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MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM - A COMPREHENSIVE AND PROMISING NOVEL DRUG DELIVERY

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ABSTRACT: Since Dr. Tsuneji Nagai of Hoshi University, Japan in the early 1980's used the concept of bio adhesion for the delivery of insulin across the buccal mucosa in beagle dogs; several researchers tried a large number of drugs for administration through buccal mucoadhesive dosage forms. The potential of these dosage forms have been found to be tremendous because of their ability to improve the bioavailability of many such drugs by bypassing the hepatic first pass metabolism. Because of the growing number of newer molecules in the form of peptides and proteins, the research in this field has gained the centre stage for the non-invasive drug delivery as an alternative to parenteral route. The novel design of the buccal delivery system can be achieved by the help of polymers of synthetic and natural polymers. The purpose of this review article is to establish the developments and highlight the importance of mucoadhesive buccal delivery for low bio available drugs.

INTRODUCTION: Pharmaceutical dosage form development is the combination of an art as well as a science with the sole objective to produce a dosage form that is efficacious, patient friendly, stable, economical and delivers the drug as close as possible to the intended target with minimal adverse effects. Conventional forms of drug administration, in many cases, have been supplanted by the advent of novel drug delivery systems. The pharmaceutical companies are presently seeking innovative dosage forms by way of novel drug delivery systems as they represent strategic tool for expanding markets and indications, extending product life cycles and generating newer opportunities [1].

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NDDS is no longer a theory. It is a reality and this is illustrated by the fact that around 13% of the current global pharmaceutical market is accounted for NDDS. Among the NDDS, transmucosal drug delivery market recorded second highest growth in the last five years with 171% whereas overall market growth stands at 106% [2].

Rapid developments in the field of molecular biology and gene technology resulted in generation of many new drugs in large number including peptides, proteins, polysaccharides, nucleic acids and other molecules possessing superior pharmacological efficacy and site specificity. But, the main impediment for oral delivery of these drugs is their inadequate oral absorption due to extensive presystemic metabolism and instability in acidic environment. As a result, the full therapeutic potential of many drugs cannot be realized; hence administration through highly expensive and less patient friendly parenteral route is inevitable. Further, parenteral route is most hazardous due to

incidences of anaphylaxis, extravasations and infection risk. Serious drawbacks associated with parenteral route and poor drug bioavailabilities have led to investigate new alternative drug delivery system [3]

Transmucosal Drug Delivery: Transepithelial drug delivery across skin or absorptive mucosae seems to offer many benefits such as improved bioavailability and, hence possible to lower drug doses, thereby less dose-related side effects than the oral route [3]. In comparison, transmucosal delivery systems exhibit a faster delivery than do transdermal delivery systems. Also, delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in minimal inter subject variability. In addition, these systems could potentially be used to deliver drugs that exhibit poor and variable bioavailability due to significant hepatic first-pass metabolism [4].

The absorptive mucosae include buccal, sublingual, palatal, gingival, nasal, pulmonary, rectal, vaginal and ocular routes. On the other hand, in case of nasal delivery, availability of very small surface area for absorption as well as the large variability in mucus secretion could significantly affect drug absorption. Further, severe sensitivity to drugs causes significant irreversible damage to the mucosa. In pulmonary delivery, despite the enormous surface area available for absorption, the major challenge is the reproducible placement of drug in the alveolar region due to the mucociliary clearance, hence not suitable for sustained delivery.

Vaginal, rectal and ocular mucosae offer many advantages, but poor patient compliance making them a feasible site for local applications rather than for systemic use. Sublingual mucosa is more permeable but not suitable for retentive delivery. Palatal and gingival routes are suitable for retentive drug delivery but has poor permeability coefficient [5].

Among all transmucosal sites, buccal cavity was found to be the convenient and easily accessible site for the local or systemic delivery of drugs. Because of its expanse of relatively immobile smooth muscle, abundant vascularization, direct access to the systemic circulation through the internal jugular vein that bypasses hepatic first pass metabolism, makes it highly promising for delivery of drugs exhibiting poor oral bioavailabilities. Facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious advantages of buccal adhesive systems [6].

Buccal Mucosal Structure and its Suitability: Buccal region is that part of the mouth bounded 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.Numerous racemose mucous, or serous glands are present in the submucous tissue of the cheeks [7].

Maxillary artery supplies blood and blood flow is faster and richer (2.4 ml/min/cm^2), thus facilitates passive diffusion of drug molecules across the mucosa. The turnover time for the buccal epithelium has been estimated at 5-6 days [8].

Buccal mucosa is relatively permeable, robust, more tolerant to potential allergens in comparison with the other mucosa and skin due to near absence of Langerhans cells [9]. Enzymatic activity in buccal mucosa is very negligible [10]. The permeability of the buccal mucosa was estimated to be 4-4000 times greater than that of the skin [11].

Buccal mucosa composed of several layers of different cells as shown in **Fig. 1**. The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40-50 cell layers thick [12]. Lining epithelium is the nonkeratinized stratified squamous epithelium that has thickness of approximately 500-600μm and surface area of 50.2cm^2. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer [13].

Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. Lipid analysis of buccal tissues shows the presence of phospholipid 76.3 %, glucosphingolipid 23.0% and ceramide NS at 0.72%. Other lipids such as acyl glucosylated ceramide and ceramides like Cer AH, Cer AP, Cer NH, Cer AS, and EOHP / NP are completely absent [14].

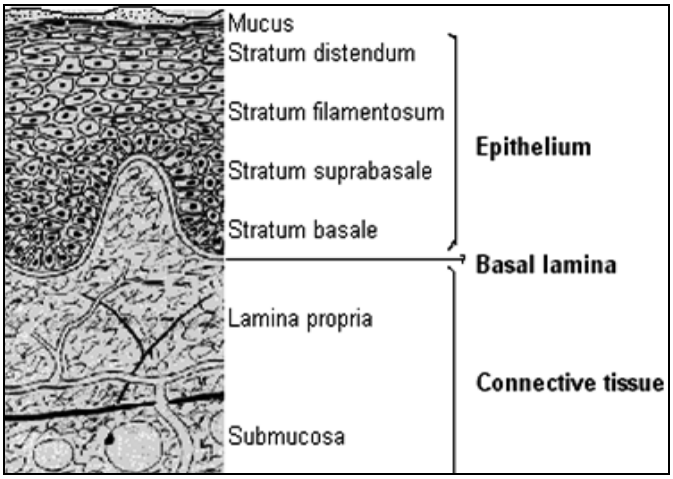

FIG. 1: CROSS-SECTION THROUGH BUCCAL MUCOSA

Absorption pathways: Drugs administered via the oral mucosa gain access to systemic circulation by passive diffusion in accordance to Fick's law [15]. Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers.

However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed[16]. It has also been found that the oral mucosa contains active, carrier-mediated transport systems for few small drugs and nutrients, such as monosaccharide and amino acids [17]. The main penetration barrier exists in the outermost quarter to one third of the epithelium [18].

Mucus: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varying from 40µm to 300µm [19]. The sublingual glands and minor salivary glands together produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa [20]. Mucus serves as an effective delivery vehicle by acting as a lubricant, allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery system [21]. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic to mucus. Mucins contain approximately 70-80% carbohydrate, 12-25% protein and up to 5% ester sulphate [22]. The dense sugar coating of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers [23].

Mucins are secreted as massive aggregates by prostaglandins with molecular masses of roughly 1 to 10 million Daltons. Within these aggregates, monomers are linked to one another mostly by non-covalent interactions, although intermolecular disulphide bonds also play a role in this process (**fig. 2**). Oligosaccharide side chains contain an average of about 8 – 10 monosaccharide residues of five different types namely L-fructose, D-galactose, N – acetyl – D - glucosamine, N – acetyl – D - galactosamine and sialic acid. Amino acids present are serine, threonine and proline [24]. Because of the presence of sialic acids and ester sulfates, mucus is negatively charged at physiological salivary pH of 5.8 – 7.4 [25].

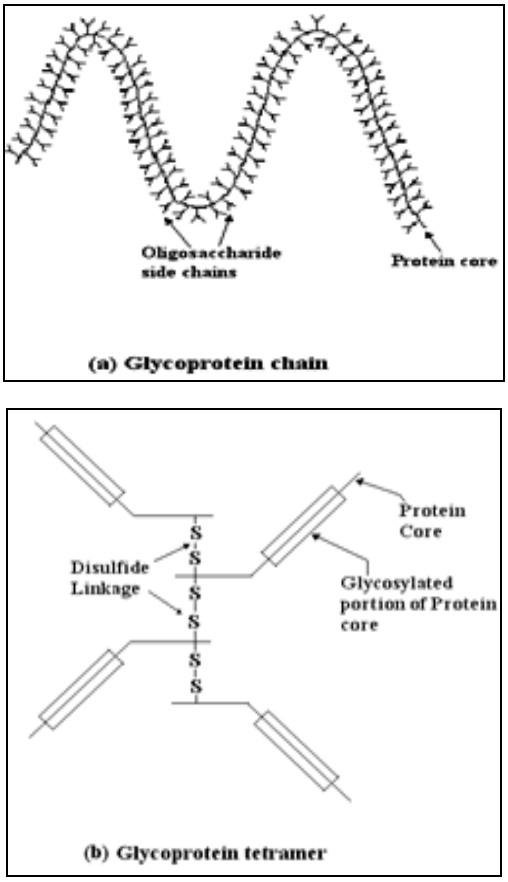

FIG. 2: SCHEMATIC REPRESENTATION OF MUCUS

Saliva: The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as unstirred layer. Within the saliva there is a high molecular weight mucin named MG1 [26] that can bind to the surface of the oral mucosa so as to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms. The major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth, submandibular under the tongue, and the sublingual through many ducts in the floor of the mouth.

Besides these glands, there are 600-1000 tiny glands called minor salivary glands located in the lips, inner cheek area and extensively in other linings of the mouth and throat [27]. Total output from the major and minor salivary glands is termed as whole saliva, which at normal conditions has flow rate of 1-2ml/min [28]. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. It is high in potassium, bicarbonate, calcium, phosphorous, chloride, thiocyanate and urea and low in sodium. The normal pH of saliva is 5.6 - 7. Saliva contains enzymes namely α - amylase (breaks 1-4 glycosidic bonds), lysozyme (protective, digests bacterial cell walls) and lingual lipase (breaks down the fats) [29].

Buccal Drug Delivery Systems: The histological features of buccal mucosa make it a feasible site for sustained release delivery systems, which could maintain a steady release of drug in the systemic circulation. Various delivery approaches have been developed to deliver drugs into the oral cavity for either local or systemic action. These include mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized transmucosal devices [30].

The simplest and oldest dosage forms are lozenges and mouthwashes. The drug is constantly washed away by a considerable amount of saliva from these non-attached delivery systems resulting into initial burst effect followed by a rapid decrease in concentrations to below therapeutic levels. Moreover, the dosage form must be palatable for a better patient compliance. Likewise, ordinary gels, pastes and even dosage forms for sustained release through buccal mucosa such as medicated chewing gums, medicated lollipops and lozenges could not overcome the salivary scavenging effect [31]. To overcome these limitations, delivery systems designed to remain in the buccal mucosa for prolonged periods based on the concept of bio/mucoadhesion have been developed [32].

Bio/mucoadhesion: Bioadhesion is the phenomenon in which a synthetic or natural macromolecule adheres to a biological tissue, which can be either an epithelial surface or the mucus layer covering a tissue and are held together for extended periods of time by interfacial forces[33]. It is a complex phenomenon and several steps have been suggested in mucoadhesive bond formation[34]. The first step is the spreading, wetting and dissolution of mucoadhesive polymer at the interface. The second step is the mechanical or physical entanglement between the polymer and the mucus, resulting in a inter-penetration layer. The next step is the result of chemical interactions, such as covalent and ionic bonds, hydrogen bonding and Van der Waal's interactions. Hydrogen bonds and hydrophobic interactions are the most desirable on developing mucoadhesive systems, since strong primary bonds (e.g. covalent bonds and ionic bonds) could cause irreversible damage of mucosal surface.

Mechanisms of polymer adherence to mucosal surfaces have not yet been fully understood and five theories have been proposed for the mucoadhesion. It is unlikely that a single, universal theory will account for all types of adhesion observed. These theories include the adsorption, diffusion, wetting, fracture and electronic theories. The 'adsorption theory' states that interfacial chemical bonds are formed upon initial contact between mucosal surface and the mucoadhesive polymer.

In the 'diffusion theory', it has been suggested that after initial contact between the mucosal surface and the mucoadhesive polymer, a physically entangled network between the polymer and the mucus is formed. The 'wetting theory' is based on the ability of the polymer to spread on biological surfaces. This theory is generally applicable to liquid bioadhesive systems. The 'fracture theory' is related to the force required for the separation of

polymers from the mucus below. According to the 'electronic theory', electron transfer occurs between mucosal surface and the mucoadhesive polymer as a result of their different electronic properties. Electrostatic interactions with the negatively charged mucin surface contribute to the formation of an intermediate inter-diffusion network [6].

Buccal Adhesive Polymers: Polymer 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*, and *meros* meaning *parts*. 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. Instead of being identical, similar monomers can have varying chemical substituents. The differences between monomers can affect properties such as solubility, flexibility, and strength. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers [6].

Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue and visco-elastic properties [35].

Ideal characteristics:

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities
- Should have good spreadability, wettability, swellability, solubility and biodegradability properties
- Should contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus
- Should have functional groups able to form hydrogen bonds
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups
- Should allow easy incorporation of the drug and provide drug release in a controlled manner
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength
- Should demonstrate acceptable shelf life
- Should not aid in development of secondary infections such as dental caries

CONCLUSION: From the article, we can conclude that the novel muco adhesive buccal delivery drug plays an important role for developing a route of administration for the low bioavailable drugs and in this manner avoids the first pass metabolism, improves the bioavailability and very much suitable for peptides and proteins .The mucoadhesive buccal delivery which will be achieved by the use of different polymers from natural and synthetic source for developing a novel dosage form. The mucoadhesive buccal delivery is suitable not only for low bio available drugs but also for peptides and proteins.

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CONFLICTS OF INTEREST: Nil

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