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Available online at: http://www.iajps.com ***Review Article***

REVIEW OF MUCOADHESIVE BUCCAL TABLET OF ALOGLIPTIN

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Abstract:

In the present project of Alogliptin mucoadhesive buccal tablets were prepared and evaluated. As Alogliptin undergoes extensive first pass metabolism its bioavailability when given through Conventional route is 30% and (80x4) doses. So, in order to improve its bioavailability, to decrease the dosing frequency and to bypass the first pass metabolism the study has been planned to prepare Alogliptin buccal tablets The gift sample of Alogliptin was analyzed by various organoleptic and spectrophotometric methods. The sample of Alogliptin possesses similar color, odor, and taste and texture s given in officials. The melting point of procured sample was analyzed by capillary fusion method and found 180oC. The qualitative solubility of Alogliptin was determined by various solvent systems.

Keywords: Mucoadhesive, Alogliptin, Buccal delivery system.

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1. INTRODUCTION:

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bio adhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bio adhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used.

Mucoadhesive drug delivery systems can be delivered by various routes:

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

1.1 Mucoadhesive Oral Drug Delivery Systems

Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oral cavity can be subdivided as:

- **Sublingual delivery:** This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- **Buccal delivery:** This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa).
- **Local delivery:** This is drug delivery into the oral cavity. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic drug delivery.

Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery. This is because the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems. Thus, the buccal mucosa is more appropriate for sustained direction of drug delivery

1.1.1 Advantages of Oral Mucoadhesive Drug Delivery Systems:

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance.

1.1.2 Disadvantages of Mucoadhesive Drug Delivery Systems:

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcer genic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste and irritancy.
- Eating and Drinking is prohibited.

1.2 Theories of Bioadhesion and Mucoadhesion

Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed "bioadhesion"; furthermore, if this adhesion occurs on mucosal membranes, it is termed "mucoadhesion". Bioadhesion is defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. Bioadhesion and Mucoadhesion have been widely promoted as a way of achieving targeted drug delivery to an active site of choice through the incorporation of bioadhesive hydrophilic polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API). The rationale being that the formulation will be 'held' on or at the biological surface and the API will be released close to the absorptive membrane, with a consequent enhancement of bioavailability

Many theories have been proposed to describe mucoadhesion, namely adsorption theory, wetting theory, diffusion theory, electronic theory, and fracture theory In the "adsorption theory", primary and secondary chemical bonds of the covalent and non-covalent types are formed upon initial contact between the mucous and the mucoadhesive polymer[3]. The "wetting theory" is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the spreadability of the drug delivery system across the biological substrate. The basis of the "diffusion theory" is chain entanglement between glycoproteins of the mucous and the mucoadhesive polymer to create a semi-permanent adhesive bond. The "electronic theory" describes that adhesion occurs by means of electron transfer between the mucous and the mucoadhesive system arising through differences in their electronic structures. The "fracture theory" is perhaps the most widely used theory in studies on the mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established

1.3 Anatomy of the buccal mucosa- considerations for development of mucoadhe-sive buccal drug delivery systems (MBDDS)

The primary role of the buccal mucosa, like the skin, is to protect underlying structures from foreign agents. The surface of the buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by an undulating basement membrane This stratified squamous epithelium consists of differentiating layers of cells (keratinocytes) which change in size, shape, and content as they travel from the basal region to the superficial region, where the cells are shed. Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. The epithelium, as a protective layer for the tissues beneath, is divided into (a) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks, and (b) keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity. The epithelial cells, originating from the basal cells, mature, change their shape, and increase in size while moving towards the surface.

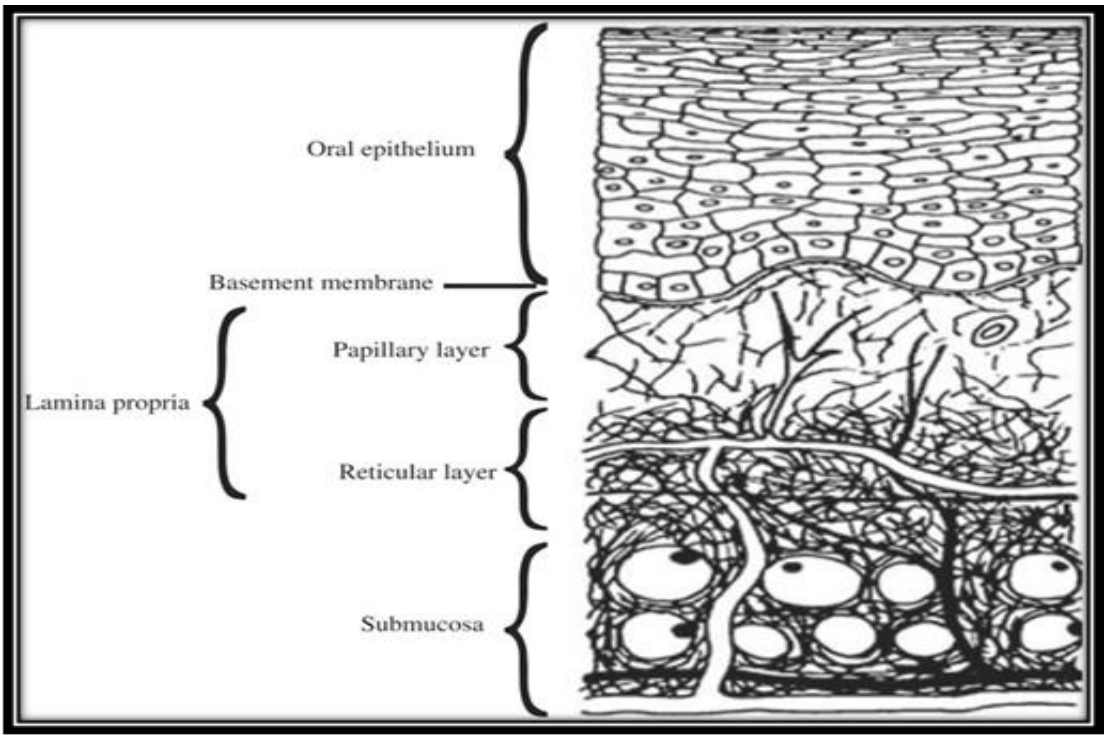

Fig. No 1: A cross section of the oral Mucosa.

The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues, and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa

1.3.1 Mucus

The tissue layer responsible for formation of the adhesive interface is mucous. Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans.The thickness of the mucous blanket is determined by the balance between the rate of secretion and the rate of degradation and shedding, and is site dependent. This matrix may actually play a role in cell-cell adhesion, also acting as a lubricant allowing cells to move relative to one another. Similarly, mucus generally plays a critical role in the bioadhesion of mucoadhesive drug delivery systems. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands. At physiological pH, mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins contain approximately 95% water, 0.5-5% glycoproteins and lipids, 1% mineral salts and up to 1% free proteins. Mucous glycoproteins are high molecular proteins possessing attached oligosaccharide units. The mucous layer, which covers the epithelial surface, has various roles.

The oral mucosa is robust and shows short recovery times after stress or damage. Drug absorption is facilitated by the continuous washing action of saliva (0.5-2 liters per day) over the mucosal surface. This route also allows for accessibility and easy removal of the system in case of an adverse drug reaction. Furthermore, the drug is not subjected to the destructive acidic environment of the stomach; therapeutic serum concentrations of some drugs can be achieved more rapidly. In addition, the drug enters the general circulation without first pass metabolism in the liver. The rich blood supply (20.3 mL/min/100 g tissue) of the oral mucosa offers high permeability to various therapeutic agents (e.g. nitroglycerine). The other functional properties of the buccal mucosa are the relatively high surface area (50.2 cm2) and lower value for membrane thickness (thin membrane) of approximately 500-600 µm, which can, potentially, enhance the rate of drug uptake. A combination of the above factors leads to higher bioavailability. Consequently, these factors support the oromucosal cavity as a highly feasible and rational site for systemic drug delivery [16],[61].

1.4 Mucoadhesive Dosage Forms: A Prologue

Although the buccal mucosa as a novel drug delivery route is being widely explored recently, its potential as a route for drug delivery was known to mankind centuries ago. Modern day researchers are therefore exploring the various routes available for drug delivery, especially through the oral mucosa, and coming up with novel drug delivery systems.

1.4.1 Tablets

Tablets are small, flat, and oval, with a diameter of approximately 5-8 mm. Unlike conventional tablets, mucoadhesive tablets allow for drinking and speaking without major discomfort. These are placed directly onto the mucosal surface for local or systemic drug delivery. These soften, adhere to the mucosa, and are retained in position until dissolution and or release is complete. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages. For example, it offers efficient absorption and enhanced bioavailability of the drugs due to a high surface-to-volume ratio and facilitates a much more intimate contact with the mucous layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue, including those found in the stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs

In the case of tablets, like other non-wetting solid MDDS, mucoadhesion arises as a result of dehydration of an area of the mucosa. Commercially available tablets are characterized by slow dissolution and maintenance of a therapeutic concentration of the active ingredient in patient's blood for prolonged periods: from 1-2 (Buccastem®) to 8 or more hours (Striant®). Despite the demonstrated efficacy of the local application of mucoadhesive buccal tablets, for example, in the treatment of candidiasis of the oral cavity, the main restriction to their wide use arises from their size and shape, as there is the need for the drug delivery system to make close contact with the mucosal surface

1.4.2 Films/Patches

Mucoadhesive films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, in the case of local delivery for oral diseases, the films also help 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.

Buccal patches are described as laminates comprised of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a mucoadhesive surface for mucosal attachment. Patches may be used to deliver drugs directly to a mucosal membrane. These are similar to those used in transdermal drug delivery. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site

1.4.3 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. Certain mucoadhesive polymers, for example, sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from liquid to semisolid. This change enhances the viscosity, which results in sustained and controlled release of drugs. Hydrogels are also a promising dosage form for buccal drug delivery.

1.5 Structure and Function of Oral Mucosal Membrane:

The outermost layer of oral mucosa is stratified squamous epithelium and below it, there is a basement membrane called lamina propria which is followed by the submucosa. It also contains many sensory receptors including the taste receptors of the tongue. Lamina propria, consist of collagen fibres a supporting layer of connective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (oesophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Tissue have moist surface due to mucus which is a, viscous, gelatinous secretion and this mucus composed of glycoproteins, lipids, inorganic salts, and up to 95% water. Mucin (Glycoproteins) are the most important components of mucus and it is also responsible for gelatinous structure, cohesion, and antiadhesive properties. Mucin consist of three dimensional network with large number of loops. The main functions of the mucus are to protect and lubricate the supporting epithelial layer.

1.5.1 Permeability:

The permeability of the buccal mucosa is estimated to be 4-4000 times greater than the skin. In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non- keratinized, and the palatal intermediate in thickness but keratinized. The permeability barrier property of the oral mucosa is predominantly due to intracellular materials derived from the so called – "membrane coating granules" (MCGS). Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa while carrier mediated transport has been reported to have a small role. In buccal mucosa two routes of passive transport are found one involves the transport of compounds through the intercellular space between the cells (Para cellular) and other involves passage into and across the cells (transcellular). Another barrier to drug permeability across buccal epithelium is enzymatic degradation.

1.6 Role of Saliva:

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

1.7 Role of Mucus:

- Made up of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bio adhesion of mucoadhesive drug delivery systems

1.8 Buccal Drug Delivery and Mucoadhesive Property:

For the development of Buccal drug delivery systems, mucoadhesion of the device is the important criteria. For proper and good mucoadhesion, mucoadhesive polymer have been utilized in many different dosages form such as tablets, patches, tapes, films, semisolids and powders. Many studies showed that addition of various polymers to drug delivery systems such as gums, increased the duration of attachment of the

formulations to the mucous surface and also increased the efficacy.

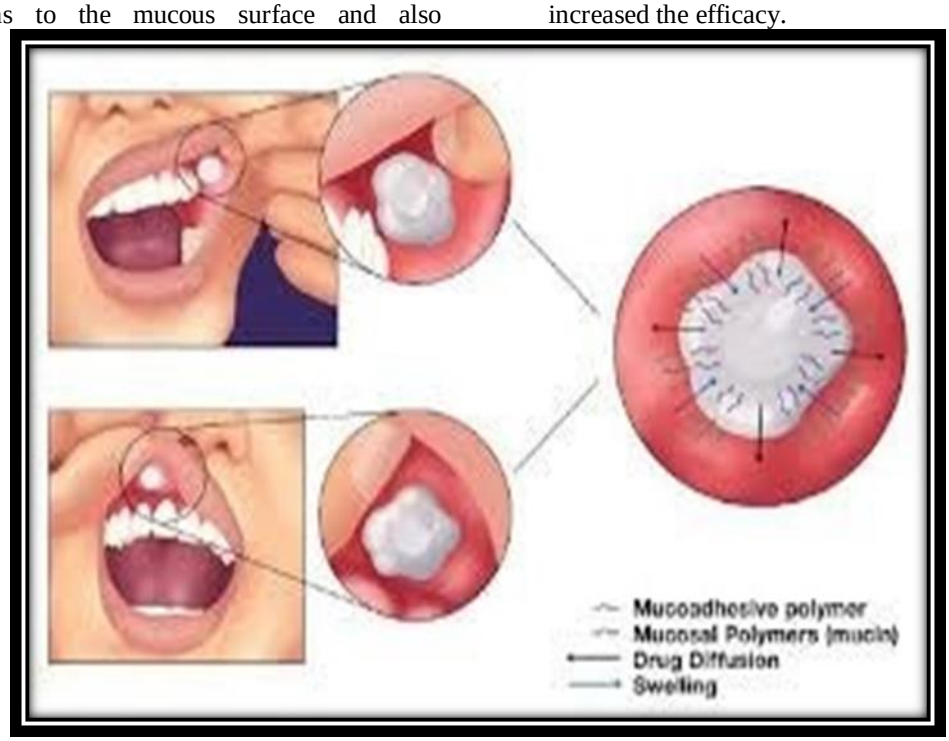

Fig. No 2. Design of buccal Mucoadhesive Tablets

The polymers should possess following general physiochemical features so as to serve as mucoadhesive polymers–

- Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spread ability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.

1.9 Theories of Mucoadhesion

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion

1.9.1 The electronic theory :

suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces**.**

1.9.2 The wetting theory:

is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid.

1.9.3 The adsorption theory:

Describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorption's theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

1.9.4 The diffusion theory:

Describes interdiffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.

1.9.5 The mechanical theory

assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide

an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect**.**

1.9.6 The fracture theory:
Differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion

1.10 Mechanisms of Mucoadhesion:
The mechanism of mucoadhesion is generally divided in two steps,

1. Contact stage
2. Consolidation stage

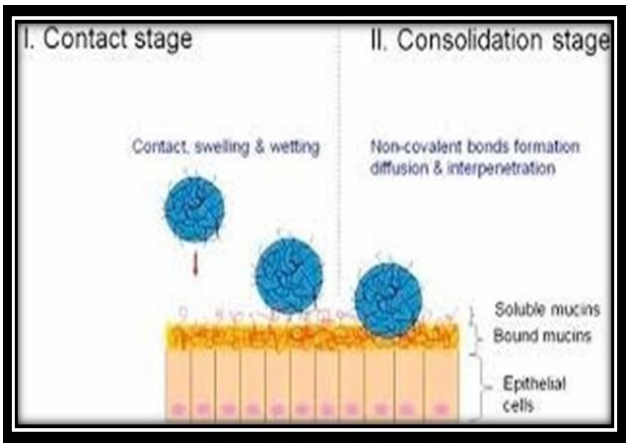

Fig.No 3: Mechanism of Mucoadhesion

The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over in other cases, the deposition is promoted by the aerodynamics of the organ to the membrane, the system is administered, such as for the nasal route. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.

Essentially, there are two theories explaining the consolidation step:

1. The diffusion theory
2. The dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions.

According to dehydration theory, materials that are able to readily gelfie in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure.

1.11 Mechanism to Increase Drug Delivery Through Buccal Route:
1.11.1 Absorption enhancer:
The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances the facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers.

The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are zone, fatty acids, bile salts and surfactants such as sodium dodecyl sulphate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextran's across a tissue culture model of the buccal epithelium while Glyceryl monolete were reported to enhance peptide absorption by a co-transport mechanism.

Mechanism: Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

1.11.2 Changing mucus rheology:
Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

1.11.3 By Overcoming Enzymatic Barrier:
These acts by inhibiting various peptidase and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier.

Inaddition, changes in membrane fluidity also alter the enzymatic activity indirectly. Increasing the thermodynamic activity of drug: Some enhancers increases the solubility of the drug and there by alters the partition coefficient. This leads to in- creased thermodynamic activity resulting better absorption
Surfactants such as anionic, cationic, non-ionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favourable properties such as biodegradability, bioavailability, and antifungal/antimicrobial properties in addition to its potential bio adhesion and absorption enhancer

Table No 1. Examples of some of permeation Enhancers:

Sr. No	Permeation Enhancers
1	Cyclodextrin
2	Lauric acid
3	Polyoxyethylene
4	Polysorbate 80
5	Sodium glycodeoxychlorate
6	Sodium lauryl sulphate
7	Sodium taurochlorate

a. General criteria for selection of drug candidate

- Buccal adhesive drug delivery systems with the size 1–3 cm2 and a daily dose of 25 mg or less are preferable13.
- The maximal duration of buccal delivery is approximately 4–8 hr14.
- Drug must undergo first pass effect or it should have local effect in oral cavity
- Drugs with biological half-life 2-8 hr will in general be good candidates for sustained release dosage forms.
- Local drug irritation caused at the site of application is to be considered while selecting the drug.
-

b. Pharmaceutical considerations: Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.

c. Muco adhesive polymers: is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, meaning parts.16
The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight, and are linked to each other during a chemical reaction called polymerization

d. Ideal Charecteristics: Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.

- Should have good spread ability, wetting, swelling and solubility and biodegradability properties.
- Polymer must be easily available and its cost should not be high.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.

Table No 2: List of buccal mucoadhesive drug delivery systems

Dosage forms	Active ingredients	Polymers	Investigators
Buccoadhesive Discs	Fluconazole	CP 974P, SCMC, sodium alginate, HPMC	Yehia et al.
Buccoadhesive Tablets	Propranolol HCl	SCMC, CP-934P	Patel et al.
Buccoadhesive Tablets	Atenolol	CP 934P and SCMC	Singh et al.
Buccoadhesive Tablets	Pravastatin Sodium	Carrageenan gum, PVP K30	Shidhaye et al.
Buccoadhesive Tablets	Lercanidipine HCl	HPMC	Charde et al.
Buccoadhesive Tablets	Nystatin	Carbomer (CB), and HPMC	Juan et al.
Buccoadhesive Tablets	Ondansetron HCl	CP 934P, sodium alginate, SCMC, HPMC	Ali et al.
Buccoadhesive Tablets	Domperidone	HPMC, CP	Bhalekar et al.
Buccoadhesive Tablets	Tizanidine HCl	HPMC K4M, SCMC	Shanker et al.
Buccoadhesive Films	Propranolol HCl	Polycarbophil (PC), sodium alginate, gellan gum	Carmen et al.
Buccoadhesive Films	Fluconazole	HPMC, HEC, chitosan, Eudragit and sodium alginate	Yehia et al.
Buccoadhesive Films	Ondansetron HCl	PVA, PVP, CP 934P	Koland et al.
Buccoadhesive Films	Glipizide	HPMC, SCMC, CP-934P and Eudragit RL-100	Semalty et al.
Buccoadhesive Films	Insulin	Ethylcellulose, chitosan	Cui et al.
Buccoadhesive Films	Myoglobin	Chitosan	Colonna et al.
Buccoadhesive Films	Progesterone	Chitosan	Jain et al.
Buccoadhesive Films	Nicotine	Sodium alginate-magnesium aluminium silicate	Pongjanyakul et al.
Buccoadhesive Films	Lidocaine	HPC	Okamoto et al.
Buccoadhesive Films	Thiocolchicoside	Gelatin and CMC	Artusi et al.
Buccoadhesive Patches	Propranolol HCl	CP 934 and PVP-K30	Patel et al.
Buccoadhesive Patches	Atenolol	CP 934 P, SCMC, HPMC	Mohanty et al.
Buccoadhesive Patches	Sumatriptan succinate	Gelatin and PVP-K30	Shidhaye et al.
Buccoadhesive Patches	Lignocaine	Proprietary mucoadhesive support system	Brook et al.
Buccoadhesive Patches	Miconazole nitrate	SCMC, chitosan, PVA, HEC, HPMC	Nafee et al.
Buccoadhesive Patches	Oxytocin	CP 974P	Li et al.
Buccoadhesive Patches	Thyrotropin-releasing hormone	Organic polymers	Li et al.

1.12 Ationalist Approach of MBBDS Towards Different Diseases

1.12.1 Cardio vascular disease

Hypertension, one of the major cardiovascular diseases, needs a lifelong therapy to remain under control. Most of the antihypertensive drugs like carvedilol, metoprolol, propranolol, isosorbide mononitrate etc. have low oral bioavailability and smaller half-life. Two main reasons for low bioavailability are poor aqueous solubility and high first pass metabolism. The buccal mucoadhesive route of drug delivery provides direct access to the systemic circulation through the internal jugular vein by bypassing the first pass metabolism, leading to high bioavailability.

The dose of carvedilol, a model antihypertensive drug, is 25 mg twice a day; however, a lower effective dose is reported to be approximately 3.125 mg. Thus, by increasing the contact time and avoiding the first pass metabolism, a lower amount of drug can effectively produce the normal dose effect. Again, by sustaining the drug release, the frequent administration of drug can be avoided, thereby increasing the patient compliance

1.12.2 Fungal/microbial infections

Oral candidiasis is an opportunistic fungal infection caused by Candida albicans. These yeast infections are usually treated locally by application of gels or suspensions. Release of drugs from these preparations involves an initial burst of activity whose level rapidly declines to subtherapeutic concentrations. Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis. The oral dose of fluconazole for the treatment of oral candidiasis (100 mg/day for 1 or 2 weeks) results in notable side effects varying from headache, nausea to liver dysfunction, and hepatic failure. Furthermore, oral fluconazole is reported to interact with a number of medications, including oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. The pathogenic yeasts in oral candidiasis are usually detected in the superficial layers of the oral mucosa. Thus, the effectiveness of the systemic fluconazole may be partially topical through its concentration in oral fluids. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of MBDDS containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a long time

1.12.3 Migraine

Migraines are thought to occur when certain blood vessels in the brain become swollen (dilated). Drugs used for the treatment include the "triptan" group, comprising of sumatriptan, zolmitriptan, and rizatriptan. These drugs work by helping blood vessels in the brain to return to normal size. It may also block pain signals in the brain. The model drug, sumatriptan is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously as two 6-mg doses over 24 hours. However, a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attack, and also low oral bioavailability (15%) due to high first-pass metabolism may make oral treatment unsatisfactory. Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution and inability of self-administration for injectables, respectively

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.

1.12.4 Nausea and vomiting

Ondansetron HCl, chosen as a model drug for treating postoperative nausea and vomiting associated with emetogenic cancer chemotherapy, possesses certain characteristics that a drug should have to get absorbed through buccal mucosa viz., biphasic solubility and low molecular weight. Moreover, the primary route of ondansetron clearance is by hepatic phase I metabolism, so its bioavailability may be improved when delivered through the buccal mucosal route. Patients may have frequent vomiting following chemotherapy and they may be unable to swallow a tablet to prevent vomiting. It justifies the need to develop a buccal patch/film of ondansetron hydrochloride, which increases patient compliance. Its bioavailability when administered by oral route is only 50% to 60% and its dose is low i.e., 4-8 mg; hence, it can be conveniently loaded onto a patch

2. DRUG PROFILE

2. Alogliptin

2.1.1 Chemical Structure

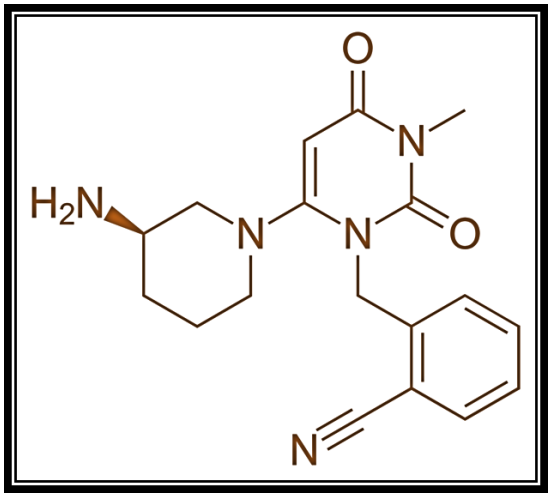

Fig No 4: Chemical Structure of Alogliptin

2.1.2 Chemical Formula- C18H21N5O2
2.1.3 Molecular Weight- 339.39 g/mol
2.1.4 Solubility- DMSO, Methanol, Water

2.1.5 Description:
Alogliptin is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke.Alogliptin works by increasing levels of natural substances called incretins. Incretins help to control blood sugar by increasing insulin release, especially after a meal. They also decrease the amount of sugar your liver makes.

2.1.6 Pharmacodynamics
Peak inhibition of DPP-4 occurs within 2-3 hours after a single-dose administration to healthy subjects. The peak inhibition of DPP-4 exceeded 93% across doses of 12.5 mg to 800 mg. Inhibition of DPP-4 remained above 80% at 24 hours for doses greater than or equal to 25 mg. Alogliptin also demonstrated decreases in postprandial glucagon while increasing postprandial active GLP-1 levels compared to placebo over an 8-hour period following a standardized meal. Alogliptin does not affect the QTc interval.

2.1.7 Mechanism of action
Alogliptin inhibits dipeptidyl peptidase 4 (DPP-4), which normally degrades the incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide 1 (GLP-1). The inhibition of DPP-4 increases the amount of active plasma incretins which helps with glycemic control. GIP and GLP-1 stimulate glucose dependent secretion of insulin in pancreatic beta cells. GLP-1 has the additional effects of suppressing glucose dependent glucagon secretion, inducing satiety, reducing food intake, and reducing gastric emptying.

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP-4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures

3. SUMMARY AND CONCLUSION:

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules increase the residence time of the dosage form at the site of absorption. Mucosal layer represents potential sites for the attachment of any bioadhesive systems because mucosal layer lines number of the body including the gastro intestinal tract, the urogenital tract, vaginal tract, the eye, ear, and nose. The mucoadhesive Bilayer tablets consisting of two various types of drug molecules and they show on set of actions at their particular sites. This review describes the structure of mucosal layer, mechanism of action of mucoadhesion, and preparation techniques of Bilayer tablets and evaluation parameters of tablets.

Drug actions can be improved by new drug delivery system, such as mucoadhesive system. This system remains in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to improvement in both local and systemic effects..

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5. CONFLICTS OF INTEREST
Authors have no conflicts of interest to declare.
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