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ENHANCING THERAPEUTIC EFFICACY WITH MUCOADHESIVE DRUG DELIVERY.

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Abstract:

The buccal region within the mucosal cavity of the mouth provides an alternative route over an oral drug administration for systemic as well as local drug delivery. As the buccal mucosa has an abundant blood supply and is relatively permeable, it can be considered as most accessible and desired location for both local and systemic drug delivery. The buccal method for medication delivery greatly helps in avoiding issues in the gastrointestinal environment, such as increased first-pass metabolism and medication degradation. Muco-adhesive systems offer varieties of advantages such as convenience in administration and termination of therapy in case of emergency, higher patient compliance, better bioavailability, rapid absorption, etc. This current review highlights the Muco-adhesive drug delivery system, its advantages and limitations, mechanisms and theories of mucoadhesion, different Muco-adhesive dosage forms, and bioadhesive polymers. It also highlights the current status on mucoadhesive drug delivery methods for the buccal cavity or Muco-adhesive systems.

Keywords: *Bioadhesion, mucoadhesion, Muco-adhesive drug delivery system, oral mucosa, first-pass metabolism, bioadhesive polymers.*

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INTRODUCTION:

Mucoadhesive drug delivery system interact along with the mucus layer covering the mucosal epithelial surface & mucin molecules & enhance the residence time of the dosage form at the site of absorption. Mucoadhesive drug delivery system remains in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action for better bioavailability and both local and systemic effects. The potential use for mucoadhesive systems as drug carriers lies in its extended the residence time at the absorption site, allowing enhance contact with the epithelial barrier. Mucoadhesive system is an approach to achieve higher bioavailability, by the use of bioadhesive polymer that can adhere to mucosal epithelial surface in the mouth. Thus, they prolong the action of the drug. The oral mucosa is highly permeable with blood vessels; hence therapeutic concentration of the drug can be achieved rapidly. Oral mucosal ulceration is a common condition with up to 50% of healthy adults suffering from recurrent minor mouth ulcers (aphthous stomatitis) [1]. Evaluation of the efficacy and tolerability of a mucoadhesive gel compared with a pain-relieving oral solution for the treatment of aphthous stomatitis. The mucoadhesive gel was found to be more effective than the oral solution.

The mucoadhesive delivery system has several advantages like prevention of first pass metabolism, better bioavailability, specific tissue targeting, rapid onset of action, elimination of enzymatic degradation, etc. Basically, it can be considered as a possible option for both systemic as well as local drug distribution. Among these, oral mucosa is perhaps the most convenient and preferred route for drug delivery. The delivery of drug over the mucosa of the mouth can be classified into three types:

1. Sublingual delivery- involves delivery of drug via the Ventra surface of the tongue and the floor of the mouth's mucosal membrane.

2. Buccal delivery- involves the delivery of drug via means of the mucosal membrane lining the cheeks i.e. buccal mucosa.

3. Local delivery- involves delivery of drug inside the oral cavity. The buccal mucosa present in the mouth cavity is highly vascularized with an abundant blood supply and is relatively permeable. Moreover, it bypasses first pass metabolism and prevents pre-systemic GI tract degradation [2].

Advantages of mucoadhesive drug delivery system:

- The buccal drug delivery provides a relatively rapid onset of action as compare to the other non-oral routes, hence, has a high patient acceptability.
- Improved patient compliance due to the easy application of dosage forms in comparison to the injections and don't provide any painful sensation
- The mucosal membranes are highly vascularized so that the administration as well as removal of a dosage form is easy.
- The sustained drug delivery can be achieved by using the mucoadhesive polymers of 'SR' grades.
- Due to the high extent of perfusion the rate of drug absorption is faster.
- The side effect that can arise due to oral administration, such as, nausea and vomiting, they can be avoided completely.
- The mucoadhesive drug delivery can be easily used in case of unconscious and less Co-operative patients.
- The drugs, which show poor bioavailability via the oral route, can their bioavailability can be enhanced by formulating their mucoadhesive delivery systems [3].

Disadvantages of mucoadhesive drug delivery system:

- The dissolution of drug due to continuous secretion of saliva (0.5-2 l/day)
- Prolonged contact of the drug possessing ulcerogenic property.
- For the in vitro screening of drugs the oral mucosal delivery is lack of good model. This is the major drawback of this drug delivery.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.
- Also has smaller surface area.
- costly drug delivery system [4]

Need for mucoadhesive drug delivery system

The sublingual process has been a research subject for the past several years, but concern over buccal drug delivery is much more recent that happens to be concurrent with the biotechnological advances. It made peptides to be available for curative uses without delay. Degradation and low absorption hinder the administration of hydrophilic high molecular weight drugs such as peptides (e.g., insulin, cyclosporine A, etc.) through the oral process. Here, buccal process turns out to be effective. Drugs having short half-lives (e.g., midazolam) necessitate repeated injections which, in turn, result in poor patient compliance. This parenteral administration is then most favored for such drugs and it also involves high production and control costs. In humans, the permeation of drugs through the buccal epithelium is said to associate both the transcellular and paracellular routes. The large surface area represented by buccal mucosa (23% of the total

surface of the oral mucosa including the tongue) makes it more fit for systemic drug delivery [5].

Drug selection:
The physicochemical properties of the drugs play a critical role in the drug selection for oral transmucosal delivery. Drugs must have unique physicochemical properties that are a proper balance between solubility and lipophilicity to deliver them transmucosally. Even though the drug has a favorable condition for oral mucosal delivery, only a few milligrams of drug can permeate it. No new classes of drugs are scientifically developed recently for oral transmucosal delivery because of the economic impulse flourishing the development of new drug formulations. For an effective transmucosal delivery to take place, in addition to the necessary physicochemical properties of the drug, there must also be a significant clinical advantage. Hence, drugs used for oral transmucosal delivery are limited to the existing products (e.g., nitroglycerine, prochlorperazine, metronidazole, etc.). The present review intends to illustrate the potential of buccal route in drug delivery, discussing the recent ways in which the technologies could improve the future treatment of mucosal and systemic disease by making use of the full advantages of the properties of the oral mucosa that makes it an ideal drug delivery site [6].

FORMULATIONS:
History of buccal drug delivery development Back in 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth, dental adhesive powders for the use of mucoadhesive polymers were used for the development of pharmaceutical formulations. Improved results were reported when carboxy methyl cellulose (CMC) and petrolatum were used for the development of formulation. Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium CMC (SCMC), pectin, and gelatin. The formulation was later marketed as OrahesiveR. Another formulation which entered into the clinical trials is OrabaseR which is a blend of polymethylene/mineral oil base. This was followed by the development of a system where polyethylene sheet was laminated with a blend of SCMC and polyisobutylene which provided an added advantage of protecting the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment [7].

General Concepts of Mucoadhesion:
Mucus is a viscous and heterogeneous biological product that covers many epithelial surfaces. Cells secreting mucus are located at various locations in the body like Gastrointestinal, Ocular, Nasal, Buccal, Reproductive and Respiratory tracts. Mucus functions as a lubricant to reduce shear stress and acting as barrier against harmful substances. Goblets cell containing Mucus are located in the epithelium. Mucus is located in large granules in the goblet cells. Mucus granules are located in the apical side of the goblet cell giving a balloon shaped appearance of these cells. It is released by the process of Exocytosis or Exfoliation of the Whole cell[8].

Transport mechanism:
Drug transport mechanism through the Buccal drug delivery is carried out by two mechanisms i.e. transcellular (intracellular) and paracellular (intercellular). Paracellular route of permeation of the drug across the buccal epithelium is carried out through the passive hydrophilic drugs i.e. protein or peptide which undergoes rapid dissolution in the aqueous fluid present in the intercellular spaces. For example caffeine is the drug which undergoes absorption via paracellular route and more often used as a marker for the paracellular absorption . Whereas in case of trancellular pathway drug is penetrated through the cells i.e. by transferring the drug through the lipodial barrier i.e. cell membrane followed by the hydrophilic content of the series lipophilic balance with a slight predominance of hydrophilic property [9].

Types of Interaction Physical or Mechanical bonds:
Physical bonds involve the entanglement of mucin glycoprotiens with the polymer chains, and the interpenetration of the mucin chains in the polymer matrix. Factors affecting these are Chain flexibility and Diffusion Coefficients[10].
Chemical Interaction: Chemical interactions include Van der Waals Dispersive Interactions or Hydrogen Bonds. Van der waals Forces are further classified into Debye Forces due to permanent dipole-induced interactions, Keesom forces due to permanent dipole-permanent dipole interactions and London forces due to induced dipole-induced dipole interactions. Hydrogen bond also plays a key role in adhesion. Groups which form Hydrogen bonds are Hydroxyl, Carboxyl, Sulfate, amino groups, and others. Covalent bonds are formed by the chemical reaction of the polymer and the substrate. This type of bond leads to permanent adhesion. Therefore, only mucus turnover

and the epithelial desquamation would result in the separation and loss of the polymer from the tissue [11].

Steps in Mucoadhesion:
In spite of the extensive research in this field, the mechanisms of mucoadhesion are not completely clear. However, it is agreed upon that mucoadhesion takes place in two steps.

The Contact Stage:
In this step the intimate contact occurs between the mucoadhesive and mucous membrane. Initially mucoadhesive and the mucous membrane come together to form an intimate contact. The gastrointestinal tract is an inaccessible mucosal surface, which means that the adhesive material cannot be placed directly onto the target mucosal surface, or delivered to the surface by organ design. Adhesion and possible blockage of the gastrointestinal tract can prove to be detrimental. For larger particles, peristalsis and other gastrointestinal movement may help to force the dosage form into contact with the mucosa. However, evidence of successful adhesion of larger dosage forms has yet been less often reported in the literature, other than the potentially dangerous case of oesophageal adhesion. For smaller particles in suspension, adsorption onto the gastrointestinal mucosa would be an essential prerequisite for the adhesion process. The physicochemical processes taking place here can be described by DLVO Theory [12].

The consolidation stages:
In this step, various physicochemical interactions occur to consolidate and strengthen the adhesive joint, resulting in a prolonged adhesion. It is proposed that in order to achieve strong or prolonged adhesion, a second 'consolidation' stage is required. For achieving strong adhesion, a change in the physical properties of the mucus layer will be required otherwise it will fail to hold on to the bioadhesive polymer on application of dislodging stress. There are two theories explaining this process. First theory based on the intermolecular interaction proposes that the mucoadhesive molecules interpenetrate and bond by secondary interactions with mucus glycoprotein. The second theory is the dehydration theory, which proposes that when a material capable of rapid gelation in an aqueous environment is brought into contact with a second gel water movement occurs between gels until equilibrium is reached. The latter theory explains why mucoadhesion occurs in a matter of seconds, while the former requires the polymers to interpenetrate several micrometer distances within a short time. The rheological studies suggest that interpenetration of mucus and mucoadhesive polymer leads to formation of a surface gel layer, which will substantially inhibit any further interpenetration [13].

Mucoadhesion Theories of Polymer attachment:
Numerous theories have been present to explain this complex process of Mucoadhesion. These numerous theories should be considered as complementary processes during the entire mucoadhesion process. Therefore, they should be considered together while explaining mucoadhesion

Wettability Theory:
This theory holds good for liquid or low viscosity mucoadhesive systems. It essentially measures the "spreadability" of the Bioadhesive polymer on the mucus. It proposes that the adhesive component penetrates the surface irregularities, hardens, and anchors itself to the surface. Essential characteristics for the Bioadhesive materials include zero or nearly zero contact angle, relatively low viscosity and an intimate contact that excludes air entrapment. Therefore, the interfacial energies are responsible for the contact of the two surfaces and for the adhesive strength. It can be concluded from the above equation that the mucoadhesive polymer systems that exhibit similarity in structure and functional groups with the mucin layer will show increased miscibility resulting in a greater spread across the mucosal surface. Lower water content in the polymer will facilitate the hydration of the polymer leading to more intimate contact, while hydrophilic polymer containing a lot of water will have a lower contact angle and will therefore discourage intimate contact [14]

The Electronic Theory:
Electronic Theory describes adhesion as a phenomenon in which there occurs electron transfer between the mucus and the mucoadhesive system as a result of the differences in their electronic structures. This electron transfer leads to a formation of double layer of electric charges at the mucus and the mucoadhesive interface. The result of this is the formation of attractive forces within this double layer. There is a controversy over the acceptance of this theory due to the fact that it explains the electrostatic forces, which are much weaker as the causes of bond adhesion [15].

The Fracture Theory: This theory states that the adhesive bond between the systems is force required to segregate both the surfaces from each other. In this case the force of separation of the polymer from the mucus is related to the strength of the bioadhesive bond. It is found that the work fracture is greater when

the polymer network strands are longer or the case in which the degree of cross-linking within the system is reduced[16].

The adsorption Theory: According to this theory adhesion is an outcome of different surface interactions (primary and secondary bonding) between the bioadhesive polymer and mucus substrate. Primary bonds, also stronger, such as ionic, covalent and metallic bonding leads to adhesion and is called chemisorptions. These forces are somewhat undesirable due to their permanency. Apart from these, there are secondary forces, also weaker, which constitute the van der waals forces, hydrophobic interactions and hydrogen bonding. These interactions are weak in nature requiring less energy to break. But as the mucoadhesion requires being a transient event, it is desirable to have these forces [17].

The Diffusion-interlocking theory:
This theory postulates that mucoadhesive polymer chains diffuse into the glycoprotein chain network of the mucus layer in a time-dependent manner. In the process of interpenetration, the molecules of the polymer and the glycoprotein network of the mucus come into intimate contact with each other. This leads to an establishment of a concentration gradient leading to the inter-diffusion of the both polymer inside each other. The penetration rates of this two-way diffusion process are dependent upon the diffusion coefficient of both the interacting polymers. Apart from this the miscibility also plays a crucial role. Therefore, it can be postulated that solubility parameter of polymer and glycoprotein network plays a key role in predicting the interpenetration. It is found, using the AFT-FTIR that the time at which maximum interpenetration [18].

Buccal Mucoadhesive Dosage Forms:
An ideal drug delivery system should possess the two main properties that are given below: a) Spatial placement (for targeting drug to specific organs/tissues) b) Temporal delivery (for controlling the rate of drug delivery) Today, it very difficult to formulate an ideal drug delivery. This led to development of sustained/controlled release delivery systems. Still, sustained or controlled delivery system lacks in preventing drug loss by either hepatic first pass metabolism or pre-systemic elimination like gastric, intestinal, or colonic degradation. So, several approaches have been tried to form a suitable dosage form for the above said conditions. Oral mucosal drug delivery, one of the physiological approaches, was reported to be a method to formulate these drugs into suitable dosage form with good therapeutics effect. Oral mucosal drug delivery of different drugs can be achieved by bioadhesive polymer systems [19].

General considerations in designing dosage forms:
Physiological aspects:
Due to the constant flow of saliva and regular movement of tissues present in the oral cavity the local delivery of the drugs in oral cavity is the most challenging aspect. Due to this, the residence time of the drugs for this route is very short. The buccal mucoadhesive formulations are being used to overcome this problem. The bioadhesive polymers are been use for improving the residence time in the buccal mucosa, and hence increase the absorption of drugs delivered by this route. Due to the local absorption of drugs, side effects are also being reduced as compared to in case of systemic delivery [20]

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

Pharmaceutical aspects:
The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstlythe water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increased in buccal mucosa .There are many other factors that affect the release and penetration of drug, must be optimized during formulation design [21].
On the basis of their geometry, the buccal mucoadhesive dosage forms can be categorized into three types as given below.
Type I: In this there is a single layer containing dosage form which provides multidirectional drug release. The main disadvantage of this type is that the drug loss is high by swallowing.
Type II: It contains the drug loaded bioadhesive layer covered by impermeable backing membrane. The backing membrane covers only the opposite side from the site of attachment hence preventing the drug loss from the upper surface of device [22].
Type III: In this type, all sides of drug loaded mucoadhesive layer are covered by impermeable except the side that attaches the target area. It is a unidirectional drug flow preventing all kinds of unwanted drug loss.shows various types of buccal dosage form

Physiological Factors Mucin turnover, renewal rate of mucosal cells, and disease state of mucus layer are physiological variables that may affect mucoadhesion [23].

MUCOADHESIVE POLYMERS:

Mucoadhesive drug delivery systems are based on the adhesion of a drug/ carrier to the mucous membrane. To promote this adherence a suitable carrier is required.

Ideal Characteristics of Mucoadhesive Polymers: A mucoadhesion promotoing agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva [24].

- Polymer must have a high molecular weight up to 100.00 or more. This is necessary to promote the adhesiveness between the polymer and mucus.
- Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.
- High viscosity.
- Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross linked polymers swell in presence of water and retain their structure. Swelling favours controlled release of the drug and increases the polymer/mucus interpenetration
- Spatial conformation.
- Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
- Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form.
- Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. Cationic chitosan HCl showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadhesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be attributed as anion>cation>non-ionic.
- Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.
- Optimum pH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.
- It should non toxic, economic, biocompatible preferably biodegradable.

CLASSIFICATION OF POLYMERS BASED ON GENERATION:

First Generation Of Mucoadhesive Polymers These are either natural or synthetic hydrophilic substances which have organic functional groups (carboxyl, hydroxyl, and amino groups) or hydrogen bonds. Some known mucoadhesive polymers are carbomers, cellulose derivatives, chitosan and, alginates.

They come into three types:

(a) Cationic polymers such as chitosan that have electrostatic interactions with mucin.

(b) Anionic polymers are mainly derived from poly acrylic acids, which have a negative charge.

(c) Non-ionic polymers that have weaker mucoadhesion force than anionic polymers. Among these polymers are hydroxyl propyl-methyl cellulose, hydroxyethyl cellulose and methyl cellulose [25].

Carbopol Carbopol, a lightly cross-linked polyacrylic acid (PAA), is an industry standard for mucoadhesive polymer. These days, many companies use carbopol polymers, because of some advantages such as releasing in a long period of time, being safe and effective for oral administration, increasing bioavailability, and protecting protein and peptides from degradation The role of carbopol in protecting peptides and protein is to change the velocity of degradation reaction [26].

Chitosan Chitosan is a cationic polymer (polysaccharide) that is gaining importance in developing mucoadhesive drug delivery systems, because of its good biocompatibility, biodegradability, and nontoxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Onishi and Machida showed that chitosan and its metabolized derivatives are quickly eliminated by the kidney. In the study of Ayensu et al., lyophilized chitosan wafers were prepared that contained chitosan, bovine serum albumin (as a model protein), glycerol (as plasticizer), and d-mannitol (as cryoprotectant).

Pectin Pectin is a natural polysaccharide consisting of mainly D-galacturonic acid and glycosidic units.

Pectin can be used for controlled drug delivery because of its excellent biocompatibility and unique properties. For instance, pectin can easily adhere to mucosal surfaces which improve the retention time of AMPs. Krivorotova et al. indicated the antimicrobial activity of nisin-loaded nanoparticles in vitro against two Gram-negative bacteria (E. coli and Klebsiella spp.) and two Gram-positive (Arthrobacter sp.and Bacillus subtilis), using the agar-diffusion assay[27].

Second Generation Of Mucoadhesive Polymers:
Compared to the previous one, the advantage of this generation is that they can interact with cell surfaces through specific receptors or covalent bonding, which leads to improved chemical interactions. Among this group are lectins and thiomers.

Lectins Lectins are glycoproteins or proteins of nonimmunological origin which specifically recognize sugar molecules, and therefore can bind to glycosylated membrane components. Sugars are present in glycolipids and glycoproteins of mammalian mucosa, at the surface of epithelial cells, or in mucous layers[28].

Thiolated Polymers The thiolated polymers are derivatives of hydrophilic polymers like polyacrylates, chitosan, or deacetylatedgallan gum. The presence of these polymers increases the residence time via the covalent bonds with the residuals of cysteine in mucus and also increases rigidity and cross-linking. Thiolated polymers also show an increased permeation-enhancing effect and enzyme inhibitory properties. In the studies of Langoth et al., matrix-based tablets were made that contained novel pentapeptideleu-enkephalin (pain modulating) and thiolated polymer PCP (Polycarbophil).

Manufacturing methods of the buccal tablets:
Manufacturing methods of the buccal patches/films:
Solvent casting
This method is widely used for the manufacturing of the controlled release matrix and liquid reservoir type buccal film, oral disintegrating films, pellets and granules

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

Bioadhesive microsphere: Microsphere is an important part in case of novel drug delivery system. This mucoadhesive microsphere is mainly used for purpose of targeting to specific body cavity[29].
Bioadhesive wafers: It is a newer dosage form for bioadhesive buccal delivery. It is used at the periodontal region for the treatment of infections related with periodontitis .
Bioadhesive lozenges: Bioadhesive lozenges are generally used for delivery of drugs that are antimicrobials, corticosteroids, local anesthetics, antibiotics and anti-fungals and are used topically in the buccal cavity[30].

Semisolid dosage form
Bioadhesive patch/film :Patches or film are preferred over tablet because of their comfort and flexibility. They are formulated such that it can provide contact between bioadhesive formulation and mucosa. Thickness of patch is a constraint which cannot provide control release of drug for longer period of time. In case of drug containing reservoir layer type; drug is released in controlled manner. Patches and film are mostly preferred for local action to treat oral diseases. There are many methods used for formulation of patch or films such as solvent casting method, hot melt extrusion technique, direct milling, semisolid casting, solid dispersion extrusion etc. Among that solvent casting is most popular method and widely used
Buccal gel and ointment: As the advantage of dispersion gel and ointment has come in focus. They do not have accurate dosing as unit dosage form like tablet, patches or films hence they are mostly preferred for local action where dose accuracy is less or not concern.
Medicated chewing gum: Medicated chewing gum contains drug which after chewed, offer high amount of drug to prove local action in mouth. It can also shows absorption through systemic circulation.The medicated chewing gum for nicotine replacement therapy is available. Likewise caffeine chewing gums are also available[31].
Liquid dosage form: These are available in form of solution or suspension of drug in suitable vehicle. There are many liquid dosage forms that are available in market such as mouthwashes, mouth freshener, and are generally used for local delivery of drugs. Wide varieties of polymers are use from that chitosan has greatest binding capacity than other. Viscous liquid formulations are preferred to coat buccal cavity either as vehicle or as protectant[32].
Therapeutic Approach

This delivery system shows controlled drug release, bioavailability enhancement, easy administration, dosage reduction, and usage frequency.

Anti-emetics

Ondansetron hydrochloride is a serotonin 5HT3 antagonist used to prevent nausea and vomiting as a side effect of emetic cancer chemotherapy. To prevent first-pass metabolism by the liver and increase the bioavailability of the drug, the drug should be administered orally.Ali and associates. Buccal adhesive Tablets include ondansetron, CP 934, sodium alginate (ALG), low viscosity SCMC, HPMC 15cps and ethyl cellulose[33].

Antimigraine

Sumatriptan succinate (a 5-HT1 receptor agonist) treats migraine headaches. Shidaye et al. pre-prepared double-layer mucosal patch, consisting of sumatriptan succinate, chitosan and PVP K30. The results show that increased chitosan concentration leads to enhanced mucosal adhesion of the patch. However, the increase in PVP K30 and decreased chitosan concentration leads to better release drugs. On the other hand, improve both chitosan and PVP K30, increasing the degree of plaque swelling[34].

Anti-histamine

Chlorpheniramine maleate (CPM) is a histamine H1 receptor antagonist commonly used to treat allergic conditions. In the study by Sekhar et al., external mucosal patches containing CPM and hydroxyethyl cellulose (HEC) were prepared. 1.46 times higher than the oral dosage form, indicating that the dosage form is non-irritating, not cause mucosal damage or irritation by application.

Antimicrobials

Using conventional pharmaceutical dosage forms such as suspensions, solutions, and Mouthwash is ineffective for oral cavity diseases. This may be due to the ease of removal of these forms of the drug; therefore, several attempts have been made to clinical treatment of oral cavity complications

Cardio Vascular Medicines

Carvedilol is a non-selective beta-adrenergic antagonist used to treat hypertension and stable angina. To treat hypertension, Yamsani Corporation has manufactured carvedilol mucin tablets, consisting of carbopol 934 and hydroxypropyl methylcellulose (HPMC K4M and K15M), to achieve controlled, out-of-order Release. The results showed that increasing the polymer concentration in the formulations resulted in sustained Release of carvedilol.

Hypoglycemic Agents

In a study by Semalty et al., Mucoadhesive buccal films containing glipizide, HPMC, CP-934, SCMC and Eudragit RL-100 were formulated. The results indicated that therapeutic levels of glipizide may be adequate via buccal delivery. Mujib and others. Different HPMC grades were used to prepare mucoadhesive buccal films of glibenclamide. The results showed that the matrix integrity depended on the drug's amount and properties[35].

Smoking deterrents

The nature of the smoking habit is partly due to the presence of the psychostimulant consumed. The route of nicotine use (NCT) is through the skin and mucous membranes such as the nose and mouth. It's neutral, and protonated NCT can easily permeate through mucous membranes[36].

Anti-inflammatory drugs

Inflammation is one of the leading causes of diseases of the oral cavity. To manage this problem, topical anti-inflammatory drugs such as flurbiprofen, flufenamic acid, ibuprofen, etc., are used. In these treatments, drug dosage is reduced, and systemic side effects are minimized. In the study of Anahita Ghorbani et al., Mucus tablets have been prepared.

CONCLUSION:

Buccal regions provide a convenient route for both local and systemic delivery of drugs. Muco-adhesive systems offers several advantages over other delivery systems such as easy administration and withdrawal of delivery system, higher patient compliance, prevention of first-pass metabolism, cost effectiveness and so on. It allows for close contact between the dosage form and the buccal cavity. and ensures longer residence time which offers prolonged drug release. Many new developments and works are still going on all around the world on mucoadhesive buccal drug delivery system. The future direction of Muco-adhesive drug delivery system lies in vaccine formulation and delivery of small proteins and peptides.

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Discloure of conflict of interest

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REFERENCES:

1. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, Lockhart PB, Patton LL, Porter S, Thornhill MH. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Adv Drug Deliv Rev. 2012;64(1):16-28. doi: 10.1016/j.addr.2011.02.008, PMID 21371513.

2. Hoogstraate JAJ, Wertz PW, Wertz PW. Drug delivery via the buccal mucosa. Pharm Sci Technol Today. 1998;1(7):309-16. doi: 10.1016/S1461-5347(98)00076-5.
3. Mathias NR, Hussain MA. Non-invasive systemic drug delivery: develop ability considerations for alternate routes of administration. J Pharm Sci. 2010;99(1):1-20. doi: 10.1002/jps.21793, PMID 19499570.
4. Shojaei AH. Buccal Mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30. PMID 10942969.
5. Lis Fontinele de Sa L, Nogueira NC, Da Silva Filho EC, Figueiras A, Veiga F, Nunes LCC, Lamartine Soares-Sobrinho J. Design of buccal mucoadhesive tablets: understanding and development. J Appl Pharm Sci. 2018;8:150-63.
6. Venkataswamy R, Lavanya Nallaguntla. Review article on pulsatile drug delivery system. Asian J Pharm Clin Res. 2021;14:48-59.
7. Carvalho FC, Bruschi ML, Evangelista RC, Gremião MPD. Mucoadhesive drug delivery systems. Braz J Pharm Sci. 2010;46(1):1-17. doi: 10.1590/S1984-82502010000100002.
8. Puri V, Sharma A, Maman P, Rathore N,singh I, Overview of mucoadhesive biopolymers for buccal drug delivery systems.Int J App Pharm .2019; 11:18-29.
9. Datir M. Recent advances in mucoadhesive buccal drug delivery system and its marketed scope and opportunities. IntJAdv PharmSci, 2018; 1: 86-104.
10. Laffleur F. Mucoadhesive therapeutic compositions: a patent review (2011-2014). Expert opinion on therapeutic patents. 2016; 26(3):377-88. DOI:10.1517/13543776.2016.1145209.
11. Xu W, Ling P, Zhang T. Polymeric micelles, a promising drug delivery system to enhance the bioavailability of poorly water-soluble drugs ,Journal of drug delivery. 2013;2013 DOI:10.1155/2013/340315.
12. Mantaj J, Vllasaliu D. Recent advances in the oral delivery of biologics, Pharmaceutical Journal. 2020. DOI: 10.1211/PJ.2020.20207374
13. Golshani S, Faramarzi MA. Expected Impact of Biosimilar on the Pharmaceutical Companies, Iranian Journal of Medical Sciences, 2021;46(5):399. DOI: 10.30476/ijms.2021.92314.2356
14. N.k.Jain. Advances in controlled and Novel drug delivery published by CBS publisher and distributors pvt .Ltd, first edition-2001, 249-282
15. Garly DM, Ismail S, Ibrahim HK, Ghorab MM. Mucoadhesive gel of carvedilol nanoparticles for enhanced dissolution and bioavailability .journal of drug delivery science and technology .2018;47;151-8.DOI:10.1016/j.jddst.2018.07.009
16. Mamatha K, Venkatesh P. A revieyw on mucoadhesive drug delivery systems,Journal of Innovations in Applied Pharmaceutical Science (JIAPS). 2022:32-6.
17. Adikwu MU. A review on Mucins and their potentials, Trop J Pharm Res. 2006; 5:581-2.
18. Roy S.K, Prabhakar B. Bioadhesive polymeric platforms for transmucosal drug delivery systems-a review. Tropical Journal of Pharmaceutical Research, 2010; 9(1):91-104. https://doi.org/10.4314/tjpr.v9i1.52043
19. Mortazavi S.M, Sayed A.M. Propranolol Hydrocholoride Mucoadhesive tablet: Development and In-vitro Evaluation, Iranian Journal of Pharmaceutical Research, 2020; 19(2):22-33.
20. Praveen G. Development and in-vitro evaluation of Mucoadhesive tablets of losartan potassium. The Pharma Innovation, 2012; 1(5):63-70.
21. Patel A.R, Patel D.A, Chaudhry S.V. Mucoadhesive buccal drug delivery system. International Journal of Pharmacy and Life Sciences, 2011; 2(6):848-856.
22. Qidra R.K. In-depth recent advances in buccal mucoadhesive drug delivery system. European Journal of Pharmaceutical and Medical Research, 2018; 5(3):81-103.
23. Puratchikody A, Prasanth V.V, Mathew S.T, Kumar A. Buccal drug delivery: past, present and future- a review. International Journal of Drug Delivery, 2011; 3:171-184.
24. Park, Kinam, and Joseph R. Robinson. "Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion." International journal of pharmaceutics 19.2 (1984): 107-27. Print.
25. Patel, Niketkumar, et al., "Influence of Electronic and Formulation Variables on Transdermal Iontophoresis of Tacrine Hydrochloride." Pharmaceutical development and technology 20.4 (2015): 442-57. Print.
26. Patel, Niketkumar, et al., "Application of Design of Experiments for Formulation Development and Mechanistic Evaluation of Iontophoretic Tacrine Hydrochloride Delivery." Drug development and industrial pharmacy 42.11 (2016): 1894-902. Print.
27. Ponchel, Gilles, and Juan-Manuel Irache. "Specific and Non-Specific Bioadhesive Particulate Systems for Oral Delivery to the

Gastrointestinal Tract." Advanced Drug Delivery Reviews 34.2 (1998): 191-219. Print.
28. Rieger, Christiane, et al., "Characterization of Different Carbon Nanotubes for the Development of a Mucoadhesive Drug Delivery System for Intravesical Treatment of Bladder Cancer." International journal of pharmaceutics 479.2 (2015): 357-63. Print.
29. Serra, Laura, Josep Doménech, and Nicholas A. Peppas. "Engineering Design and Molecular Dynamics of Mucoadhesive Drug Delivery Systems as Targeting Agents." European journal of pharmaceutics and biopharmaceutics 71.3 (2009): 519-28. Print.
30. Ramana MV, Nagdaand C, Himaja M (2007) Design and Evaluation of Mucoadhesive Buccal Drug Delivery Systems containing Metoprolol Tartrate. Ind J of P'ceutical Sci 69: 515-518.
31. Kolli CS, Gannu R, Yamsani VV, Kishan V, Yamsani MR (2008) Development of Mucoadhesive Patches for Buccal Adminstration of Prochlorperazine: Evaluation of in–vitro Release and Mechanical Properties. Int J of P'eutical Sci and Nanotech 1: 64-70.
32. Dr.Yajaman Sudhakar ,Dr.K.N.Jayaveera , Introduction to Novel Drug Delivery System S.D.Chand publication, page no. 20-21.
33. Velmurugan S, Deepika B, Nagaraju K, Vinushitha S (2010) Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam. Int J of Pharm Tech Res 2: 1958-1968.
34. Naga Raju K, Velmurugan S, Deepika B, Vinushitha S (2011) Formulation and in-vitro Evaluation of Buccal Tablets of Metoprolol Tartrate. Int J of Pharm and P'ceutical Sci 3: 239–246.
35. Deshmukh GJ, Varma MM, Manjunath YS (2011) Development and evaluation of Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive Agent obtained from the Fruits of Ficus carica L. Indo American Journal of Pharmaceutical Research 1: 69-79.
36. Mishra S, Kumar G, Kothiyal P (2012) Formulation and Evaluation of Buccal Patches of Simvastatin by Using polymers. The Pharma Innovation 1: 87-92.