CHAPTER – 1

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]. 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% where as 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 non-invasive drug delivery systems [3].

1.1. Transmucosal drug delivery:

Transepithelial drug delivery across skin or absorptive mucosa 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].

1.2. 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 and 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].

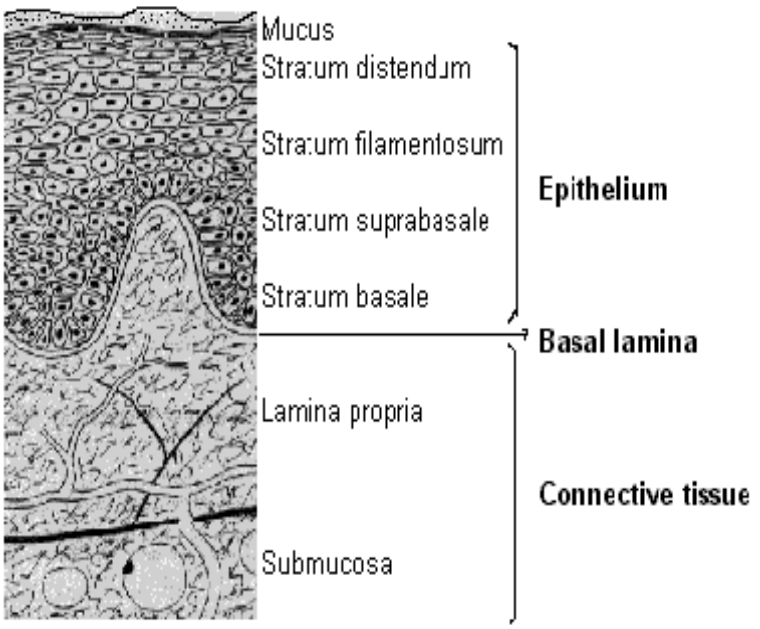


FIG 1. CROSS-SECTION THROUGH BUCCAL MUCOSA

1.3. 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 monosaccharides and amino acids [17]. The main penetration barrier exists in the outermost quarter to one third of the epithelium [18].

1.4.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 the adhesion of mucoadhesive drug delivery systems [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. 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].

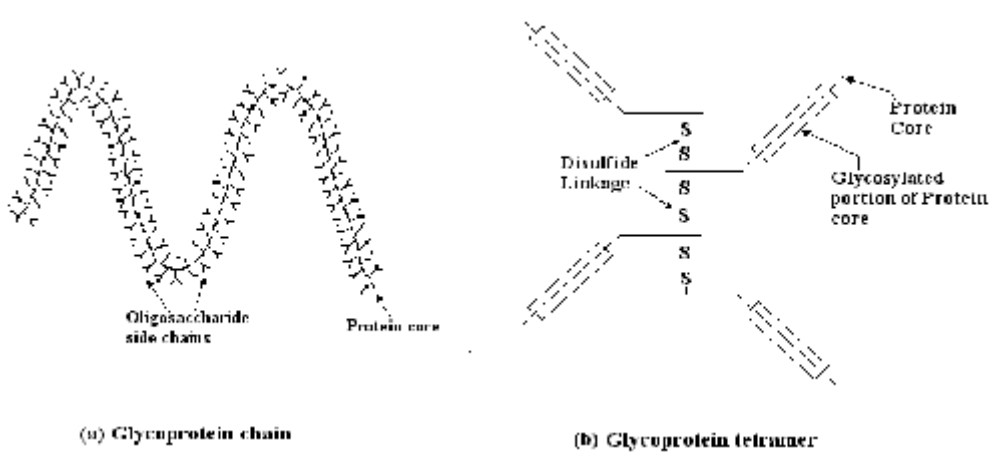


FIG 2. COMPOSISTION OF MUCUS

1.5. 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].

1.6. 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 b

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].

1.7. 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 an 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].

1.8. 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].

1.8.1. Ideal characteristics for mucoadhesive polymers [6]

- 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

In general, adhesive polymers can be classified as natural or synthetic, water-soluble or water insoluble, charged or uncharged polymers. A wide range of polymers has been investigated as mucoadhesive in order to enhance buccal drug absorption by increasing the contact with the buccal mucosa for prolonged periods and were enlisted in Tables 1 & 2.

TABLE 1. MUCOADHESIVE POLYMERS IN BUCCAL DRUG DELIVERY

SOURCE	EXAMPLES
Natural/Semi-synthetic	Agarose, chitosan, Carrageenan, Hyaluronic acid, various gums (guar, hacka, xanthan, gellan, carragenan, pectin and sodium alginate)
Synthetic	**Cellulose derivates** [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methyl-hydroxyethyl-cellulose]
	Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG].
	Others Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), PEG, polyoxyethylene, PVA, PVP, thiolated polymers, phospholipid polymers , polyvinyl alcohol.

TABLE 2. MISCELLANEOUS CLASSIFICATION OF BIOADHESIVE POLYMERS

Criteria	Categories	Examples
Aqueous solubility	Water-soluble	CP, HEC, HPC (water 38.8°C), HPMC (cold water), PAA, sodium CMC, sodium alginate.
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Aminodextran, chitosan, diethylaminoethyl (DEAE)-dextran, trimethylated, chitosan.
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum.
Potential bioadhesive forces	Non-ionic Covalent Hydrogen bond Electrostatic interaction	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP. Cyanoacrylate Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA. Chitosan.

1.8.2. Some representative mucoadhesive polymers:

Hydrogels

Hydrogels often called as "wet" adhesives because they require moisture to exhibit the adhesive property. They are usually considered to be cross linked water swollen polymers having

water content ranging from 30% to 40% depending on the polymer used. These are hydrophilic matrices that absorb water when placed in an aqueous media. This may be supplied by the saliva, which may also act as the dissolution medium. They are structured in such a manner that the cross linking fibers present in their matrix effectively prevent them from being dissolved and thus help them in retaining water. When drugs are loaded into these hydrogels, as water is absorbed into the matrix, chain reaction occurs and drug molecules are released through the spaces or channels within the hydrogel network. Polymers such as poly acrylates (carbopol and polycarbophil), ethylene vinyl alcohol, polyethylene oxide, poly vinyl alcohol, poly (N-acryloylpyrrolidine), polyoxyethylenes, self cross linked gelatin, sodium alginate, natural gums like guar gum, karaya gum, xanthan gum, locust bean gum and cellulose ethers like methyl cellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose etc form part of the family of hydrogels [36].

COPOLYMERS

Researchers are currently working on carrier systems containing block copolymers rather than using single polymeric system. Copolymerization with two or more different monomers results in chains with varied properties. A block copolymer is formed when the reaction is carried out in a stepwise manner, leading to a structure with long sequences or blocks of one monomer alternating with long sequences of the other. These networks when composed of hydrophilic and hydrophobic monomers are

Called polymer micelle. These micel 12 uitable for enclosing individual drug molecules. Their hydrophilic outer shells help to he cores and their contents from chemical attack by aqueous medium. Most micelle-based systems are formed from poly (ethylene oxide)-b-polypropylene-b-poly (ethylene oxide) triblock network.

There are also graft copolymers, in which entire chains of one kind (e.g., polystyrene) are made to grow out of the sides of chains of another kind (e.g., polybutadiene), resulting in a product that

is less brittle and more impact-resistant. Thus, block and graft copolymers can combine the useful properties of both constituents and often behave as quasi-two-phase systems [37].

Multifunctional polymer

These are the bioadhesive polymers having multiple functions. In addition to the possession of bioadhesive properties, these polymers will also serve several other functions such as enzyme inhibition, permeation enhancing effect etc. Examples are polyacrylates, polycarbophil, chitosan etc.

Thiolated polymers

These are the special class of multifunctional polymers also called thiomers. These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Due to these functional groups various features of well established polymeric excipients such as poly (acrylic acid) and chitosan were strongly improved [38]. Thiolated polymers designated thiomers are capable of forming disulphide bonds with cysteine-rich subdomains of mucus glycoproteins covering mucosal membranes [39]. Consequently, the bridging structure most commonly used in biological systems is utilized to bind drug delivery systems on the mucosal membranes. By immobilization of thiol groups the mucoadhesive properties of poly (acrylicacid) and chitosan, was improved to 100-fold to 250-fold [40, 41].

Thiomers are capable of fo[illegible]tra- and interchain disulphide bonds within the polymeric network leading to stro[illegible]roved cohesive properties and stability of drug delivery systems such as matrix tablets. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process. Zinc dependent proteases such as aminopeptidases and carboxypeptidases are inhibited by thiomers.

The underlying mechanism is based on the capability of thiomers to bind zinc ions and this property is highly beneficial for oral administration of protein and peptide drugs. They also exhibit permeation-enhancing effects for the paracellular uptake of drugs based on a glutathione-mediated opening process of the tight junctions [42, 43].

Milk Protein

A particular example is a milk protein concentrate containing a minimum of 85% of proteins such as Prosobel L85, LR85F at concentration of 15% to 50%, preferably 20% to 30% in a bioadhesive tablet showed good bioadhesive property [44].

Pharmaceutical properties of mucoadhesive polymers

- Cationic and anionic polymers bind more effectively than neutral polymers.
- Anionic polymers with sulphate groups bind more effectively than those with carboxylic groups.,
- Polyanions are better than polycations in terms of binding potential, toxicity.
- Water-insoluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers.
- Degree of binding is proportional to the charge density on the polymer.

1.9. Important factors for mucoadh

The mucoadhesive strength of a polymer or blend of polymers is affected by the nature of the polymer and also by the nature of the surrounding media. Polymer related factors such as molecular weight, concentration of active polymer, flexibility of polymer chains and spatial

configuration; environment related factors such as pH, applied strength, initial contact time, selection of the model substrate surface and swelling; physiological variables like mucin turnover and disease state are to be considered while developing a bioadhesive dosage form [45].

1.10. Measurement of mucoadhesive strength

To ensure compatibility, physical and mechanical stability, surface analysis and bioadhesive bond strength, these tests are important during the design and development of a mucoadhesive release system [6].

Qualitative methods are useful for preliminary screening of the respective polymer for its bio or mucoadhesion, compatibility and stability. However, these methods are not useful in measuring the actual bioadhesive strength of the polymers. These methods include viscometric method, analytical ultracentrifuge criteria, atomic force microscopy, electrical conductance, fluorescent probe method, lectin binding inhibition technique, thumb test, colloidal gold staining method, direct staining method etc [6].

Quantitative methods are also called macroscopic methods. The majority of the quantitative bio and/or mucoadhesion measurement methods found in the literature are based on measuring the force required to break the adhesive bond between the model membrane and the adhesive. Depending on the direction in which the adhesive is being separated from the substrate, peel, shear, and tensile forces can be measured. These methods usually measure the force required to break the adhesive bond between a model membrane and the test polymers.

The instruments usually employed are modified balances or tensile testers. The results of the study provides important information [15] g the effect of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion [6].

1.11. Buccal mucoadhesive dosage forms

Nagai et al. [46] was the pioneer in the bioadhesive drug delivery system in the early 1980's by administering insulin across the buccal mucosa in beagle dogs. The desirable attributes of an buccal adhesive system for prolonged systemic delivery are: a high drug loading capacity, no irritancy, good mucoadhesion, smallness in size and enough flexibility to be acceptable by users [47].

According to the mechanism by which the drug is released from the device, buccal dosage forms can be classified as monolithic (or 'matrix') and reservoir type. In monolithic systems, the drug is uniformly dispersed or dissolved in the polymer matrix and drug release occurs by diffusion trough the polymer network. In the reservoir (or membrane controlled) systems, a drug reservoir is entrapped between an impermeable backing layer and a polymeric membrane, which controls the drug release rate [48]. The first step in the development of a patch/film is the selection and characterization of a polymer either alone or in combination with appropriate bioadhesive properties and drug release control [49]. Several polymers such as polyacrylates, polyoxyethylenes, CMC, HPC, HPMC, natural gums (guar, xanthan, locust bean, sodium alginate) were used as polymers [50].

1.11.1. Adhesive semi-solid systems

These systems were developed by the incorporation of hydrogels in the formulation [51] in order to minimize poor retention of dosage form at the site of application. Hydrogels, often called as 'wet' adhesives, are hydrophilic polymers capable of being hydrated in aqueous environment [52]. Normally, hydrogels are cross-linked molecules. Upon contact with water, they would not dissolve in the aqueous medium but swells rapidly, so that and physically entrapment of drug molecules takes place.

After gel hydration, chain re[illegible]n occurs and the drug molecules are slowly released by diffusion through channels within the hydrogel network, by degradation of the polymeric matrix or by a combination of the both [53]. To date, major application of adhesive gels in the oral cavity is local drug delivery, in particular for treatment of periodontitis [54].

1.11.2. Adhesive patches and films

Adhesive films and laminated patches are relatively new types of buccal delivery systems, promising especially for systemic drug delivery [55]. Several investigators have studied [56] a number of polymers and different geometries for developing patches for the delivery of different peptides across buccal mucosa. Bioadhesive patches are laminates consisting of a polymeric drug-loaded layer, an impermeable backing layer to promote unidirectional drug release and, generally, mucoadhesive components with or without release retardants and additives, such as penetration enhancers or enzyme inhibitors [57]. Bioadhesive films are similar to laminated patches in terms of manufacturing process, advantages and drawbacks. The buccal films have also been developed recently for mucosal immunization that allows for needle-free administration of cost-effective vaccines [58].

These dosage forms provide a better flexibility, leading to a higher patient compliance and comfort, in comparison with adhesive tablets. In addition, they provide better residence times than oral gels. Moreover, a polymeric adhesive film is able to protect the underlying surface, thus reducing pain and treating the oral disease more effectively [59]. However, despite having advantages, long manufacturing times, high costs, environmental concerns due to the solvents used are the major disadvantages connected with these dosage forms. Representative research on buccal adhesive patches and films are summarized in Table 3.

TABLE 3. DEVELOPMENTS IN BUCCAL ADHESIVE PATCHES/FILMS

DRUG	BIOADHESIVE POLYMER USED	REF
Plasmid DNA	Noveon, Eudragit S-100	60
β- galactosidase	Noveon, Eudragit S-100	60
Ipriflavone	PLGA,Chitosan	61

Chlorhexidine gluconate	Chitosan	62
Chlorphineramine maleate	Polyoxyethylene	63
Protirelin	HEC, HPC, PVP, PVA	64, 65
Buprenorphine	CP-934, PIB & PIP	66
Isosorbide dinitrate	HPC, HPMCP	67
Lidocaine	HCP, CP	68
Miconazole nitrate	SCMC, chitosan, PVA, HEC & HPMC	69
Nifedipine	Sodium alginate	70
Acyclovir	[P (AA-co-PEG)]	71

1.11.3. Adhesive tablets

Buccal adhesive tablets are small, flat and oval with a diameter of approximately 5-8 mm and about 2 mm in thickness [72]. In presence of saliva, they adhere to the mucosal surface until dissolution and/or drug release is complete and allows drug permeation across the buccal mucosa. After a short time following application in the mouth, the patient is not aware of its presence, allowing speaking, drinking and eating without any discomfort. Adhesive buccal tablets can be applied to different sites in the oral cavity, including the palate, the mucosa of the cheeks or in any comfortable position between lip and gum in case of patient wearing dentures [73]. They are a feasible dosage form for the transmucosal absorption of systemically acting drugs, which are ineffective when administered by conventional routes. Buccal tablets are designed to erode slowly since the buccal route is generally used in the treatment of chronic disorders when a prolonged release of the active substance is required.

In order to prevent drug loss from the top surface of the dosage form, specialized tablets with two layers have been developed. They contain a drug-loaded bioadhesive layer and an impermeable backing layer to promote unidirectional drug absorption and to minimize drug leakage in the oral cavity. Several investigators have reported on the development of buccal adhesive tablets containing a fast-release and a controlled-release layer. The fast release layer contains poly(vinyl pyrrolidone) (PVP) as the bioadhesive component a

to the buccal mucosa and the controlled release layer consists of a mixture of PVP and poly(acrylic acid) [74]. In order to achieve unidirectional release with minimal drug loss, the drug release can be restricted to occurs only from the face of the tablet in contact with the buccal mucosa and other faces are coated with water impermeable hydrophobic substances such as ethyl cellulose, oil etc. Large number of drugs has been investigated and reported by several groups are summarized in Table 4

TABLE 4. DEVELOPMENTS IN BUCCAL ADHESIVE TABLETS

DRUG	BIOADHESIVE POLYMER USED	REF
Ketoprofen	Chitosan & Sodium alginate	75
Nifedipine	Chitosan, Polycarbophil, Sodium alginate, Gellan gum	76
Propranolol	CP, HPMC, PC, SCMC, PAA	77
Propranolol	HPMC, CP 934	78
Propranolol	HPMC, PC	79
Diltiazem	CP, HPMC, PC, SCMC, PAA	80
Diltiazem	CP 934 & PVP K-30	81
Metaclopromide	CP, HPMC, PC, SCMC, PAA	82
Nystatin	Carbomer, HPMC	83
Verapamil	HPC-M, CP 934	84
Triamcilone	HPC, CP-934	85
Triamcilone	HPMC, PADH	86
Lidocaine	CP-934, HPC-H	87
Metronidazole	CP-934, HPMC	88
Sodium fluoride	Modified starch, PAA	89
Miconazole	Modified starch, CP-934	90
Pentazocine	CP-934P, HPMC	91
Chlorpheneramine	Hakea gum	92
Calcitonin	Hakea gum	93
Omeprazole	Sodium alginate, HPMC, CP-934P, PC	94

DRUG	BIOADHESIVE POLYMER USED	REF
Nicotine	HPC, CP-934P, PVP	95
Clotrimazole	CP 974P, HPMC K4M	96
Nicotine hydrogen tartrate	Anionic, cationic and nonionic polymers	97
Citrus oil & Magnesium salt	Cross linked PAA & HPC	98
Buspirone HCl	CP 974 HPMCK4M	99
Omeprazole	Sodium alginate & HPMC	100
Hydrocortisone acetate	HPMC (Methocel K4M), carbopol934P, polycarbophyl	101
Ergotamine tartrate	PVA	102
Hydralazine Hcl	CP 934P & CMC	103
Prednisolone	Polycarbophil & CP 934P	104
Buprenorphine	HEMA & Polymeg	105
Morphine sulphate	Carbomer & HPMC	106
Propranolol	CP-934P, HPMC K4M	107

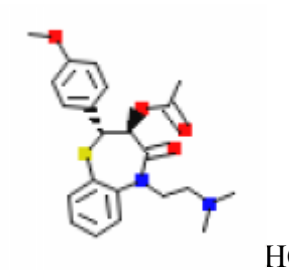
In order to improve bioavailability of administered drug across the buccal mucosa, several bioadhesive tablet systems have been the subject of a growing interest [6]. Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%. Some of the commercially available buccal adhesive formulations are listed in Table 5.

TABLE 5. COMMERCIALLY AVAILABLE BUCCAL ADHESIVE DOSAGE FORMS

Commercial Name	Company	Dosage form

Buccastem	Rickitt Benckiser	Tablet
Suscard	Forest	Tablet
Gaviscon liquid	Rickitt Benckiser	Oral liquid
Orabase	ConvaTech	Oral paste
Corcodyl gel	Glaxo smithkline	Oromucosal gel
Corlan pellets	Celltech	Oromucosal pellets
Fentanyl Oralet™	Lexicomp	Lozenge
Miconazole Lauriad	Bioalliance	Tablet
EmezineTM	BDSI's	Buccal tablet
BEMA Fentanyl	BDSI's	Buccal soluble film
Straint™ SR	Ardana	buccal adhesive tablet
Zilactin	Zila	Buccal film
Luborant	Antigen	Artificial saliva
Saliveze	Wyvern	Artificial saliva
Tibozole	Tibotec	Tablet

1.12.DILTIAZEM HYDROCHLORIDE



HCl

The chemical name for diltiazem Hydrochloride is (+)-cis-3-(Acetoxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-ethoxyphenyl)-1,5-benzothiazepin-4(5H)one hydrochloride.

Molecular formula : $C_{22}H_{26}N_2O_45$, HCL

Molecular weight : 450.98g/mole

Appearance, odor and taste:

Diltiazem Hydrochloride is white crystalline powder. It is odorless and has bitter taste.

Solubility:

Freely soluble in water chloroform, formic acid and methanol sparingly, soluble in dehydrated alcohol insoluble in benzene.

Optical rotation:

It possesses two asymmetric carbons and is therefore optically active. The dextrorotatory enantiomer is the more potent biologically active form. The optical rotation of a 1% w/v solution in water at 25^0c [$\alpha^{25}{}_0$] is between $+100^0$ and $+ 116^0$.

Melting Point:

210^0C ($207.5\ ^0$C– $217\ ^0$C)

pH:

The pH of saturated solution in water is 3 and 1% w/v solution has pH of 4.2.

Stability:

In the solid state, it is reported to highly stable. Storage of the drug under condition of room temperature and 33% or 79% relative humidity for 57 days did not cause any physical or chemical degradation.

Storage:

Preserve in tight, light resistance containers.

Mechanism of action:

Diltiazem exert their effect by blocking voltage-sensitive calcium channels in the heart and in the blood vessels. This prevents calcium levels from increasing as much in the cells when stimulated, leading to less contraction. This decreases total peripheral resistance by dilating the blood vessels, and decreases cardiac output by lowering the force of contraction. Because resistance and output drop, so does blood pressure. With low blood pressure, the heart does not have to work as hard; this can ease problems with cardiomyopathy and coronary disease. Unlike with beta-blockers, the heart is still responsive to sympathetic nervous system stimulation, so blood pressure can be maintained more effectively. Diltiazem have an increased effect on AV nodal conduction compared to that of the dihydropyridines; while they also cause vasodilation via relaxation of vascular smooth muscle, their vasodilatory effects are only one-tenth the magnitude of nifedipine. It also interfere somewhat with blood coagulation by inhibiting platelet aggregation.

Angina*:*

The precise mechanism by which diltiazem relieve angina has not been fully determined but it is believed to be brought about largely by its vasodilatory effects on the coronary and peripheral vasculature. This increases blood flow to the ischemic area of the myocardium and reduces oxygen demand by decreasing the afterload.

Arrhythmia*:*

Diltiazem depress AV nodal conduction and prolong functional refractory periods, which is the basis for their use in supraventricular arrhythmias.

Hypertension:

The mechanism by which diltiazem reduces arterial blood pressure involves direct peripheral arterial vasodilation and reduction in peripheral vascular resistance.

Absorption and Fate:

Diltiazem is rapidly and almost completely absorbed from the gastro intestinal tract following oral administration, but undergoes, extensive first pass hepatic metabolism. The bioavailability has been reported to be about 40–44%, although there is considerable inter individual variation in plasma concentrations. About 80% of diltiazem is bound to plasma proteins, it is extensively metabolized in the liver, one of the metabolites; desacetyl diltiazem has been reported to have 25-50% of the activity of parent compound. The half-life as reported to about 3 to 5 hrs. Approximately 2-4% of a dose is excreted in urine as unchanged diltiazem with the reminder excreted as metabolites in bile and urine.

Studies on the pharmacokinetics of diltiazem in healthy subjects after single and multiple doses indicating that bioavailability was increased after multiple doses, probable because of decreased pre systemic elimination.

Therapeutic Uses:

Diltiazem, is a slow calcium-channel blocker, modulator and antagonist that acts by interfering with calcium mediated events in excitation - contraction coupling in smooth muscles and in particular arteries. It is used in humans and animals for the treatment of supraventricular dysrhythmias and for heart rate control in patients with atrial fibrillation, atrial flutter, atrioventricular nodal reentry and angina. It is also used as vasodilator, blood platelet aggregation inhibitor, antiarrhythmic, antithrombotic, antiischemic and in the management of mild or moderate systemic hypertension.

Dose:

30-120mg for management of angina thrice in a day. 60-120mg twice a day as sustained release tablets for management of hypertension.

1.13.Need for Novel Buccal Adhesive Ta[illegible] Diltiazem hydrochloride

On oral administration, CYP3A of cytochrome P-450 enzymes group metabolizes and adversely affects bioavailability of diltiazem during hepatic first pass. Diltiazem is a highly suitable candidate for retentive buccal delivery because of its poor oral bioavailability (<40%), short biological half-life (4hrs), optimum partition coefficient (150.8) and small molecular weight (450.98 g/mole) [6]. Several research groups have studied delivery of diltiazem via the buccal route in the form of conventional matrix tablets, films, bilayered systems, and hydrogel systems. Though there is remarkable improvement in the bioavailability (upto 65%), some serious limitations such as non-unidirectional release leading to no protection against salivary scavenging and non-masking of taste makes it unpalatable because of bitterness of diltiazem had remained as obstacles for successful development of dosage forms at commercial scale.

In an attempt to overcome these limitations, Novel Buccal Adhesive Tablets (NBATs) as core in cup fashion was prepared to deliver the drug unidirectionally towards buccal mucosa using water-soluble fraction of mucilaginous materials from the natural edible sources as mucoadhesive agents.