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Buccal Patches: Boon To Oral Drug Delivery System

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ABSTRACT

Buccal administration of drug provides a convenient route of administration for both systemic and local drug actions. The preferred site for retentive oral transmucosal delivery systems and for sustained and controlled release delivery device is the buccal mucosa. Rapid developments in the field of molecular biology and gene technology resulted in generation of many macromolecular drugs including peptides, proteins, polysaccharides and nucleic acids in great number possessing superior pharmacological efficacy with site specificity and devoid of untoward and toxic effects. However, the main impediment for the oral delivery of such drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Direct access to the systemic circulation through the internal jugular vein bypasses drug from the hepatic first pass metabolism leading to high bioavailability. The objective of this article is to review the developments in buccal adhesive drug delivery system as patches.

Keywords: Buccal mucosa, buccal patches, mucoadhesion, permeation.

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INTRODUCTION

The effect of a drug can now be reinforced as a result of the development of new release systems. Controlled release consists of techniques that make the active chemical agents available for a target, providing an adequate release rate and duration to produce the desired effect. The main controlled drug delivery systems currently available include matrices, pellets, floating systems, liposomes, microemulsions, liquid crystals, solid dispersions, nanosuspensions, transdermal systems, cyclodextrin inclusion complexes, osmotic pumps and bioadhesive systems.[1] The extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time to get the desire benefit, not only for local targeting of drugs but also for the better control of systemic drug delivery.[2]

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration.[3] The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival) . With the advances and progress in biotechnology, hydrophilic high molecular weight therapeutic agents such as proteins and peptides are readily available for therapeutic use. However, when administered by the oral route, these agents suffer from problems such as degradation and poor absorption. To overcome these obstacles and for successful delivery of proteins and peptides, the buccal route of drug delivery has acquired significant attention.[4]

Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration. The mucoadhesive drug delivery system is delivery system 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. Buccal cavity has wide variety of functions and it acts as an excellent site for the absorption of the drugs. It provides direct entry of drug molecules into the systemic circulation, and avoids hepatic first pass metabolism and gastrointestinal drug degradation.[5]

Advantages of Buccal Drug Delivery System[6, 7, 8]

Drug administration via buccal mucosa offers several distinct advantages:

1) The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2) Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
3) Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.

4) Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5) High patient acceptance compared to other non-oral routes of drug administration.
6) Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers.
7) Increased residence time combined with controlled API (Active Pharmaceutical Ingredient) release may lead to lower administration frequency.
8) Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
9) As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
10) Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.
11) It offers a passive system of drug absorption and does not require any activation.

Disadvantages [6, 7, 8]

The main challenges of buccal administration are:

1) Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm of which ~50 cm represents non-keratinized tissues, including buccal membrane.
2) Barrier properties of the mucosa.
3) The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
4) The hazard of choking by involuntarily swallowing the delivery system is a concern.
5) Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.
6) Drugs with large dose are difficult to be administered.

OVERVIEW OF ORAL CAVITY[9]

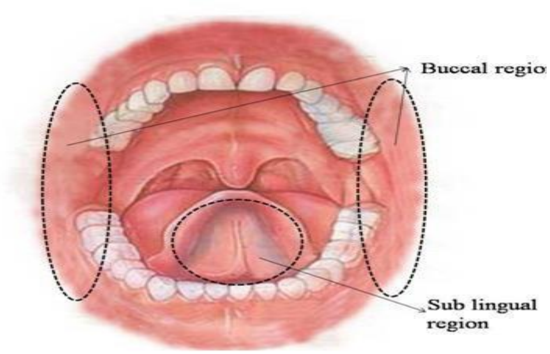

Figure 1: Anatomy of Oral Cavity

The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly-vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via net of capillaries and arteries lying underneath.

1) The mucus-secreting regions consisting of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinized epithelium.
2) The hard palate and the gingiva are the regions of the masticatory mucosa and have a normally keratinized epidermis.
3) Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

Buccal Mucosa[10, 11, 12]

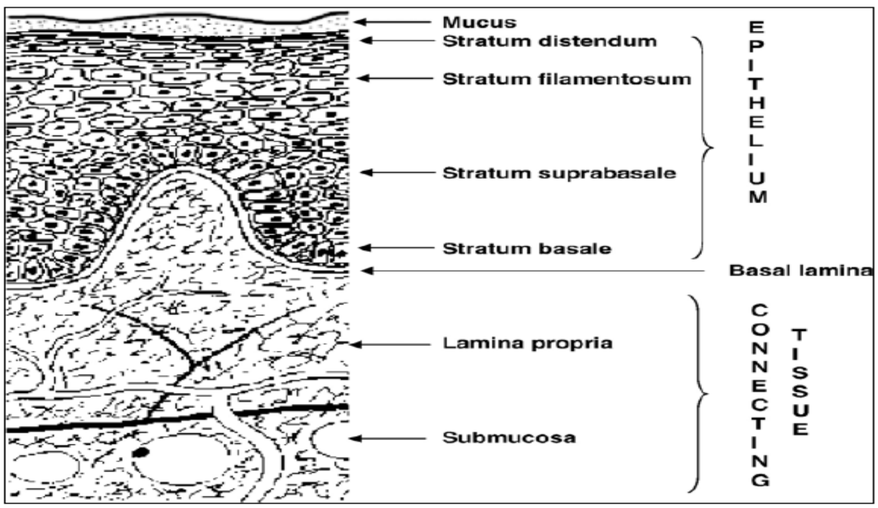

Figure 2: Cross Section of Buccal Mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelium of the buccal mucosa is about 40-50 cell layers thick. The turnover time for the buccal epithelium has been estimated at 5-6 days. The oral mucosal thickness varies depending on the site; the buccal mucosa measures at 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongued, and the gingivae measure at about 100-200µm. The mucosae of the soft palate, the sublingual, and the buccal regions, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function.

The non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides. They also contain small amounts of neutralbut polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia. In the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor glands. At physiological pH the mucus network carries a negative charge (due to sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer.

Saliva[4]

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 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. Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral mucosa.

Saliva serves multiple important functions:

1) It moistens the mouth, initiates digestion and protects the teeth from decay.
2) It also controls bacterial flora of the oral cavity.
3) Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions.
4) It protects the teeth by forming “protective pellicle”. This signifies a saliva protein coat on the teeth, which contains antibacterial compounds.

The Mucus Layer[9]

Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological state. However, it has the following general composition

1. Water - 95%
2. Glycoproteins and Lipids - 0.5 to 5%
3. Mineral salts - 0.5 to 1%
4. Free Proteins - 0.5 to 1%

Mechanism of Drug Transport[13, 14, 15, 16]

The mechanisms by which the drugs cross biologic lipid membranes are passive diffusion, active transport, and pinocytosis. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion, although facilitated diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of low concentration within the buccal tissues. Further diffusion then takes into the venous capillary system, with the drug eventually reaching the systemic circulation via jugular vein.

The basic drugs transport mechanism for the buccal epithelium is the same as that for other epithelia in the body. Two major routes are involved: Transcellular (intracellular) and Paracellular (intercellular).

The transcellular route may involve permeation across the apical cellmembrane, intracellular space and basolateral membrane either by passive transport (diffusion, pH partition) or by active transport (facilitated and carrier-mediated diffusion, endocytosis). The transcellular permeability of a drug is a complex function of various physicochemical properties including size, lipophilicity, hydrogen bond potential, charge and conformation. Transportation through aqueous pores in the cell membranes of the epithelium is also possible for substances with low molar volume (80 cm/mol).

The second route, available to substances with a wide range of molar volumes, is the intercellular route (paracellular route).within the intercellular space, hydrophobic molecules pass through the lipidic bilayer, while the hydrophilic molecules pass through the narrow aqueous regions adjacent to the polar head groups of the lipids.

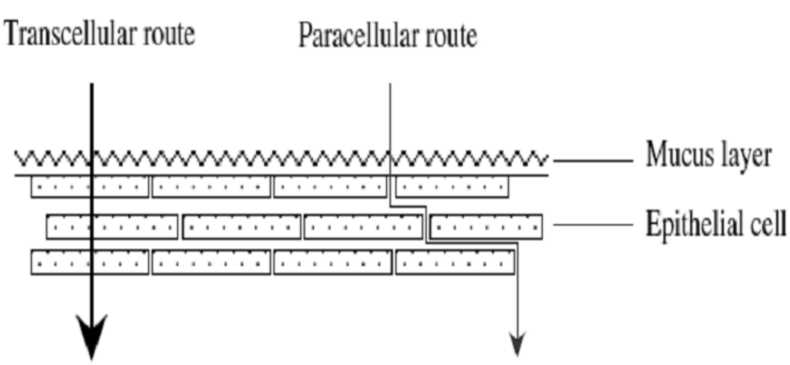

Figure 3: Mechanism of Drug Transport

BUCCAL PATCHES [17, 18]

Buccal patch is a non dissolving thin matrix modified-release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time.

TYPES OF BCCCAL PATCHES[1, 17]

Matrix type (Bi-directional): The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth.

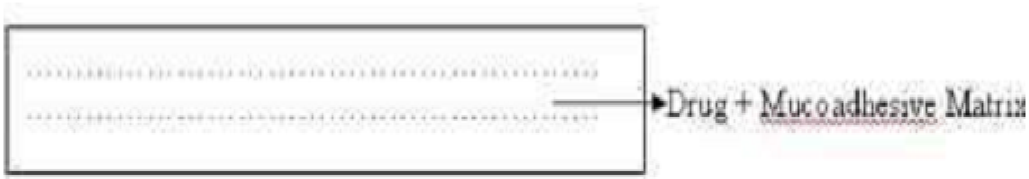

Figure 4: Bi-Directional Buccal Patch

Reservoir type (Unidirectional): The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

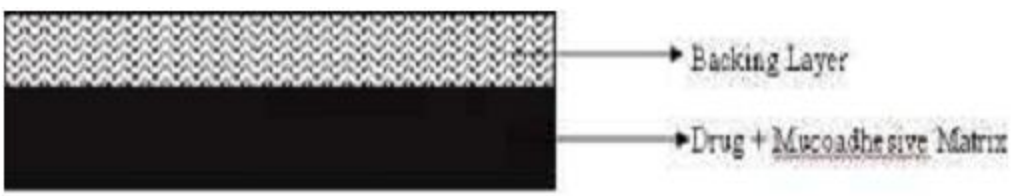

Figure 5: Unidirectional Buccal Patch

Basically unidirectional types of buccal patches are used for drug delivery in the buccal cavity for local as well as systemic effect.

Characteristics of an Ideal Buccal Patch[9, 19, 20]

An ideal buccal adhesive system should possess the following characteristics:

1) Quick adherence to the buccal mucosa and sufficient mechanical strength.
2) Drug release in a controlled fashion.
3) Facilitates the rate and extent of drug absorption.
4) Should have good patient compliance.
5) Should not hinder normal functions such as talking, eating and drinking.
6) Should accomplish unidirectional release of drug towards the mucosa.

7) Should not aid in development of secondary infections such as dental caries.
8) Possess a wide margin of safety both locally and systemically.
9) Should have good resistance to the flushing action of saliva.

Table 1: Composition of Buccal Patches

Active ingredient	
Mucoadhesive Polymers	HPMC, HPC, HEC, Carbopol, Eudragit, PVP, PVA, Chitosan, Sodium CMC, Thiolated Polymers
Backing Membrane	Ethyl Cellulose
Penetration Enhancers	Glycol, Polysorbate 80, Sodium Lauryl Sulphate, etc
Plastcizer	Polyethylene Glycol, Propylene Glycol, Glycerol,Etc

Active Pharmaceutical Ingredient

For buccal drug delivery, it is cardinal to prolong and augment the contact between API and mucosa to obtain the desired therapeutic effect. Buccal adhesive drug delivery systems with the size 1-3 cm and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6 h.[19]

The important drug properties that affect its diffusion through the patch as well as the buccal include molecular weight, chemical functionality and melting point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties.[20]

Following are the critical properties for candidature to Buccal Mucoadhesive Drug Delivery:

1) The conventional single dose of drug should be low.
2) The drug should not adversely affect the natural microbial flora or oral cavity.
3) Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

Mucoadhesive polymers (Mucoadhesives)

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: poly meaning many and mermeaning parts. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus.[19]

The adhesion of materials with mucosa can be considered as the result of the following steps: Polymer hydration, wetting of mucosa, diffusion into the mucus and chemical bonding with glycoprotein. Hydrated polymer wets the mucus when interatomic and intermolecular forces occur at the interface. The formulation of an assembly is determined by a liquid-solid contact step and thus, the criteria of good wetting and free energy of interaction between the two materials should be considered.

After the initial contact between the hydrated polymer and the mucus, the mucoadhesion strength is determined by the formation of secondary chemical bonds due to polymer chain/mucin interpenetration, which is affected by polymer flexibility and mobility. Hence, the ideal bioadhesive polymer should have satisfactory surface energy and chain flexibility favoring its spread and diffusion into the mucus and functional groups forming secondary chemical bonds (for examples, ionic and hydrogen bonds)[14]

New generation of mucoadhesive polymers (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to the mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. Examples of such are the incorporation of L-cysteine into thiolated polymers and the target-specific, lectin mediated adhesive polymers.

Thiolated polymers or designated thiomers are mucoadhesive basis polymers, which display thiol bearing side chains. These polymers are obtained by addition of conjugated sulfidryl groups. Thiolated polymers are a type of second-generation mucoadhesive polymer derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The thiolated polymers help to increase the mucoadhesive property.[6]

Table 2: Mucoadhesive Polymers for Buccal Patches[11, 19, 21]

Criteria	Categories	Examples
Source	**Semi-natural/Natural**	Agarose, chitosan, gelatin Hyaluronic acid Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	**Cellulose derivatives** CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose **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), polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous Solubility	**Water soluble**	CP, HEC, HPC (water < 38ºC), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	**Cationic**	Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan

	Anioic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Nonionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive Forces	**Covalent**	Cyanoacrylate
	Hydrogen Bonding	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

Characteristics Of Ideal Mucoadhesive Polymers[22, 23, 24]

An ideal polymer for buccoadhesive drug delivery system should have the following characteristics:-

1) The polymer and its degradation products should be non-toxic and non-absorbable from the GIT.
2) It should be non-irritant to the mucous membrane.
3) It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.
4) It should adhere quickly to moist tissue and should possess some site specificity.
5) It should allow easy incorporation of the drug and offer no hindrance to its release.
6) The polymer must not decompose on storage or during the shelf life of the dosage form.
7) The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Backing Membrane[25]

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.

Permeation Enhancer[14]

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers.One of the major disadvantages associated with buccal drug delivery is the low flux of drugs across the mucosal epithelium, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration and absorption enhancers to increase the flux of drugs through the mucosa. Because the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosa have been shown to improve buccal drug penetration. Drugs investigated for buccal delivery using various permeation and absorption enhancers vary over a wide range of molecular weight and physicochemical properties.

Mechanisms of Action of Permeation Enhancers[10, 15]

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

1) **Changing mucus rheology**:

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

2) **Increasing the fluidity of lipid bilayer membrane**:

   The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.

3) **Acting on the components at tight junctions**:

   Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

4) **By overcoming the enzymatic barrier**:

   These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

5) **Increasing the thermodynamic activity of drugs**:

   Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

Table 3: Example of Permeation Enhancers: [19, 26]

Category	Examples
Surfactants	**Ionic** Sodium lauryl sulfate, Sodium laurate, Polyoxyethylene-20-cetyl ether,Laureth-9, Sodium dodecyl sulfate(SDS), Dioctyl Sodium sulfosuccinate **Non-ionic** Polyoxyethylene-9-lauryl ether (PLE) , Tween 80, Nonylphenoxypolyoxyethylene (NP-POE), Polysorbates, Sodium glycocholate.
Bile Salts and Derivatives	Sodium deoxycholate, Sodium taurocholate, Sodium taurodihydrofusidate (STDHF), Sodium glycodihydrofusidate, Sodium glycocholate, Sodium deoxycholate.
Fatty acids and Derivatives	Oleic acid, Caprylic acid,Mono(di)glycerides,

	Lauric acid, Linoleic acid, Acylcholines, Acylcarnitine, Sodium caprate, Oleic acid.
Chelating Agents	EDTA, Citric acid, Salicylates.
Sulfoxides	Dimethyl sulfoxide(DMSO), Decylmethyl sulfoxide
Polyols	Propylene glycol, Polyethylene glycol, Glycerol, Propanediol.
Monohydric Alcohols	Ethanol, Isopropanol.
Others	Urea and derivative, Unsaturated cyclic urea, Azone (1-dodecylazacycloheptan-2-one), Cyclodextrin, Enamine derivatives, Terpenes, Liposomes, Acyl carnitines and cholines.

Plasticizers[25]

These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. Usually the percentage of polymer falls in the range of 10-50% of total polymer weight. The plasticizers help in release of the drug substance from the polymer base as well as act as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer- polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity.

Preparation Of Mucoadhesive Patches[27, 28]

Mucoadhesive buccal patches can be prepared by the following methods:-

Solvent Casting Method:

Mucoadhesive patches are prepared by solvent casting method. All ingredients were accurately weighed and mixed in pestle and mortal. 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 20-25ºC 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.

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.

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.

EVALUATION OF BUCCAL PATCHES

The following tests are used to evaluate the Buccal Patches: Drug Content Uniformity, *Ex-vivo* Residence Time, Thickness Testing, *In-vitro* drug permeation studies, *In-vitro* release studies, Moisture absorption studies, Surface pH study, *In-vitro* bioadhesion measurement, Stability in human saliva, etc.

Physical evaluation[29, 30]

It includes- Weight uniformity, Content uniformity, Thickness- uniformity, mass uniformity. Mass uniformity tested in different randomly selected patches from each batch and patch thickness measured at 5 different randomly selected spots using a screw gauge.

Surface pH[31, 32]

Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.

Folding endurance[33]

To determine folding endurance, a strip of patch is cut and repeatedly folded at the same place till it broke. The number of times the patch could be folded at the same place without breaking gives the value of folding endurance.

Swelling Index[34, 35]

Buccal adhesive dosage forms were weighed individually (w1) and placed separately in Petri dishes containing 4ml of phosphate buffer ph 6.6 at regular intervals(0.5,1,2,3,4,5,6 hours).

The dosage forms were removed from the Petri dishes and excess surface water was removed using filter paper. The dosage form were reweighed (w2) and swelling index (SI) was calculated as follows, SI= (W2-W1)/W1

Ex-vivo bioadhesion test[28, 36, 42]

The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.

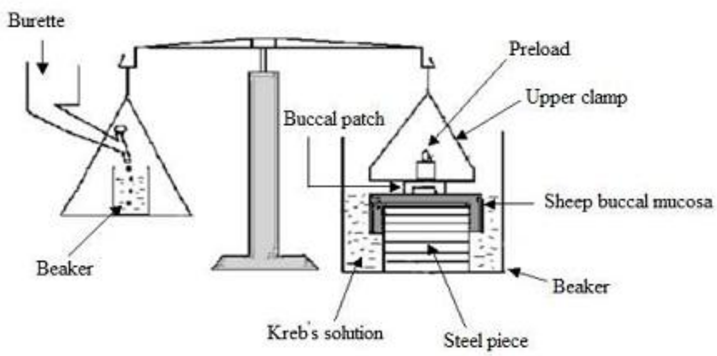

Figure 6: Ex-vivo bioadhesion test apparatus

Measurement of Mucoadhesive strength

In vitro drug release[17, 37, 40]

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution.

In vitro drug permeation studies[13, 28]

The *in-vitro* buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer.

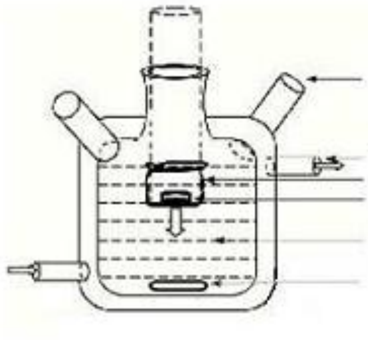

Figure 7: Keshary-Chien/Franz Diffusion Cell

Ex-vivo Mucoadhesion Time[28, 38]

The *ex-vivo* mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch and drug content is noted.

Stability Studies in Human Saliva[17, 28, 39]

The stability study of buccal patches is performed in natural human saliva. The human saliva was collected from humans (age 18-50 years). Buccal patches placed in separate Petri dishes containing 5 mL of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the patches are examined for change in colour, shape and drug content.

Ageing[17, 31]

Patches subjected to accelerated stability testing. Patches packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5°C and 75±5% RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored bioadhesive patches investigated after 1, 2, 3, 4, 5, and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope.

FUTURE TRENDS

Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. The future challenge in the development of buccoadhesive dosage forms is to modify the permeability barrier of the mucosa using safe and effective penetration enhancers. Mucoadhesive drug delivery systems available in the market include aftach tablet (Triamcinolone acetonide), suradrintablet (Nitroglycerin), Buccostem tablet (prochlormperazine maleate), Salcoat powder sprays (Beclomethazone- dipropionate), Rhinocort powder spray (Beclomethazone Dipropionate) and sucralfate (Aluminum hydroxide). Though there are only a few mucoadhesive formulations available currently, it can be concluded that drug delivery using mucoadhesive formulations offers a great potential both for systemic and local use in the near future. Various strategies are being employed to achieve oral absorption of peptides. These strategies include manipulation of the formulation (e.g. inclusion of penetration enhancers or protease inhibitors etc.), maximizing retention of the delivery system at the site of absorption, and alteration of the peptide so as to optimize affinity for endogenous transport systems, build in chemical and metabolic stability, minimize the size and optimize the balance between lipophilicity and hydrogen bonding potential.

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. Studies on mucoadhesive systems have focused on a broad array of aspects. It is a growth area whose goal is the development of new devices and more “intelligent” polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon. Mucoadhesive buccal patches is a novel drug delivery system because it has several advantages over the conventional drug delivery system. The drugs delivery via the buccal route is safe, because drug absorption can be promptly terminated in case of toxicity by removing buccal dosage form from buccal cavity and number of drugs can be administered through mucoadhesive buccal patches. The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their deliver rates, biodegradation, and site specific targeting can be predicted, monitored and controlled.

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