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Analysis of the Buccal Patch Drug Delivery System, Development, and Clinical Trials..

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ABSTRACT: The mouth is a promising medication delivery location because drugs taken orally bypass the digestive system and first-pass metabolism, where they might be degraded. Delivery of medications via the buccal mucosa to produce systemic pharmacological effects is what is meant by the term "buccal drug delivery."Advantages of buccalbioadhesive films over conventional dosage forms may be seen in the treatment of numerous disorders due to the controlled and gradual release of topical medications in the mouth cavity.The buccal patch is a non-dissolving, thin-matrix, modified-release dosage form designed for the supine and uncooperative patient.[1] The buccal mucosa's accessibility, smooth, and inflexibility make it an ideal location for a bioadhesion system. Consequently, medications having a limited half life in the body. Oral flexible patches have been created to address the problems associated with taking pills. The purpose of this review is to educate readers about buccal patches and the buccal medication delivery mechanism. Review the criteria used to assess buccal patches.

KEYWORDS: buccal drug system , buccal patch , Method of buccalpatchs , Evaluation of buccalpatch.

I. INTRODUCTION

Buccal drug delivery: The pharmaceutical business is now a significant player in the healthcare sector, having attracted significant attention. The pharmaceutical industry'sinnovations have improved people's lives by allowing them to live longer and healthier lives. When compared to oral administration for systemic drug delivery, transmucosal routes, which include the nasal, rectal, vaginal, ocular, and oral mucosal linings, provide exceptional chances and possible benefits.[1]

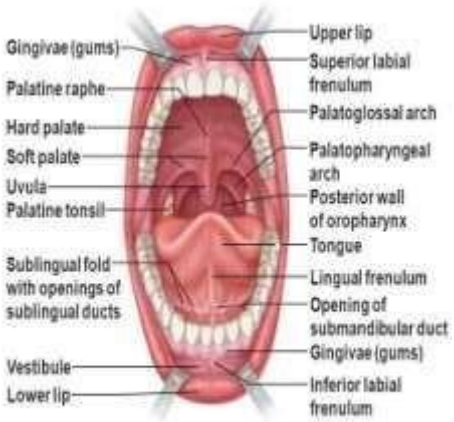

Fig : 1 oral cavity

Muco adhesive drug delivery system

Advantages of mucoadhesive drug delivery systemsinclude increased bioavailability of therapeutic agents due to the circumvention of some of the body's natural defense mechanisms and increased residence time of the drug at the site of application compared to conventional delivery methods.[2]The capacity to "mucoadhere," or stick to

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the mucus gel layer, is a crucial factor in the development of thesedrug delivery systems. Since the buccal mucosa hasa large blood supply and is moderately permeable,it is an appealing route for systemicdelivery of medicines. By using the buccal route, you can avoid issues like high first-pass metabolism anddrug degradation in the harsh gastrointestinal environment, and if there are any signs of toxicity, you can quickly stop the absorption of the drug by simply removing the dosage form from the buccal cavity.

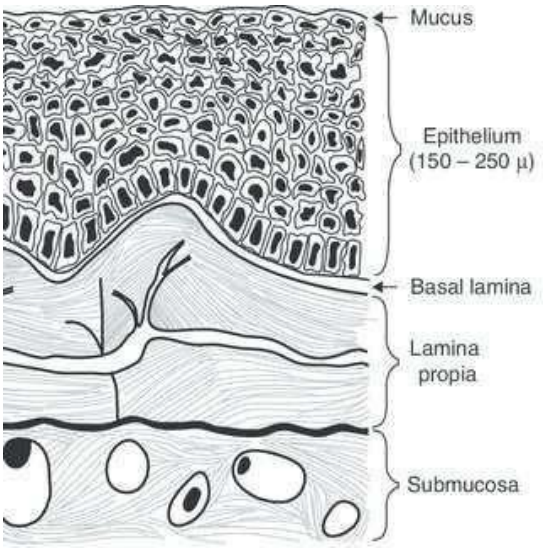

Fig:2 Oral mucosa

Structure of Oral Mucosa:

The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It also contains many sensory receptors including the taste receptors of the tongue.[3]

Table 1: Thickness and surface area of oral cavity

Oral cavity membrane	Thickness (mm)	Surface area (cm^2)
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.1

The mucoadhesive drug delivery system in the mucus membrane of oral cavity can be categorized into three delivery systems:[11]

- Sublingual delivery
- Buccal delivery
- Local delivery

These oral sites provide the high blood supply for the greater absorption of drug with sufficient permeability. From these three sites of oral mucoadhesive drug delivery system, the buccal delivery is the most convenient site.

ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM[10]

Mucoadhesive via buccal route offers followingadvantages: -

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- Ease of drug administration and termination of drug action can be easily accomplished.
- Permits localization or retention of the drug to the specified area of oral cavity forextended period of time.
- Bypass hepatic first pass metabolism.
- Drugs with poor bioavailability owing to the high first pass metabolism can be administeredconveniently.
- Ease of drug administration to unconscious patients.
- Water content of saliva is being capable to ensure drug dissolution.

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM:[3]

Matrix type: The buccal patch designed in amatrix configuration contains drug, adhesive, and additives mixed together.

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

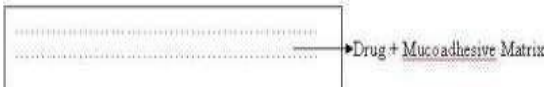

Fig. 3: Buccal patch designed for bidirectional drug

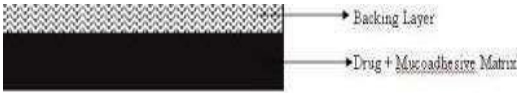

Fig. 4: Buccal patch designed for unidirectionaldrug

TYPES OF BUCCAL DOSAGE FORM:

Tablets designed to adhere to the buccal mucosa are called buccalbioadhesive tablets, and they must be moistened before being placed in touch with the mucosa. Using bioadhesive polymers and excipients, double and multilayered tablets may be manufactured. Two buccalbioadhesive tablets, Bucastem (Nitroglycerine) and SuscardbuccaP (Prochloroperazine), are now on the market in the United Kingdom.[10]

Bioadhesive buccal patches and films are made up of two poly laminates or a multilayered thin film that is either round or oval in shape and mostly consists of bioadhesive. medication delivery in one direction across the buccal mucosa thanks to a polymeric layer and an impermeable backing layer. Buccalbioadhesive films arc formulated by incorporating the drug in alcohol solution of bioadhesive polymer.[10]

Table 2: List of permeation enhancers[8]

Permeation Enhancers	
Chelators	EDTA, Citricacid , Sodium salicylate, Methoxy salicylates.
Surfactants	Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bro-mide.

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Bile salts	Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxychol Sodium taurodeoxychola

An ideal polymer for buccoadhesive drug delivery systems should have followingCharacteristics.[4]
It should be inert and compatible with the environment.
• The polymer and its degradation products shouldbe non-toxic absorbable from the mucouslayer.
• It should adhere quickly to moist tissue surfaceand should possess some site specificity.
• The polymer must not decompose on storageorduring the shelf life of the dosage form
The polymer should be easily available in themarket and economical..
• It should allow easy incorporation of drug intothe formulation.

Advantages of Buccal Patches: [4]

One, the mouth mucosa receives a lot of blood. Drugs are taken into the bloodstream through the deep lingual veins after being absorbed by the mouth mucosa.

entering the systemic circulation through the internal jugular vein, the face vein, or the braciocephalic vein.

By using the buccal route, the medicine is able to enter the systemic circulation without going via the liver first. Many medications, including insulin and other proteins, peptides, and steroids, may not be stable if exposed to the digestive juices of the gastrointestinal system. Neither the presence of food nor the pace at which the stomach empties affects the rate at which a medicine is absorbed.

The buccal membrane region is big enough to accommodate placement of a delivery system atseveral time points, and there are two buccal membrane areas per mouth, allowing placement ofa drug delivery system on either the left or right buccal membrane.

The membranes that border the mouth canal are easily reached with a buccal patch, making the process of applying the patch painless and pleasant.

5. In the event of an emergency, the patient may halt treatment and take charge. Drugs may be simply placed in the buccal cavity using buccal medication administration devices. Patients are more likely to take their medicine when it comes asa buccal film.

Limitation of buccal drug administration[10]There is certain limitation via drug administeredthrough buccal route: -

- Drugs with ample dose are often difficult to be administered.
- Possibility of the patients to swallow the tablets being forgotten.
- Eating and drinking may be restricted till the end of drug release.
- This route is unacceptable for those drugs, which are unstable at pH of buccal environment.
- This route cannot administer drugs, which irritate the mucosa or have a bitter orunpleasant taste.
- Limited surface area is available for absorption

Mechanism ofbioadhesion: Bioadhesion is aninterfacial phenomenon in which two materials, atleast one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material andbiological substrate, such as adhesion between polymer and/or copolymer and a biological membrane. In case of polymer attached to the mucin layer of the mucosal tissue, the term "mucoadhesion" is employed. "Bioadhesive" is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of t

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ime.[21]

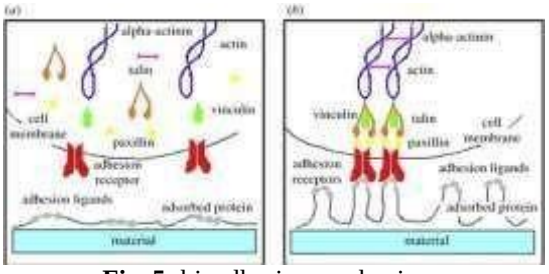

Fig. 5: bioadhesive mechanism

Characteristics of an Ideal BuccoadhesiveSystem:[10]

An ideal buccal adhesive system should possessthefollowing characteristics:

1. Quick adherence to the buccal mucosa andsufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should have good patient compliance.
5. Should not hinder normal functions such astalking, eating and drinking.
6. Should accomplish unidirectional release ofdrugtowards the mucosa.
7. Should not aid in development of secondaryinfections such as dental caries.
8. Possess a wide margin of safety both locallyandsystemically.
9. Should have good resistance to the flushingaction of saliva.

Advantages of Buccal Drug Delivery System:[3] Drug administration via buccal mucosa offers several distinct advantages:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
3. Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.
4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5. High patient acceptance compared to other non- oral routes of drug administration.
6. Tolerance (in comparison with the nasal mucosaand skin) to potential sensitizers.
7. Increased residence time combined with controlled API release may lead to lower administration frequency.
8. Additionally significant cost reductions may beachieved and dose-related side effects may be reduced due to API localization at the disease site.
9. As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower APIconcentrations for disease treatment.
10. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.
11. It offers a passive system of drug absorption and does not require any activation.
12. The presence of saliva ensures relatively largeamount of water for drug dissolution unlike in case of rectal or transdermal routes.

Disadvantages of Buccal Drug Delivery System:[7]

The main challenges of buccal administration are: 1. Limited absorption area- thetotal surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues,including buccal membrane.

2. Barrier properties of the mucosa.
3. The continuous secretion of the saliva (0.5- 2/day) leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

II. METHOD OF PREPARATION

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Two methods are used to prepare adhesive patches.

1. Solvent casting: In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation 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 size and geometry evaluated.

2. Direct milling: In this, patches are manufactured without the use of solvents. 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 rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

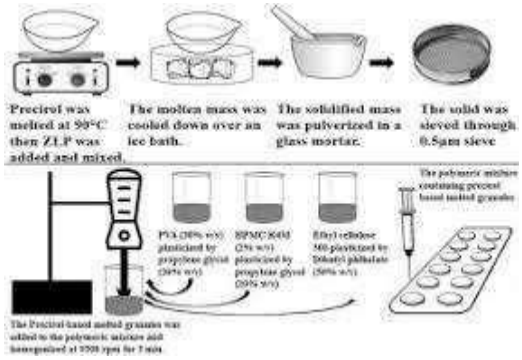

Fig:6 preparation of buccal patch

Composition of Buccal Patches:[15]

A. Active ingredient.

B. Polymers (adhesive layer): Hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. Sweetening agents: Sucralose, aspartame,mannitol, etc.

E. Flavouring agents: Menthol, vanillin, cloveoil,etc.

F. Backing layer: Ethyl cellulose, Poly vinylalcohol etc.

G. Penetration enhancer: Cyano acrylate, etc.

H. Plasticizers: PEG-100, 400, propyleneglycol,etc

III. EVALUATION PARAMETERS

The following tests are used to evaluatethe Buccal Patches:

Drug Content Uniformity, Ex-Vivo Residence Time, Thickness Testing, In-vitro drug permeation studies, In-vitro release studies, Moisture absorption studies, Surface pH study, In-vitro bioadhesion measurement, In-vitro permeation through porcine buccal membrane, Stability in human saliva, FTIR studies etc water (15:85, v/v).

The flow rate was 2.0 ml/min and the run time 15 min. The retention time of TPL was 3.1 min. The TPL calibration curve, at concentrations varying from 5_g/ml to 100_g/ml.[1]

1. Surface pH: Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[24]

2. Thickness measurements: The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.[24]

3. Swelling study: Buccal patches are weighed individually (designated as W1), and placed separately in 2%

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agar gel plates, incubated at 37°C
± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper.

$$SI = \frac{(W2 - W1)}{W1} \times 100$$

4. Water absorption capacity test: Circular Patches, with a surface area of 2.3 cm2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na2HPO4,
0.19 gKH2PO4, and 8 g NaCl per litter of distilled wateradjusted with phosphoric acid to pH6.7), and kept in an incubator maintained at 37°C
± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3 and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature then the finalconstant weights are recorded. Wateruptake (%) is calculated using the following equation,

$$\text{Water uptake (\%)} = \frac{(W_w - W_f)}{W_f} \times 100$$

Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured.[27]

5. Ex-vivo bio adhesion test: The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted intoa glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. [30]

The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.[30]

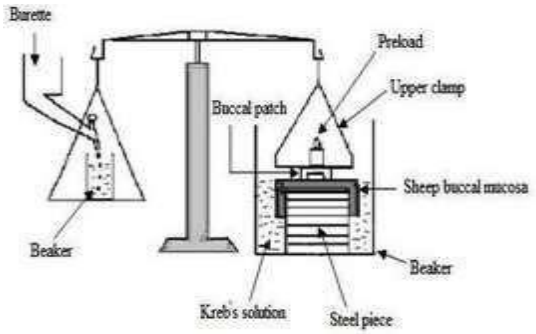

FIG.7: Measurement of mucoadhesive

6. In vitro Drug Release: The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution.[15]

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

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The donor compartment is filled with buffer [24]

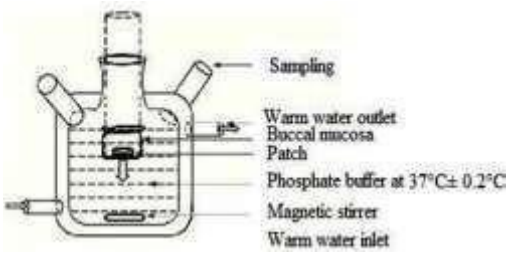

Fig.8: Schematic chematic diagram of franzdiffusion cell for buccal patch

7. **Permeation study of buccal patch:** The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.
8. **Ex-vivo Mucoadhesion Time:** The ex-vivomucoadhesion time performed after application ofthe buccal patch on freshly cut buccal mucosa(sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filledwith 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours.[15] The time for changesin colour, shape, collapsing of the patch and drug content is noted.
9. **Measurement of mechanical properties:** Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with thedimensions of 60 x 10 mm and without any visualdefects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designedto secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break, the force and elongation of the film at the point when the trip break is recorded. [15]

IV. CONCLUSION

The buccal mucosa provides several benefits for sustained, regulated medication administration. First-pass metabolism in the liver and pre-systemic circulation ensure that the mucosa receives a constant supply of oxygen and nutrients. The digestive system is bypassed, preventing systemic excretion. The location seems to be agreeable to the patient and would work well for a retentive device. Drug penetration into the mucosa may be regulated and optimized with careful consideration of dosage form design and formulation. For the purposes of systemic distribution of orally ineffective medications, and as a viable and appealing option for non-invasive delivery of powerful peptide and protein therapeutic molecules, buccal drug delivery is a promising topic for future investigation. Mucoadhesivebuccal patches employing differentnatural polymer are still the subject of much research and development. This study aims to provide a concise summary of current research and to outline potential future directions for the development of natural polymer-based mucoadhesive buccal patches.The location seems to be agreeable to the patient and would work well for a retentive device. Drug penetration into themucosa may be regulated and optimized with careful consideration of dosage form design and formulation.

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