MUCOADHESIVE DRUG DELIVERY SYSTEMS-AN UNUSUAL MANEUVER FOR SITE SPECIFIC DRUG DELIVERY SYSTEM

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ABSTRACT

Mucoadhesion is a field of current interest in the design of drug delivery systems. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and/or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects. In this paper main prominence on gastrointestinal dosage forms along with concepts, mechanism of mucoadhesion, factors affecting mucoadhesion, anatomy of gastrointestinal tract, permeation enhancers and evaluation methods and also some review regarding research work already been carried.

Key words: Mucoadhesion, residence time, buccal route, therapeutic performance, permeation enhancers.

INTRODUCTION

For systemic delivery, the oral route has been the preferred route of administration for many systemic actively drugs. When administered by the oral route, however, many therapeutic agents have been reportedly subjected to extensive presystemic elimination by gastrointestinal degradation and/or hepatic metabolism. Results of low systemic bioavailability, short duration of therapeutic activity, and/or formation of toxic and inactive metabolite have been often reported.

Mucoadhesive drug delivery systems are delivery systems which utilized the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. [1]
Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug. The mucoadhesive drug delivery system includes the following: \[2\]

1. Buccal drug delivery system
2. Sublingual drug delivery system
3. Vaginal drug delivery system
4. Rectal drug delivery system
5. Nasal drug delivery system
6. Ocular drug delivery system

**MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS:**

Drug delivery via the membranes of the oral cavity can be subdivided as sublingual delivery, buccal delivery and local delivery.

These oral mucosal sites differ greatly from one another, on terms of anatomy, permeability, to an applied drug, and their ability to retain a drug delivery system for desired length of time.

What aspects make the oral mucosa, mainly the buccal site rather attractive?

1. Because of easily accessibility it permits localization of the system.
2. Since the patients are well adapted to oral administration of drugs in general, patient acceptance and compliance is expected to be good.
3. Its ability to recover after local treatment is pronounced and hence allows a wide range of formulations to be used e.g. bioadhesive patches and ointments \[3,4\].

**Advantages of mucoadhesive buccal drug delivery:**

Drug administration via the oral mucosa offers several advantages

1. Easy of administration and termination of therapy in emergency.
2. Permits localization of the drug for a prolonged period of time.
3. Can be administered to unconscious and trauma patients.
4. Offers an excellent route for the systemic delivery of drug which by passes first pass metabolism, thereby offering a greater bioavailability.
5. Significant reduction in dose can be achieved, there by reducing dose, dose dependent side effects, and eliminates peak-valley profile.
6. Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered.

7. It offers a passive system for drug absorption.

8. It can be made unidirectional to insure only buccal absorption.

9. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective uses of therapeutic agents like peptides, proteins and ionized species can be achieved.

10. Flexibility in physical state, shape, size and surface.

11. Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.

12. It satisfies several futures of the controlled release system.

13. The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.

14. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.

15. Rapid onset of action\textsuperscript{[4],[5]}

**Limitations of Buccal Drug Administration:**

1. Drugs which are unstable at buccal pH cannot be administered.

2. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.

3. Only drug with small dose requirement can be administered.

4. Only those drugs which are absorbed by passive diffusion can be administered by this route.

5. Eating and drinking may become restricted.

6. There is an ever present possibility of the patient swallowing the dosage form.

7. Over hydration may lead to slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.

8. Drugs contained in the swallowed saliva follows the pre-oral and advantages of buccal route are lost\textsuperscript{[4],[6]}.
ANATOMY AND NATURE OF ORAL CAVITY:

The oral cavity may be divided into two regions, the outer oral vestibule, bounded by the lips and cheeks and the oral cavity itself the borders being, and formed by the hard and soft palates, the floor of the mouth and tonsils.

Physical Description of Oral Cavity:

The mucosa that lines the oral cavity may be divided into three types, classified according to their function as;

1. Masticatory mucosa: Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.

2. Lining mucosa: Which covers the lips, cheeks, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non-keratinized epithelium.

3. Specialized mucosa: covering the dorsum of the tongue with highly keratinization.[7]

Regional variation in the composition of oral mucosa:

The membrane that lines the oral cavity has a total area of 200 cm² and shows difference in structures thickness and blood flow depending on their location. Keratinized and non-keratinized tissue occupies about 50% and 30% respectively[5],[3].

Table 1: Regional variation in the composition of oral mucosa

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Structure</th>
<th>Epithelial thickness (µm)</th>
<th>Residence time</th>
<th>Blood flow (ml/min/cm²)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>Non-keratinized</td>
<td>500-600</td>
<td>+</td>
<td>2.40</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Non-keratinized</td>
<td>100-200</td>
<td>--</td>
<td>0.97</td>
</tr>
<tr>
<td>Gingival</td>
<td>Keratinized</td>
<td>200</td>
<td>+</td>
<td>1.47</td>
</tr>
<tr>
<td>Palatal</td>
<td>Keratinized</td>
<td>250</td>
<td>--</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Oral mucosa:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 cell layers thick), a lamina propria followed by the submucosa as the innermost layer (Figure-1).

The composition of the epithelium varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramide \[^8\].

Composition of Mucus Layer:

Mucus is a translucent and viscid secretion which forms a thin, contentious gel, mean thickness of this layer varies from about 50-450 µm in humans secreted by the globet cells lining the epithelia or by special exoivic glands with mucus cell acini. It has the following general composition.

- Water -95%
- Glycoprotein and lipids – 0.5-3.00%
- Mineral salts – 1%
- Free proteins – 0.5-1.0%

Figure 1
Structure of the oral mucosa.
Functions of Mucus Layer:

1. Protective: resulting particularly from its hydrophobicity.
2. Barrier: The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.
3. Adhesion: Mucus has strong cohesion properties.
4. Lubrication: It is to keep the mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules [7], [8].

Salivary secretion:

There are mainly three glands which secrets saliva in the oral cavity, parotid, sublingual and sub-mandibular.

Functions of saliva: Moisten the oral cavity, aid the digestion of foods, lubricate the food for mastication and swallowing, provides protection to the tissue from abrasion by rough materials that may enter into mouth.

Saliva is composed of 99% water and is a complex fluid containing organic and inorganic material. Secretion of saliva is highest during the working hs. The amount of saliva produced throughout the day is 1-1.5L but this flow is variable according to researchers. The pH of saliva ranges from 5.8 to 7.4 the saliva of oral cavity has a low buffering capacity [4], [8].

Bioadhesion:

Bioadhesion 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 polymer and/ or copolymer and a biological membrane. In case of polymer attached to the mucin layer of the mucosal tissue, the term ‘mucoadhesion’ is employed [9].

‘Bioadhesive’ is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time. Bioadhesive are classified into three types.

Type-1: Between biological layers without involvement of artificial materials. Cell diffusion and cell aggregation are good examples.
Type-2: Bioadhesion can be represented by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.

Type-3: Adhesion of artificial substances to biological substrate such as adhesion of polymer to skin or other soft tissue.[7], [8], [9].

Mechanism of Bioadhesion:

For Bioadhesion to occur, three stages are involved.

Stage-1: An intimate contact between a Bioadhesive and a membrane either from a good wetting of the Bioadhesive and a membrane or from the swelling of bioadhesive.

Stage-2: Penetration of the bio-adhesive into the service of the tissue takes place.

Stage-3: Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bounds can then settle.

Figure 2

Interpenetration of Bioadhesive and mucous polymer chain[10]

The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electro static interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

THEORIES OF BIOADHESION/ MUCOADHESION: [4, 9]

Several theories have been proposed to explain the fundamental mechanism of adhesion.

1. Wetting:

Wetting theory is predominantly applicable to liquid bioadhesive systems and analyzes adhesive and contact behavior in terms of a liquid or a paste to spread over a
biological system. The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm$^2$ released when an interface is formed.]

According to Dupres equation work of adhesion is given by

$$W_a = Y_A + Y_B - Y_{AB}$$

Where A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$W_c = 2Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

2. Diffusion:

According to this theory the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The polymer chains penetrate the mucous; the exact depth of penetration depends, on the diffusion co-efficient, time of contact, molecular weights and decreases rapidly as the cross linking density as shown by Peppas.

3. Electronic:

According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucous glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layers.

4. Fracture:

Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon / L)^{1/2}$$

Where: E- Young’s modules of elasticity

$\varepsilon$- Fracture energy

L- Critical crack length when two surfaces are separated
5. Absorption:

According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds such as Primary covalent (permanent) and secondary chemical bonds (including electrostatic forces, Vander Waals forces and hydrogen and hydrophobic bonds)

**Factors affecting muco/ bioadhesion:**

Structural and physicochemical properties of a potential bioadhesion material influence bioadhesion.

**a. Polymer related factors:**

1. Molecular weight:

   The bioadhesive force increases with molecular weight of polymer, up to 1, 0000 and beyond this level there is no much effect. To allow chain interpenetration, the polymer molecule must have an adequate length.

2. Concentration of active polymers:

   There is an optimum concentration of polymer corresponding to the best bioadhesion infect, in concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous, for solid dosage forms such as tablets showed that the higher the polymer concentration the stronger the bioadhesion.

3. Flexibility of polymer chain:

   Flexibility is an important factor for interpenetration and enlargement. As water-soluble polymers become cross linked, the mobility of individual polymer chain decreases. As the cross linking density increases, the effective length of the chain which can penetrate into the mucous layer decreases further and mucoadhesive strength is reduced [9].

**b. Environment related factors:**

1. pH:

   pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH because of difference in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide back bone.
2. Applied strength:
   To place a solid bioadhesive system, it is necessary to apply a defined strength.

3. Initial contact time:
   The mucoadhesive strength increases as the initial contact time increases.

4. Selection of the model substrate surface:
   The viability of biological substrate should be confirmed by examining properties such as permeability, electrophysiology of histology.

5. Swelling:
   Swelling depends on both polymers concentration and on presence of water. When swelling is too great a decrease in bioadhesion occurs[9].

c. Physiological Variables:
1. Mucin turnover:
   The natural turnover from the mucus layers is important for at least two reasons.
   a. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers.
   b. Mucin turnover results in substantial amounts of soluble mucin molecules.

2. Diseased states:
   Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye [7],[8],[9].

Method used to study bioadhesion:

   Several test methods have been reported for studying bioadhesion. These tests are important during the design and development of bioadhesion controlled released system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesion bond strength.

The tests can be broadly classified into 2 major categories

1. In-vitro / Ex-vivo methods

2. In-vivo methods

1. In-vitro / Ex-vivo methods:
   Most in-vitro methods were based on either tensile or shear stress.
a. Modified balance or tensile testers.

b. Wilhelm plate method (shear stress).

c. Other in-vitro methods

A number of other methods including thumb test method, adhesion weight method, fluorescent probe method, flow channel method, falling liquid film method, colloidal gold staining method, have been used for the determination of bioadhesion.

2. In-vivo methods:

Rathbone et al. has discussed several methods to study rate and extent of drug loss from human oral cavity. These include buccal absorption test, disks methods and perfusion cells. These methods have provided information on mechanism by which drugs are transported across the oral cavity membranes\(^1\),\(^9\).

**Permeability of oral mucosa:**

A primary function of the oral mucosa is to provide a barrier. At the same time, the oral mucosa shares with the gut, the ability to maintain a moist surface.

**Nature of permeant:**

Molecular size: For hydrophilic substances, the rate of absorption is a function of the molecular size. Small molecules (75-100 Da) appear to cross the mucosa rapidly, but permeability fall rapidly as molecular size increases.

Lipid solubility: For any series of unionizable compounds, their relative permeabilities are function of their oil-water co-efficient with the more lipid-soluble compounds having higher permeabilities.

Ionization: The degree of ionization of a permeant is a function of both its pKa and the pH of the mucosal surface. For many weak acids and weak bases, only the unionized form possesses appreciably lipid solubility. Absorption is observed to be highest when pH values dictate that the drug is present predominantly in the non-ionized form and as the degree of ionization increases with a change in solution pH, the absorption decreases in a characteristic sigmoid fashion.

In general higher fluxes will be obtained by maintaining the pH so that the drug is in the non-ionized form. This can be achieved by inclusion of pH modifiers to the formulation\(^9\).
Possible routes for drug transport across the oral mucosa:
Two potential routes of material transport across the epithelium are:

- The Paracellular pathway
- The Transcellular pathway

The paracellular route involves passage of molecules through the inter-cellular space, while transcellular route involving passage into and across the cell (intracellular). Substances with a high solubility in lipid are expected to transverse the oral mucosa more easily through the inter cellular spaces.

Passive diffusion is undoubtedly the major transport mechanism for drugs; the nutrients from the mouth are shown to be absorbed by carrier systems i. e. facilitated diffusion.

Transmucosal permeation of polar molecules, such as peptide based pharmaceuticals, may be by way of paracellular route, however several barriers exists during the course of paracellular permeation \(^9\).

Permeation enhancers:

Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity.

Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination \(^5,^6\).

Categories and examples of membrane permeation enhancers

A. Bile salts and other steroidal detergents: Sodium glycocholate, Sodium taurocholate, Saponins, Sodium tauro dihydro fusidate and Sodium glycol dihydro fusidate.

B. Surfactants:
   1. Non- ionic: Laureth-a, Polysorbate-9, Sucrose esters and do-decyl maltoside
   2. Cationic: Cetyl trimethylammonium bromide
   3. Anionic: sodium lauryl sulfate

C. Fatty acids: oleic acid, lauric acid, caproic acid
D. Other enhancers:

1. Azones
2. Salicylates
3. Chelating agents
4. Sulfoxides e.g. Dimethyl Sulfoxide (DMSO)

Mechanism of Buccal Absorption Enhancer:

The mechanism by which enhancers act are been poorly understood. Surfactants such as sodium lauryl sulphate interact at either the polar head groups or the hydrophilic tail regions of the molecules comprising the lipid bilayer disrupting the packing of the lipid molecules, increasing the fluidity of the bilayer and facilitating drug diffusion. Interaction of enhancers with the polar head groups may also cause or permit the hydrophilic regions of adjacent bilayers to take up more water and more apart, thus opening the Para cellular pathway. Non ionic surfactants and long chain acids and alcohols also increase membrane components, thereby increasing the permeability. Agents such as DMSO, polyethylene glycol, and ethanol can, if present insufficient high concentrations in the delivery vehicle enter the aqueous phase of the stratum corneum and alter its solubilizing properties, thereby enhancing the partitioning of drugs from the vehicle into the skin\cite{5, 6}.

✔ Mechanisms by which permeation enhancers are thought to improve mucosal absorption include the following:

- Changing mucus rheology
- Increasing fluidity of lipid bilayer membrane
- Affecting the components involved in the formation of intracellular junctions
- Overcoming the enzymatic barrier
- Increasing the thermodynamic activity of drugs

Some review regarding the work done on Mucoadhesive Buccal Drug Delivery Systems:

Oral cavity was studied as a site for bioadhesive drug delivery. The review focuses on an overview of oral mucosa, bioadhesion, formulation factors,
residence time, and bioadhesive dosage forms different bioadhesive polymers, theories of bioadhesion, measurement of bioadhesion. The various bioadhesive dosage forms discussed were adhesive tablets, adhesive gels, patches, and ointments.\textsuperscript{[11]}

Buccal mucosa was studied as a route for systemic delivery. The objective was to review buccal drug delivery by discussing the structure and environment of the oral mucosa and the experimental methods used in assessing buccal drug permeation or absorption.\textsuperscript{[12]}

Buccal tablets of Diltiazem hydrochloride were studied. They were prepared and evaluated for in-vitro drug release. In situ testing was done using bovine cheek pouch membrane in a Franz diffusion cell. Maximum drug release was 86% obtained.\textsuperscript{[13]}

Drug release was studied from oral mucosal adhesive tablets of Diltiazem were prepared by directly compressing the drug with a mixture of chitosan and sodium alginate. In-vitro adhesion studies indicated adhesion properties comparable to those of a commercial formulation.\textsuperscript{[14]}

Sustained release and buccal adhesive Propranolol hydrochloride tablets prepared by direct compression technique. The formulation containing 20% hydroxypropyl methylcellulose yielded good sustained release matrix tablets. Buccal adhesive controlled release tablets were prepared by compression of HPMC with polycarbophill, the adhesion force was affected by mixing ratio of HPMC and PAA in the tablet and the weakest adhesion force was observed at ratio of 1:1 (HPMC: PAA) as compared to the conventional Propranolol (40mg), a single dose of 20% HPMC (160mg) produced smoother plasma level profile, with lower and delayed peaks.\textsuperscript{[15]}

In-vitro release and permeation of Oxytocin from a mucoadhesive buccal patch by using rabbit buccal mucosa mounted on diffusion cell was studied.\textsuperscript{[16]}

Absorption of Thyrotropin- Releasing Hormone was studied in rats using a mucoadhesive patches by in-vitro and in-vivo studies in rats. TRH patches placed
on the buccal mucosa of anesthetized rats demonstrated rapid stimulation and release of Thyroid-stimulating hormone (TSH) from the anterior pituitary.\[17\]

Mucoadhesive buccal films of Clotrimazole was designed and evaluated for oral Candida infections. The buccal films were formulated using solvent casting technique by using various polymers, Carbopol 934P, Carbopol 974, HPC-M, HPMC-E4M, Eudragit NE-30D, Eudragit RL PM and propylene glycol as an plasticizer. A number of different bioadhesive films were evaluated on the basis of their physical characteristics, bioadhesive performances, release characteristics, surface pH, folding endurance, and stretch ability.\[18\]

In-vitro studies on buccal strips of Glibenclamide using chitosan, Eudragit and polyvinyl Pyrrolidone, and propylene glycol as a plasticizer was studied. Prepared strips were evaluated for physical characteristics, percentage swelling and in-vitro release studies in dissolution apparatus type-2 (paddle method).\[19\]

Buccal mucoadhesive films and mucoadhesive gels of Theophylline using hydroxypropyl methylcellulose, ethyl cellulose and Carbopol was designed. The drug release pattern and stability studies of these formulations were studied. \[20\]

Mucoadhesive films of Acyclovir for transbuccal delivery for systemic action by using novel mucoadhesive, copolymers of acrylic acid and poly (ethylene glycol) was designed. Films were prepared for unidirectional release and evaluated for in-vitro permeation studies using porcine buccal mucosa up to 20 hours with a time lag.\[21\]

Transmucosal sustained-delivery of Chlorpheniramine maleate in rabbits was studied and demonstrated using a novel, natural mucoadhesive gum (Hakea gibbose) as an excipient in buccal tablets.\[22\]

Mucoadhesive buccal disks made from HPC, ethyl cellulose, and Carbopol 934 was developed for novel Nalbuphine prodrug controlled delivery and studied for effect of formulation variables on drug release and mucoadhesive performance.\[23\]

Diltiazem hydrochloride buccal patches was prepared and evaluated by solvent casting technique using hydroxyl propyl methyl cellulose, polyvinyl Pyrrolidone, polyvinyl alcohol, ethyl cellulose and hydroxypropyl cellulose in various
proportion and combination with two different plasticizer, glycerol and castor oil.[24]

Mucoadhesive films of Miconazole was developed and evaluated by using various polymers, Carbopol 934P, HPMC-E15, HPMC-E4M, HPC-L, HPC-M, HPMC and propylene glycol as a plasticizer. [25]

Systemic absorption of Propranolol hydrochloride from buccoadhesive films was studied by using sodium carboxy methyl cellulose, Carbopol, polycarbophill, in different ratio and combinations with unidirectional drug release were applied to rabbit oral mucosa and inhibition of isoprenaline-induced tachycardia was achieved. [26]

Buccoadhesive tablets of Miconazole nitrate was formulated and evaluated. They were developed using Carbopol 934P in combination with second polymer which was hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose, hydroxypropyl cellulose or sodium alginate.[27]

Polymeric film dosage forms of Lidocaine for buccal administration was developed. Films were prepared by three different methods, direction compression of physical mixture (DCPM), direct compression of spray-dried powder, and by solvent evaporation and characterized the different formulations in different compressing pressure as well as lubricant effect on release rate. [28]

Mucoadhesive tablets of Lignocaine hydrochloride was developed by using Carbopol 934P, sodium carboxy methylcellulose, and polyvinylpyrrolidone-K30 and evaluated for surface pH, swelling studies, in-vitro as well as in-situ release studies.[29]

Indomethacin microcapsules was prepared and evaluated with a coat consisting of alginate and a mucoadhesive polymer such as sodium carboxymethylcellulose, methyl cellulose, Carbopol and hydroxypropylmethylcellulose by an emulsification-ionic gelation process.[30]

Buccal delivery of Thiocolchicoside was studied by using different parameters likes’ in-vitro (through porcine mucosa) and in-vivo (buccal tissue of pigs) release studies were carried out and the in-vitro in-vivo correlation was established[31]
Mucoadhesive films of nystatin were prepared. The design and formulation of the films were based on the mucoadhesive properties of carbomer 934P (CB) and carboxymethycellulose (NaCMC), and also on the plasticizer properties of polyethylene glycol 400 (PEG400). A surfactant (ascorbyl palmitate, ASC16) was added to the system to aid in nystatin dispersion.[32]

Mucoadhesive drug delivery systems were proposed. Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. [33]

The drug delivery using buccal adhesive systems were proposed. The buccal mucosa has been investigated for local drug therapy and the systemic delivery of the therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. [34]

The oral availability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism lead to poor patient compliance was proposed. [35]

Optimized the process variables on drug encapsulation efficiency, release rates, size, and morphology of polymeric microspheres of gellan gum and poly (vinyl alcohol) by the emulsion cross-linking method were prepared. Carvedilol, an antihypertensive drug, was successfully loaded into these microspheres prepared by changing the experimental variables such as ratio of gellan gum: poly (vinyl alcohol). [36]

Unidirectional buccal films of Isosorbide dinitrate were developed and characterized. The films were formulated by solvent casting method using different bioadhesive polymers like Carbopol 934P and polyvinyl Pyrrolidone by using two different plasticizers propylene glycol and diethyl phthalate. [37]

Matrix type transdermal therapeutic systems were developed containing Carvedilol with different ratios of hydrophilic and hydrophobic polymeric
combinations like ethyl cellulose, Eudragit RL, Eudragit RS and polyvinylpyrrolidone by the solvent casting technique. \[38\]

Buccal patch for systemic administration of Carvedilol were developed and evaluated in the oral cavity using two different mucoadhesive polymers like HPMC E 15, HPC JF and propylene glycol as a plasticizer. \[39\]

CONCLUSION

There is no doubt that the oral route is the most favored and probably most complex route of drug delivery. Critical barriers such as mucus covering the GI epithelia, high turnover rate of mucus, variable range of pH, transit time with broad spectrum, absorption barrier, degradation during absorption, hepatic first pass metabolism, rapid luminal enzymatic degradation, longer time to achieve therapeutic blood levels, and intrasubject variability, are all possible issues with oral route. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing.

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