop a red colour on the surface.

**Direct staining method:**

It is a novel technique to evaluate polymer adhesion to human buccal cells following exposure to aqueous polymer dispersion an in vivo and invitro methods. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer treated cells by image analysis.

**Shear stress method:**

The measurement of the shear stress gives an direct correlation to the adhesion strength in a simple shear stress measurement based methods two smooth,polished plexi glass boxes were selected one block was fixed with adhesive araiditeon a glass plate with was fixed on level table. The level was adjusted with the spirit level.to the upper block, a

thread was tied and the thread was passed down through a pulley, The length of the thread from the pulley to the pan was 12cm.at the end of the thread a pan of weight 17gms was attached into which the weights can be added.

#### Detachment force measurement :

The Whilhelmy plate method is one of the traditional method for the measurement of the force of adhesion of various bioadhesive dosage forms. The method involves the measurement of the dynamic contact angle and utilizes a microtensiometer and a micro

balance.The CAHN dynamic contact angle analyzer is used for this purpose.

#### Stability study in human saliva:

The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from the humans(age 18 to 50 years) buccal patches are in separate petri dishes containing 5ml of human saliva and placed in a temperature in controlled oven at 37degree centigrade for 6 hours .at regular time intervals (0,1,...6 hours) the dose formulations with better bioavailability are needed .

#### EVALUTION PARAMETERS OF BUCCOADHESIVE FORMULATIONS:[55]

SNO	DRUG USED	SIZE AND SHAPE(mm)	THICKNESS	WEIGHT(mg)
1	Propranolol hydrochloride(tab)	11FC	1.5-1.6	150
2	Theophyline(tab)	7FC	40	250
3	Prednisoline	10FC	ND	112-152
4	Ergotamine tartrate(gel in tab)	10.6	2/1	150
5	Testosterone(tab)	9FC	ND	200
6	Ibuprofen(patch)	10FC	0.1-0.27	105-350
7	Omeprazole	7FC	ND	100
8	Nifedipine	9FC	1.9	125
9	Triamcinolone acetonide	13FC	1.7	200
10	propranololHCL	9FC	ND	162
11	Sodium fluoride	8FC	ND	120
12	nicotin	12FC	ND	150
13	Diclofenac sodium	13FC	ND	175
14	Metaprolal tarate	-	ND	200

#### CURRENTLY USED FORMULATIONS:

Many novel formulations have been advanced to various stages of development and approval and have met with varying manufacturing and marketing successes:

- a.Tablet
- b.Sprays
- c.Mouth washes
- d.Gels
- e.Paste
- f.Patches
- g.Wafers or films

#### a.Tablets:

Lozenges,troches and tablets for systemic delivery across the oral mucosa are currently commercially available for drugs including nitroglycerin and fentanyl. Solid formulations such as tablets and lozenges dissolve into the saliva utilizing the whole surface area of the oral cavity for absorption.

Drawbacks of the tablet and lozenges include variations due to the differences in saliva production and sucking intensity . Muco adhesive tablet

formulation are better in this respect as they adhere to the mucosa increasing exposure time .

#### b.Sprays:

glyceryltrinitrate is a small molecule that can be rapidly delivered across the sublingual oral mucosa using a spray for angina relief.the generex biotechnology corporation as developed a rapid mist spray which is of capable of delivering large molecules such as insulin across the oral mucosa.other applications of the rapid mist system in development include vaccination against cancer and influenza pain management and weight loss.

#### c.Mouth washes:

The current literature on mouth washes and oral rinses predominantly focuses on their use in the local delivery of antimicrobial agents.the substantivity allows significant antibacterial effect up to 7 hours after the mouth rinse.several naturally occurring antimicrobials such as lactoperoxidases ,lysozymes and lactoferrin have also been investigated in a mouth wash form. The effectiveness of essential oil containing anti microbial mouth washes is thought to

relate their anti oxidant properties. The management of vesiculoulcerative conditions frequently involves the topical delivery of various steroid preparations and anti microbials in mouth wash form.

#### **d.Gels:**

Gels have been investigated as a means of control drug delivery since 1980s.the primary goal of bioadhesive control drug delivery is to localized a delivery device with in the body in enhance the drug absorption process in a site specific manner . Others are at the stage of animal or ex-vivo studies .few clinical studies have been performed and those that have are often small in size for the delivery of systemic analgesics and antihypertensives and the drug for treating cardiovascular diseases as well as the topical delivery of antifungal agents and muco protective agents to the oral mucosa.

#### **e.Paste:**

the paste have been utilized in the delivery of anti microbial agents for improved extractions socket healing after tooth extractions in patients HIV disease and for the delivery of controlled release triclosan in oral care formulations .paste are also been used for the local delivery and retension of slow release minocycline in the formulation.

#### **f.Patches:**

several different patch systems that adhere to oral mucosa and designed to deliver drugs have been developed. There are basically three different types oro-adhesive patches.patches with a dissolvable matrix for drug delivery to the oral cavity .they slow and completely dissolved during use living nothing to remove. However significant amounts of drug will be

lost to oral cavity .they are better used therefore for delivery drugs more generally in to the oral cavity than into the oral mucosa to which they are applied .

#### **g.Wafers:**

Thin strips of polymeric films capable of loading upto 20mg of drugs. dissolve on the tongue in less than 30 sec and delivered the drugs which are able to cross the permeability barrier directly to the blood supply for rapid treatment.

### **RECENT APPLICIONS IN AN ORAL MUCOADHESIVE DRUG DELIVERY:[56]**

Oral muco adhesive drug delivery has widespread applications for many drugs which an oral administration results in poor bioavailability and are rapidly degraded by the oral mucoadhesive drug delivery provides advantages of high accessibility and low enzymatic activity.

The hydrophilic polymers like SCMC ,HPC and polycarbophil were used for the treatment of periodontal disease but now the trend is shifting towards the utilization of effective system to the delivery of peptides, proteins,and polysaccharides. semisolids offer more ease in administration but tablets are also been formulated. tablets include matrix device or multilayered systems containing a muco adhesive agent.the buccal cavity has additional advantages of high patient compliance the first generation mucoadhesive paste has been used as barrier system for mouth ulcers .the tablet is kept under the upper lip to avoid clearance mechanism of the salivary gland.

### **BUCCOADHESIVE APPROVED UNDER CLINICAL TRAIL FORMULATIONS:[57]**

S.NO	ACTIVE SUBSTANCE	BRAND NAME	COMPANY	POLYMER USED	FORMULATION
1.	Prochlorperaxime maleate	buccastem	Reckitt banckiser	Xanthangum and povidine	Tablet
2.	Hydrocortisone sodium succinate	corlanpelletes	UCB pharma	acaciagum	Pellets
3.	Triamcinolone acetonide	aphtach	Teijin limited	HPMC,PAA	Tablet
4.	Testosterone	striant	Columbia lab	HPMC,CP	Tablet
5.	miconazole	daktarin	Janssen cilag	undisclosed	Tablet
6.	fentayl	fentora	Cephalon inc	Modified food starch	Tablet
7.	Glyceryl trinitrate	suscard	Forest lab	HPMC	Tablet

#### **Buccal mucoadhesive dosage forms may be classified into three types:**

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

**LIST OF PATENTS:[58]**

S.NO	TYPE OF FORMULATION	PATENT NO.	TITLE OF THE PATENT	YEAR OF PATENT	SELECTION OF THE PATENT
1.	microspheres	US6235313B1	bioadhesive Micro spheres and there use as DDS.	May2001	to establish the correlation between the chemical nature.
2.	Nano particles	US6235313B1	Bio adhesive microspheres and there use as DDS.	May2003	Site specific CDS over extended period of time.
3.	Multi particulate	US0281007A1	Mucoadhesive oral formulations of high permeability and solubility.	December 2007	To increase the oral bio availability of BCS class one.
4.	Multi particulate	US5571533A	Control release muco adhesive pharmaceutical composition oral administration of furosemide	November 1996	Eliminates diursis peak or reduces intersubject response variability with the conventional treatment
5.	Nano composite	US0232899A1	Mucoadhesive nanocomposite delivery system	Sep 2009	Delivery of the drug by adding with chitoson of silica nanocomposite during the in-situ relation of colloidal silica.
6.	Muiti particulate	US0280183A1	Multiparticulate form of administration compresing nucleic acid containing mucoadhesive active ingredients	November 2009	It comprising mucoadhesively formulated nucleic acid ingredients and to process for producing the pharmaceutical form
7.	Tablet	USO26824A1	Bio adhesive rate controlled oral dosages formulations	October 2008	Polymers with improved bioadhesive properties and methods for improving the release pattern of monolithic system .
8	Semisolid dosage forms	USO240111A1	Semisolid mucoadhesive formulations	October 2006	To improve the technical and organoleptical charecteritics by vaginal applications
9	nanoparticles	US0323977A9	Mucoadhesive nanoparticles for cancer treatment	December 2010	Chitosin monofatty acids and cancer therapeutics agent based nanoparticles
10	Nanoparticles	US6235313V1	Microspheres and their use as drug delivery and imaging systems	May2003	Delivery over a extended period of time for active ingredients or sensory markers.
11	Multi particulate	USO19643A1	Pentaprazole,multi particulate formulations	August 2007	To avoid sticking to nanogastric and gastronomy.

**CONCLUSION:**

Buccal mucoadhesive drug delivery system is becoming popularity .The main objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit daily once dosing. The use of natural polymers is increasing in the formulation of buccal tablets and as a carrier for buccal drug delivery can be used to improve the health of all living things and to minimize the unwanted effect of synthetic polymers. The area is well suited for a retentive device and appears to be acceptable to the patient .the mucosa is well supplied with both vascular and lymphatic drainage and first pause metabolism in the liver and pre-systemic elimination in the GIT is avoided. This review

focuses on the preparation of the novel drug delivery systems which will provide least adverse effects and maximal therapeutic response, with advent of new molecules especially therapeutic proteins and peptides there is requirement of specialized delivery systems to reach the target sites. This is also evident by the numbers of the products which coming to the market and there in the pipeline for clinical trials.

**MARKETED PRODUCTS:[59]**

1) FENTANIL buccal formulations (Fentora and actiq)are design to adhere in buccal mucosa for certain period of time followed by its swallowing .This produces initial rapid absorption when formulation is in oral cavity and prolonged absorption when formulation is swallowed and reaches toGIT.

2) STRINAT is only buccal formulation available providing long duration of adhesion .it involves patented “progressive hydration technology. This tablet is taken twice a day.

3) APHTHACH is the tablet developed by nagri et for local treatment of aphous stomatitic which is recurrent discrete painful areas of ulceration.

4) EMEZINE is developed for emesis and found to be more effective than oral tablet.

5) SUSCARD is used to quick action to treat and prevent the chest pain caused by angina pectoris by passing the oral dissolution and absorption step in the GIT.

6) LAURIAD and TIBOZOLE are indicated for the oropharyngeal candidiasis by delivering antifungal drug designed to enable once daily dosing for local treatment of the oral cavity.

7) CORLAN pellets are indicated in the mouth ulcer and are directed not to be sucked but be dissolved in close contact with ulcer for its topical application.

8) Corlan-hydrocortisone succinate,bonjela – hypromellose,daktarin-miconazole.

9) buccal mucosa formulation : buccastem-nausea,vomiting ,vertigo.

#### ACKNOWLEDGMENT:

I would like to express my special thanks to Mr.Dibyalochan Mohanty, Anurag group of institutions group of institutions, school of pharmacy for his support and encouragement, guidance to successfully complete my review article as well as great thanks to our Dean Dr Vasudha Bakshi for her constant support for our research work.

#### REFERENCES:

1. Ganesh NS,Ambale SM ramesh B,deshpande KB ,an overview on lamitations of gastrotentive drug delivery system international journal of pharmaceutical science review and research .2011;8(2):0-23.
2. Bindu MB,zulkar NK MHAMMAD ,Ravinder NA ,david banji:mucoadhesive drug delivery system,an overview of journal of advanced pharmaceutical technology and research 2010;1(4)381.
3. Ganesh GN, Pallaprola M, Gowthamarajan K,et al. Design and development of buccal drug delivery system for labetalol using natural polymer.Int J Pharm Res and Dev 2011;3:37-49.
4. Randhawa MA, Malik SA, Javed M, et al Buccal absorption of weak acidic drugs is not related to their degree of ionization as estimated from the Henderson-Hasselbalch equation .Pak J. Med. Res.,2003;42:116.
5. Singh R,Sharma D, Garg R, Review on Mucoadhesive Drug Delivery System with

Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery of Pharmaceuticals .Journal of Developing Drugs ,2017;6(1):1-12.

- 6.Monali,sonawaneal,dattatreya,shinkar2,ravindrasaud agar ,mucoadhesive buccal drug delivery system: review article Int J Curr Pharm Res.,9(4): 1-4.
7. Santanu Roychowdary, Rajesh Gupta and Sourav Saha. A Review on Buccal Mucoadhesive Drug Delivery System .Indo- Global Journal of pharmaceutical science ,2011; 1(3):223-233.
8. 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 researches,5(6),2011,291-303.
9. Arshad Bashir Khan ,Rajat Mahamana and Emili Pal, Review on Mucoadhesive Drug Delivery System: Novel Approaches in Modern Era ,RGUHS J Pharma Sci.,Oct –Dec,2014;4:4.
10. Rossi S, Sandri G,Caramella CM.Buccal drug delivery :a challenge already wom?Drud Dis today .2005;2:59-65.<http://dx.doi.org/10.1016/j.ddtec.2005.05.018>; PMID :24981756.
11. Flavia CC.marcos LB raul CE,maria PD mucoadhsive drug delivery system .brazilian journal of pharmaceutical science 2010;46(1):1-17.
12. Kisore D ,Utpal RW ,shripal A.A Review on study of buccal drug delivery system. Innovative systems design and Engineering.2011;2(3):0-9.
13. Sachin Shankar Lokhande and Sandeep S.Lahoti,Bucoadhesive Drud Delivery System: Need. Asian Journal of biomedical And Pharmaceutical Sciences, 2012;(14):29-36.2012:14.
14. Ankaj Kaundal, Pravin Kumar And Archana Chaudhary. A Review On Mucoadhesive Buccal Tablets Prepared Using Natural and Synthetic polymers.World journal of Pharmacy And Pharmaceutical Sciences,2015;4: 07.
15. Sidharth Malagounda Patil and Swati S. Kulkarni. Review on Buccal Mucoadhesive Drug Delivery Systems .International Standard Serial Number.(ISSN):2249-6807.
16. Phaninda B, B Krishna (2013) Recent advances in mucoadhesive drug delivery system:A review .Int.J Pharm. Med and Sc.1-15.
17. 36.Roy S, Pal K, Anis A, Pramanik K, Prabakar B. Polymer In Mucoadhesive Drug Delivery system.A Brief Note Designed monomers and polymers 2009;12(6):483-95.
18. Anay R.Patel, dhagesh A, patel and sharad V.chaudary .mucoadhesive buccal drug delivery



- system. *Int. J. of Pharm. and Life Science (IJPLS)*, June : 2011;2(6):848-856848.
19. chen JL, Cyr GN, Composition producing adhesion through hydration in mainly adhesion in biological system. *New York, Academic Press* 163-181.
  20. chng H, Park H, Kelly P, Robison JR, bioadhesion polymers as platform for oral controlled drug delivery. *J. Pharm. Science* 1985;74:399-405.
  21. bhatt JH designing and evaluation of mucoadhesion microspheres of metronidazole for oral controlled drug delivery.
  22. seema bhadana, naveenth garud akansha gaurd (2013) colon specific drug delivery of mesalamine using eugradth s 100 coated chitosan microspheres for the treatment of ulcerative colities. *International Current Pharmaceutical Journal* 42 45.
  23. Amir H Shojei, buccal mucosa as a route for systemic drug delivery A Review. *J Pharm, pharmaceutical science*. 1998 1(1) 15-30.
  24. surender V mahima K aruna R sapna S An overview on buccal drug delivery system (IJPSR) 2011;6:1303-21.
  25. Aleksovski A, dreu R, gasperlin M, planinsek O. mini tablets :a contemporary system for oral drug delivery in targetted patient groups. *Expert Opin Drug Delivery* . 2015;12(1)65-84.
  26. Reineke J, cho DY, dingle yl, cheifetz p, laulicht B, lavin D, et al .can bioadhesive nanoparticles allow for more effective particles uptake from the small intestine ?J, controlled release 2013;170(13):477-84.
  27. collins AE1, deasy PB. bio adhesive losenger for the improved delivery of ce-typridinium chloride *J pharm science* 1990;79(2):116-9.
  28. KV. Shijith1, Sarath Chandran C, KV. Vipin and Ann Rose August And K. Premaletha. A Review On Basics Behind Development Of Muco Adhesive Buccal Drug Delivery Systems. *IJAPBC*, Apr-Jun, 2013; 2(2). ISSN: 2277-4688.
  29. Ahagon, AN. Gent, Effect of interfacial bonding on the strength of adhesion, *J. Polym. Sci. Polym. Phys.*, 1975; 13: 1285-1300.
  30. Abolfazl A, Farnaz R. Medicated chewing gum, a novel drug delivery system. *J Res Med Sci*. 2015;20(4):403-11. PMID:26109999 PMID:PMC4468459.
  31. Nayak BS, Rout PK, Nayak UK, Bhowmik BB. Development and Characterization of Bio adhesive Gel of Microencapsulated Metronidazole for Vaginal Use. *Iran J Pharm Res*. 2010;9(3):209-19.
  32. Caon T, Jin L, Simões CM, Norton RS, Nicolazzo JA. Enhancing the Buccal mucosal delivery of peptide and protein therapeutics. *Pharm Res*. 2015;32(1):1-21. <http://dx.doi.org/10.1007/s11095-014-1485-1> ;
  33. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive Buccal drug delivery systems. *J Biomed Res*. 2014;28(2):81-97. PMID:24683406.
  34. Phaninda B, B Krishna (2013) Recent advances in mucoadhesive drug delivery system:A review .*Int.J Pharm. Med and Sc.*1-15.
  35. Flavia CC,marcos LB raul CE,maria PD mucoadhsive drug delivery system .*brazilian journal of pharmaceutical science* 2010;46(1):1-17.
  36. seema bhadana, naveenth garud akansha gaurd (2013) colon specific drug delivery of mesalamine using eugradth s 100 coated chitosan microspheres for the treatment of ulcerative colities. *international current pharmaceutical journal* 42 45.
  37. Inman LR, Cantey JR. Specific adherence of Escherichia coli (strain RDEC-1) to membranous (M) cells of the Peyer's patch in Escherichia coli diarrhea in the rabbit. *J Clin Invest*. 1983;71(1):1-8. <http://dx.doi.org/10.1172/JCI110737>; PMID:PMC436831.
  38. Woertz C, Preis M, Breikreutz J, Kleinebudde P. Assessment of test methods evaluating mucoadhesive polymers and dosage forms: an overview. *Eur J Pharm Bio Pharm*. 2013;85(3):843-53. <http://dx.doi.org/10.1016/j.ejpb.2013.06.023>; PMID:23851076.
  39. Park CR, Munday DL. Evaluation of Selected Polysaccharide Excipients in Buccoadhesive Tablets for Sustained Release of Nicotine Drug Development and Industrial Pharmacy. 2004;30(6):609-17. PMID:15285334.
  40. Davidovich-Pinhas M, Bianco-Peled H. Mucoadhesion: a review of characterization techniques. *Expert Opin Drug Deliv*. 2010;7(2):259-71. <http://dx.doi.org/10.1517/17425240903473134>; PMID:20095946.
  41. Satheesh MNV, Semwal R, Semwal DK, Semwal RB. Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route. *Expert Op in Drug Deliv*. 2012;9(6):629-47. <http://dx.doi.org/10.1517/17425247.2012.679260>; PMID:22512535.
  42. Khutoryanskiy VV. Advances in mucoadhesion and mucoadhesive polymers. *Macromol Biosci*. 2011;14-11(6):748-64.
  43. Guha SS, Banerjee R. Intravesical drug delivery: Challenges, current status, opportunities and

- novel strategies. *J Control Release*. 2010;148(2):147-59.
44. Inman LR, Cantey JR. Specific adherence of *Escherichia coli* (strain RDEC-1) to membranous (M) cells of the Peyer's patch in *Escherichia coli* diarrhea in the rabbit. *J Clin Invest*. 1983;71(1):1-8.  
<http://dx.doi.org/10.1172/JCI110737>;  
PMCID:PMC436831.
45. Leitner V, Walker GA. Bernkop-Schnürch. Thiolated polymers. evidence for the formation of disulphide bonds with mucus glycoproteins. *Eur J Pharm Bio pharm*. 2003;56:207-214.  
[http://dx.doi.org/10.1016/S0939-6411\(03\)00061-4](http://dx.doi.org/10.1016/S0939-6411(03)00061-4).
46. Woertz C, Preis M, Breitzkreutz J, Kleinebudde P. Assessment of test methods evaluating mucoadhesive polymers and dosage forms: an overview. *Eur J Pharm Bio Pharm*. 2013;85(3):843-53.  
<http://dx.doi.org/10.1016/j.ejpb.2013.06.023>;  
PMid:23851076.
47. International journal of pharma medicine and biological science ISSN 2278-5221  
[www.ijpmbs.com](http://www.ijpmbs.com) Vol.2,No. 1,January 2013 all rights reserved.
48. International journal of pharma medicine and biological science ISSN 2278-5221  
[www.ijpmbs.com](http://www.ijpmbs.com) Vol.2,No. 1,January 2013 all rights reserved.
49. Cui F, He C, Yin L, Qian F, He M, Tang C, Yin C. Nanoparticles incorporated in bilaminated films, a smart drug delivery system for oral formulations. *Biomacromolecules*, 2007, 8, 2845–2850.
50. Cui F, He C, Yin L, Qian F, He M, Tang C, Yin C. Nanoparticles incorporated in bilaminated films, a smart drug delivery system for oral formulations. *Biomacromolecules*, 2007, 8, 2845–2850.
51. Yong CS, Jung JH, Rhee JD, Kim CK, Choi H.G. Physicochemical characterization and evaluation of buccal adhesive tablets containing omeprazole. *Drug Dev Ind Pharm*, 27(5), 2001, 447-455. 27.
52. Kamel AH et al. Micromatrical metronidazole benzoate film as a local mucoadhesive delivery system for treatment of periodontal diseases, *AAPS Pharm Sci Tech*, 8(3), 2007, 75.
53. International journal of pharma medicine and biological science ISSN 2278-5221  
[www.ijpmbs.com](http://www.ijpmbs.com) Vol.2,No. 1,January 2013 all rights reserved.
54. Patel DA, Patel MR, Patel KR, Patel NM. Buccal Mucosa as a Route for Systemic Drug Delivery, a Review. *Int J Drug Dev Res*, 2012, 4(2), 99-116.
55. Gavin P Andrews, Thoma P Lavery and David S Jones. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur J Pharm Bio Pharm*, 71, 2009, 505-518.
56. International journal of pharma medicine and biological science ISSN 2278-5221  
[www.ijpmbs.com](http://www.ijpmbs.com) Vol.2,No. 1,January 2013 all rights reserved.
57. H.H. Sigurdsson, T. Loftsson and C-M. Lehr, International Journal of Pharmaceutics, 2006, 325, 1-2, 75.
58. International journal of pharma medicine and biological science ISSN 2278-5221  
[www.ijpmbs.com](http://www.ijpmbs.com) Vol.2,No. 1,January 2013 all rights reserved.
59. Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Cocker D. The efficacy of nonopioid analgesic for postoperative dental pain: a meta-analysis. *Anesth Prog*. 1997;44:119–126.
60. International journal of pharmaceutics ,mucpadhesive drug delivery system:march2009.
61. Advances in controlled and novel drug delivery ,N.K.JAIN,1<sup>st</sup> edition .