Review Article

Overview of Buccal Drug Delivery System

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ABSTRACT

The Buccal medication Delivery System (BDDS) is a modern way to medication delivery that aims to replace traditional drug administration routes. The occurrence of drug side-effects can be significantly minimised, and the targeted distribution of drugs can be effectively performed using BDD (Bio Distribution and Drug distribution). Significant advancements have been achieved in Bucco-adhesive drug administration to address specific challenges, such as first pass metabolism and low bioavailability, associated with regularly utilised dosage forms and controlled drug delivery for extended periods of time. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal delivery.

Keywords: Buccal drug delivery system (BDDS), Evaluation of BDDS, medication delivery.

INTRODUCTION

The oral route is the most suitable method for administering medication to patients and the safest means to transfer it to the circulatory system. The lack of monitoring and identification of the gastrointestinal tract (GIT) process has been hindered by the oral administration of nearly all medications in conventional dosage forms.[1] The Buccal drug Delivery System (BDDS) is a modern way to medication delivery that aims to replace traditional drug administration routes. The occurrence of drug side-effects can be significantly minimised, and the targeted distribution of drugs can be effectively performed using BDD (Bio Distribution and Drug distribution). The administration of medications through the buccal mucosa (BM) has garnered significant attention due to its simple accessibility. Despite being the most popular method for administering large medications, the oral route has some disadvantages, including local gastrointestinal distress, enzymatic breakdown inside the GI tracts, and first pass metabolism in the liver.[2] Significant advancements have been achieved in Bucco-adhesive drug administration to address specific challenges, such as first pass metabolism and low bioavailability, associated with regularly utilised dosage forms.

Anatomy of oral mucosa

Oral mucosa:[2] The oral mucosa is composed of an outermost layer of stratified squamous epithelium (fig 1). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer can be seen in figure. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 µm.

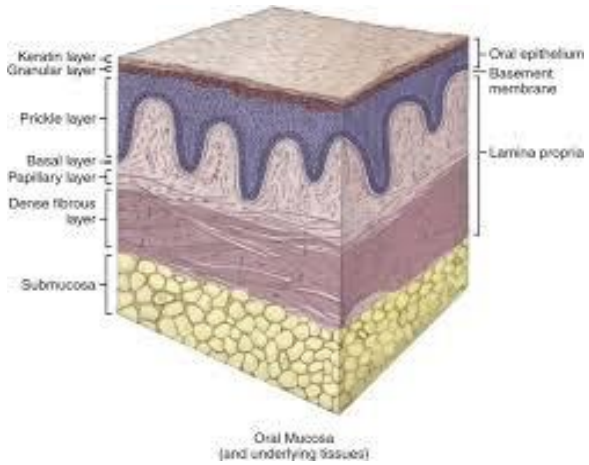

Figure 1: Oral Mucosa

Permeability: It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than the skin. The differences in permeability between different region of the oral cavity because of diverse structures and functions of the different oral mucosa. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non keratinized, and the palatal intermediate in thickness but keratinized.

Passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, carrier mediated transport has been reported to have a small role. In buccal mucosa two routes of passive transport are found:

Paracellular: It involves the transport of compounds through the intercellular space between the cells.

Transcellular: It involves passage into and across the cells.[3]

Buccal drug delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Since the drug content within the buccal formulations can be considerably lower than tablets and capsules, toxicity or undesired side effects will potentially be significantly reduced.

Buccal patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. Buccal drug delivery is a highly effective way to increase bioavailability. This is because the buccal mucosa has a rich in blood supply which facilitates the direct entry of the drug into the systemic circulation.

MECHANISM OF BUCCAL DRUG DELIVERY SYSTEM

Mechanism of buccal absorption: Buccal drug absorption occurs by passive diffusion of the non-ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membranes and the more lipophilic the drug molecule, the more readily it is absorbed. The dynamics of buccal absorption of drugs could be adequately described by first-order rate process. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth.

The linear relationship between salivary secretion and time is given as follows:

$$\frac{dm}{dt} = \frac{Kc}{ViVt}$$

Where,

M - Mass of drug in mouth at time t

K - Proportionality constant

C - Concentration of drug in mouth at time

Vi - The volume of solution put into mouth cavity and Vt - Salivary secretion rate

Mechanism of Mucosal Adhesion: Several theories purposed the mechanism of mucoadhesion by the interaction of polymer and mucus. The mechanism of mucoadhesion is divided into two steps, first is contact step and second is consolidation step. In the first step the mucus layer come in contact with mucoadhesive and mucous membrane and the formulation swell and spread over mucus membrane. In the second consolidation step the moisture activates the mucoadhesive material, this plasticizes the system, this allows to mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step. The diffusion theory is the mutually interacting of mucoadhesive molecules and glycoprotein of mucus and building of secondary bonds by interpenetration of their chains. Two steps of Mucoadhesion Process According to the dehydration theory the material get gelify when it come in contact with the mucus in the aqueous environment. The drawing of water into the formulation due to concentration gradient until the osmotic balance is reached. This process increases the contact time of mucous membrane with the mixture of formulation and mucus. So it is not the interpenetration of the macromolecules chains, it is the water motion that lead to the consolidation of the adhesive bond. The dehydration theory is not applicable for highly hydrated forms or solid formulations. (fig 2)

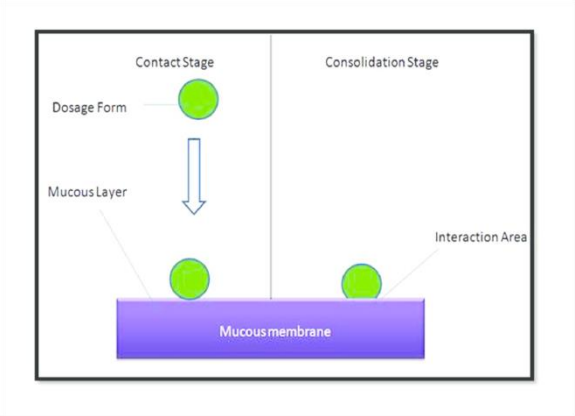

Figure 2: Mechanism of Mucosal Adhesion

The mechanisms of bioadhesion are explained by the following theories.

1. Wetting theory.
2. Theory of diffusion.
3. Theory of Adsorption.
4. Theory of fractures.
5. The theory of absorption
6. Theory of electronics.[4]

Manufacturing Methods of Buccal Patches

Following manufacturing methods are used in constructing mucoadhesive buccal patches:

Solvent casting method: In solvent casting method mucoadhesive polymers in required quantity is treated with solvent and polymer swell after vortexing. The measured quantity of plasticizer added in polymer mixture and again vortexed. The quantity of drug that needed liquefied in small volume of solvent system and added to

the polymer solution and mixed well. Then entrapped air is removed and blend is transferred into a cleaned petri plate (fig 3). The patches developed are stored in a desiccator till the evaluation tests are performed.[5]

Direct milling method: In this process, patches are fabricated deprived of the usage of solvents. Direct milling or kneading methods are used for motorized mixing drug and excipients without the existence of any liquefied solution. The desired thickness is accomplished by rolling the consequential material. The backing material is then laminated. The solvent-free process is chosen because there is no probability of residual solvents and health issues produced by solvents.[6]

Hot melt extrusion method: In hot melt extrusion method blend of pharmaceutical ingredients is molten and different shapes yielded by forcing mixture through an orifice. Hot melt extrusion has been used for the fabrication of controlled release matrix tablets, pellets, granules, oral disintegrating films dosage forms. Solid dispersion extrusion immiscible components are extruding with drug and then solid dispersions are formulated. Finally, the solid dispersions are shaped into films by means of dies.

TYPES OF BUCCAL PATCHES

a) Matrix type (Bi-directional)

b) Reservoir type (Unidirectional)

Composition of buccal patches:

A. Active ingredient.

B. Polymers (adhesive layer): HEC, HPC, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluents for its high aqueous solubility, its flavoring characteristics, and its physicomechanical properties, which make it suitable for direct compression. Another example: microcrystalline starch and starch.

D. Sweetening agents: Sucralose, Mannitol, etc.

E. Flavouring agents: Menthol, vanillin, clove oil, etc.

F. Backing layer: EC etc.

G. Penetration enhancer: Cyano acrylate, etc

H. Plasticizers: PEG-100, 400, propylene glycol, etc.,

Permeation enhancers:

These are substances added to pharmaceutical formulation in order to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity. Examples: Dimethyl sulfoxide (DMSO), Decylmethyl sulfoxide, Propylene glycol, Glycerol, etc.

Mechanism of Penetration Enhancers

1. Changing Mucus Rheology

2. Increasing the fluidity of lipid bilayer membrane

3. Action at tight junction's components

4. By overcoming the enzymatic barrier

5. By enhancing the thermodynamic action of drugs. [7]

EVALUATION OF BUCCAL PATCHES

The following tests are used to evaluate the Buccal Patches:

1. Weight uniformity: Five different randomly selected patches from each batch are weighed and the weight variation is calculated.

2. Thickness uniformity: The thickness of each patch is measured by using digital vernier caliper at five different positions of the patch and the average is calculated.

3. Folding Endurance: The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.

4. Surface pH: The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petri dish till gelling at room temperature. The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

5. Drug content uniformity: For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content of is estimated spectrophotometrically. The averages of three determinations are taken.[8]

6. Swelling Index: Buccal patches are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8. The patches are removed from the petri dishes and excess surface water is removed using filter paper. The patches are reweighed (W2) and swelling index (SI) is calculated as follows:

$$SI = \frac{W2-W1}{w1} \times 100$$

7. Moisture Content and moisture absorption:

The buccal patches are weighed accurately and placed in a dessicator containing 100 ml of saturated solution of aluminium chloride, which maintains 76% and 86% humidity (RH). After 3 days, films are taken out and weighed. The moisture absorption is calculated using the formula:

$$\textit{Moisture content} = \frac{Initial\ weight - Final\ weight}{Final\ weight} \times 100$$

8. *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 are then filtered through wattman filter paper and analyzed for drug content after appropriate dilution.

9. *Ex-vivo* mucoadhesion time: The *ex-vivo* mucoadhesion (residence) time is determined by locally modified USP disintegration apparatus using 800 mL of simulated saliva (pH 6.2) and the temperature is maintained at (37±1) °C. A porcine buccal mucosa obtained from local slaughter house within 2 h of slaughter is used to mimic the human buccal mucosa in the *in-vivo* conditions. The mucosal membrane is carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane is washed with deionized water and then with simulated saliva (pH 6.2). Porcine buccal mucosa (3 cm diameter) is glued on the surface of a glass slab. One side of the buccal patch is hydrated with one drop of simulated saliva (pH 6.2) and brought into contact with porcine buccal mucosa by gentle pressing with a fingertip for few seconds. The glass slab is vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch is completely immersed in simulated saliva at the lowest point and is out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface is recorded as ex-vivo mucoadhesion time.

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal deliver.

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