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Mucoadhesive Buccal Patch: A Novel Approach for the Delivery of Anti-Diabetic Drugs

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ABSTRACT:
Diabetes mellitus is a chronic illness in which the pancreas either produces insufficient amounts of insulin or is unable to use the insulin it produces efficiently. Injection insulin and oral hypoglycemic drugs remain to be the core components of diabetic treatment. Patient compliance is frequently low with them. The buccal region inside the oral cavity is a desirable location to administer the preferred medication. There have been developed sustained release formulations that are becoming more and more appreciated by medical professionals. Drug was placed in sustained-release buccal patch to enhance bioavailability and inhibit first pass metabolism. Since it is simple to administer and non-invasive, the buccal route is considered as patient-friendly. The primary objective of this review is to provide an overview of composition & formulation method of buccal patch as well as advantages of buccal drug delivery system.
Keywords: Diabetes, Insulin, Drug delivery system, Buccal Patch, Sustained Drug Delivery.

I. INTRODUCTION

The preferred and most popular method of medicine delivery is oral ingestion. It has a number of benefits, including as being more patient-friendly, painless, easy to self-medicate, and enabling variable and controlled dose schedules than the majority of other drug delivery methods. Even though the oral route is preferred for drug administration, it also has significant drawbacks, including the first pass effect, gastrointestinal enzymatic degradation, and a delay between administration and absorption, which is harmful for medications that need to take effect quickly. These challenges have promoted researchers to consider different drug delivery methods, including pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. For systemic drug delivery, transmucosal routes which include the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities offer good options and possible benefits over peroral administration. Depending on the specific medicine, these benefits may include a better enzymatic flora for drug absorption, the potential bypass of the first pass effect, and prevention of presystemic clearance inside the GI tract. [1]

Compared to other devices, buccal patches provide more flexibility and comfort. Additionally, since oral gels are rapidly removed by saliva, a patch can solve the issue of the relatively short residence period of oral gels on mucosa. Buccal route drug delivery provides the direct entry to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. [2]

Diabetes Mellitus (DM) is a chronic, multifactorial health disorder that can be driven on by a number of genetic and/or environmental causes. Type 2 diabetes mellitus (DM), a chronic metabolic condition, is becoming more common everywhere in the world. The disease is characterized by high blood sugar levels, due to a deficiency of concentration and/or of activity of insulin, the pancreatic hormone involved in managing glycaemia. [28]

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

1. Improved patient compliance due to the elimination of associated pain with injections.
2. A relatively rapid onset of action can be achieved relative to the oral route.
3. The formulation can be removed if therapy is

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required to be discontinued.
4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5. The residence time of dosage form at the site of absorption is prolong, hence increases the bioavailability.
6. High blood supply and good blood flow rate cause rapid absorption.[3]

DISADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

As compared to the sublingual membrane the buccal membrane has low permeability.
1. Limited surface area is available for absorption.
2. This route cannot administer drugs which irritate the mucosa or have a bitter or unpleasant taste or anoxious odour. [4]
3. This route is unacceptable for those drugs which are unstable at pH of buccal environment.
4. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
5. Drugs with large dose are difficult to be administered.[5]

BUCCAL PATCHES

Buccal patch is a non-dissolving thin matrix modified-release dosage form. The patch is composed of one ormore polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release).The patch is removed from the mouth and disposed of after a specified time.[7]

IDEAL CHARACTERISTICS OF BUCCAL PATCHES

- The drug should get release in a controlled fashion.
- Normal functions should not be disturbed like talking and drinking.
- The patch should get attached to the site of application for few hours.
- The patch should not cause irritation at the site of application.
- The patch should provide drug release in a unidirectional way towards mucosa.
- Should provide the rate and extent of drug absorption.[6]

TYPES OF BCCCAL PATCHES:

- **Matrix type (Bi-directional):** The drug, adhesive, and additives are incorporated together in the matrix-shaped buccal patch. Drug release via bi-directional patches occurs in the mouth and mucosa.
- **Reservoir type (Unidirectional):** The reservoir-style buccal patch has a cavity for the drug and additives that 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. In general, unidirectional buccal patches are utilized for local and systemic delivery of medications in the buccal cavity. [7,12]

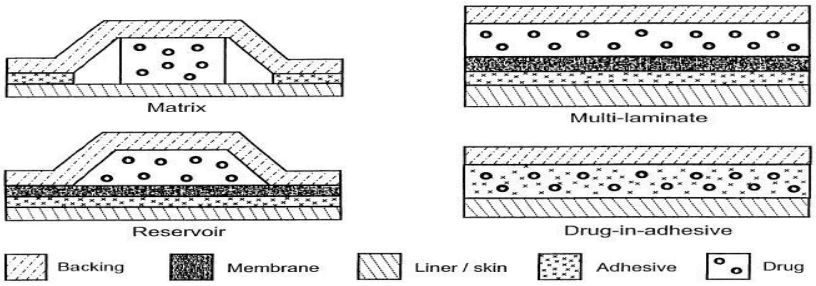

FIGURE 1: MATRIX AND RESERVOIR TYPE BUCCAL PATCHES

Composition of buccal patches: [3, 7]

The basic components of buccal bio adhesive drug delivery system are:
1. Active Pharmaceutical Ingredient
2. Mucoadhesive polymers
3. Backing membrane
4. Penetration enhancers
5. Plasticizers

ACTIVE PHARMACEUTICAL INGREDIENT(API):

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To achieve the intended therapeutic impact with buccal drug delivery, it is crucial to extend and increase the interaction between API and mucosa. Molecular weight, chemical activity, and melting point are crucial pharmacological qualities that influence how well a medication diffuses through a patch and the buccal mucosa.

The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on following characteristics:

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

MUCOADHESIVE POLYMERS: [8, 9]

Mucoadhesives are synthetic or natural polymers that interact with the primary molecules making up the majority of the mucus and the mucus layer covering the mucosal epithelial surface. The first step in the development of mucoadhesive dosage forms is these lection and characterization of appropriate mucoadhesive polymers in the formulation. Additionally, polymers are utilized in matrix devices, where the drug is incorporated in a polymer matrix that regulates the timing of drug release. commonly used polymers are Aminodextran, chitosan, dimethyl amino ethyl-dextran, trimethylated chitosan Chitosan-EDTA, CP, CMC, pectin, PAA,PC, sodium alginate, sodium CMC.

Characteristics of Ideal Mucoadhesive Polymers:

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

- The polymer and its degradation products should be non-toxic and non-absorbable from the GIT.
- It should be non-irritant to the mucus membrane.
- It should preferably form strong non-covalent bond with the mucin epithelial cell surfaces.
- Itshouldadherequicklytomoisttissuesurfaceands houldpossesssomesitespecificity.
- Itshouldalloweasyincorporationofthedrugandof fernohindrancetoitsrelease.
- 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.

BACKING MEMBRANE:

Bioadhesive devices are mostly attached to the mucus membrane by the backing membrane. The backing membrane's materials need to be harmless, impermeable to the medication, and penetration-enhancing. The commonly used materials in backing membrane include carbopol, HPMC, HPC, CMC etc. [10]

PENETRATION ENHANCERS: [11]

Permeation enhancers are substances which assist in permeation through buccal mucosa. The limited drug flux across the mucosal epithelium, which results in low drug bioavailability, is one of the main drawbacks of buccal drug delivery. To boost the flux of medications through the mucosa, various substances have been researched for their potential use as buccal penetration and absorption enhancers. Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows

a. Changing mucus rheology
b. Increasing the fluidity of lipid bilayer membrane
c. Acting on the components at tight junctions
d. By overcoming the enzymatic barrier
e. Increasing the thermodynamic activity of drugs

Commonly used penetration enhancers are Oleic acid, Caprylic acid, Mono (di) glycerides, Urea and derivative, Unsaturated cyclicurea, Azone (1-dodecylazacycloheptan-2-one), Cyclodextrin , Di methyl sulfoxide (DMSO), Decyl methyl sulfoxide.

PLASTICIZERS:

These compounds are used to make thin films of polymer or a polymer blend soft and flexible. Examples of common plasticizers used are glycerol, propylene glycol, PEG200, PEG 400, castor oil etc. The plasticizers serve as penetration enhancers and aid in the release of the medicinal component from the polymer basis. The choice of plasticizer depends on how well it can solvate the polymer and change the interactions between the polymers. By reducing the molecular rigidity when utilized in the proper ratio with the polymer, these compounds impart flexibility.

METHOD OF PREPARATION:

(1) **Solvent casting:** This approach involves coating a sheet of release liner with an organic

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solvent that contains both the drug and all patch excipients. After the solvent has evaporated, a thin layer of protective backing material is fused onto the coated release liner sheet to create a laminate, which is then die-cut to create patches with the specified size and geometry.

(2) Direct milling: This eliminates the need for solvents in the manufacturing of patches. Direct milling or kneading are typically used to mechanically combine the drug and excipients without the use of any liquids. The finished product is rolled on a release liner until the necessary thickness is reached after the mixing process. Following that, the backing material is laminated as previously said. [2, 7]

EVALUATIONS OF BUCCAL PATCH:

1) Surface pH: Buccal patches are placed on the surface of an agar plate and allowed to swell for two hours. A pH paper is applied to the surface of the swollen area in order to test the surface pH.[13]

2) Thickness measurements: Using an electronic digital micro-meter, the thickness of each film is measured at five separate positions (the center and four corners). [14]

3) Swelling study: All buccal patches (W1) are weighed separately, then each is put in a separate 2% agar gel plate. The plates are then incubated at 37°C ± 1°C, and any physical changes are checked. Patches from the gel plates are taken off at regular 1-hour intervals until the three-hour mark, and any remaining surface water is carefully wiped away with the filter paper. The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula. SI= (W2-W1) X 100 /W1 [15,16]

4) Folding endurance: The folding endurance of patches is determined by repeatedly folding 1 patch at the same place until it breaks or is folded up to 200 times without breaking.[17]

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 into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right hand side pan until the patch detached from the mucosal surface.[15] The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.[18,19]

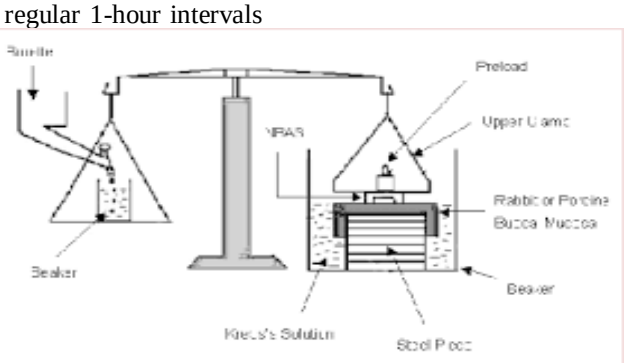

FIGURE 2: MEASUREMENT OF MUCOADHESIVE STRENGTH

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

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content after appropriate dilution. The in- vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C±0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer [20, 21, 22]

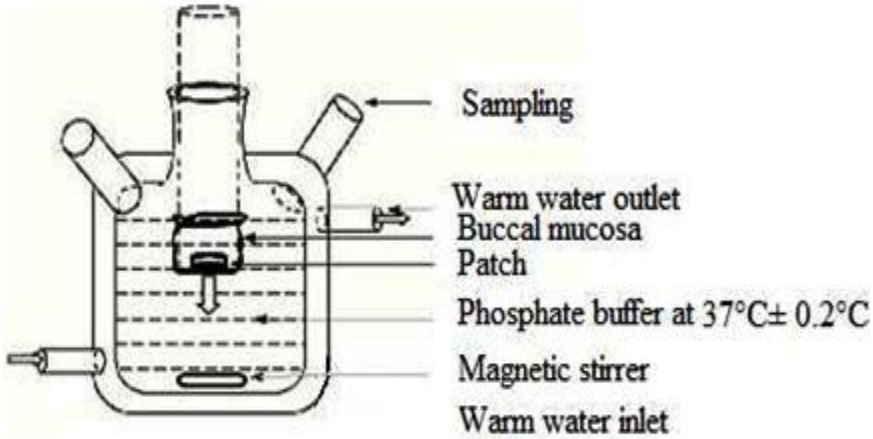

FIGURE 3: SCHEMATIC DIAGRAM OF FRANZ DIFFUSION CELL FOR BUCCAL PATCH

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 analysed for drug content [23].

8) Ex-vivo mucoadhesion time

The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch, and drug content is noted. [24,25]

9) Stability study in human saliva

The stability study of optimized bi-layered and multi-layered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate Petri dishes containing 5ml 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 dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dose required and minimize side effects that may be due to systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. [26, 27]

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II. CONCLUSION AND FUTURE PERSPECTIVE:

Since diabetes mellitus is a chronic condition that necessitates continuous medication administration and glucose level monitoring, an innovative development in diabetes treatment approaches would be much appreciated. We expect an enormous shift in the treatment of diabetes if the manufacturing difficulties associated with the buccal patch are resolved, since buccal drug delivery systems are believed to be an effective way of improving patient outcomes when compared to conventional dosage forms.

Better drug bioavailability can be attained, which means diabetes patients won't need to take their medications as frequently as they would if they used conventional oral drugs twice a day. One further notable benefit is that patients will have a simpler treatment option, which is the application of a buccal patch to the buccal region with a predetermined release rate. Researchers are increasingly interested in exploring and venturing into buccal drug delivery because various approaches involving buccal patches have demonstrated highly desirable advantages in terms of improving drug bioavailability, lowering dosage frequency, preventing side effects, and offering a painless and simple administration method that improves patient compliance. To overcome the drawbacks of conventional dosage forms and an increasing number of patients with diabetes, a stronger effort should be made toward developing buccal patches for antidiabetic medications.

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