Review Article

Buccal Drug Delivery System: An Effective Potential in Pharmaceuticals

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ABSTRACT

In the field of drug delivery systems, scientists and researchers work on many novel drug delivery systems that are easily handled and available for therapeutic use. The main purpose of these studies and research is to develop a drug delivery system that targets the desired organs or sites. This means it reduces the side effects and loss of drug in the systemic circulation. The silent point of this topic is to discuss the various advantages of the buccal drug delivery system (BDDS) extremely over the conventional and systemic formulation. In this system bioavailability of the drugs is enhanced via bypassing the first pass metabolisms. The oral mucosal route helps in the better absorption and prolonged residence time of drug because the formulation remains in touch with the mucosal surface. This review discusses the various advantages and disadvantages of the buccal drug delivery system, several anatomies of the oral part especially mucosal, transportation route of drug, and the role of ideal polymers in the buccal drug delivery system. This review even has some details regarding the out there marketed products including tablets, films, patches, gels, and ointments for the buccal drug delivery system.

Keywords: Buccal drug delivery, oral mucosa, residence time, bioavailability.

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INTRODUCTION

Amongst all dosage forms, the oral route is the most preferable route to patients. The disadvantages of the oral route of administration are hepatic 1st pass metabolism and enzymatic degradation of drug or formulation between the GI tract, in which few classes of drugs like proteins and peptides are eliminated[1]. So for overcomes to these problems, the formulation scientists working on such types of problems and developed an alternative way to delivered drugs without degrading in GI tract i.e. via transdermal, buccal, sublingual, intranasal, pulmonary routes, etc. In these alternative routes, Transmucosal routes for drug delivery proposed several advantages over the oral route of drug administration. In this route, mucoadhesion plays a most important role in the drug delivery[2, 3]. Mucoadhesion is a phenomenon that uses the property of bioadhesion of several water-soluble polymers that act as an adhesive when hydrated so this can be used to target a drug into a particular area of the body for a longer period of times. Delivery of the drug through the mucosal layer is now a novel approach that can provide better and effective treatments including topical as well as systemic ones. This special type of dosage forms, that can be used on the thick gel-like structure called mucin, so all bioadhesives need to interact with the mucin layer while the progression of attachments. Transmucosal routes for drug delivery mainly consists of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity that tends to outstanding opportunities and potential advantages[4]. Delivery of drugs throughout the oral mucosa can be divided into three different types[5, 6].

1. **Sublingual drug delivery** – Before going to the systemic delivery, sublingual is the early route of administration. This route avoids the first-pass metabolism and provides faster drug entry to the systemic circulation. In this route, the drug is placed 'under the tongue' region where the present blood vessel provides rapid absorption of the drug as compared to the digestive tract.
2. **Buccal drug delivery** – It comprises of the inner check, where drugs are placed in the mouth between the upper gum or gingivitis and check for treatment of disease locally and systemic.
3. **Local drug delivery** – It comprises of routes of administration from locally or orally.

Advantages of Buccal drug delivery[7]

The administration of the drug through this route has broad advantages, which are as follow-

1. One of the major advantages of this route is that it avoids the 1st pass metabolism and also provides cover from the GI tract's fluids that increase drug bioavailability.
2. As it is consists of many permeable blood vessels near oral mucosa it gives rapid absorption of the drug and faster delivery to the systemic circulations.

3. It developed a better performance of drugs so that they may act as prolonged contact time with the mucosal layer.
4. Due to its flexibility, small size, and prolonged retention time make it better for the patient's compatibility as compared to other routes of administration.
5. The drug that is having higher molecular weight like proteins & peptides, drugs that are unstable in the acidic and alkaline environment are easily administered through these routes.
6. As the absorption is relatively higher so that dose reduction can be easily achieved, this means fewer side effects.
7. Due to this alternative route, numerous types of drugs are administered such as enzymatic, analgesics, narcotics, steroids, cardiovascular agents.

Disadvantages of buccal drug delivery systems[8, 9]

Despite various advantages, these routes have certain challenges and incompatibility. Such are as follow:

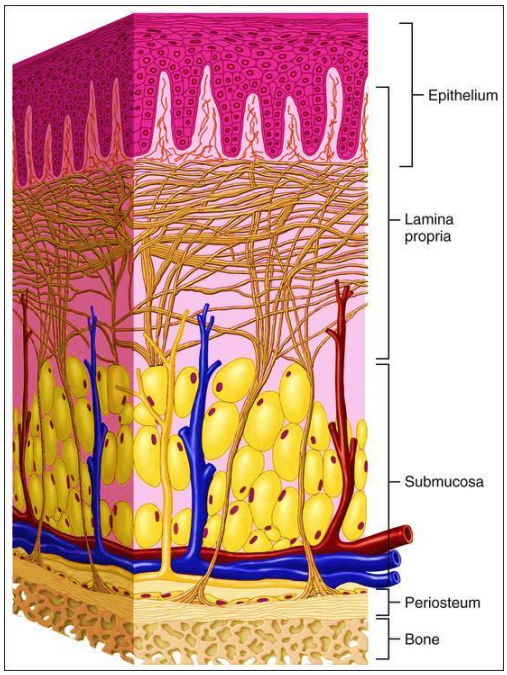
1. One of the major disadvantages of the BDDS is that it has a limited surface area for absorption.
2. While taking buccal dosage form, patients are restricted for eating and drinking.
3. The unremitting secretion of saliva (0.5–2 L/day) results in dilution of the drug (Gandhi and Robinson, 1994).
4. Those drugs that have a bitter taste, unpleasant smell, and odor are not suitable for this route and may causes certain discomfort in the oral mucosa.
5. The pH of buccal also creates problems for those drugs that are unstable at buccal pH and cannot be delivered through these routes.
6. Due to unremitting secretion of saliva which also results in loss of suspended particles and dissolving drugs.
7. Drugs that are absorbed only by the process of passive diffusion can be used & administered through this route.

Overview of the Oral mucosa

Anatomy of oral mucosa- Inside oral mucosa, some various layers and regions provide deep knowledge about the permeation of drug reaches the systemic circulations.

A. **Structure[9]** :

While demonstration under light microscopy, it seems various patterns of maturation in the epithelium taken from human oral mucosa. (Fig.1)

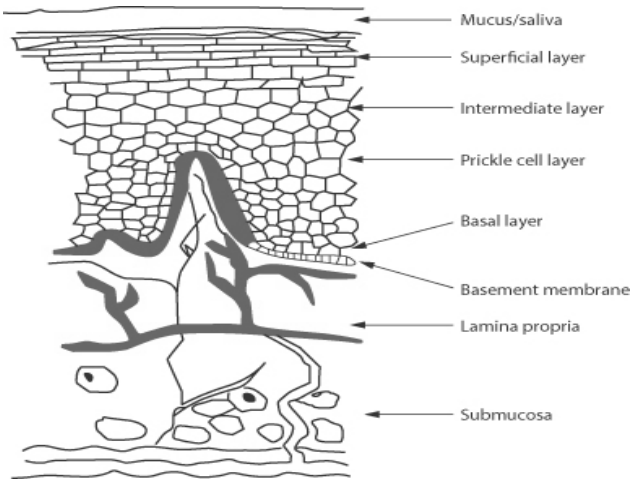


(https://pocketdentistry.com/12-oral-mucosa/)

Figure 1: Microscopic View of Layer Present in Oral Cavity

The oral mucosa is divided into three different layers:

1. Oral epithelium
2. Basement membrane &
3. Connective tissue or Lamina propria



(https://basicmedicalkey.com/drug-absorption-basics-and-the-oral-route/)

Figure 2: Lateral View of Layer of Oral Mucosa

The arrangement of oral mucosa is started with the epithelium, below that a supporting system of the basement membrane is present. This supporting system is again supported with the help of various layers collectively call as connective tissues or lamina propria. (Fig. 2)

1. **Epithelium** – It is also known as a protective layer of the oral mucosa. The epithelium is further divided into – keratinized epithelium and non – keratinized epithelium.

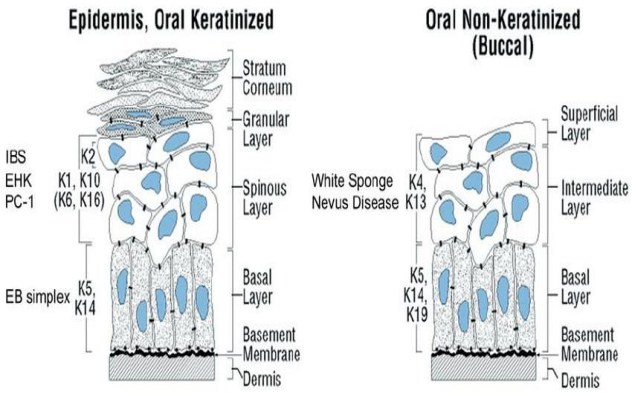


Figure 3: Layers inside of A. Keratinized & B. Non – keratinized Epithelium

a. **Keratinized epithelium**- In keratinized oral mucosa, the epithelium consists of four layers(Fig.3)[10]:

- Stratum basale (basal layer)
- Stratum spinosum (prickle layer)
- Stratum granulosum (granular layer)
- Stratum corneum (keratinized layer)

It protects the surface from abrasion by keratin. It also prevents dehydration and kept hydrated. Keratinized epithelium work as waterproof because it is consists of many layers of dead squamous cells, which are textured to be waterproof and decrease evaporation from underlying tissues. It is lining between the ventral surfaces of the tongue, at the floor of the mouth, lips, cheeks[11].

b. **Non – keratinized epithelium** - In non-keratinized epithelium(Fig.3), there are two deep layers i.e. basale and spinosum which remain the same as keratinized epithelium but the outer layers are named as *intermediate* and *superficial* layers. It is found on the soft palate, on the inner lips, inner cheeks, and the floor of the mouth, and ventral surface of the tongue.

2. **Basement membranes** – This membrane consists of the extracellular matrix that is found in all epithelium tissues. It provides the structural support to the epithelial tissue and makes a mechanical connection between epithelial and lying beneath connective tissue. Basement membrane helps in the regulation of metabolism, proliferation, survival characterization of epithelial cells. Due to the lack of its blood supply, the basement membrane act as a filter that passes all small molecules and derived gases from blood[12].

3. **Connective tissue or Lamina propria** – The deeper layer of the epithelium tissue is known as connective tissue (Lamina propria). It is composed of two layers named as papillary & dense. The surface of the papillary layer consists of loose connective tissue along with the nerve tissue and blood vessels. The deepest tissue i.e. dense layer that contains an abundant amount of fibers. Among the papillary layer and the dense tissue of the lamina propria is a capillary plexus that supplies nutrition to every layers of the oral mucosa[13].

B. **Composition of oral mucosa** – Oral mucosa is mainly composed of 'Mucus', it is a translucent – viscous fluid secreted within oral mucosa and this is a thin gel which works as an adhesive agent on the mucus surface. The epithelial cell which is present in buccal mucosa is occupied by the mucus. The thickness of mucus is approximately 30mm – 310 mm and it varies from region to region.

C. **The function of mucus**[14, 15]

Mucus worked as:

- Barrier
- Bioadhesion
- Lubrication
- Cell-cell adhesion
- Protective

D. **Saliva** –The mucosal membrane covered with the layer of saliva with a coating thickness about to be 75 µm thick. Inside the saliva, mucin is presently named with MG1 which having high molecular weight. This MG1 mucin worked as lubrication, as to maintain hydration inside the oral mucosa. It is composed of 99.5 % of water and consists of glycoproteins, electrolytes, and proteins. The normal saliva is having a pH of 5.6- 7[16]. Saliva plays multiple roles in the oral cavity such as

- It helps in the food digestion by mixing with them.
- It helps in the protection of teeth from decay.
- It also helps in moistening of mouth.
- It protects the teeth by the formation of a 'protective pellicle'.

Mucoadhesion

Mucoadhesion is known as the adhesion between the two surfaces of the materials, at least one of the surface is a mucosal surface. It is use for the adhesion of synthetic and biological macromolecules to biological tissue. It interacts primarily with the mucus layer after applied to the mucosal epithelium and this is called mucoadhesion[17].

Various theories of mucoadhesion

Mucoadhesion involves various types of bonding mechanisms and it is the interaction between every process that allows for the process of adhesion.

1. **Adhesion theory**: In this theory, the bioadhesive materials adhere between two surfaces it is done due to the force acting on the surface between the atoms on both surfaces. According to this theory it helps in the adherence of tissue due to the net results of one or more secondary forces like van-der wall's forces, hydrogen-hydrogen bonding, and hydrophobic bonding[18].

2. **Wetting theory**: This is one of the most oldest and popular theories of mucoadhesion. This theory is applied to the liquid and less viscous mucoadhesive system and practice it is a way to measure the spreadability of active pharmaceutical ingredients that are used across the biological substrate. The measuring technique used in this theory such as the contact angle. In general, rules state that the lower the contact angles than the greater the affinity. For adequate spreadability, the contact angle should be equal or closer to zero[19].
3. **Diffusion theory:** These theories discuss the polymeric chain from the bio-adhesive penetrated into glycoprotein- mucin chain and reaches into adequate depth between the opposite matrix which allows the formation of a semi-permanent bond. This penetration depends on the diffusion coefficient. This process can be visualized at the point of initial contact[19].
4. **Mechanical theory**: This theory is the most accepted theory among all of the others. Within this theory, it analyses the force which is required to detach two surfaces after adhesion[20]. The maximum tensile strength produced while detachment can be calculated by

   The maximum force of detachment [Fm]/ Total surface area [Ao]
5. **Electronic theory**: In this theory, the electrostatic forces are applied between the glycoprotein with mucin network and the bioadhesive materials. Due to different electronic properties of the mucoadhesive polymers and the mucus glycoprotein, which starts electron transfer between these two surfaces[21].

Physiological factors affecting buccal bioavailability[22]:

1. **The thickness of the epithelium**: As the oral epithelium varies in thickness according to the oral cavity. Thickness affects bioavailability where more thickness less bioavailability. The thickness of buccal mucous measures approximately 500-800µm.
2. **Blood supply**: In oral mucosa, lamina propria rich with blood supply and lymphatic network that covers the oral cavity, therefore the drug substance which passes – over the oral epithelium is easily absorbed and reaches the systemic circulation.
3. **Metabolic activity**: When drugs are delivered through the oral mucosa, drug substances are absorbed by the oral epithelium and delivered directly to the systemic circulation and avoid the first-pass metabolism of the liver and gut walls. This property of oral mucosa attracts many enzymatically labile drugs for delivered through these routes such as therapeutic proteins and peptides.
4. **Saliva & mucosa** – In the oral mucosa, there is a continuous production of saliva that results in regularly washed with saliva. The daily production of saliva is approximately 0.5- 2 liters/day. Inside oral mucosa, the sublingual portion is always exposed to a lot of salivae that result in it enhances drug dissolution and that leads to an increase in bioavailability.
5. **Ability to retain delivery system** - The oral mucosa enriches with the smooth and relatively immobile surface due to which it is preferably suited for the use of retentive drug delivery systems.
6. **Transport routes and mechanism** -The drug permeated through the oral epithelium barrier by two main routes(Fig 4) –

   ❖ **The paracellular routes** -In between adjacent epithelium cells.

   ❖ **The transcellular routes**- Apart from epithelial cells that can take place by any of the following mechanisms i.e. passive diffusion, carrier-mediated transport, and via the endocytic process.

Mainly drug administered through buccal mucosa crosses through the paracellular routes via the intercellular lipids that produced by a membrane- coating granules[23].

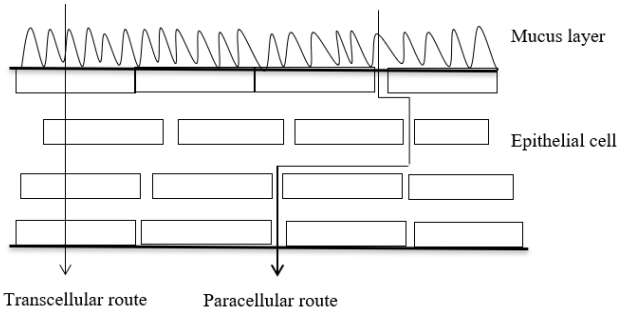


Figure 4: Paracellular and Transcellular Routes Lining Across the Mucosal Membrane for Permeation of Drug Role of Polymers in buccal drug delivery

Polymers play the most important role in buccal drug delivery by controlling the drug release at the target sites. It is a broadly used class of biomaterials that are extensively used in medicines and biotechnology. It is very difficult to classify a polymer for their use as biomaterials become more challenging. Before developing a buccal dosage form, the 1st step is the selection and evaluation of suitable polymer. While selecting a polymer for use as biomaterials it can be both types i.e. naturally occurring and synthetic or a combination of both. Based on easily adhesion to the mucin epithelial surface, a polymer can be divided into three broad categories[24]:

1. A polymer shows its properties of bioadhesion and becomes sticky when it is placed in water.
2. A polymer which adheres to non-specific, non-covalent interaction, that is already electrostatic in Nature.
3. A polymer that easily binds with the specific receptor sites which are present on the surface of cells.

Mucoadhesive polymers:

Mucoadhesive polymers are the most important constituents that are used in the oral delivery dosage forms. The main function of these polymers is to interact with the mucosal layer present at the target sites. The most commonly used polymer used in the buccal drug delivery includes PAA (Polyacrylic acid), PVA (Polyvinyl alcohol), SCMC (Sodium carboxymethyl cellulose), HPMC (Hydroxypropylmethylcellulose), HPC (Hydroxypropyl cellulose) and sodium alginates[25, 26].

Future generation polymer gives a new level of promising for adherence directly to the cell surface instead of the mucosal surface. These types of polymers directly contact with the cell surface with the help of some specific surface receptor present on the target sites or via covalent bonding. Under these classes of polymer grant new possibilities for the delivery of new drug molecules, macromolecules, and also in improving the delivery of specific target sites.

Generally mucoadhesive can be classified into different categories as (Table 1)[27] natural or synthetic; water-soluble or water-insoluble; cationic- anionic or non – ionic, etc.

Table 1: Classification of Mucoadhesive Polymer Used in Buccal Drug Delivery

Criteria	Class	Examples
On the basis of Origin	Natural/semi-natural	Chitosan, gelatin, Hyaluronic acid, various gums (for example- xanthan, pectin, guar, gellan, sodium alginate, hakea, etc.)
	Synthetic	Cellulose Derivatives – CMC, thiolated CMC, HPMC, sodium CMC, Methylhydroxyethylcellulose, etc.
		Others – Polyoxyethylene, PVA, PVP, thiolated polymers
		Poly(acrylic acid)- based polymers polyacrylates, poly(2-hydroxyethyl methacrylate), poly(acrylic acideo- ethylhexylacrylate) etc.
On the Basis of solubility	Water-soluble	PVA, PVP, HPC, HPMC, sodium alginates, SCMC,MC, etc.
	Water-insoluble	Carbopol, polyacrylic acid, PEG, methacrylic acid, EC, PC, etc.
On the basis of Charge	Cationic or Anionic	Pectin, PAA, PC, Carbopol, sodium alginate, CMC, Amino dextran, trimethylated chitosan, etc.
	Non- ionic	Hydroxylated starch, HPC, PVP, PVA, etc.
On the basis of the bonding mechanism	Covalent	Cyanoacrylate
	Hydrogen bonding	PVA, CP, PVA, Acrylate, etc.
	Electrostatic bonding	Chitosan

Characteristics of an ideal polymer that is used for mucoadhesive drug delivery[28, 29]

An ideal polymer used for mucoadhesive drug delivery systems should have the following properties:

- The property of polymer and its degradation products should be non-toxic and non-absorbable in the GI tract.
- It should be a non-irritant to the oral mucosa or mucus membranes. It should ideally form a strong non-covalent bond with the cell surfaces of mucin epithelial.
- It should easily adhere to moist tissue and should get some site-specificity.
- It should permit easily incorporation of the drug and proposed non-hindrance to its release.
- The polymer doesn't decompose on storage or during the shelf life of the dosage form.
- The polymer must be cost-effective.

Role of Penetration enhancers:

Most of the drugs that are delivered through the buccal routes are dependent upon the permeation via the mucosal surfaces. To overcomes these problems penetration enhancers play a supportive role in getting permeation of drug inside buccal routes. Buccal permeation enhancers have properties to disable the penetration barrier of the buccal mucosa. It helps the drug to safely penetrate the barrier inside the buccal drug delivery. There is a various penetration enhancer that improved the drug for easy permeation such as surfactants, bile sites, fatty acids, chelators, ethanol, and chitosan, etc.

Ideal characteristics of buccal penetration enhancer

- It should be non-irritant
- It should be non- toxic
- There should not interaction with either drug or excipients.
- It should be inert.
- There should be not any pharmacological activity within the body.
- It should be compatible with both drugs and excipients.

Buccal mucoadhesive dosage forms

The mucoadhesive dosage form can be categorized as sublingual, buccal, or gingival systems for systemic drug delivery or local drug delivery at any specific site. Inside the oral cavity, the buccal region has been considerably explored and shows promising effects for certain drugs[30].

Based on the geometry the three classes of mucoadhesive dosage forms are as follow (Fig.5)[24, 31]

- **Type I:** In this type, the dosage form is a single layer device with a multi-directional drug release. These dosage forms sustain significant drug loss because of swallowing.
- **Type II:** These types of dosage form consist of a superimposed backing layer which is impermeable placed on top of the drug loaded bioadhesive layer. By forming a double layer device that interrupts drug loss from the top surface inside the oral cavity
- **Type III:** It is a dosage form that releases the drug in unidirectional. That provides the minimal loss of drug due to the drug due to the drug released only from the side adjacent to the oral mucosa. This dosage form is developed by coating every side except the one which is in contact with the buccal mucosa.

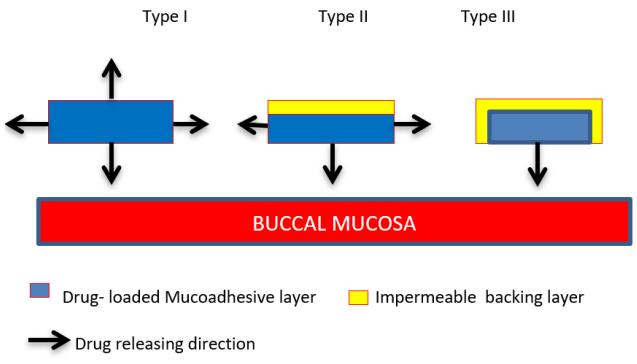


Figure 5: Texture of Different Buccal Mucoadhesive Dosage Forms

These buccal dosage forms can also be grouped as either a 'reservoir' or 'matrix'. In the reservoir, the dosage forms the drug present in excessive amounts and is surrounded by a reservoir i.e. a polymeric membrane. This membrane controls the drug's release rate. While in matrix type systems, it contains a polymer matrix in which drugs are uniformly dispersed. In the system, the drug release is controlled via a polymer network by diffusion method[16].

Buccal dosage forms

Buccal tablets: Tablets are one of the most popular and commonly used dosage forms. The buccal tablets are of different shape and size such as small, flat, and oval-shaped, and similar to conventional tablets, they also make free for drinking and speaking without any major inconvenience.

Different techniques are used for the preparation of bioadhesive tablets which includes direct comparison or wet granulation techniques. In the case of buccal drug delivery, the tablet that is inserted into the buccal patch may dissolve or erode. So that they must be formulated and compared with sufficient pressure only to give a hard tablet. For the achievement of the unidirectional release of drugs, it uses water-impermeable materials, such as ethyl cellulose, hydrogenated castor oil, etc. by applying comparison or by spray coating to coat every face of the tablet except the one that is in contact with the buccal mucosa[32].

Buccal patches: Buccal patches are a non-dissolving thin matrix modified release dosage form. It is composed of more than one polymer film or containing a layer of drug or other specific excipients. As it is used in buccal, it may contain a mucoadhesive polymer layer that helps to bind to the oral mucosa, gingiva, or teeth for the controlled release of the drug into the oral cavity. If it is placed in oral mucosa it worked as unidirectional or when it is kept to the oral cavity it acts as both i.e. bidirectional release. While preparation of the buccal patch it is recommended that it may be dissolved in the mouth and disposed of after a specific time. Two popular methods are used for the preparation of buccal patch:

1. Solvent casting method
2. Direct milling method

In the **solvent casting method**, the solvent were evaporated and the solution of the drug and polymer casted onto a backing layer sheet and from intermediate sheets patches was punched out.

In the **direct milling method**, formulation components are uniformly mixed and compressed to the required thickness, and patch of predetermined size and shape are then obtained by cutting or punched out.

Buccal Film: While the different dosage forms of buccal drug delivery such as tablets, patches, gels, ointments, disc etc. are already available in the market[33, 34, 35, 36]. Instead of that, buccal films are getting more demand because of patient's compliance and convenience. Due to these properties of buccal film, they are highly preferred over other mucoadhesive dosage forms. Because it is comfortable and flexible, they assure more accurate dosing delivery and having higher residence time as compared to gels and ointments. These films are also helping to reduce the pain by covering the wound surface and hence increase

the treatment importance[37]. An ideal buccal film should possess flexibility, elasticity, softness, and strong enough to remain unchanged due to stress from actives in the mouth. The buccal film should also have the property of good mucoadhesive strength, which helps a film to be retained in the mouth for the desired duration[38].

Buccal gels and ointments: Generally, gels are clear, transparent, semisolids which contain solubilized active substances. The main advantage of gel and ointments are they easily dispersed throughout the oral mucosa. The disadvantage of gels and ointments formulation is that they having poor retention at the application sites but this problem has been overcome by using bioadhesive formulation. In this bioadhesive formulation, certain bioadhesive polymer is used such as sodium carboxymethylcellulose[39] that passes off by a phase change that converts a liquid into a semisolid. The transformation increases or improves the viscosity, which results in sustained or controlled release of drugs.

Various parameters on which buccal dosage forms are evaluated

1. **Drug excipients interaction studies:** Preparation of pharmaceutical dosage form containing both API and a greater quantity of excipients may lead to the chance of certain interaction between them due to certain compatibility of the drug. Therefore, evaluation of this interaction between an active drug substance and different excipients play an important role during the stage of development of solid dosage form. Certain technology is available for the study of drug excipient interaction. Some of them are FTIR (Fourier Transform Infra-red spectrum), DSC (Differential Scanning Calorimeter), TLC (Thin Layer Chromatography), XRD (X-Ray Diffraction), etc. Among all of these, DSC is more preferably used technology due to its fast evaluation of possible incompatibilities. It shows if there is any change in appearance, the shift of melting endotherms and exotherms, or any variation in the corresponding enthalpies of the reaction[40].

2. **Physical evaluation:** Physical evaluation of any solid dosage form was done by measuring its weight variation, content uniformity, disintegration, dissolution etc. Among all of these, weight variation can be measured by taking average weight of at least 10 patches from random batch with an individual. Thickness measurement of any film was processed by measuring the film from five direction including center. The mean thickness of a film was calculated by taking variation greater than 5% rest was discarded from analysis. During this evaluation 3 patches were selected individually in 100 ml of volumetric flask , then the 100 ml of phosphate buffer having pH 6.8 added to the film and continuously stirred for 24hrs. The prepared solution was then filtered and diluted suitably. The remaining solution was analyzed by UV – Spectrometer and by taking average the final reading was prepared[41].

3. **Surface pH:** It is necessary to confirm the pH of the buccal patch to avoid any side effects. If the dosage forms either acidic or alkaline pH then it may irritate the buccal cavity. To overcome these problems, the patches are kept to be as close to neutral if possible[42]. To getting this pH, a combination of glass electrodes was used. For this study, the selected patches were kept for swelling with 1ml of distilled water having a pH between 6.5 ± 0.05 for 2hours at room temperature. For the reading of pH, the electrode is brought to contact with the surface of the patch then allowing it to equilibrium for 1min [43].

4. **Swelling studies:** Swelling study is generally the study of increasing wright due to swelling. For this studies take a drug-loaded patch of dimension 1x1 cm^2 and weigh it before the study. Then cover with a pre-weighed coverslip that is kept in a Petri dish. A solution of 50 ml phosphate buffer having pH 6.6 was added to the Petri dish. Interval of every 5 minutes the coverslip was removed and measure the weight for about 30 minutes. After the final minutes, the difference in weight gives the increased weight due to the absorption of water and swelling of the patch[44].

   In another case, swelling studies are defined by an increase in the area due to swelling. For this evaluation, first, select a drug-loaded patch having size 1x1 cm^2 then cut according to requirement and placed in the Petri dish. Within the interval of 5 min for 1hr, the increase in the length and breadth of the patch was noted. The percent swelling (%S) was calculated by applying this equation[45]

$$\% S = \frac{Xt - Xo}{Xo} \times 100$$

Where Xt is the weight or area of the swollen patch after time't'

And Xo is the original patch weight or area at zero time't'

5. **Stability studies in Human saliva:** The stability study of a buccal film is related to the time of dissolving film. This study is performed for the entire batch according to the guidelines by ICH. Under this study, the evaluation was carried out for the drug content after a predetermined time interval including disintegration time and physical appearance[46]. A drug-loaded mucoadhesive patch is performed at 40º C, 37º ± 5º C, and 75 ± 5% RH for at least 3 months[47].

6. **Folding endurance:** Folding endurance of a buccal patch was studied by continuously folding a patch at the same place until it breaks or if possible folds up to 300 times handily. This is one of the good measuring properties of an ideal patch. For calculating the values of the folding endurance of a patch, count the number of times in which the patch is folded at the same place without breaking. At least 5 patches were needed for this evaluation[48].

Marketed mucoadhesive dosage form

Different buccal dosage form that is available in the market are listed below (Table 2)[27]

Table 2: Marketed Mucoadhesive Dosage Form

Brand name	Active drugs	Marketing company	Dosage form	Uses
Nitrocot	Nitroglycerin	Thomson Healthcare Products	Sublingual tablets	Anti- angina
Buccastem	Prochlorperazine	Reckitt Benckiser	Buccal tablets	Nausea, Vomiting
Suscard BT	Glyceryl trinitrate	Forest Pharmaceuticals	Buccal tablets	Anti- angina
Fentora	Fentanyl citrate	Wolters Kluwer Health	Buccal tablets	Opioid analgesics
Buprenorphine HCL	Buprenorphine	Roxane Laboratories	Sublingual tablets	Opioid analgesics
Sitavig	Acyclovir	Cipher Pharmaceuticals	Buccal tablet	Herpes labialis (cold sores)
Onsolis	Fentanyl base	Meda Pharmaceuticals	Buccal soluble film	Opioid pain reliever
Breakyl	Fentanyl citrate	Mylan IRE Healthcare	Buccal film	Pain reliever
Nicoderm CQ	Nicotine	Pfizer	Oral patch	Smoking cessation agent
Anadrol 50	Androgen	Thomson Healthcare Products	Oral patch	Hormonal agent
Isordil	Isosorbide dinitrate	IPCA Laboratories Ltd.	Sublingual tablets	Chest pain (angina)
Ativan	Benzodiazepines	Pfizer	Sublingual tablets	Anxiety, seizure
Aquoral	Dibasic sodium phosphate/ monobasic sodium phosphate/ calcium chloride/sodium chloride	Jazz pharmaceuticals	Oral spray	Dry mouth
PreviDent 5000	Sodium fluoride/ Potassium nitrate	Colgate Oral Pharmaceuticals	Oral paste	Sensitive teeth
Listerine	Cool mint	Pfizer	Buccal film	Mouth freshener

Future prospective

As the buccal drug delivery promises numerous advantages related to bioavailability as well as economically and better patient compliance with easy handling. Currently, scientists are working on many traditional polymers for novel drug delivery. Many polymers are under process for using dosage form including a novel buccal adhesive delivery system for better consideration of bioavailability. Many buccal dosage forms are available in the market like tablets, gels, liquids, which are easily accepted by patients. Delivery of protein - peptides, and vaccines are still challenging. Globally, scientists working on the future formulation of vaccines and protein peptides loaded drug via mucosal delivery. Nanoparticles and microparticles drug delivery through oral mucosa is also an interesting field of research that provides better therapeutic effects related to better and enhanced absorption with increased contact time.

CONCLUSION

Buccal drug delivery dosage forms like patches or films are showing a greater absorption rate of rate and these systems avoid the first-pass metabolism in the liver and pre-systemic elimination in GIT was also seen. The mucosal drug delivery system is a developing and promising area that gives many advantages for better systemic delivery of that drug which are effective via these routes. The mucoadhesive polymer also plays an important role in safe and effective buccal permeation absorption with the combination of permeation enhancers. Also, the buccal adhesive dosage form is very useful in targeting local disorders inside the oral cavity such as mouth ulcers that are easily cured by reducing the overall dosage and providing minimum side effects. Buccal routes becoming the most interesting area in the research field in the delivery of various proteins and peptides as well as antibodies and gene therapy across the oral mucosa. If it is possible to deliver through suitable sites, it changes the way for treating many diseases either orally and systemically.

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