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Buccal Drug Delivery System: A Review

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ABSTRACT: Bioadhesion is a phenomena of interfacial molecular attractive forces within the centre of the surfaces of biological substrates and therefore natural or synthetic polymers that causes the polymer to cling to the biological substrate for an extended period of your time . he buccal area of the oral mucosa provides an adorable channel of systemic medication distribution within the mouth mucosa. Because buccal drug delivery systems prolong the duration of dosage form at things and thus contribute to improved and/or better therapeutic performance of t, the mucosa of the cavity was found to be the most convenient and simply approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage form among the various transmucosal sites available. The main focus of this study is on the oral mucosa, route, barriers to drug entry, alternative dose forms, and evaluation methodologies; this may be valuable in avoiding formulation design challenges.

Keywords: Bioadhesion, Barriers, Pathway, Transmucosal Dosage Form.

INTRODUCTION

Bioadhesion is a phenomenon of interfacial molecular attractive forces within the middle of the surfaces of biological substrate and thus the natural or synthetic polymers, which allows the polymer to stick to biological surface for an extended period of your time . Among the several drug delivery routes, the oral route is perhaps the most popular among patients and clinicians. However, there are several drawbacks to taking medicine orally, such as hepatic first-pass metabolism and enzymatic breakdown in the gastrointestinal (GI) tract. which make it illegal to take certain types of drugs, particularly peptides and proteins, by mouth. As a result, alternative absorptive mucosas are being examined as prospective drug administration sites. The mucosa is somewhat permeable, has a plentiful blood supply, is tough, and recovers quickly after stress or damage. Local and systemic drugs have been delivered through the mouth. Gingivitis, oral candidiasis, oral lesions, cavities, and xerostoma are all treated with local therapy, whereas asthma and angina are treated with systemic delivery. The use of systemic activity in the treatment of disorders including angina and asthma is being studied.

Bioadhesive Delivery of Drug System in mouth

- **Sublingual delivery** Which is systemic delivery of medicine through the mucosal membranes lining the ground of the mouth.
- **Buccal delivery** Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa)
- **Local delivery** Which is drug delivery into the mouth .

Overview of the Oral Mucosa

A. Structure The outermost layer of stratified epithelium makes up the oral mucosa. A basement memrane, a lamina propia, and the submucosa, the innermost layer, are found below. The epithelium is similar to the stratified squamous epithelia seen throughout the body. There's a mitotically active basal cell layer there, which progresses through a variety of differentiating intermediate layers to the superficial layers, where cells are lost from the epithelium's surface. The buccal mucosa epithelium has roughly 40-50 cell layers, while the sublingual epithelium has less. As they progress from the basal to the superficial layers, epithelial cells grow in size and become flatter. The buccal epithelium has been estimated to have a turnover time of 5- 6 days, which is often reflective of the oral mucosa as a whole. The buccal mucosa measures 500-800m, while the mucosal thickness of the hard and soft palates, the base of the mouth, the ventral tongue, and thus the gingiva measures 100-200m.

B. Role of Saliva

- Protective fluid for all tissues of the mouth .
- Continious mineralization of the enamel .

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- To hydrate oral mucosal dosage forms.

C. Role of mucus

- Made from proteins and carbohydrates.
- Cell –cell adhesion.
- Lubrication.
- Bioadhesion of mucoadhesive drug delivery system.

D. Permeability

The oral mucosa is a absorbent epithelia that lies somewhere between the epidermis and the intestinal mucosa..It is believed that buccal mucosa is 4-4000 times more permeable than that of the skin. The oral mucosa's permiabilities decline in order of sublingual greater than buccal, buccal greater than palatal, and buccal greater than palatal. The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, and the palatal mucosa is intermediate in thickness but keratinized..

E.Structure and style of Buccal Dosage Form

The buccal patch designed

1. Matrix type: During a matrix configuration buccal patch contains drug, adhesive, and additives mixed together.

2. Reservoir type: During a reservoir system the buccal patch designed contains a cavity for the drug and additives break away the adhesive. To regulate the direction of drug delivery, an impermeable backing is applied , to scale back patch deformation and disintegration while within the mouth; and to stop drug loss.

F. Permeability of medicine through Buccal Mucosa

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa

i. Transcellular (intracellular, passing through the cell).

ii. Paracellular (intercellular, passing round the cell).

Permeation across the buccal mucosa has been reported to be mainly by the Para cellular route through the intercellular lipids produced by membrane-coating granules.

Advantages of buccal drug delivery system

Mucoadhesive via buccal route offers following advantages:

1. Relatively large area
2. Accessibility
3. Rich blood Supply
4. Low metabolic activity
5. Robust
6. Prolonged retention
7. Intestinal alternative
8. Zero-order controlled release
9. simple use and Low variability.

Limitations of buccal drug delivery system

1. Large dose of drug is difficult to be administered.
2. There is a restriction of drinking and Eating.
3.The patien has the possibility to swallow the tablet.
4. The drugs, which are unstable at buccal pH are not administered by this route.
5. The drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor are not
admistered by this route.
6. For absorption there is a small area.

Mechanism of Buccal Absorption

Buccal drug absorption occurs via passive diffusion of nonionized species across the epithelium's intercellular gaps, which is principally mediated by a degree gradient. The principal transport mechanism is the movement of non-ionic species across the cavity's lipid membrane. The buccal mucosa, like many other mucosal membranes, has been described as a lipoidal barrier to the passage of medicine, and as a result, the more lipophilic the drug molecule, the more quickly it is absorbed. A first order rate process could accurately capture the kinetics of drug absorption in the mouth. There are a number of potential impediments to buccal medication absorption that have been identifiedSalivary secretion changes the buccal absorption kinetics from drug solution by modifying the concentration of drug within the mouth, according to Dearden and Tomlison (1971). The following is the linear relationship between salivary secretion and time:

$$\frac{-dm}{dt} = \frac{KC}{ViVt}$$

Where,

M - Mass of drug in mouth at time

K - Proportionality constant

C - Concentration of drug in mouth at time

Vi - the quantity of solution put into mouth cavity and

Vt - Salivary secretion rate.

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Physiological factors affecting buccal bioavailability

1. **Inherent Permeability Of Epithelium:**The permeability of the oral mucosal epithelium lies halfway between that of the skin epithelium, which is highly specialised for barrier function, and the gut, which is highly specialised for adsorptive function. The buccal mucosa is less permeable than the sublingual mucosa within the mouth.
2. **Thickness of Epithelium:**The thickness of the oral epithelium varies a lot depending on where you are in the mouth. The thickness of the buccal mucosa ranges from 500 to 800 millimetres.
3. **Blood Supply:**The mouth is served by a well-developed blood supply and lymphatic network within the lamina propria, thus drug molecules that pass through the oral epithelium are quickly absorbed into the circulation.
4. **Metabolic Activity:**Drug moieties adsorbing on the oral epithelium are transported straight into the bloodstream, bypassing the liver's and gut wall's first-pass metabolism. As a result, oral mucosal administration may be particularly appealing for enzymatically labile medicines such as therapeutic peptides and proteins.
5. **Saliva and mucous:** Because of the exocrine gland's activity, a stream of saliva, ranging from 0.5 to 2 litres per day, is constantly washed over the oral mucosal surfaces. The sublingual area, in particular, is exposed to a large amount of saliva, which may help to improve drug breakdown and hence bioavailability.
6. **Ability to retain delivery system:** Because the buccal mucosa has a smooth and relatively immobile surface, it is well suited to the use of retentive delivery systems.
7. **Species distinctions:** Rodents have a highly keratinized epithelium, making them unsuitable as animal models for research into buccal medication delivery.

Buccal Formulations

The size of the delivery system varies depending on the formulation; for example, a buccal tablet could be 5-8mm in diameter, while a flexible buccal patch could be 10 -15cm2 in area. Buccal patches that are mucoadhesive and have a surface area of 1–3 cm2 are ideal. The total amount of medication given over the buccal mucosa in a single day via a $2cm^2$ system is expected to be between 10 and 20 mg. The shape of the delivery system can also vary, while an ellipsoid shape appears to be the most appropriate for buccal drug administration. The delivery device's thickness is usually limited to a few millimetres. the situation of the delivery device also must be considered. The maximal duration of buccal drug retention and absorption is approximately 4-6 h because food and/or liquid intake may require removal of the delivery device. The physiology of the mucus membrane under illness conditions must be taken into account (e.g.: Cancer patients suffer from oral candidiasis).

Novel Buccal Dosage Forms

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

A.Buccal mucoadhesive tablets

Buccal mucoadhesive tablets are dry dosage forms that must be moistened before being placed against the buccal mucosa. Example: a double-layer tablet with an inner core of cocoa butter containing insulin and a penetration enhancer and an adhesive matrix layer of Hydroxy Propyl, cellulose, and polyacrylic acid.

B.Patches and Films: Buccal patches consists of two laminates, with a solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then dig the specified oval shape. a completely unique mucosal adhesive film called "Zilactin" – consisting of an alcoholic solution of hydroxyl Propyl cellulose and three organic acids. The film which is applied to the oral mucosal are often even when challenged with fluids, it must be kept in place for a minimum of 12 hours.

C. Preparations that are semisolid (Ointments and Gels)

Patient acceptance of Bioadhesive gels or ointments is lower than that of solid Bioadhesive dosage forms, and most of these dosage forms are only utilised for localised drug therapy within the mouth. Orabase, one of the first oral mucoadhesive delivery methods, is made up of finely ground pectin, gelatin, and sodium carboxy methyl cellulose distributed in a poly (ethylene) and an oil gel base that may be kept at the application site for 15 to 150 minutes.

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D. Powders : The hydroxypropyl cellulose and beclomethasone in powder form are sprayed into the oral mucosa of rats, there is a significant increase in duration compared to an oral solution, with 2.5 percent beclomethasone remaining on the buccal mucosa for nearly 4 hours.

Characterization

1. **Interaction investigations between drugs and excipients**

The evaluation of potential incompatibilities between a live drug component and various excipients is an important part of the formulation stage in the case of a solid dosage form. The Fourier Transform Infrared Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography, and X Ray Diffraction (XRD) are all commonly used to check for pharmacological excipient interactions. Because it displays changes in appearance, shifts in melting endotherms and exotherms, and variation within the related enthalpies of the reaction, DSC enables for quick evaluation of probable incompatibilities.

2.Physical Evaluation: Weight uniformity, Content uniformity, and Thickness uniformity are all included. Weigh variation was investigated by weighing the averages of 10 randomly selected patches from each batch and comparing them to individual patches. Five points on the film sample should be measured for thickness (centre and 4 corners), As a result, the average thickness is determined. Air bubbles, nicks, or tears, as well as samples with a mean thickness variation of more than 5%, are removed from the study. In separate 100 ml volumetric flasks, three patches (20mm diameter) of each formulation were placed, 100 ml of pH 6.8 phosphate buffer was added, and the mixture was constantly agitated for twenty-four hours. The solutions were filtered, appropriately diluted, and analysed with a UV spectrophotometer. As a final reading, the average of three patches was used.

3. The pH of the surface

The buccal patch's surface pH was chosen to investigate the possibility of any in vivo side effectsBecause an acidic or alkaline pH can irritate the buccal mucosa, it was decided to keep the pH of the surface as close to neutral as possible24. For this, a composite glass electrode was used. The patches were allowed to swell for two hours at room temperature after being in contact with 1 ml of water (pH 6.5 0.05), and pH was measured by placing the electrode on the patch's surface and allowing it to equilibrate for one minute.

4. Swelling studies

Weight gain as a result of swelling: On a preweighed cover glass, a drug-loaded patch measuring 1x1 cm2 was weighed. It had been stored in a petridish, and 50 mL of pH 6.6 phosphate buffer had been added. The duvet slip was removed every five minutes and weighed for up to a half-hour. Because of the differential in weights, the load increases due to water absorption and patch26 swelling.

Swelling causes an increase in surface area: During a petridish, a 1x1cm^2 drug-loaded patch was cut and put. To live the rise within the area, a paper was placed beneath the petridish. In the petridish, 50 mL of phosphate buffer, pH 6.6, was added. The area was calculated after seeing a rise in the patch's length and breadth at five-minute intervals for 60 minutes.. The percentswelling (%S) was calculated using the subsequent equation:

$$\% S = \frac{Xt - Xo}{X_0} \times 100$$

Where, Xt is that the weight or area of the swollen patch after time t

TXo is that the original patch weight or area at zero time.

5. Palatability Test : After bitterness and physical appearance, palatability research is undertaken on the concept of taste. According to the standards, each batch is assigned an A, B, or C grade. When a formulation receives at least one A grade, it is considered average. When a formulation receives two A grades, it is deemed nearly as good, and the formulation that receives all three A grades is called superb.

6.Mucoadhesive strength (Ex- vivo)

The ex vivo mucoadhesive strength is determined using a modified balance method. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose material. The membrane rinsed with water then with phosphate buffer pH 6.8 at 370 C. The buccal mucosa dig sections and rinsed with phosphate buffer pH 6.8. a portion of buccal mucosa was connected to the glass\svial, which was stuffed with phosphate buffer. Before the

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investigation, the two sides of the balance were kept equal by keeping a 5g weight on the right-hand pan.

A 5g weight was far away from the right-hand pan, lowering it along with the tablet across the mucosa. For a total of five minutes, the equilibrium was maintained in this posture. The water (equal to weight) was steadily added to the righthand pan with an infusion set (100 drops/min) until the tablet separated from the mucosal surface. The mucoadhesive strength of the buccal tablet was calculated using this detachment force. The buccal tablet was glued to the lower edge of a rubber stopper using cyanoacrylate adhesive after the glass vial was snugly put into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C 1°C).

7.Mucoadhesive time (in vivo)

The ex vivo mucoadhesion time was measured after the buccal patch was applied to freshly sliced buccal mucosa (sheep and rabbit). The fresh buccal mucosa was tied on the glass slide, and the mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa with a light-weight push for 30 seconds with a finger tip. The glass slide was then placed into a beaker containing 200 ml of phosphate buffer pH 6.8 and held at 37°C 1°C. To imitate the cavity environment, a 50 rpm stirring rate was introduced after 2 minutes, and tablet adhesion was evaluated for 12 hours. Because of the mucoadhesion time, the time it took for the pill to disengage from the buccal mucosa was recorded.

8. Drug release(in vitro)

The rotating paddle method of the US Pharmacopeia (USP) XXIII was chosen to investigate medication release from bilayered and multilayered tablets. Phosphate buffer pH 6.8 is used in the dissolving media. The release was carried out at a temperature of 370 C 0.50 C at a rotational speed of fifty rpm. The buccal tablet's backing layer was adhered to the glass disc with instant adhesive (cyanoacrylate adhesive). The disc was assigned to the dissolving vessel's rock bottom. At predetermined intervals, samples (5 ml) were extracted and replaced with fresh medium. After proper dilution, the samples were filtered through Whatman paper and examined using UV spectrophotometry at a suitable nm.

9. Drug permeation (in vitro)

The Keshary-Chien/Franz type glass diffusion cell was used in an in vitro buccal drug permeation research of medicine via the buccal mucosa (sheep and rabbit) at 37°C 0.2°C. Between the donor and receptor compartments, fresh buccal mucosa was placed. Because the core of the buccal tablet was placed against the mucosa, the compartments were clamped together. 1 mL of phosphate buffer pH 6.8 was stuffed into the donor chamber. Phosphate buffer pH 7.4 was poured into the receptor compartment, As a result, by stirring with a magnetic bead at 50 rpm, the hydrodynamics within the receptor compartment are maintained. A 1 ml sample is frequently taken at specified intervals and tested for drug content using a UVspectrophotometer at a suitable nm.

10. Human saliva stability research

In accordance with ICH requirements, a stability study of fast dissolving films is performed on all batches. The films are assessed for drug content, disintegration time, and physical appearance after predefined time intervals. 33. For three months, the stability of an optimised mucoadhesive patch formulation was tested at 400°C, 37°C, and 75% RH. After three months, the value of all parameters remained the same, with modest changes in the value of volume entrapment efficiency, percent elongation, and abortifacient release after 8 hours, which was significant.

11.Measurement of mechanical properties

The patches' mechanical properties were assessed using a microprocessor-based advanced force gauze and a motorised test platform (Ultra Test, Mecmesin, West Sussex, UK) with a 25kg load cell. A film strip of 60 x 10 mm and free of optical flaws was cut and positioned between two clamps spaced by 3 cm. Clamps were created to hold the patch in place during the test without crushing it. Because the bottom clamp remained stationary, the strips were dragged apart at a rate of 2mm/sec by the higher clamp, which moved at a rate of 2mm/sec until the strip broke. The film's force and elongation at the point where the strip broke were recorded. The formula was used to calculate the lastingness and elongation at break values.

$$\text{Tensile strength (kg. mm}^2\text{)} = \text{ForcFf} \quad \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

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Elongation at break (%.mm^2) = $\frac{\text{Increase long (mm)T} \times 100}{\text{Original length Cross sec tionalarea (mm}^2\text{)}}$

12.Folding strength

Folding endurance of the patches was determined by folding one patch at a similar location until it broke or manually folding up to 300 times, which was deemed sufficient to indicate desirable patch qualities. The value of the folding endurance is determined by the number of times the patch can be folded at an equivalent location without breaking. This test takes five patches to complete.

13.Viscosity

Aqueous solutions containing both the polymer and the plasticizer at the same concentration as the patches. The viscometer was a Brookfield type LVDV-II attached to a helipath spindle number 4. At 20 rpm and temperature, the viscosity was measured.

14.Ageing

Patches were put through a series of rapid stability tests. Patches were put on glass Petri dishes lined with aluminium foil and incubated for six months at 370.5°C with 755 percent RH. Changes in the stored drug's appearance, duration, release behaviour, and drug content After 1, 2, 3, 4, 5, and 6 months, bioadhesive patches were examined. The information displayed the average of three determinations. A scanning microscope was used to examine fresh and aged medicated patches after 6 months of storage.

CONCLUSION

Buccal adhesive systems provide numerous benefits in terms of accessibility, administration, and withdrawal, retentivity, low enzymatic activity, cost, and patient compliance. This overview of mucoadhesive buccal patches may prove to be a useful tool in the development and characterization of mucoadhesive buccal patches. Mucoadhesive buccal patches have a variety of uses, including avoiding first-pass metabolism in the liver and preventing pre-systemic evacuation in the alimentary canal. The world looks to be compatible with a retentive device and acceptable to the patient. The permeability within the local environment of the mucosa can often be managed and manipulated with suitable dosage form design and formulation to accommodate medication permeation. Buccal drug delivery could be a potential topic for future research, with the goal of systemic distribution of orally ineffective medications, as well as a viable and appealing alternative for noninvasive delivery of powerful peptide and protein therapeutic molecules. he need for safe and effective buccal permeation absorption enhancers, on the other hand, may be a critical component for the future of buccal drug delivery. Mucoadhesive systems may play a larger role in the creation of new pharmaceuticals as a result of the influx of new compounds resulting from pharmacological research**.**

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