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A REVIEW WITH SPECIAL PROMINENCE ON MUCOADHESIVE BUCCAL DRUG DELIVERY FOR PEPTIC ULCER

Raoof Ali*, Disha Dutta and Ashok Kumar

Devsthali Vidyapeeth College of Pharmacy Lalpur, Rudrapur Uttarakhand India 263148.

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***Corresponding Author**
Raoof Ali
Devsthali Vidyapeeth College of Pharmacy Lalpur, Rudrapur Uttarakhand India 263148.

ABSTRACT

Around the novel drug delivery system such as a mucoadhesive and buccal system has made accessible a lot of beneficial in the field of pharmacy. Mucoadhesive buccal drug delivery systems are novel drug delivery system, which utilize the property of bioadhesion of polymers that happen to adhere on hydration, these drug delivery system can be used for targeting a drug to the exacting region of the body for an extended period of time. Mucoadhesion is an interfacial process in which polymers bind to the mucus through the covalent bond, and the polymers act as a drug delivery vehicle in the mucoadhesive drug delivery system. Peptic ulcer is a chronic developmental disease in human, in which imbalance take place between aggressive factor and defensive factor resulting erosion of the lining of the stomach, or the upper duodenum. It has been mostly established diseases in the world and it has a multifactor etiology. Some environmental elements such as spicy food, warring lifestyle, alcohol and nicotine can increase the acid and bicarbonate secretion and these factors inhibit or reduce the secretion of mucus in the digestive tract.

KEYWORDS: Mucoadhesive buccal drug delivery system, bioadhesion, polymer, peptic ulcer.

1. INTRODUCTION

The primary aim of oral controlled drug delivery system is to deliver drug for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But sometime this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process narrow absorption window and stability problem in the intestine. To overcome these problems includes the bioadhesive or mucoadhesive system.[1]

Mucoadhesion is a process in which polymer binds to the mucus membrane through the covalent bond, and the drug is released from diffusion process to a controlled manner. In the mucoadhesive drug delivery system polymer act as drug delivery vehicle. Mucoadhesion has been an extensively adapted approach for achieving site specific drug delivery through the amalgamation of mucoadhesive polymer within pharmaceutical formulations along with the active pharmaceutical ingredient. The concept of mucoadhesive was introduced into the control drug delivery in the early 1980's. Mucoadhesive polymers are synthetic or natural polymers, which interact with the mucas layer covering the mucosal epithelial surface and mucin molecule constituting a major part of mucus. They propound the treatment more effective and safe, not only for local action, but also for systemic action.[2]

Buccal drug delivery is a topical administered medicine in the form of a tablet or patch that apply between the gum and chick to deliver the drug for a prolonged period of time for the treatment of local and systemic problem. The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity, therefore mucoadhesive dosage forms are suggesting for oral drug delivery system.

Peptic ulcer is a disease of chronic development, characterized by an imbalance between the factors that damages the mucosa and those for its protection, resulting in a lesion of the lining (mucosa) of the upper digestive tract. The word 'peptic' refers to pepsin a stomach enzyme that breaks down proteins, typically in the stomach or duodenum caused by the digestive action of pepsin and stomach acid.[3]

2. Mucoadhesive drug delivery system

The concept of mucosal-adhesive or mucoadhesive was introduced into the controlled drug delivery in the early 1980's. Mucoadhesive polymers are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. They give the treatment more effective and safe, not only for local action, but also for systemic problems. These dosage forms are self-administrable, cheap and have superior patient compliance. With the right dosage form design, local environment of the mucosa can be controlled and manipulated in order to optimize the rate of drug dissolution and permeation. The buccal delivery is defined as the drug administration through the mucosal membranes lining the cheeks (buccal mucosa). The main impediment to

the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption.[1,4]

1. Advantages[1,5]

- Buccal mucosa has the excellent accessibility, an extension of smooth muscle and relatively stable mucosa, hence suitable for the administration of retentive dosage forms.
- The drug directly enters into the systemic circulation through the internal jugular vein bypasses drugs from hepatic first pass metabolism leading to high bioavailability.
- Easy to drug administered and termination, low enzymatic activity, can be used permeation enhancers, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration.
- Insensitive environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
- The drug can be administered to unconscious patients; drug administration can be terminated in case of emergency.
- Both hydrophilic and lipophilic drugs can be permeated through this route.

2. Disadvantages[1,5,6]

- Smaller surface area, low permeability of the buccal membrane, specifically when compared to the sublingual membrane.
- The swallowing of saliva can also potentially pilot to the loss of dissolved or suspended drug and eventually, the spontaneous removal of the dosage form.
- Drugs which are unstable at buccal PH cannot be administrated, In addition to the swallowing; there is another inconvenience of such dosage form during drinking and eating by the patient.
- Drugs which have a bitter taste or unpleasant taste or an obnoxious odour, irritate the mucosa cannot be administrated by this route.

3. Buccal mucosal structure and its suitability

The buccal area is that part of the mouth delimited anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. The maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm2) than that in the sublingual, gingival and palatal regions thus facilitate passive diffusion of drug molecules across the mucosa. The buccal mucosa consist of several layers of different cells, the

outermost layer is stratified squamous epithelium, below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer, epithelium act as a protective layer for the tissues beneath and is divided into

1. **Epithelium**

a. Stratum distendum
b. Stratum filamentosum
c. Stratum super basal
d. Stratum basal

2. **Basal lamina**
3. **Connective tissue**

a. Lamina propria
b. Submucosa

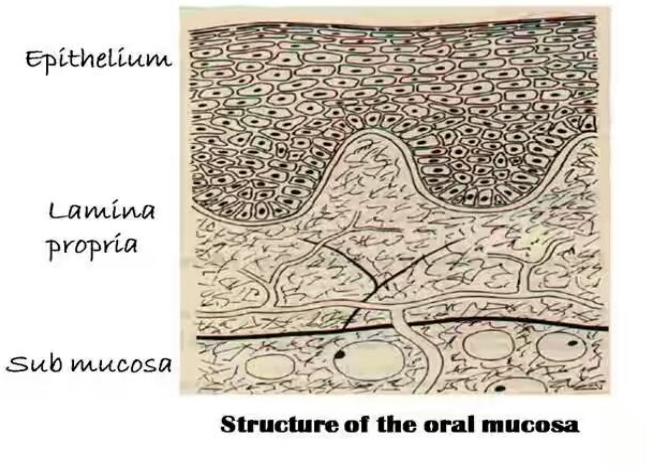

Figure No.1- structure of oral mucosa.

3.1. THE MUCUS LAYER

The oral epithelium cell surrounded by the ground substance mucus, it is a translucent and viscid secretion, which forms a thin continues gel adherent to mucosal epithelium surface made up of glycol proteins located various body cavities from respiratory, 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.[1,6]

3.2. Composition of mucus

S.No	Composition	Percentage
1	Water	90%
2	Glycoprotein and lipid	0.5-5%
3	Mineral salt	1%
4	Free proteins	0.5-5%

3.3. Function of mucus layer

The primary functions of the mucus layer are:

Protective: It protects the epithelium surface from acid diffusion through the lumen resulting particularly from its hydrophobic.

Barrier: The role mucus layer as a barrier in tissue absorption of drugs and it also decreases the bioavailability of the drugs.

Adhesion: Mucus has firm cohesional properties and rigidly binds to the epithelial cell surface as a continuous gel layer.

Lubrication: Moisture is present in the mucus which provides lubrication to mucosal layer**,** an important role of the mucus layer is to keep the mucosal membrane slightly wet.

3.4. Saliva

The oral cavity is marked by the presence of saliva produced by the salivary gland. The saliva within the oral cavity makes it very difficult for the drugs to be retained for a significant amount of the time to facilitate absorption in this site.

Role of saliva: Saliva continuous mineralization of the tooth enamel and it act as protective fluid in all tissues of the oral cavity. It hydrates the oral mucosa of the dosage forms.

4. Mucoadhesive buccal drug delivery systems

The oral cavity is an attractive site for drug delivery due to ease of administration and termination, avoid the possibility of drug degradation in the gastrointestinal tract, and first-pass metabolism. Within the oral mucosal cavity, delivery of drugs is classified into three categories.[1]

Sublingual delivery: in which the drug administration via mucosal membrane lining the floor of the mouth i.e., sublingual mucosal to the systemic circulation.[2]

Buccal delivery: in which administration of the drug between the gum and cheeks i.e., buccal mucosa to the systemic circulation.[3]

Local delivery: for the treatment of oral cavity problem, such as Aphthous Ulcers, fungal conditions and Periodontal diseases by administration of the bioadhesive system either to the palate, the gingiva or the cheek.[7]

5. Mechanism of Bioadhesion

The mechanism of bioadhesion can be described in three successive steps: Steps involved in the process of bio/mucoadhesion are as follows.[1,8]

- Wetting and swelling of polymer to permit intimate contact with biological tissue.
- Interpenetration of bioadhesive polymer chains & entanglement of polymer mucin chains.
- Formation of weak chemical bonds between entangled chains.

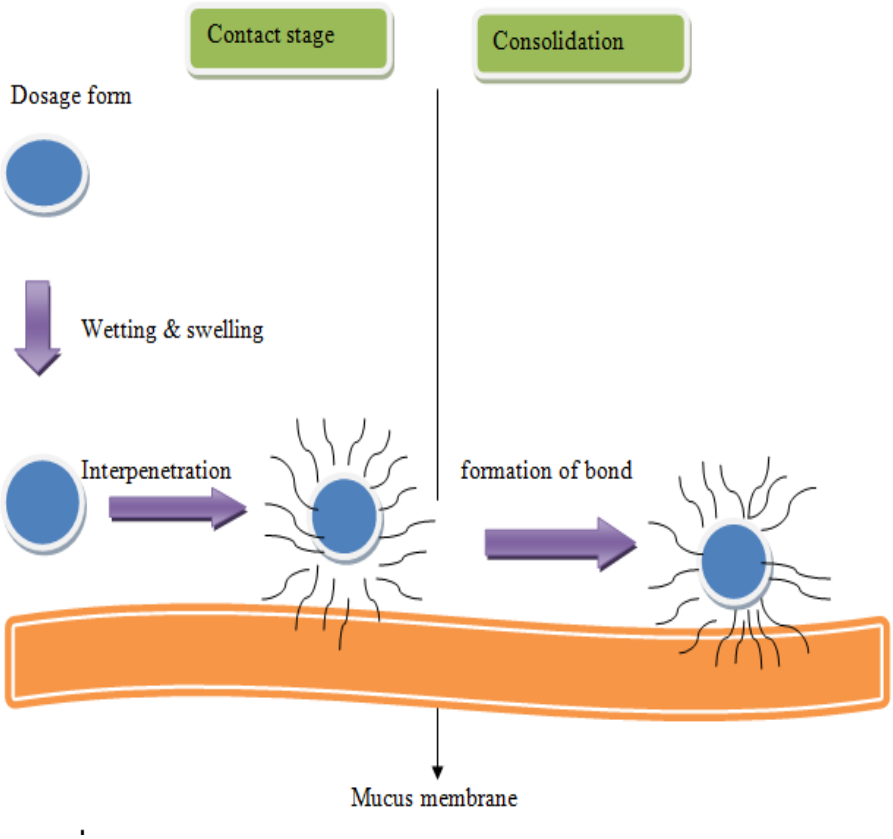

Figure No.2: Mechanism of bioadhesion.

6. Drug delivery pathway

There are two permeation pathways for passive drug transport across the oral mucosa:

a. Paracellular routes

b. Transcellular routes

The permeation of drug through these two routes simultaneously; however, one route is usually preferred over the other depending on the physicochemical properties of the drug. The intercellular spaces and cytoplasm are hydrophilic in character; lipophilic compounds would have low solubility in this atmosphere. The cell membrane is lipophilic in nature and hydrophilic solutes will have complexity permeating through the cell membrane due to a short partition coefficient, the intercellular spaces cause as the main barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Oral epithelium stratified, solute permeation may occupy an incorporation of these two routes.[1,9]

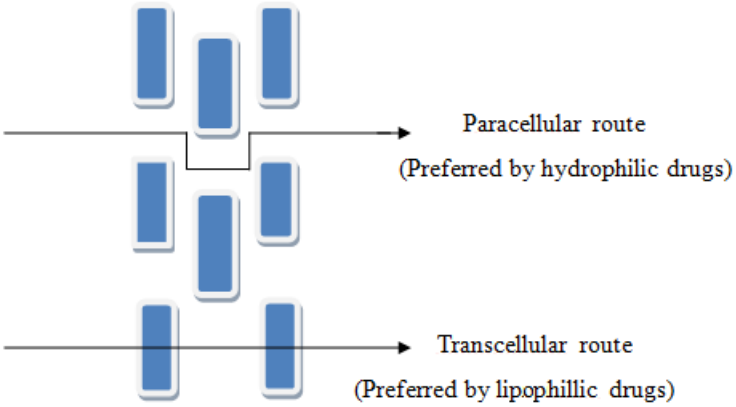

Figure No.3: Drug delivery pathway

7. Mechanism of drug release[1,11]

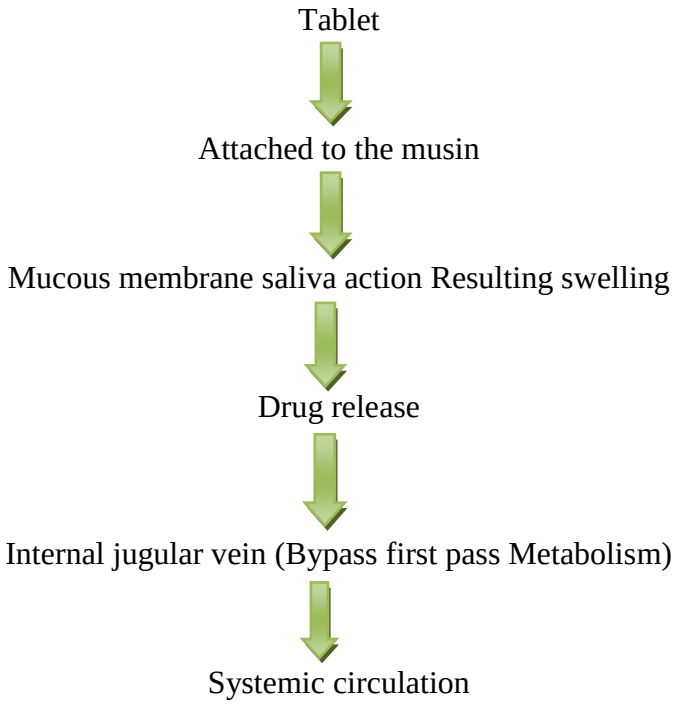

Figure No.4: Mechanism of drug release.

8. Mucoadhesive Polymer used in buccal drug delivery system

Mucoadhesive buccal delivery systems are being explored for the localization of the active agents to a particular site, in mucoadhesive drug delivery system polymer act as drug delivery vehicles and its play an important role in designing such systems in order to increase the residence time of the active agent at the desired location. Mucoadhesive polymers have properties of water soluble and water insoluble. They attach to mucus membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions.[1,5,12]

An ideal mucoadhesive polymer has the following characteristics.

- It should non-toxic and non-absorbable from the gastrointestinal tract.
- It should be non-irritant to mucous membrane.
- It should form a strong non covalent bond with mucin epithelial cell surfaces.
- It should be adhered rapidly to moist tissue and should acquire site specificity.
- Permit to easy incorporation of the drug and offer no obstacle to its release.
- It must not decompose on storage or during the shelf life of the dosage form.
- It should be cost effective Mucoahesive polymers are classified as follows:

Hydrophilic polymers

These categories of polymers are called as water soluble polymer, it is swell when put into an aqueous medium with the subsequent dissolution of the matrix. These polymers consisted carboxylic group and possess admirable mucoadhesive properties. These polymers are directly compressed with the drugs to get an excellent mucoadhesive delivery system. These are such as poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methyl cellulose (SCMC), Hydroxy propyl cellulose (HPC), Xantham gum and other cellulose derivative.

Hydrogels

They are three-dimensionally cross-linked polymer chains which have the capability to hold water within its porous structure and swell by means of adhesion with the mucus that covers epithelia. The capacity of water holding of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. Hydrogels are further classified into sub categories on the basis of their charge and on the basis of their source.[12]

Anionic polymers Carbopol, Polyacrylates

Cationic polymers Chitosan

Neutral/nonionic polymers

Eudragit analogues on the basis of source hydrogels are classified into following categories:

Synthetic polymers Cellulose derivatives, Carbopols etc.

Natural polymers

Tragacanth, Pectin, Gelatin, Sodium alginate, Acacia.

Novel mucoadhesive polymers

That new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by corium technologies. The polymer complex have been prepared by non covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends.[12]

S. NO.	Name of Polymer	Molecular Weight	Description	Application
1.	Polyvinyl Pyrolidine	2500-3,000,000	White , odourless And hygroscopic Powder	Good emulsifying agent, thickening agent, binding agent
2.	Carbopol	7×105 to 4× 109	White, fluffy, acidic, hygroscopic powder with slight characteristics odour	Excellent thickening, emulsifying, gelling, binding agent, possess good bioadhesive 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, fibrous powder or granules. It is odorless and Tasteless	It is used in oral and topical pharmaceutical formulation and 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 in oral.
6.	Chitosan	10,000-1,000,000	Odorless, white or creamy-white powder or flakes	It is used in cosmetics and pharmaceutical formulations and used as acompoment of mucoadhesive dosage form, flims, gels, tablet and beads
7.	Eudragit Analogue	47,000	Transparent or pale yellowish colour, odourless	Good Emulsifying, binding agent

9. Factors affecting mucoadhesion

1) Polymer Related Factors[1,6,15]

a) Molecular weight: Interpenetration of polymer molecules into the mucus layer is erratic, for low molecular weight polymers penetration is greater than high molecular weight polymers because entanglements are superior in high molecular weight polymers.

b) Concentration of active polymer: the concentration of polymer in solid dosage forms such as tablets, higher the concentration of polymer, the stronger the bioadhesion force.

c) Spatial Conformation: The bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear, helical conformation of polymers may shelter many active groups, primarily liable for adhesion, thus reducing the mucoadhesive strength of the polymer.

d) Chain flexibility of polymer: The chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more cross linked, mobility of the individual polymer chain decreases, also as the cross linking density increases, the effective extent of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced.

e) Degree of Hydration: The important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under condition, where the amount of water is limited.

2) Environmental – Related Factors[1,8,17]

a) PH of mucoadhesive site: The pH influences the charge on the surface of both mucus and polymers. Mucus will have an unusual charge density depending on pH, because of variation in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may influence adhesion.

b) Applied strength: The solid bioadhesive system is necessary to apply a defined strength, the polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.

c) Initial contact time: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases.

d) Selection of the model substrate surface: The conduct and handling of biological substrates during the testing of mucoadhesive is an important factor, physical and biological changes may arise in the mucus gels or tissues under the experimental conditions.

3) Swelling index: Swelling feature is related to the polymer itself, and its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. Additional the swelling of polymeric matrix higher the adhesion time of polymers.

4) Physiological variables: The Mucin turnover and disease state of mucus layer are physiological variables, which may concern bioadhesion.

10. Mucoadhesive dosage form

The incidence of a smooth and relatively stationary surface for placement of a mucoadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using mucoadhesive systems. The sublingual and buccal routes avoid first-pass metabolism. These regions consist of a non-keratinized epithelium, resulting in a more permeable tissue than the skin, drugs with a short biological half-life requiring a sustained release effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to be delivered by the oral cavity.[19,20]

Tablets

Mucoadhesive buccal tablets are dry dosage forms and it is to be moistened prior to placing in contact with buccal mucosa. It is double layer tablet, consisting of adhesive matrix layers of polyacrylic acid and hydroxy propyl, cellulose with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate), thus offering the possibilities of localized as well as the systemic controlled release of drugs. These are widely used because they offer a prolonged release of drug from the dosage form, and improve the patient compliance and reduce frequency of drug administration**.**

Films

Mucoadhesive buccal films may be favored over adhesive tablets in terms of flexibility and comfort. They can avoid the relatively short residence time of oral gels on the mucosa, which are easily washed away and unconcerned by saliva. Moreover, in the case of local delivery for oral diseases, the films also help to protect the wound surface, thus helping to reduce pain, and treat the disease more effectively. An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good mucoadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film should not be too extensive in order to prevent discomfort.

Patches

Muadhesive patches are laminates consisting of an impermeable backing layer, drug-containing reservoir layer from which the drug is released in a controlled manner, and a mucoadhesive surface for mucosal attachment. The patch systems are parallel to those used in transdermal drug delivery. Mostly two methods used to prepare adhesive patches incorporate solvent casting and direct milling. The impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize warping and disintegration of the device during the application period.

Gels and ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using mucoadhesive formulations.

Powders

Hydroxpropyl cellulose and Beclomethasone in powder for when sprayed onto the oral mucosa of rats, a significant increase in the residence time virtual to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.

Buccal sprays

The generex bio technologies have been introduced insulin spray. That technology is being used to extend a formulation for buccal delivery of insulin for the treatment of type - 1diabetes Buccal spray delivers a mist of fine droplets onto mucosal membrane may be on to mucin layer.

11. Peptic ulcer

Peptic ulcer is defined as a disruption of the mucosal integrity of the stomach and duodenum leading to a local defect or excavation due to active inflammation. The word ‘peptic’ refers to pepsin a stomach enzyme that breaks down proteins. Peptic ulcer is a disease of chronic development, characterized by an imbalance between the aggressive factors like acid, pepsin, bile and the defensive factors such as bicarbonate (HCO_3^-) and nitrogen oxide (NO) that damages the mucosa and those for its protection, resulting in a lesion of the lining of the upper digestive tract. It has been one of the most prevalent diseases in the world, the ulcer has a multifactor etiology. Environmental elements such as spicy food, sedentary lifestyle,

alcohol and nicotine can inhibit or reduce secretion of mucus and bicarbonate, increasing acid secretion.[2,12]

Peptic ulcer disease (PUD), Zollinger-Ellison Syndrome (ZES) and gastro esophageal diseases (GRD) are upper gastrointestinal disorders sharing a common abnormality: too much acid and pepsin activity for the degree of local tissue resistance. Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract mucosa and muscularis mucosa. Peptic ulcer has unquestionably been a disease of the twentieth century. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. There are different types of ulcers most common are peptic ulcer: gastric ulcer, which appeared to be due to damage to the lining of the stomach, and duodenal ulcer, which was associated with excessive acid secretion by the stomach. The etiology of peptic ulcer was fiercely debated.[23,24]

- **Causes of peptic ulcer**

The causes of peptic ulcer disease include Helicobacter pylori infection, non-steroidal anti inflammatory agents (NSAIDs) and malignancy.

H.pylori

H.pylori is a very powerful producer of urease and may cause ulceration by causing hydrolysis of urea which leads to generation of cytotoxic ammonia.

NSAIDs

When administered orally cause local irritation, allow back diffusion of acid into the gastric mucosa and induce tissue damage, parenterally administered NSAIDs can also cause gastric mucosal damage and bleeding correlated with the inhibition of the biosynthesis of gastric prostaglandins (PG) mainly PGI and PGE.

Alcohol consumption

The non distilled and fermented alcohol beverage increase gastrin level and acid secretion. Alcoholic drink containing succinic maleic acid, also stimulate gastric acid secretion.

Smoking and tobacco

Relationship between the secretion pepsin and the smoking habits of patients has been investigated, significantly more cigarette smokers with peptic ulceration secreted pepsin in greater than trace amounts after histamine than non smokers with ulceration.

Fasting condition

The fasting condition causes gastric empty which in some cases causes gastric ulcers.

- **Regulation of gastric acid secretion**

Terminal enzyme H^+k^+ATPase secrets H+ ions in the apical canaliculi of the parietal cell, and can be activated by histamine, acetylcholine and gastrin acting by their own receptors located on the basolateral membrane of these cells. The histamine act on H_2 receptor and acetylcholine and gastrin acts either may act directly through muscarinic receptors, respectively or my act indirectly by releasing histamine from histaminocytes. Gastrin is secreted from the antrum in retort of antral pH, food constituents and vegal mediated reflexes.[25]

- **Types and symptoms of peptic ulcers**

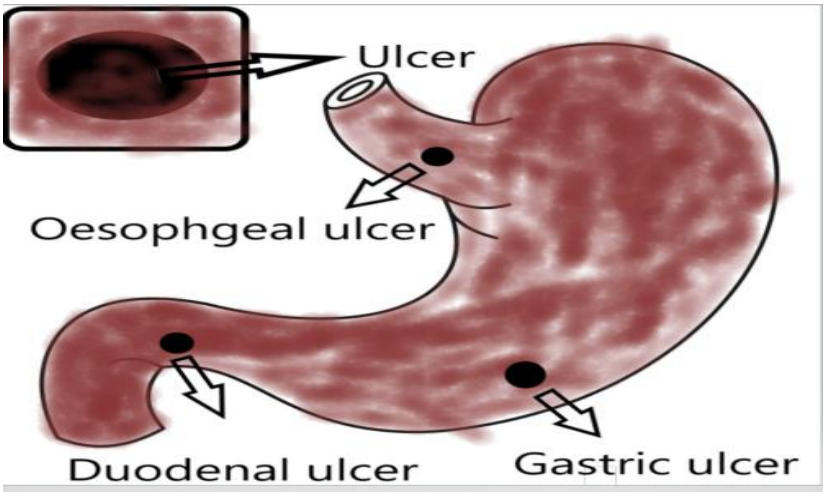

Figure No.5: Types of ulcer.

The three most common types of peptic ulcer are called ‘gastric ulcer’ and ‘duodenal’ oesophageal ulcer. A person may have both gastric and duodenal ulcers at the same time.

Gastric ulcer: Gastric ulcer is located in the stomach, characterized by pain (especially in the abdomen) and common in older age groups (especially in female). Eating may increase pain rather than relieve pain, other symptoms may include nausea, vomiting and weight loss.

Duodenal ulcer: Duodenal ulcer is found at the beginning of the small intestine (duodenum) and characterized by severe pain in the upper abdomen and chest area with burning sensation in the upper abdomen that awakens patients from sleep. Generally, pain occurs when the stomach is empty and relieve after eating.

Oesophageal ulcer: Oesophageal ulcer is found in oesophagus it is developed by reflex movement of gastric acid from the stomach to the oesophagus and causes erosion on the upper digestive tract.[2,12,25]

12. Antiulcer drugs used in the mucoadesive drug delivery system

Several antiulcer drugs are used for treatment of peptic ulcer, generally these classes of drug are significantly used such as proton pump inhibitor, antihistamines, anticholinergic, antacid, ulcer protective agent. Peptic ulcer is a chronic developmental disease in which imbalance between the aggressive factor such as acid, peptic, bile and protective factors such as bicarbonate ions, nitrogen oxide, resulting lesions of the lining of the upper digestive tract. Mucoadhesive buccal drug delivery system is one of the important tool for the treatment of peptic ulcer, from this route the drug is delivered directly into the system circulation for a longer period of time and to achieving the better bioavailability, circumvent the first pass metabolism and gastrointestinal fluctuation. Example of antiulcer drug which is used in mucoadhesive drug delivery system for the treatment of peptic ulcer[1,2,24]

S.NO	Brand Name	Active Ingredients
1.	Nifediac cc	Nifedipine
2.	Zegerid otc	Omeprazole
3.	Aciphex	Rabeprazole
4.	Almagate	Flatcoat antacid
5.	Topalkan	Aluminium magnesium antacid
6.	Nexium	Esomeprazole

CONCLUSION

Extensive research efforts have recently been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose dependent side effect. Buccal delivery of the drug provides an attractive alternate to other conventional methods of systemic drug administration. It is a potent drug delivery system for the treatment of peptic ulcer.

The aim of this study to deliver the drug for a prolonged period of time, and to achieving the better bioavailability and reducing the dosing frequency and side effects, they give the treatment more effective and safe not only for local but also for systemic problem, these dosage forms are self administrable cheap and having a superior patient compliance. Mucoadesive buccal drug delivery system applies between the gum and inner chick that

deliver the drug to a predetermined rate or a control rate, mucoadhesive buccal drug delivery system is suitable for both lipophilic and hydphilic drug.

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