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Mucoadhesive Dosage Form: A Review

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ABSTRACT
The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. The oral cavity is the most accessible portion of the human digestive system, and it provides an appealing route of drug administration for local and systemic treatment because to its high accessibility and fair patient compliance. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combination of polymers, absorption enhancers.

Keywords: Buccal Delivery, Oral Cavity, Oral Mucosa, Theory of Mucoadhesive.

I. INTRODUCTION

The delivery of medications utilising different pharmaceutical dosage forms, such as tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as carriers, has been the mainstay of treating acute diseases or chronic illnesses for many decades. The oral route is likely the one that both patients and doctors favour among the many medication delivery methods. Some medications, however, have issues with this method. GI fluid enzymes, GIT-pH circumstances, and enzymes attached to GIT membranes are just a few of the causes of the bioavailability issues. Poor bioavailability of the medicine results from first-pass metabolism caused by direct transport of the drug to the liver by the blood that drains the GIT. In certain instances, the drug's intrinsic issues can be resolved.(1)

The capacity of new medication delivery methods to increase a medicine's bioavailability has sparked interest in them in recent years. Such an innovative method of medication delivery is the buccal route employing bioadhesive dosage forms. By giving the medication via the buccal route, extensive first-pass metabolism and drug degradation in the hostile gastrointestinal environment can be avoided.(2)

Due to the simplicity of administration, prevention of potential drug degradation in the gastrointestinal tract, and first-pass metabolism, the oral cavity is a desirable location for drug delivery. Three kinds of medication administration are distinguished inside the oral mucosal cavity:

1) Sublingual delivery : which is the systemic administration of medication via the mucosal membranes lining the mouth's floor.
2) Mucoadhesive delivery : which involves the administration of medication through the cheeks' mucosal membranes (Mucoadhesive mucosa).
3) local delivery: which is drug delivery into the oral cavity.(3)

Characteristics of an Ideal Bucoadhesive system

1. Quick adherence to the buccal mucosa and sufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should accomplish unidirectional release of drug towards the mucosa.
5. Should have good resistance to the flushing action of saliva.
6. Should not interfere normal functions such as talking, eating and drinking.
7. Should not cause any irritation or inconvenience to the patient.(4)

1.1 : Drug delivery via buccal route

When a dosage form is put in the outer vestibule between the buccal mucosa and gingiva, buccal delivery, or medication release, can take place. The following are some benefits and other details of this route that are clarified.

Advantages of buccal drug delivery

1. Buccal mucosa is richly vascularized and more accessible for the administration and removal of a dosage form.
2. High patient acceptability compared to other nonoral route of drug administration.
3. Compared to harsh environmental factors that exit in oral delivery of drugs, mucosal lining of

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buccal tissue provided a much milder environment for drug absorption.
4. Low enzyme activity in the buccal mucosa compared to other mucosal routes.
5. Avoids acid hydrolysis in the gastrointestinal tract and bypass the first-pass effect.

Disadvantages of buccal drug delivery

1. Low permeability of buccal mucosa.
2. Small surface area: 170 cm^2 is the total surface area of the membrane out of which approximately 50 cm^2 is nonkeratinized tissues, including the buccal membrane.
3. Continuous salivary secretion in oral cavity leads to washing and dilution of drug in the buccal form.
4. Swallowing of saliva can also potentially leads to the loss of dissolved or suspended drug ultimately, the involuntary removal of the dosage form.
5. Hazard of choking by involuntarily swallowing in the delivery system.
6. Buccal delivery system may be inconvenient while eating or drinking.[5]

1.2 : Anatomy and Nature of Oral cavity

1.2.1: Oral cavity:

Due to its exceptional accessibility and reassuring patient compliance, the oral cavity is the most important component of the human digestive system. Additionally, the oral mucosa offers an alluring route of drug administration for both local and systemic treatment.

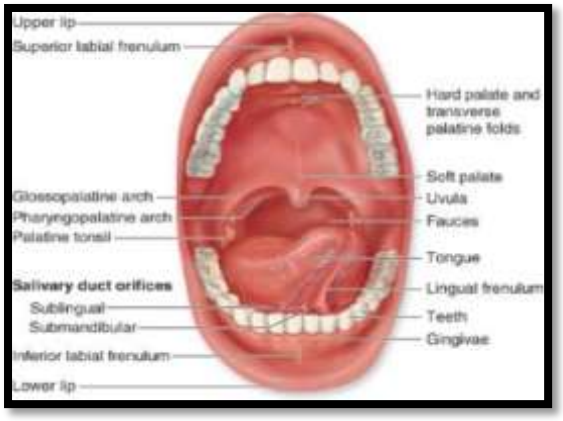

Fig 1: Structure of buccal cavity

1.2.2: Overview of oral cavity

The region of the mouth called the oral cavity is defined by the lips, cheeks, hard palate, soft palate, and floor of the mouth. There are two areas of the oral cavity.

1. The outer oral vestibule, which is enclosed by the gingiva, teeth, lips, and cheeks (gums).
2. The actual oral cavity, which includes the hard and soft palate as the roof and runs from the teeth and gums back to the faces (which open to the throat). From the cavity's floor, the tongue swells.

Through a network of arteries and capillaries, the medication given through the mouth mucosa enters the systemic circulation. The external carotid artery is the principal blood vessel feeding the mouth cavity. Through capillary and vein branches, the venous backflow is eventually absorbed by the jugular vein.

1.3: Oral mucosa

1.3.1: Anatomy and Physiology of the oral mucosa

The mucosa that lines the oral cavity may be divided into three types and classified according to their function as:

1. Masticatory mucosa: The mucosa that lines the teeth is included in this. These can be found, among other locations, on the hard palate and in the area around the teeth. In various places, keratinized epithelium can be found.
2. Lining mucosa: Lips, cheeks, and nose are all covered by this mucosa. Base of the oral cavity, fornix, lowest portion of the tongue. These regions, as well as the buccal mucosa and the soft palate The epithelium does not have keratin.
3. Mucosa specialised: covers the tongue's dorsum. Based on different areas of the oral cavity, highly keratinized tongue light microscopy reveals a number of diverse patterns of maturation in the epithelium of the human oral mucosa. The epithelium, basement membrane, and connective tissues are the three separate layers that make up the oral mucosa. The basement membrane serves as support for the epithelium that lines the mouth cavity. Connective tissues in turn support the basement membrane (Fig 2). The basal cell-derived epithelial cells develop, changing their appearance and enlarging as they migrate to the surface. It has been established that the buccal epithelium in humans, dogs, and rabbits ranges in thickness from 500 to 800 µm. The connective tissues and the epithelium are separated by the basement membrane, which creates a discrete layer. It serves as a mechanical support for the epithelium and provides the necessary adhesion between the epithelium and the underlying connective tissues.[6]

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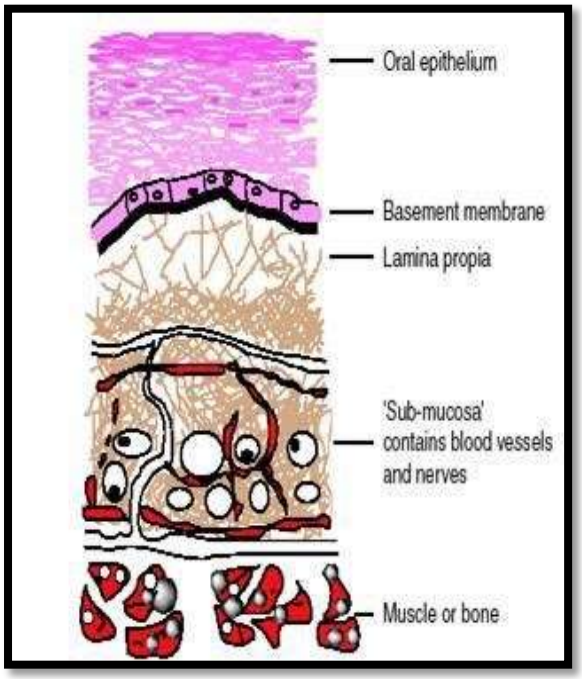

Fig 2: Structure of Buccal mucosa

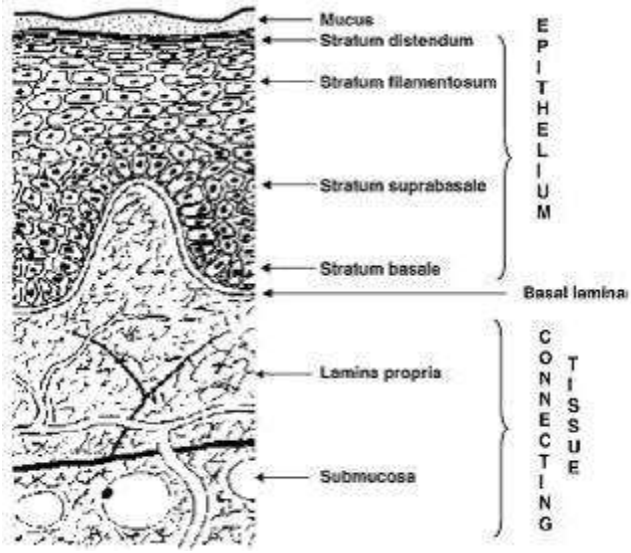

Fig 3: Cross-section of Mucoadhesive mucosa

Table 1: Cross-section of Mucoadhesive mucosa

Tissue	**Structure**	**Thickness (µm)**	**Blood flow (ml/min/cm^2)**
Mucoadhesive	Non - keratinized	500 – 600	2.4
Sublingual	Non - keratinized	100 – 200	0.9
Gingival	Keratinized	200	1.5
Palatal	Keratinized	250	0.9

1.4: Mucoadhesive drug delivery system

The phenomenon of interfacial molecular attractive forces between the surfaces of the biological substrate and the natural or artificial polymers is known as bioadhesion, and it enables the polymer to stick to the biological surface for a long time. These systems have long been employed in the creation of goods for diverse biomedical uses.

1.4.1: Theories of Mucoadhesive

1. **Diffusion Theory**: This theory core principle is that chains of the substrate and adhesive interpenetrate sufficiently deeply to form a semi-permanent adhesive connection. The diffusion coefficients of the two interacting polymers, which are known to be influenced by molecular weight and cross-linking density, are what determine the penetration rate. Additionally, it's crucial to take into account aspects like segment mobility, bioadhesive polymer flexibility, mucus glycoprotein, and the extended nature of both networks.

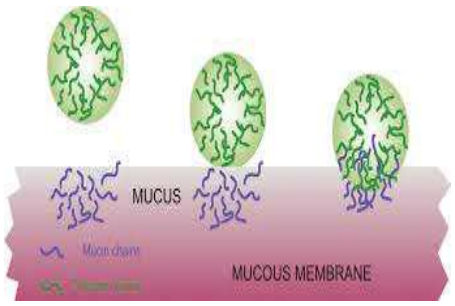

Fig 4: Secondary interaction between mucoadhesive device and mucus

2. **Electronic Theory**: Mucus often has distinct electrical properties from sticky polymers. An electrical double layer is created at the interface between these two surfaces when they come into contact, and adhesion results from the attractive force of electron transfer across the electrical double layer.

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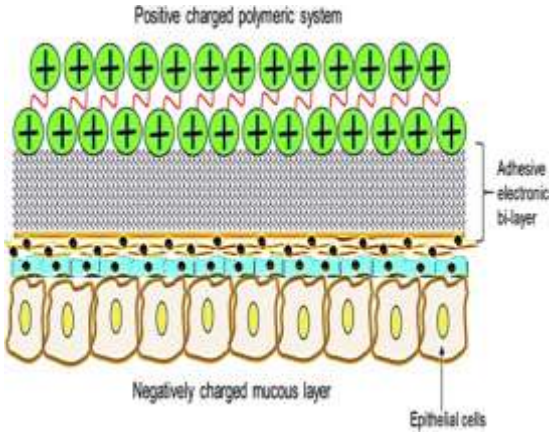

Fig.5: Electronic theory

3. Adsorption Theory: According to the adsorption hypothesis of bioadhesion, a polymer's adherence to a biological tissue is caused by:

I. Primary bonds, which are unfavourable for bioadhesion since they are rather permanent.

II. Hydrogen, hydrophobic, electrostatic, and Vander Waals forces all work together to create secondary chemical connections.

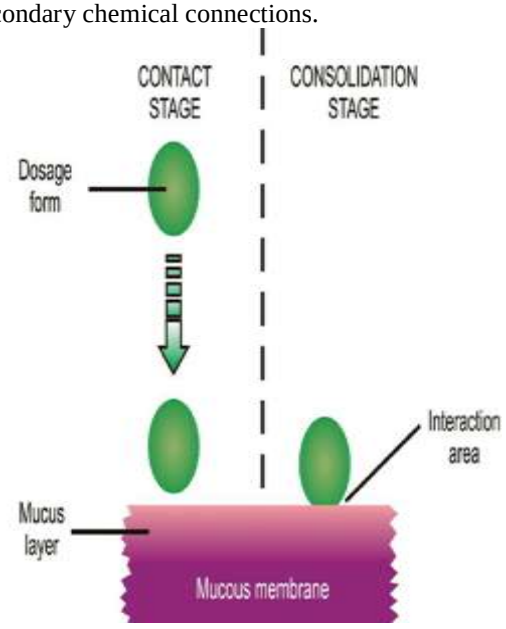

Fig 6: The process of consolidation

4. Wetting Theory: The wetting hypothesis, which has its main relevance to liquid bioadhesive systems, stresses the close contact between the adhesive and mucus. Therefore, structural similarity, the amount of cross linking in the sticky polymer, or the presence of a surfactant all affect how wet a surface is. The energy per cm^2 released when an interface forms is known as interfacial tension (Y), and it is used to represent the work of adhesion.

The Dupres equation for adhesion's work is Wa = YA + YB - YAB.

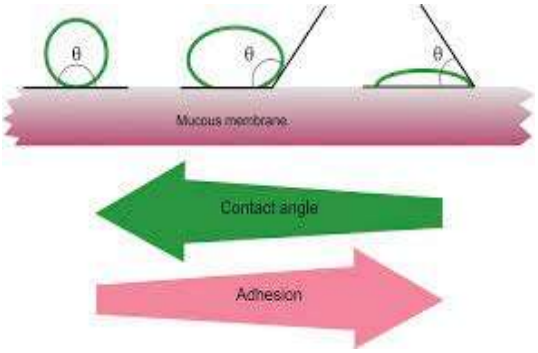

Fig 7: Influence of contact angle on mucoadhesion

5. Fracture Theory: The separation of two surfaces following adhesion is connected to the fracture hypothesis of adhesion. According to, the fracture strength is equal to the adhesive strength.

$G = (E\varepsilon / L)\ ½$

Where: E=Young's modules of elasticity

ε =Fracture energy

L=Critical crack length when two surfaces are separated.[7]

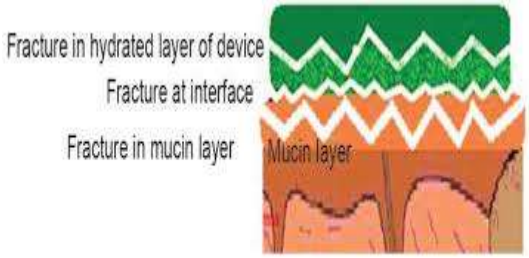

Fig 8: Fractures occurring for Mucoadhesion

1.5: Type of buccal drug delivery system

Numerous mucoadhesive dosage forms have been reported for drug delivery through the buccal region. Because the buccal region has a smooth, largely immobile surface on which to place a mucoadhesive dosage form, it seems to be better suited for the sustained delivery of therapeutic agents using a mucoadhesive system. Following is an explanation of the numerous types of buccal medication delivery systems:

1. Buccal Tablets
2. Buccal Patches and Films
3. Buccal Semisolids (ointments and gels)
4. Buccal Powders

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1. Buccal Tablets

- Adhesive tablets are held between the gum and cheek.
- Generally flat, elliptical or capsule-shaped.
- Troches & lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat.
- Bucoadhesive tablet may be monolithic or bilaminated system.
- Monolithic is multidirectional release.
- Bilayered containing core layer & backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer.
- Backing layer avoids sticking of the tablet to the finger during application.

Limitation of buccal tablets

- The small surface of contact with mucosa.
- Their lack of physical flexibility.
- It is difficult to get high release rate, which is required for some drugs.
- The extent and frequency of contact may cause irritation following chronic application of the buccal mucosa.

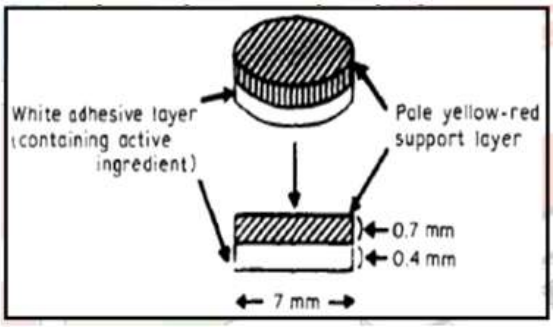

Fig 9: Adhesive tablet

Table 2: List of investigated mucoadhesive buccal tablets

Active ingredient	Polymer used
Propranolol HCL	HPMC and PC
Promethazine	Sodium CMC and Carbopol 934P
Theophylline	CP 974P
Curcumin	Anacardium accidentale
Nifedipine	CMC and CP
Glipizide	Carbopol 974P, Methocel K4M and Methocel
Lisinopril	Carbopol-934, HPMC, HEC
Carvedilol	HPMC K4M, SCMC and Carbopol-934
Clarithromycin	Carbopol 974P, HPMC K15, HPMC K4M

2. Buccal Patches and Films

Buccal patches consist of two-ply laminates or multilayered thin film round or oval as consisting of basically of bioadhesivc polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhcsivc films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Example:

- Isosorbid dinitrate in the form of unidirectional errodible buccal film are developed and characterised for improving bioavailability.
- Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma.
- Buccoadhesive film of clindamycin used for pyorrhoea treatment.

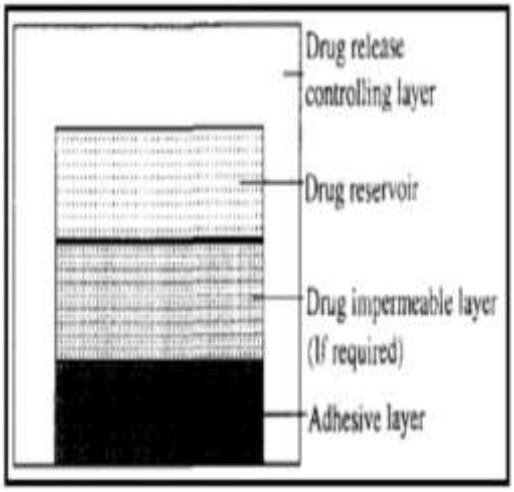

Fig 10: Bioadhesive sustained dosage form

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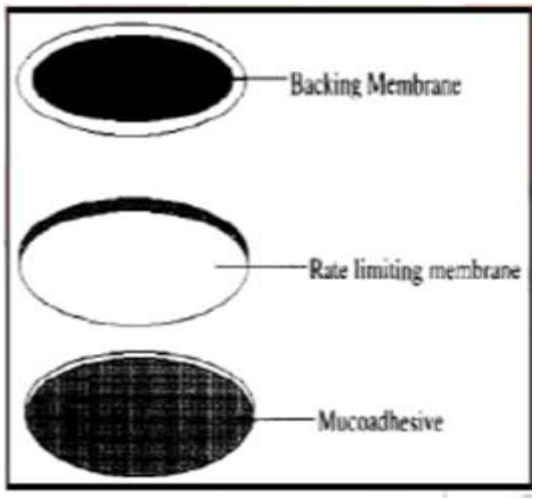

Fig 11: Prototype buccal mucoadhesive system

Table 3: List of investigated buccal mucoadhesive patches

Active ingredient	Polymers used
Domperidone	HPMC, PVP30, Eudragit RLPO, PEO
Miconazole nitrate	Sodium CMC, chitosan. PVA, HEC, HPMC
Sumatriptan succinate	Gelatin, PVP
Carvedilol	HPMC E15
Zolmitriptan	PVA and HPMC E-15

Table 4: List of investigated buccal mucoadhesive films

Active ingredient	Polymers used
Domperidone	PEO N750 and HPMC E5 LV
Insulin	Gelatin and CP 934P
Fluconazole	HPMC, HEC, chitosan, Eudragit and sodium alginate
Prednosolone	HPMC Carbopol 940 and Eudragit NE 40 D.

3. Buccal Semisolid Dosage Forms

A buccal semisolid dosage form consists of finally powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution. Example: Gels, Ointments, orabase

- Gels are usually clear, transparent, semisolids containing solubilized active substances. Forming hydrophilic polymers is typically used to prepare lipid-free semisolid dosage forms.

E.g: Methylcellulose, carbopols, hydroxyl ethylcellulose etc.

- Vehicles containing therapeutic agents are especially useful for application to mucus membranes and ulcerated or burned tissues, because their high water content reduces irritancy.
- Due to plastic rheological behaviour, they can remain to the surface of application for a reasonable duration before they are washed off.
- In comparison to solutions, gels can significantly prolong residence time and hence improve bioavailability. Eg. Glibenclamide
- One of the original oral mucosal-adhesive delivery systems- "orabase" consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.

Table 5: List of investigated buccal mucoadhesive gels

Active ingredient	Polymers used
Ibuprofen	Carbopol 980 and polycarbophil
Ergotamine tartrate	PVA
Diclofenac sodium	Hydroxyethyl methacrylate
Lidocaine	PEG, CP 934P
Celecoxib	Chitosan

4. Buccal Powder Dosage Forms

Buccal bioadhesive powder dosage forms are a mixture of bioadhesivc polymers and the drug and are sprayed onto the buccal mucosa.[8-11]

CLASSIFICATION OF MUCOADHESIVE POLYMERS USED IN BUCCAL DRUG DELIVERY

Semi-natural/natural:

E.g. Agarose, chitosan, gelatin, Hyaluronic acid, various gum, (guar, hakea, xanthan, gellan, carrageenan, pectin and sodium alginate)

Synthetic:

- **Cellulose derivatives**

E.g. Carboxymethyl cellulose (CMC), thiolated CMC, sodium CMC, Hydroxyethy cellulose (HEC), Hydroxypropyl cellulose (HPC),

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Hydroxypropyl methylcellulose (HPMC), Methylcellulose (MC), methylhydroxyethylcellulose.

- **Poly(acrylic acid)-based polymers**

E.g. Carbopol (CP), Polycarbophil (pc), Polyacrylates, Poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methylacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and polyethylene glycol (PEG)

- **Others**

E.g. Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, PVA, PVP, thiolate polymers.

Water-soluble:

E.g. CP, HEC, HPC (water<38°C), HPMC (cold water), PAA, Sodium CMC, sodium alginate

Water-insoluble:

E.g. chitosan (soluble in dilute aqueous acid), Ethyl cellulose (EC), PC.

Cationic:

E.g. Aminodextran, chitosan, dimethyl aminoethyl (DEAE)-dextran, trimethylated chitosan

Anionic:

E.g. Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum

Non-ionic:

E.g. Hydroxyethyl starch, HPC, poly (ethylene oxide), PVA, polyvinylpyrrolidone (PVP), Scleroglucan.[12]

II. CONCLUSION:

Buccal drug delivery specifically refers to the delivery of drugs through buccal mucosa to affect local/systemic pharmacological actions. This review briefly describes advantages and limitations of buccal drug delivery, selection criteria of drugs and mucoadhesive and bioadhesive polymers, mechanism of permeation enhancers and various types of buccal delivery formulations.

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