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A Review on Mucoadhesive Buccal Patch

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ABSTRACT:

The buccal region of the oral cavity is an attractive site for drug delivery. Through this route, it is possible to carry out the administration of mucosal (local side effects) and transmucosal drugs (systemic side effects). In the first case, the goal is to obtain a specific release of the drug site to the mucosa, while the second case involves absorption of the drug through the mucous barrier to reach the systemic circulation. Absorption through the buccal mucosa exceeds premature drug degradation due to enzymatic activity and pH of the gastrointestinal tract, avoiding active drug loss due to presynaptic metabolism, acid hydrolysis, and therapeutic plasma drug concentration rapidly achieved. The adhesive properties of such drug delivery platforms can reduce enzymatic degradation due to the larger intimacy between the delivery vehicle and the absorbing membrane. However, for oral administration of drugs, there are disadvantages such as the first-pass metabolism of hepatic and enzymatic degradation within the gastrointestinal tract, which inhibits the oral administration of certain classes of drugs, in particular, peptides and protein. As a result, other absorbent mucous membranes are considered potential sites for drug administration. Transmucosal drug delivery routes offer unique advantages in oral administration for systemic drug delivery.

KEY WORDS: Buccal Delivery, Mucoadhesion, Buccal Patch, Mucoadhesive Polymers, Permeation Enhancer, Evaluation of Buccal Patch.

INTRODUCTION

Oral drug delivery has been the main route for drug delivery over the decades. For systemic delivery, the oral route was the preferred route of administration for many systemically active drugs[1,2].

Recent research efforts have recently focused on positioning a drug delivery system in a particular body region to maximize the availability of biological drugs and minimize dose-dependent side effects. Buccal drug delivery provides an alternative to other conventional methods of systemic drug delivery since the buccal mucosa is relatively permeable with a rich blood supply and serves as an excellent site for drug absorption[3,4].

In oral administration of drug product, drug molecule directly enters into the systemic circulation, avoiding first-pass metabolism and drug degradation in the difficult gastrointestinal environment, which are often associated with oral administration[5-8]. The oral cavity is easily accessible for self-medication, so it is safe and well accepted by patients because the buccal patches can be easily administered and even removed from the application site, interrupting the acceptance of the drug whenever required. Furthermore, buccal patches offer more flexibility than other drug deliveries.

Oral Mucosal Sites

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

- Sublingual delivery
- Buccal delivery

- Local delivery

Sublingual delivery

This is systemic delivery of drug through the mucosal membrane lining the floor of the mouth[9]. Buccal delivery and Local delivery: for the treatment of conditions of the oral cavity. The oral cavity is the foremost part of the digestive system of the human body. It is also referred to as "buccal cavity". It is accountable for various primary functions of the body.

The oral cavity can help in the development of a suitable mucoadhesive drug delivery system. The buccal mucosa lies in the inner cheek, and formulations are placed in the mouth between the and cheek and upper gums to treat local and systemic conditions. The buccal route provides one of the conceivable routes for small drug molecules as well as conventional for typically large proteins, oligonucleotides, and polysaccharides. The oral cavity has been used as a site for local and systemic drug delivery[10].

Buccal delivery

Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo the first-pass effect[11]. The stratified squamous epithelium supported by a connective tissue lamina propria, which is present in buccal mucosa[12], was targeted as a site for drug delivery several years ago. Problems accompanied with the oral route of administration such as extensive metabolism by the liver, drug degradation in the gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route[13,14]. The buccal route appears to offer a number of advantages, like good accessibility, the robustness of the epithelium, usage of the dosage form in accordance with need, and comparatively less susceptibility to enzymatic activity. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets[15,16], adhesive gels[17,18], and adhesive patches[19].

The permeation of hydrophilic drug through the membrane is one of the major limiting factors for the development of bioadhesive buccal delivery devices. The epithelium that lines the buccal mucosa is the main barrier for the absorption of drugs[20]. In order to improve buccal absorption, several approaches have been introduced. Increased permeation of the drug through the buccal membrane and prevention of the drug degradation by enzymes was achieved by changing the physicochemical properties of the drug[21]. Alternatively, improving the adhesion and release characteristics of buccal delivery devices increases the amount of drug available for absorption[22]. The incorporation of absorption enhancers to the buccal formulation is one interesting approach. Substances that facilitate the permeation through buccal mucosa are referred to as permeation enhancers[23]. Different types of potential permeation enhancers have been studied for the buccal route to increase the penetration of drugs[24,25]. The complexation of steroidal hormones with cyclodextrins was not effective in increasing the permeation through buccal route, whereas condensation products of cyclodextrin with propylene oxide or epichlorohydrins were able to form complexes with estradiol, testosterone, and progesterone, thereby enhancing absorption through the buccal membrane in humans[26]. The delivery of hydrophilic macromolecular drugs via buccal membrane was made possible by the incorporation of absorption or permeation enhancers, which could reduce barrier properties of the buccal epithelium[27]. The aim of the present study was to discuss oral mucosa and approaches for buccal drug delivery system.

Local delivery

It is drug delivery into the oral cavity[28].

POTENTIAL ADVANTAGES OF BUCCAL PATCH[29]

The oral mucosa has a rich blood supply. The drugs are absorbed through the oral mucosa and transported through the deep or facial vein of the tongue, the internal jugular vein, and the brachiocephalic vein into the systemic circulation.

- Buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first-pass effect. Avoid contact with the digestive fluids of the gastrointestinal tract, which may be unsuitable for the stability of many drugs, such as insulin or other proteins, peptides and steroids. In addition, the rate of ingestion or emptying of the stomach does not affect the rate of absorption of drugs.
- The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per month, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.

- The oral buccal patch is well known for its good accessibility to the membranes that cover the oral cavity, which makes the application painless and comfortable.
- Patients can monitor the period of administration or end the delivery in case of emergency.
- Oral drug delivery systems are easily inserted into the oral cavity.
- The novel buccal dosage forms exhibit better patient compliance.

LIMITATION[30]

- The area of the absorptive membrane is relatively smaller. If the effective area for absorption is dictated by the dimensions of a delivery system, this area then becomes even smaller.
- Saliva is constantly released in the oral cavity by diluting drugs at the absorption site, which leads to low drug concentrations on the surface of the absorbent membrane. Involuntary use of saliva leads to the fact that a significant part of the released drug is dissolved or suspended and removed from the absorption site. In addition, there is a risk of swallowing the delivery system.
- Drug characteristics may limit the use of the oral cavity as a place for drug administration. Taste, irritation, allergies, and adverse properties such as discoloration or erosion of the teeth may limit the list of drug candidates for this route. The usual type of oral drug delivery system did not allow the patient to eat, drink or, in some cases, speak at the same time.

MUCOADHESIVE DRUG DELIVERY SYSTEM

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology [31]. adhesion can be defined as a relationship between a pressure-sensitive adhesion and a surface. The American Society for Testing and Materials has defined it as a condition in which two surfaces are held together by interfacial forces, which may consist of valence forces, interconnected actions, or both. Mucoadhesive drug delivery systems extend the residence time of the dosage form at the site of absorption. They facilitate close contact of the dosage form with the underlying absorbent surface and, thus, improve the therapeutic characteristics of the drug. In recent few years, mostly such mucoadhesive dosage form has been developed for the oral, buccal, nasal, rectal and vaginal routes for both local and systemic effects[32].

Dosage forms intended for the delivery of mucoadhesive preparations should be small and flexible enough to be acceptable to patients, and should not cause irritation. Other desirable characteristics of the mucoadhesive dosage form include controlled drug release (preferably unidirectional release), high drug loading ability, smooth surface, tasteless, good mucoadhesive properties and convenient use. Destructible formulations may be useful because they do not require systemic extraction at the end of the desired dosage interval. A number of suitable mucoadhesive dosage forms have been developed for various drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, were delivered through the mucous membrane, although with relatively low bioavailability (0.1–5%)[33], due to their hydrophilicity and high molecular weight . as well as congenital permeability and enzymatic mucosal barriers.

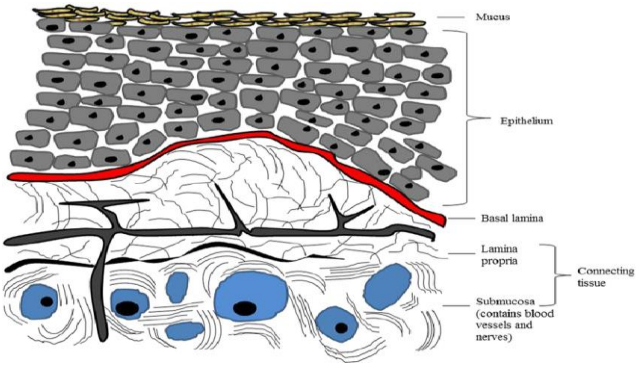

Figure 1: Structure of buccal mucosa

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained the therapeutic effect. They can be removed from the absorption site before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of the presence of dosage form and the sustained release at the site of absorption. In this regard, our review is high lighting a few aspects of mucoadhesive drug delivery systems.

Mucus Membranes

Mucous membranes (mucosae) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single-layered (e.g. the stomach, small and large

intestines, and bronchi) or multilayered/stratified (e.g. in the esophagus, vagina, and cornea). The former contains goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a luminal soluble or suspended form or as a gel layer adherent to the mucosal surface. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of their weight, making them a highly hydrated system[34]. The major functions of mucus are that of protection and lubrication.

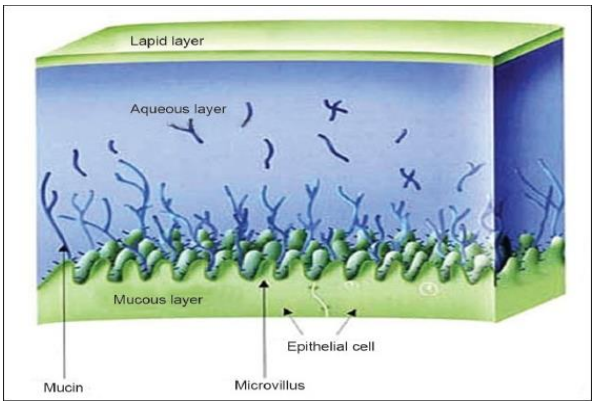

Figure 2: Mucus membrane structure

Mechanisms of Mucoadhesion

The mucoadhesion mechanism is generally divided into two steps: the contact stage and the consolidation stage. The first stage is distributed by the contact between the mucous membrane and mucoadhesive, with spreading and swelling of the formulation, initiating its deep contact with the mucous layer[35].

In the consolidation step, the presence of moisture may activate mucoadhesive materials. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, mucoadhesive molecules and mucous glycoproteins interact with each other through the interpenetration of their chains and the construction of secondary bonds. For this to take place, the mucoadhesive has characteristics that favor chemical and mechanical interactions. For example, molecules with hydrogen bonding groups (–OH, –COOH), an anionic surface charge, high molecular weight molecular chains, and surfactant properties, which help spread through the mucous layer, can have mucoadhesive properties[35-39].

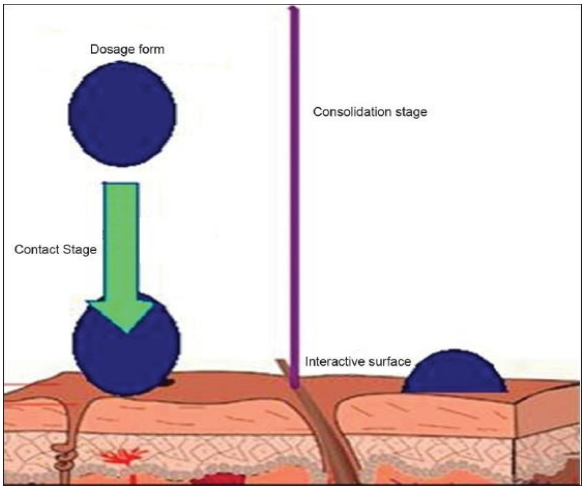

Figure 3: The process of contact and consolidation

METHOD(S) OF PREPARATION

Two methods used to prepare adhesive patches include:

Solvent Casting

In this, all patch excipients including the drug co dispersed in an organic solvent and coated onto a sheet of the release liner. After evaporation of the solvent, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired shape and geometry. 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[40,41].

Water-soluble ingredients are dissolved in H2O and API and other agents are dissolved in:

Suitable solvent to form a clear viscous solution
↓
Both the solutions are mixed
↓
The resulting solution is poured into a film and allowed to dry
↓
Film is collected

Direct Milling

These patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is wound on a release liner until it reaches the desired thickness. An impermeable backing membrane may also be applied to control drug release direction, prevent loss of drug, and minimize disintegration and deformation of the drug product during application period[42].

API and excipients are blended by direct milling
↓
The blended mixture is rolled using rollers
↓
The backing material is laminated
↓
Film is collected

While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent related health issue.

TYPES OF BUCCAL PATCH[43-46]

Matrix Type (Bi-Directional)

The designed of the buccal patch in a matrix configuration contains drug, adhesive and additives mixed together.

Reservoir Type (Unidirectional)

the designed of the buccal patch 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 prevent drug loss and to reduce patch disintegration and deformation while in the mouth.

CHARACTERISTICS OF AN IDEAL BUCCAL PATCH [47,48]

An ideal buccal mucoadhesive system should possess the following characteristics:

- Quick adherence to the buccal mucosa and adequate mechanical strength.
- Should release the drug in a controlled fashion.
- Should facilitate the rate and extent of drug absorption.
- Should possess good patient compliance.
- Should not hinder normal functions such as talking, eating and drinking.
- Should accomplish unidirectional release of drug towards the mucosa.
- Should not aid in the development of secondary infections such as dental caries.
- Should possess a wide margin of safety both locally and systemically.
- Should have good resistance to the flushing action of saliva.

COMPOSITION OF BUCCAL PATCHES

The basic components of the buccal bioadhesive drug delivery system is:

- Active Pharmaceutical Ingredient
- Mucoadhesive polymers
- Backing membrane
- Penetration enhancers
- Plasticizers

Active Pharmaceutical Ingredient (API)

For buccal drug delivery, it is important to prolong and increase the contact between API and mucosa to obtain the desired therapeutic effect. The important drug properties that affect its diffusion through the patch, as well as the buccal mucosa, include molecular weight, chemical functionality, and melting point[48].

The selection of a suitable drug for the design of buccal mucoadhesive drug delivery system should be based on following characteristics[49].

- The conventional single dose of the drug should below.
- The drugs having a biological half-life between 2-8 hours are good candidates for controlled drug delivery.
- The drug absorption should be passive when given orally.
- The drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

Mucoadhesive Polymers

Mucoadhesives are natural or synthetic polymers that interact with the mucus layer that covers the epithelial surface of the mucosa and form an important part of the main mucus molecule[48].

The first step in the development of mucoadhesive dosage forms is the selection and characterization of appropriate mucoadhesive polymers in the formulation. In matrix devices, a polymer is also used in which the drug is embedded in the polymer matrix, which regulates the duration of release of drugs.

Characteristics of ideal mucoadhesive polymers[50,51]

Ideal characteristics of polymer for mucoadhesive drug delivery system are the following:

- The polymer and its degradation products should be non-toxic and non-absorbable from the GIT.
- It should be non-irritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.
- It should adhere quickly to the moist tissue surface and should possess some site-specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.

TABLE 1: MUCOADHESIVE POLYMERS FOR BUCCAL PATCHES[48,52,53]

CRITERIA	CATEGORY	EXAMPLES
Source	**Semi-Natural/Natural**	Agarose, Chitosan, Gelatine, 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, Methyl hydroxyl ethyl cellulose. **Poly(acrylic acid)-based polymers** CP, PC, PAA, Polyacrylates, Poly(methylvinylether-co-methacrylic acid), Poly (2-hydroxyethylmethacrylate), Poly (acrylicacid-coethylhexylacrylate), Poly (methacrylte), Poly(alkylcyanoacrylate),Poly(isohexylcyanoacrylate), Poly (isobutylcyanoacrylate), Copolymer of acrylic acid and PEG **Others** Poly (N- 2- hydroxypropylmethacrylamide), Polyxyethylene, PVA, PVP, Thiolated polymers.
Aqueous solubility	**Water soluble**	CP, HEC, HPC (water < 38ºC), HPMC (cold water), PAA, sodium CMC,
	Water insoluble	Sodium alginate, Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	**Cationic**	Aminodextran, chitosan, dimethylaminoethyl-dextran, trimethylated chitosan
	Anionic	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

Backing Membrane

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucous membrane. the backing membrane material should be inert, and impermeable to the drug and penetration enhancer. The commonly used materials in the backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc[54].

Penetration Enhancers

Substances that facilitate the permeation through buccal mucosa are referred to 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[55].

Mechanisms of action of permeation enhancers[56, 57]

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

Changing mucus rheology

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

Increasing the fluidity of lipid bilayer membrane

the drug absorption mechanism is mostly acceptable through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components.

Acting on the components at tight junctions

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

By overcoming the enzymatic barrier

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

Increasing the thermodynamic activity of drugs

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

TABLE 2: EXAMPLE OF PERMEATION ENHANCERS[48,58]

Category	Examples
Surfactant	**Ionic** Sodium lauryl sulfate, Sodium laurate, Polyoxyethylene20cetylether, Laureth9, Sodium dodecylsulfate(SDS), Dioctyl Sodiumsulfosuccinate **Non ionic** Polyoxyethylene-9-lauryl ether, Tween 80, Nonylphenoxypolyoxyethylene, Polysorbates, Sodium glycolate.
Bile salts and derivatives	Sodium deoxycholate, Sodium taurocholate, Sodium taurodihydrofusidate, Sodium glycodihydrofusidate, Sodium glycocholate, Sodium deoxycholate.
Fatty acid and derivatives	Oleic acid, Caprylic acid, Mono(di)glycerides, Lauric acid, Linoleic acid, Acylcholines, Acylcarnitine, Sodium caprate.

Chelating agent	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:

These are materials used to achieve smoothness and flexibility of thin films of polymer or blend of polymers. the common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil, etc. The plasticizers help in the 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[59].

EVALUATION OF BUCCAL PATCHES

The following tests are used to evaluate the Buccal Patches:

Weight uniformity

Five different randomly selected patches from each batch are weighed and the weight variation is calculated.

Thickness uniformity

The thickness of each patch is measured by using digital vernier calipers at five different positions of the patch and the average is calculated

Folding Endurance

The folding endurance of each patch is determined by repeatedly folding the patch at the same place until it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties[60].

Surface pH

The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature[51]. The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of the three readings is recorded[61].

Drug content uniformity

For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content of is estimated spectrophotometrically. The averages of three determinations are taken[62].

Swelling Index

Buccal patches are weighed individually (W1) and placed separately in Petri dishes containing phosphate buffer pH 6.8. The patches are removed from the Petri dishes and excess surface water is removed using filter paper. The patches are reweighed (W2) and swelling index (SI) is calculated as follows[63,64].

SI = (W2-W1)/W1

Moisture Content and moisture absorption[65]

The buccal patches are weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula:

Moisture content (%) = (Initial weight - Final weightx100)/ Final weight

The buccal patches are weighed accurately and placed in a desiccator containing 100 ml of a saturated solution of aluminum chloride, which maintains 76% and 86% humidity (RH). After 3 days, films are taken out and weighed.

The moisture absorption is calculated using the formula:

Moisture absorption (%) = (Final weight-Initial weightx100)/ Initial weight

In-vitro drug release

To study the drug release from the bilayered and multilayered patches, the United States Pharmacopeia (USP) XXIII-B rotating paddle method is used and 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 the 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 are then filtered through Whatman filter paper and analyzed for drug content after appropriate dilution[66].

Ex-vivo mucoadhesion time

The ex-vivo mucoadhesion (residence) time is determined by locally modified USP disintegration apparatus using 800 mL of simulated saliva (pH 6.2) and the temperature is maintained at (37±1) °C. A porcine buccal mucosa obtained from local slaughterhouse within 2 h of slaughter is used to mimic the human buccal mucosa in the in-vivo conditions. The mucosal membrane is carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane is washed with deionized water and then with simulated saliva (pH 6.2)[67]. Porcine buccal mucosa (3 cm diameter) is glued on the surface of a glass slab. One side of the buccal patch is hydrated with a drop of simulated saliva (pH 6.2) and exposed to the porcine buccal mucosa by gentle pressing with a fingertip for a few seconds. The glass slab is vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch is completely immersed in simulated saliva at the lowest point and is out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface is recorded as ex-vivo mucoadhesion time[68].

Ex-vivo mucoadhesive strength

The force required to detach the attachment of mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive strength and it was carried out on a specially fabricated physical balance assembly. The porcine buccal mucous membrane of the pig's cheek was applied to the dry surface of the Petri dish, placing the surface of the mucous membrane outward, and moistened with a few drops of artificial saliva (pH 6.2). The right side pan of the balance was replaced by a glass disc glued with a buccal patch of 3 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (w1) was removed from the left pan, which lowered the pan and buccal patch was brought in contact with pre-moistened mucosa for 5 min. Then the weight was slowly increased to the left pan until the attachment broke (w2). The difference in weight (w2-w1) was taken as mucoadhesive strength[68].

The mucoadhesive force was calculated from the below equation:

Mucoadhesive force (kg/m/s) = (Mucoadhesive strength (g) x acceleration due to gravity) / 1000 Here, acceleration due to gravity 9.8 m/s−1

Ex-vivo permeation study

The ex-vivo buccal permeation through the porcine buccal mucosa is performed using a modified Franz glass diffusion cell. The porcine buccal mucosa is obtained from a local slaughterhouse and used within 2 h of slaughter. The freshly obtained porcine buccal mucosa is mounted between the donor and receptor compartments. The patch is placed on the smooth surface of the mucosa by gentle pressing and the compartments are clamped together. The donor compartment is moistened with 1 ml of simulated saliva (pH 6.2) and the receptor compartment is filled to touch the membrane with a mixture of 100 ml of ethanol and isotonic phosphate buffer (20:80)[69,70]. The fluid motion in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. The temperature is maintained at (37±0.2) °C by water jacket surrounding the chamber. At predetermined time intervals, a 2 ml sample is withdrawn (replaced with the fresh medium) and analyzed spectrophotometrically. The permeation study is performed in triplicate.

Stability Studies in Human Saliva

The stability study of buccal patches is performed in natural human saliva. Human saliva is collected from humans (age 18-50 years). Buccal patches are 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 color, shape and drug content[71].

CONCLUSION

The buccal mucosa offers several advantages for controlled delivery of drugs over the long term. The mucosa is well supplied with both vascular and lymphatic drainage and avoids the first-pass metabolism in the liver and pre-systemic removal of the gastrointestinal tract. The area is suitable for a maintenance device and appears acceptable to the patient. With proper dosage form design and formulation, the permeability and local mucosal environment can be controlled and manipulated to facilitate drug permeation.

The release of buccal drugs is a promising area for ongoing research with the aim of systematically delivering poor oral drugs, as well as a viable and attractive alternative to the non-invasive release of powerful peptide molecules and proteins. However, the need for safe and effective vestibular permeation/absorption of enhancers is an important component for a promising future in the area of vestibular drug delivery.

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