BUCCAL PATCH: A TECHNICAL NOTE

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ABSTRACT

Rapid developments in the field of molecular biology and gene technology resulted in generation of many macromolecular drugs including peptides, proteins, polysaccharides and nucleic acids in great number possessing superior pharmacological efficacy with site specificity and devoid of untoward and toxic effects. However, the main impediment for the oral delivery of these drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parentral route of administration is the only established route that overcomes all these drawbacks associated with these orally less/inefficient drugs. But, these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. This paper aims to review the developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

Keywords: Buccal mucosa, Permeation, Transmucosal, Drug delivery.

INTRODUCTION

The mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery[1]. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal tract and depending on the particular drug. A better enzymatic flora for drug absorption.[2,3]

Components or structural features of oral cavity:

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions[4].

• Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).

• Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate.
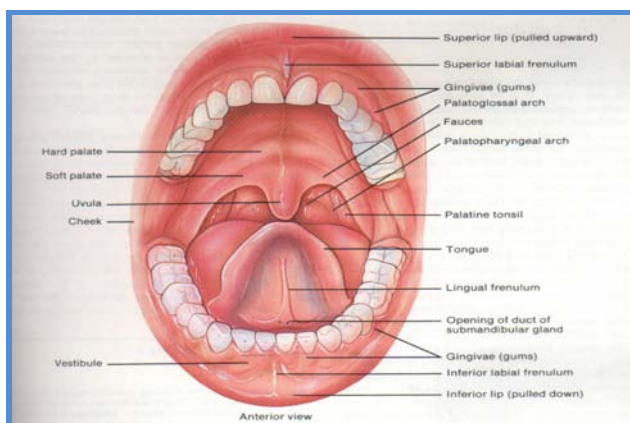
The tongue projects from the floor of the cavity.

Figure 1: Structure of oral cavity

BUCCAL PATCHES

Buccal patch is a nondissolving thin matrix modified-release dosage form composed of one or more 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[5,6].

TYPES

1. Matrix type (Bi-directional): The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional (Figure 1) patches release drug in both the mucosa and the mouth
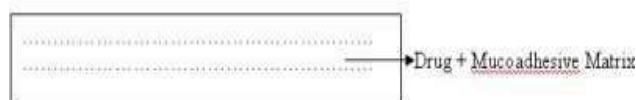

Figure 2: Buccal Patch designed for Bidirectional drug release

2. Reservoir type (Unidirectional): 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[7].
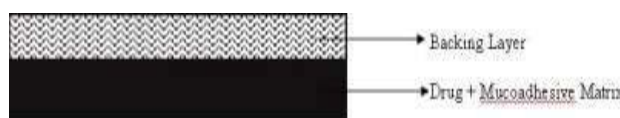

Figure 3: Buccal Patch designed for Unidirectional drug release

COMPOSITION

- Active ingredient
- Polymer (adhesive layer): hydroxyethylcellulose, hydroxypropylcellulose, poly (vinylpyrrolidone) and poly(vinylalcohol). (Carbopol 934 and PVP). And other mucoadhesive polymer[8].
- Diluents: Lactose CD selected as diluent for its high aqueous solubility, its flavoring characteristics, and its physical mechanical properties, which make it suitable for direct compression. MCS, Starch, DCP, etc.
- Sweetening agent; Sucralose, Aspartame, Mannitol, etc
- Flavoring agent: Menthol, Vanillin, Clove Oil, etc.
- Backing layer: Ethyl Cellulose, etc
- Penetration enhancer:
- Plasticizer: PEG-.100,400, Propylene Glycol, etc

IMPORTANT CONSIDERATION

In these cases, the adhesive polymer serves either as a drug carrier itself, or an adhesive layer link between a drug-loaded layer and the mucosa, or a shield to cover a drug-containing disc. The design of these patches provides either unidirectional or bidirectional release of the drug.

The size of such systems typically varies from 1 to 16 cm, depending on the specific purpose of the application. Usually, 1 to 3 cm, patches is commonly used because of convenience and comfort[9,10,11].

However, the administration site is also a factor. Large-size patches can be administered at the central position of the buccal mucosa, (i.e., center of the cheek), whereas the sublingual and gingival sites require a rather small-sized patch[12].

A variety of polymers can be used for oral mucosal patches. This includes water soluble and insoluble polymers of both ionic and nonionic types. With soluble polymer systems, drug release is accompanied by dissolution of the polymer; therefore the overall drug release rate and duration are determined by both polymer dissolution and drug diffusion, whereas in a nonsoluble hydro gel system, drug release follows fickian or nonfickian diffusion kinetics, depending on design[13,14].

A preferred mucoadhesive and elastomer are polyacrylic acid (PAA) and polyisobutylene (PIB), respectively[15].

The duration of mucosal adhesion of different bioadhesive patches varies from minutes to days depending on the type of polymer used, its amount per patch, and additional factors such as the drying technique used to prepare the patches[16].

METHOD OF PREPARATION

Two methods used to prepare adhesive patches include

Solvent casting

In this, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of 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[17].

Direct milling

In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids[18]. 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[19].

While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues[20].

EVALUATION

Physical evaluation

It includes- Weight uniformity, Content uniformity, Thickness- uniformity, ass uniformity. Mass uniformity tested in different randomly selected patches from each batch and patch thickness measured at 5 different randomly selected spots using a screw gauge[21].

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible[22].

The method adopted by Bottenberg et al was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

Swelling index:

Buccal patches were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at $37^0C \pm 1^0C$. At regular 1- hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen

tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula given in equation.

$$\text{Swelling Index} = \frac{(W2-W1) \times 100}{W1}$$

Ex vivo mucoadhesive strength

A modified balance method used for determining the ex vivo mucoadhesive strength as shown in figure 3. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 37^0C. The buccal mucosa cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time[23]. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive[24].
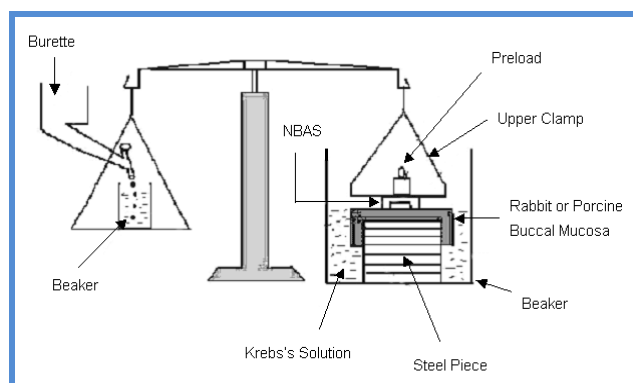

Figure 4: Measurement of mucoadhesive strength.

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 was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 mL of the phosphate buffer pH 6.8, and kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for

the tablet to detach from the buccal mucosa was recorded as the mucoadhesion time.

In vitro drug release

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consisted of phosphate buffer pH 6.8. The release was performed at 37-C ± 0.5-C, with a rotation speed of 50 rpm. The backing layer of buccal tablet attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm.

In vitro drug permeation

The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37°C ± 0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 mL of phosphate buffer pH 6.8.
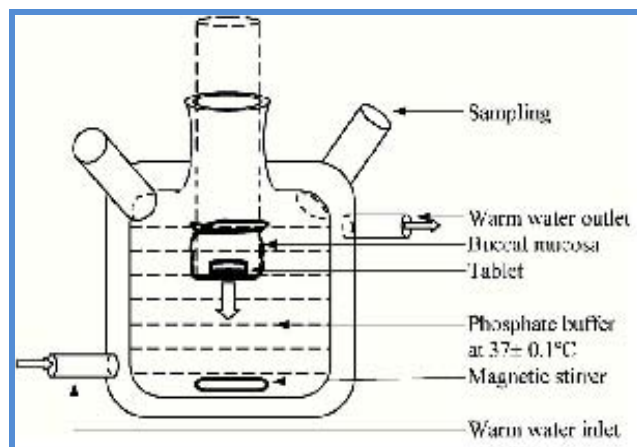

Figure 5: Schematic Diagram of Franz Diffusion Cell for Permeation Study of Buccal tablet.

The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A 1-mL sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UV-spectrophotometer[25].

Stability Study in Human Saliva

The stability study of optimized bilayered and multilayered tablets performed in natural human saliva. The human saliva was collected from humans (age 18-50 years). Buccal tablets placed in separate Petri dishes containing 5 mL of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the

tablets examined for changes in color and shape, collapsing of the tablets, and drug content[26,27].

Measurement of Mechanical Properties

Mechanical properties of the films (patches) includes tensile strength and elongation at break evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand equipped with a 25 kg load cell OR The istronâ tensile tester[28].

Film strip with the dimensions 60 x 10 mm and without any visual defects cut and positioned between two clams separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke recorded. The tensile strength and elongation at break values were calculated using the formula[29].

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

Folding Endurance

The folding endurance of patches was determined by repeatedly folding 1 patch at the same place till it breaks. The experiments performed in triplicate, and average values reported[30,31].

Viscosity

Aqueous solutions containing both polymer and plasticizer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number 4 used. The viscosity measured at 20 rpm at room temperature. The recorded values the mean of three determinations[32,33].

Ageing

Patches subjected to accelerated stability testing. Patches packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5°C and 75±5% RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored bioadhesive patches investigated after 1, 2, 3, 4, 5, and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope[34].

CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. From both a financial and global healthcare perspective, finding ways to administer injectable medications is costly and some time leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailabilities 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 totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, 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 dosage required and minimize side effects that may be caused by 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

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