REVIEW ARTICLE

BUCCAL DRUG DELIVERY A TECHNICAL APPROACH

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ABSTRACT

Over the last few years Pharmaceutical scientists are trying to explore transdermal and transmucosal routes as an alternative to injections. Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s. Conventional dosage forms for delivery of drugs via the oral mucosa include solutions, erodible or chewable, buccal or sublingual tablets and capsules. Unfortunately, a major portion of the drug in these systems may be unavailable due to involuntary swallowing and a very short residence time, because of mastication, speech etc and hence sustained release is usually not within the scope of such Formulations and development of Novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations. We formulated buccal drug delivery, the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Because buccal Adhesive 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 limited absorption surface and thus contribute to improved better therapeutic efficacy of the drug. Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions. Buccal drug delivery has gained significant attention and momentum since it offers remarkable advantages. This review article is an overview of buccal drug delivery systems encompassing a review of oral mucosa, active ingredient delivered via buccal route by different mucoadhesive formulations. Including, commercial technologies and future prospects of this route of drug delivery are discussed.

Keywords: Mucoadhesion, Mucoadhesive polymers, Microspheres, Controlled drug delivery

INTRODUCTION

The pharmaceutical industry has made considerable interest making it a major participant in the healthcare industry. The advances and progress made by pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life[1]. Amongst the various routes of drug delivery, the oral route is most preferred to the patient and the clinician alike. However, peroral administration of drugs has Disadvantages such as hepatic first pass metabolism and enzymatic degradation within the gastro intestinal (GIT), that prohibit oral administration of certain classes of drugs especially peptides and proteins. Other absorptive mucosae, are considered as potential site for drug administration. Transmucosal routes of drug delivery (mucosal linings of nasal, rectal, Vaginal, ocular and oral cavity) offers distinct advantages over peroral administration for Systemic drug delivery. These advantages include possible bypass of first pass effect, Avoidances of pre-systemic elimination within GIT and better enzymatic flora for drug absorption[1-3]. In buccal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa. One of the reasons is that buccal mucosa is less permeable and is thus not able to elicit a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral transmucosal drug delivery. Over the past few decades, the concept of use of bioadhesive polymers to prolong the contact time has gained remarkable attention in transmucosal drug delivery. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another. Bioadhesion may be defined as the state in which two materials, at least one of which is biological membrane, are held together by means of interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion[4]. Drug absorption into the oral mucosa is mainly via passive diffusion into the lipoidal membrane. Compounds with partition coefficient in the range 40-2000 and pKa 2-10 are considered optimal to be absorbed through buccal mucosa. Compounds administered by buccal route include steroids, barbiturates, papain, trypsin etc[5].

In 1980's, Professor Joseph R. Robinson at the University of Wisconsin pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer which covers epithelial tissues makes such polymers very useful excipients in drug delivery[6]. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Buccal patches are more accurate dosing than gels and ointments[7]. Mucoadhesive drug delivery systems are delivery systems which utilize the

property of bioadhesion of certain polymers, which become adhesive on hydration. The attachment as adhesion could be 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. The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, ear, nose and eye. These represent potential sites for attachment of any bioadhesive system and hence, the mucoadhesive drug delivery system includes: Buccal drug delivery, Oral drug delivery, vaginal drug delivery, rectal drug delivery, nasal drug delivery and ocular drug delivery[8].

BUCCOADHESIVE DRUG DELIVERY SYSTEM

The buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral mucosa can be distinguished according to five major regions in the oral cavity.

- The buccal mucosa (cheeks)
- The gum (gingival)
- The palatal mucosa
- The inner side of the lips
- The floor of the mouth (sublingual region)

In oral cavity, delivery of drugs can be classified into three categories[10]:

- Buccal delivery
- Sublingual delivery
- Local delivery

IDEAL CHARACTERISTICS OF BUCCAL DRUG DELIVERY[11]

- Should have good wetting and solubility and biodegradability properties
- Polymer and its degradation products should not be non-toxic, and free from leachable impurities
- Should adhere quickly to buccal mucosa and should posses sufficient Mechanical strength, Should posses peel, tensile and shear strength at the bio adhesive range
- Polymer should be easily available and its cost should not be high
- Should show bioadhesive properties in both dry and liquid state
- Should demonstrate local enzyme inhibition and penetration enhancement properties, should posses adhesively active groups
- Should have optimum molecular weight
- Should demonstrate acceptable shelf life
- Should have required spatial confirmation
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups

ADVANTAGES OF BUCCAL DRUG DELIVERY

Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism, Improved patient compliance due to the elimination of associated pain with injections, Sustained drug delivery and a relatively rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. Increased ease of drug administration, The large contact surface of the oral cavity contributes to rapid and extensive drug absorption, Extent of perfusion is more therefore quick and effective absorption, nausea and vomiting are greatly avoided. Used in case of unconscious and less cooperative patients. Drugs, which show poor bioavailability via the oral route, can be administered conveniently, ex; drugs which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine[12, 13,14].

DISVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY

Once placed at the absorption site & the dosage form should not be disturbed. The drug swallowed in saliva is lost. Properties like unpleasant taste or odour, irritability to the mucosa & stability at salivary pH possess limitations to the choice of drug. Only drugs with small dose can be administered, eating and drinking may become restricted[15, 16].

MECHANISM OF 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. "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.

In the study of adhesion generally, two steps in the adhesive process have been identified, which have been adapted to describe the interaction between mucoadhesive materials and a mucous membrane as shown below **(Fig 1):**

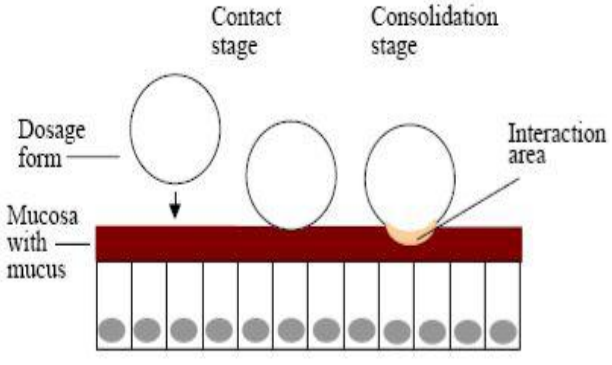

Figure 1: Stages in mucoadhesion (Adopted from N.S. Miller *et al*; Adv Drug Del Rev; 2005)[13]

Type 1. Contact Stage

An intimate wetting occurs between the mucoadhesive and mucous membrane. In some cases these two surfaces can be mechanically brought together, e.g. placing and holding a delivery system within the oral cavity, eye or vagina.

Type 2. Consolidation Stage

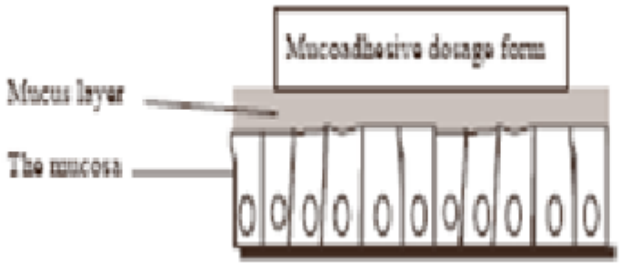

Figure 2: The three regions within a mucoadhesive joint (Adopted from J.D. Smart *et al*., Adv Drug Del Rev; 2005)[4]

Different physicochemical interactions happen to combine and toughen the adhesive joint, leading to long-lasting adhesion **(Fig 2).** Mucoadhesive materials adhere most strongly to solid dry surfaces as long as they are activated by the presence of moisture and will effectively plasticize the system allowing mucoadhesive molecules to become free, conform to the shape of the surface and bond predominantly by hydrogen and weaker van der Waal bonding.

Type 3. The Removal Mechanism

Adhesive failure will normally occur at the weakest component of the joint. For weaker adhesives this would be the mucoadhesive-mucus interface, for stronger adhesives this would initially be the mucus layer, but later may be the hydrating mucoadhesive material. The possible regions for mucoadhesive joint failure are shown in **Fig 3.**

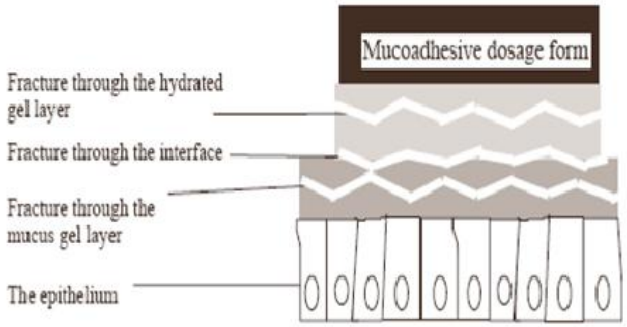

Figure 3: The possible regions for mucoadhesive joint failure (Adopted from JD Smart *et al*, Adv Drug Del Rev; 2005)[4]

THEORIES OF BIOADHESION

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

Wetting theory: 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 (γ) being defined as energy per cm^2 released when an interface is formed). According to Dupres equation.

Diffusion theory: According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between cross links and decreases significantly as the cross linking density decreases.

Electronic theory: According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucus 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 layer.

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

Adsorption theory: 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) are involved in the adsorption process[18].

FACTORS AFFECTING BIOADHESION

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

Polymer related factors

Molecular weight: The bioadhesive force increases with molecular weight of polymer up to 10,000 and beyond this level there is no much effect. To allow chain interpenetration, the polymer molecule must have an adequate length.

***Concentration of active polymers*:** There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous.

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 mucus layer decreases further and mucoadhesive strength is reduced.

Environment related factors

pH: The 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.

Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength.

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

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

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

Physiological variables

Mucin turnover: The natural turnover from the mucus layer is important for at least two reasons.

- The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers.
- Mucin turnover results in substantial amounts of soluble mucin molecules.

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[19,20].

FORMULATIONS FOR BUCCAL DRUG DELIVERY

Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–6 h.

Buccal adhesive polymers

Mucoadhesive polymers are the important component in the development of buccal delivery systems. These polymers enable retention of dosage form at the buccal mucosal surface and thereby provide intimate contact between the dosage form and the absorbing tissue. These formulations are often water soluble and when in a dry form attract water from the biological surface which in turn leads to a strong interaction between the dosage form and mucosal layer.

An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.

- The polymer and its degradation products should be nontoxic and nonabsorbable in the gastrointestinal tract
- It should be nonirritant to the mucus membrane
- It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces
- It should adhere quickly to moist tissue and should possess some site specificity
- It should allow easy incorporation of the drug and offer non hindrance to its release.
- The polymer must not decompose on storage or during shelf-life of the dosage form

Criteria followed in polymer selection

- It should form a strong non covalent bond with the mucin/epithelial surface
- It must have high molecular weight and narrow distribution

It should be compatible with the biological membrane[21]. The polymers that are commonly used as Bioadhesive in pharmaceutical applications are in Table. 01

Table: 1 Mucoadhesive polymers used in the oral cavity[43]

Criteria	Categories	Examples
Source	**Semi natural**	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate)
	Cellulose derivatives [CMC, thiolated CMC, Sodium CMC, HEC, HPC, HPMC, MC, MHEC]	Thiloated CMC,HEC,HPC, **Poly(acrylic acid)-based polymers** [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), PVA
Aqueous solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate,sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan

GENERAL CONSIDERATIONS IN FORMULATION DESIGN

Physiological considerations

The designing of buccal dosage form physiological factors such as surface of buccal mucosa, limiting device size, drug load, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered. Saliva contains certain enzymes (esterases, carbohydrases, phosphatases) that may degrade some drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. Saliva has a weak buffering capacity to maintain pH value within local regions. These disadvantages can be avoided by developing unidirectional release systems with backing layer. This concept may also results in high drug bioavailability[22].

Pharmacological considerations

Buccal drug absorption depends on the partition coefficient of the drugs. Lipophilic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the paracellular route. This behaviour leads to the assumption that chemical modification may increase drug penetration through buccal mucosa. Increasing nonionized fraction of ionisable drugs increases drug penetration

through trans-cellular route. In weakly basic drugs, the decrease in pH increases the ionic fraction of drug but decreases its permeability through buccal mucosa. Other pharmacological factors include residence time and local concentration of the drug in the mucosa, treatment of oral diseases, the amount of drug transported across the mucosa into the blood. Similar dependencies on partition coefficients were obtained from acyclovir, β-adrenoreceptor blocking agents and substituted acetanilide[21].

Pharmaceutical considerations

Factors affecting the drug release, penetration through buccal mucosa, organoleptic factors, and effects of other excipients used to improve drug release pattern and absorption, irritation caused at the site of application are to be considered while designing a formulation. Excipients enhancing palatial properties are often required to improve acceptability of dosage form or masking less/desirable properties of the bioactive constituent. Some additives can be incorporated to improve drug release pattern and absorption. Ideally pharmaceutical buccal adhesive drug delivery systems should contain mucoadhesive agents, penetration enhancers and enzyme inhibitors. Mucoadhesive agents are used to maintain an intimate and prolonged contact of the formulation with the absorption site while penetration enhancers improve the drug permeation across mucosa (trans-mucosal delivery) or into deepest layers of the epithelium (mucosal delivery). The enzyme inhibitors ideally protect the drug from the degradation by means of mucosal enzymes[21].

BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal dosage forms are meant to be placed between gingival and cheek. Buccal adhesive dosage forms are those dosage forms which can deliver drugs either locally to treat conditions within the buccal cavity or systemically via the mucosa. It often requires that buccal-adhesive dosage forms should remain adhesive and allow a controlled delivery of drug for prolonged periods. Therefore, for sustained drug delivery, buccal adhesive formulations must contain elements that remain adhesive for a prolonged period, regulate the rate and direction of drug delivery[9, 21, 22]. The different types of Buccoadhesive dosage forms are

Buccal tablets

Buccal tablets are intended to be held in the mouth, where they release their drug contents for absorption directly through the oral mucosa. A buccal tablet may release drug rapidly or may be designed to release drug slowly for a prolonged effect, give improved bioavailability of drug due to avoidance of first-pass metabolism and also improves patient compliance by reducing repetitive dose. Unlike conventional buccal tablets, these tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. Tablets intended for buccal administration by insertion into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure only to give a hard tablet[23].

Buccal films

Films are the most recently developed dosage form for buccal administration. Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. Bioadhesive films are similar to laminated patches in terms of their flexibility and manufacturing process. They are usually manufactured by a solvent casting method. The drug and polymer(s) are first dissolved in a casting solvent or solvent mixture. The solution is then cast into films, dried and finally laminated with a backing layer or a release liner. The backing layer helps to retard the diffusion of saliva into the drug layer, thus enhancing the adhesion time and reducing drug loss into the oral cavity. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method[24,25].

Buccal gels and ointments

Semisolid dosage forms, such as gels and ointments have the advantage of easy dispersion throughout the oral mucosa. 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 bioadhesive formulations. Certain bioadhesive polymers, e.g. HPMC, poloxamer 407, sodium carboxymethylcellulose, Carbopol, hyaluronic acid and xanthan gum undergo a phase change from a liquid to a semisolid. This change enhances the viscosity, which results in sustained and controlled release of drugs. A highly viscous gel was developed from Carbopol and hydroxyl propyl cellulose for ointment dosage forms that could be maintained on the tissue for up to 8 h[9, 22].

Buccal patches

Patches are laminates consisting of an impermeable backing layer, the drug containing reservoir layer from which the drug is released in a controlled manner and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermal drug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness and patches of predetermined size and shape are then cut or punched out[24,25].

FORMULATION DESIGN

In the case of both mucosal and transmucosal administration, conventional dosage forms are not able to assure therapeutic drug levels on the mucosa and in the circulation. This is because of the physiological removal mechanisms of the oral cavity (washing effect of saliva and mechanical stress), to obtain the therapeutic action, it is therefore necessary to prolong and improve the contact between the active substance and the mucosa. To fulfill the

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therapeutic requirements, formulations designed for buccal administration should contain the following functional agents: mucoadhesive agents, to maintain an intimate and prolonged contact of the formulation with the absorption site; penetration enhancers, to improve drug permeation across mucosa (transmucosal delivery) or into deepest layers of the epithelium and enzyme inhibitors, to eventually protect the drug from the degradation by means of mucosal enzymes[26,19,21].

Mucoadhesive agents

Different situations for buccal mucoadhesion are possible depending on the dosage form. In the case of dry or partially hydrated formulations, polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favour polymer chain flexibility and interpenetration between polymer and mucin chains. So, depending on the type of formulation, polymers with different characteristics have to be considered,

The polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad categories:

- Polymers that become sticky when placed in water and owe their bio adhesion to Stickiness
- Polymers that adhere through nonspecific, noncovalent interactions that are primarily electrostatic in nature
- Polymers that bind to specific receptor sites on the cell surface[22].

Permeation enhancers

Penetration enhancers are also required when a drug has to reach the systemic circulation to exert its action. These must be non-irritant and have a reversible effect the epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids (that act by disrupting intercellular lipid packing), surfactants and among these bile salts (by extracting membrane protein or lipids, by membrane fluidization, by producing reverse micellization in the membrane and creating aqueous channels), azone (by creating a region of fluidity in intercellular lipids) and alcohols (by reorganizing the lipid domains and by changing protein conformation).

Categories and examples of membrane permeation enhancers

- Bile salts and other steroidal detergents
- Surfactants: Non-ionic, Cationic, Anionic
- Fatty acids
- Other enhancers: Azones, Salicylates, Chelating agents, Sulfoxides[27].

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 bilayer to take up more water and more apart, thus opening the par cellular pathway. Non ionic surfactants and long chain acids and alcohols also increase membrane components, thereby increasing the permeability.

Agents such as dimethyl sulfoxide, polyethylene glycol and ethanol, if present in sufficient high concentrations in the delivery vehicle can enter the aqueous phase of the stratum corneum and alter its solubilising properties, thereby enhancing the partitioning of drugs from the vehicle into the skin.

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[23,28,29].

METHOD OF PREPARATION OF MUCOADHESIVE PATCHES

Mucoadhesive buccal patches can be prepared by methods mentioned below;

Solvent casting method: Mucoadhesive patches are prepared by solvent casting method. All ingredients were accurately weighed and mixed in pestle and mortar. Then the mixture added gradually to magnetically stir solvent system, which contain the plasticizer. Continue the stirring until a clear solution is obtained. The solution is then transferred quantitatively to Petri-dish. The Petri-dish covered with inverted funnels to allow evaporation of the solvents. These are kept at 20 - 25 °C temperature for 24 to 48 hours depending upon the solvent system used. Size of patches are 15 to 20 mm diameter, 0.2 to 0.3 mm thick are carefully pull out from the Petri dishes [30, 31, 32].

Semisolid casting: In semisolid casting method, initially prepare a solution of water soluble film forming polymer. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which is prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtain. Finally the gel mass is cast into the films using heat control drums.

Hot melt extrusion: In hot melt extrusion method, firstly the drug is mixed with carriers in solid form. Then the extruder containing heaters are used to melt the mixture. In the end, the melt are given the shape of films with the help of dies. Hot melt extrusion have merit as patches prepared through this method have better content uniformity [33].

Solid dispersion extrusion: In this method immiscible components are extruded with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by mean of dies.

Rolling method: In rolling method a solution or suspension containing drug is rolled on a carrier. Solvent is mainly water and mixture of water and alcohol. Film is dried on the rollers and cut into desired shapes and sizes[34].

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EVALUATION OF BUCCAL PATCHES

Physical properties

Physical appearance and surface texture of patch: This parameter was checked simply with visual inspection of patches and evaluation of texture by feel or touch.

Weight uniformity of patches: Three patches of the size 10 mm diameter were weighed individually using digital balance and the average weights were calculated.

Thickness of patches: Thickness of the patches was measured using screw gauge with a least count of 0.01mm at different spots of the patches. The thickness was measured at three different spots of the patches and average was taken[35].

Folding endurance of patches: The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patches (approximately 2x2 cm) at the same place till it broke. The number of times patches could be folded at the same place without breaking gives the value of folding endurance[36].

Swelling index of patches: The swelling Index of the patches determined by immersing pre weighed patch of size 2cm2 in 50 ml water. The strip was taken out carefully at 5 &10 min. intervals, blotted with filter paper & weighed accurately[36].

Surface pH of patches: Surface pH was determined by the patches were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrating for 1 min.

Mechanical properties

Bursting strength of patches: A test for measuring the resistance of a film to bursting and reported in kilo-Pascal or pounds per square inch or Kg / cm^2. The bursting strength of all the films were evaluated by using standard bursting strength tester.

In vitro residence time of patches: The *in vitro* residence time was determined using IP disintegration apparatus. The disintegration medium was 500 mL of simulated saliva (pH 6.8), maintained at 37 ± 2 ºC. The segments of rat intestinal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using simulated saliva (pH 6.8) and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded[37].

Drug polymer interaction study of patches: There is always a possibility of drug-excipient interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Formulations were scanned by using Perkin-Elmer FTIR, by a thin film method.

***Drug content uniformity of patches*:** The patches were tested for drug content uniformity by UV-Spectrophotometric method. Patches of 10 mm diameter were cut from three different places from the casted patches. Each patch was placed in 100 ml volumetric flask and dissolved in simulated saliva pH 6.8 and 1 mL is taken and diluted with water up to 10 mL. The absorbance of the solution was measured at suitable wavelength using UV/visible spectrophotometer. The percentage drug content was determined[38].

In vitro drug release: *In vitro* release studies were carried out by attaching sigma dialysis Membrane to one end of the open cylinder which acted as donor compartment prepared buccal patches containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer and then temperature was maintained at 37 ± 1 ºC. Receptor compartment consist of 100 mL of pH6.8 simulated saliva, sample of 2 mL were withdrawn at periodic intervals from Receptor compartment & replaced with fresh phosphate buffer immediately and the drug release was analyzed spectrophotometrically at suitable wave length. Release rate was studied for all designed formulations[39, 40, 41, 42].

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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