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BUCCALFILMS: AN INNOVATIVE TECHNOLOGY FOR ORAL DRUG DELIVERY

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ABSTRACT

Buccal route is prominent route of administration for systemic drug delivery and it leads direct access to the systemic circulation through the internal jugular vein thus bypasses drugs from the hepatic first pass metabolism and provides high bioavailability. Buccalbioadhesive films, release topical drugs in the oral cavity at a slow and predetermined rate, provide several advantages over traditional dosage forms for treatment of many diseases. This article 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 overcome the problems associated with the formulation design. It also offers more patient compliance without risk of chocking in case of paediatric and geriatric patients. Present review has summarised basics of mucoadhesion, composition, method of preparation, characterisation parameters, advantages and disadvantages of buccalmucoadhesive films.

INTRODUCTION

Buccal delivery is a system which has been attracting much attention in the recent years. Although oral drug delivery such as tablets and capsules is the most convenient and preferred route for administration of therapeutic agents, paediatric and geriatric patients find it difficult to swallow them and hence do not take their medications as prescribed by physician. A great majority of population experience dysphagia leading to poor compliance with oral tablet and hence reduces the overall effectiveness of therapy. Drugs taken orally could irritate the gastrointestinal tract and this is partially counteracted by coating. Oral route may not be suitable for drugs targeted delivery to specific organs. In certain conditions like sudden episodes of allergic attack or coughing and motion sickness or patients who are travelling without havingaccess to water, swallowing tablets and capsules may become difficult. Buccal drug delivery has lately become an important route of drug administration. Although various bioadhesive mucosal dosage forms have been developed such as tablets, films, patches, disks, strips, ointments and gels, Buccal patch is preferred over others in terms of flexibility and comfort. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability.[1,2] In addition, they provide 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.[1] The process of mucoadhesion involves a complex polymeric drug delivery system that includes processes such as wetting, adsorption and interpenetration of polymer chains. The success and degree of mucoadhesion bonding of the drug and the mucous membrane is influenced by various polymer-based properties such as the degree of crosslinking, chain length and the presence of various functional groups.[1,3]

BUCCAL PATCH

Buccal patch is a thin non-dissolving dosage form which consists of a drug reservoir layer, an impermeable backing layer and a bioadhesive surface for mucosal attachment. The backing layer control direction of drug release and prevents drug loss. The mucoadhesive polymer layer binds to the oral mucosa, gingival or teeth for unidirectional release of the drug into the oral mucosa. The patch is removed from the mouth and disposed of after a specified time.[4] A broad range of drugs can be considered suitable for preparing buccal patches, which includes hypolipidemic, analgesic, anti-depressants and NSAID. The buccal patch is an ideal formulation for quick onset of action compared to conventional dosage forms. Moreover, the oral cavity is easily accessible for self-medication and can be promptly terminated in case of toxicity by simply removing the dosage form from the buccal cavity. Thus, due to low level of irritation and ease of administration, buccal delivery is associated with high patient compliance.[5]

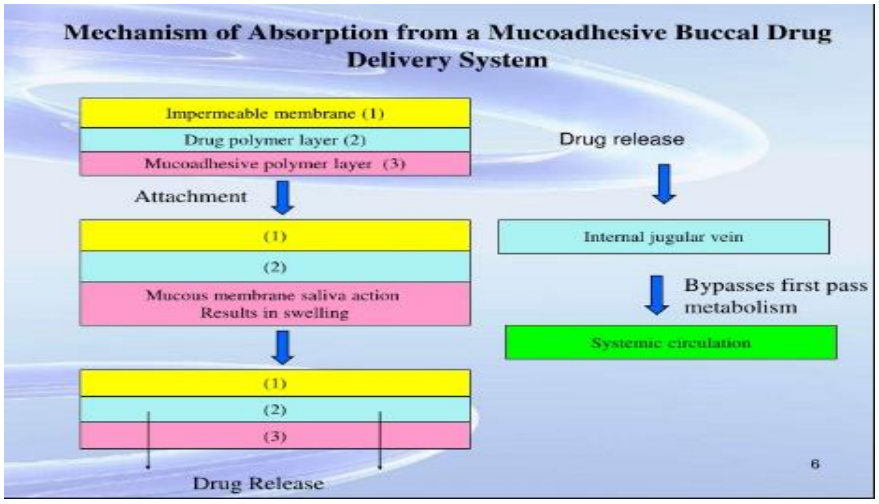

Fig 1: Mechanism of absorption in buccal Patch

CHARACTERISTICS OF BUCCAL PATCH

- Patch should easily adhere to oral cavity
- It should be elegant and thin.
- It must release drug quickly without the need of water.
- Patch should have a pleasant mouth feel

Advantages of buccal patch [1,4]

- Drugs are absorbed from oral cavity through oral mucosa which has high blood supply and get transported through internal jugular vein, braciocephalic vein, deep lingual or facial vein into the systemic circulation.
- Direct entry of drug to the systemic circulation and thereby bypassing the first pass effect.
- Stability problems or enzymatic degradation of drugs like insulin or other proteins,peptides and steroids while in contact with digestive fluids of gastrointestinal tract can be avoided by buccal route of administration. Also rate of

drug absorption will be unaffected by food or gastric emptying rate.

 Rapid onset of action

 Ease of administration in paediatric, geriatric and bedridden patients.

 Does not require water to swallow which is convenient to patients who are travelling without access to water or having difficulty in swallowing.

 Buccal patch have good accessibility to the membranes that line the oral cavity,which makes application painless and hence improved patient compliance due to the elimination of associated pain with injections. Patients can control the period of administration or terminate delivery in case of emergencies.

Limitations of buccal patches:-

 Drugs which are unstable at buccal pH cannot be administered.

 Drugs with only small dose can be administered.

 Drugs which irritate buccal mucosa cannot be administered.

 Drug must have high oral bioavailability.

 Involuntary swallowing of saliva may results in removal of drug from the site of absorption.

 Allergy, Taste, irritancy and adverse properties such as discoloration or erosion of the teeth may limit buccal route of administration.[6]

Theories of Mucoadhesion [6]

There are five different theories, which explain phenomenon of mucoadhesion:

Electronic theory

This theory is based on fact that both mucus layer and biological materials have opposing electrical charges that able to create double electronic layer at the edge and thus helps in determination of mucoadhesive strength.

Wetting theory

Liquid or less viscous molecules enter into mucosal surface and fix themselves by counteracting the surface tension at the interface. This property relates to contact angle, wetting and spread ability capacity of molecule. (Figure 2) Contact angle (θ) and interfacial tension (γ) can be determined from following equation:22$\gamma SG = \gamma SL + \gamma LG\cos S = \gamma SG - (\gamma SL - \gamma LG)$ Where γLG is liquid–gas surface tension, γSL is solid–liquid surface tension and γSG is solid–gas surface tension.

Diffusion Theory

This theory suggests that mucoadhesive polymer diffuses into mucus layer by breaking glycoprotein chain network (Figure 3). This diffusion is time dependent and depends on diffusion coefficients and molecular weight of both phases.23 Adsorption Theory Weak Vander Waals forces and hydrogen bond mediated adhesion involved in adsoption theory is most accepted theory of mechanism of mucoadhesion. It involves primary and secondary bonding in exhibiting semi permanent surface interactions.

Fracture Theory

This is the second most accepted theory, which explains the forces required to detach the two surfaces following adhesion. This force is called as tensile stress or fracture strength and can be determined by following equation: $Sm= Fm/Ao$ Where Sm: Tensile stress, Fm: maximum force of detachment andAo: surface area OR $Sf= (gcE/c)$ ½ Where Sf: fracture strength, gc: fracture energy (Wr + Wi = work done to produce new fracture surfaces + irreversible work of adhesion), E: Young's modulus of elasticity and c: critical crack length. Each and every theory (Figure 4) is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

Mechanism of Drug Absorption By Buccal Route[8,9]

Simple diffusion: It involves random movement of molecules of substance from

higher concentration to lower concentration placed on mucosa.

Facilitated diffusion: It involves carrier systems to facilitate transportation

Intercellular diffusion: The passage of substances occurs through loose junctions of oral epithelium.

Endocytosis: The drug is absorbed directly to systemic circulation by phagocytosis.

FACTORS AFFECTING BUCCAL ABSORPTION [3]

a)Membrane Factors:

 Degree of keratinization

 surface area available for absorption

 mucus layer of salivary pellicle

 intercellular lipids of epithelium, basement membrane

 absorptive membrane thickness, blood supply/ lymph draina

b)Salivary glands: The salivary glands located in epithelial or deep epithelial region of buccal mucosa constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it acts as a potential barrier to drug penetration. c. Movement of buccal tissues: Buccal region of oral cavity shows less active movements. Therefore the mucoadhesive polymers are incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.[3]

COMPOSITION OF BUCCAL PATCH:

 Active pharmaceutical ingredient (API)

 Polymers

 Diluents

 Plasticizers

 Sweetening agents

 Surfactants

 Flavouring agents

 Backing layer [4]

a)Active pharmaceutical ingredient (API)

The buccal patch has the potential for delivery of variety of APIs. 5% w/w to 30% w/w of active pharmaceutical ingredients can be incorporated in the buccal patches. The drug can be incorporated as milled, micronized and nanocrystal form based on the release profile. It improves film texture, dissolution and uniformity.

Choice of drug candidate:

 Lipophilic drugs are preferred due to high permeability across oral mucosa.

 Drug dose of less than 40 mg is suitable.

 Drug should have good solubility in water and saliva and should not have bitter taste.[4][2]

b**) Polymers**

Polymer selection is vital for a successful development of buccal patch. The polymers can be used alone or in combination as per the requirement. The robustness of film depends on the type and quantity of polymer in the film. The film formed should be tough enough to avoid damage during handling and transportation. The polymer hydration and consequently the mucus diffusion of drug promotes mucoadhesion.Swelling should favor polymer chain flexibility and interpenetration between polymer and mucin chains.[4][3]

Ideal properties of polymers

 It should be water soluble with low molecular weight.

 Facilitate rapid and easy disintegration.

 Should have satisfactory surface energy and chain flexibility favoring its spreadability and diffusion into the mucus and functional groups forming secondary chemical bonds (ionic and hydrogen bonds).

 It should have good flexibility and high tensile strength and low water permeation.

 They should be stable on long storage maintaining their initial physical properties.

 It must have good spreadability and wetting property.

 It must not be very expensive.

 It must be non-irritant, non-toxic and readily available.

 It should exhibit sufficient shear strength.[5]

Classification of polymers

Natural Polymers: Polymers of plants and

animal origin mostly found in nature are called natural polymers.

a. **Polysaccharides**- Starch and cellulose, the polymers of glucose are very common examples of polysaccharides. Starch is a chief food reserve of plants while cellulose is chief structural material of plants.

b. **Proteins** - These are the polymers of α-amino acids which are building blocks of animal cells. They are an indispensable part of our food.

c. **Nucleic Acids** - These are the polymers of various nucleotides. RNA and DNA are common examples of nucleic acids. d. Natural Rubber - It is a natural polymer of 2-methyl buta-1, 3-diene (isoprene) obtained from latex.

Semi-Synthetic Polymers: These are obtained from naturally occurring polymers by carrying out chemical treatment or modification to improve their physical properties like lustrous nature and tensile strength. Eg: cellulose acetate, cellulose nitrate. Synthetic Polymers: The polymers which are prepared in the laboratory from low molecular weight compounds are referred to as synthetic polymers or man-made polymers.

They possess new functional groups, high molecular weight and charged groups. Eg: polyethylene, polystyrene, nylon, PVC, bakelite, teflon, orion, etc.[10]

c) Diluents

They improve the consistency and applicability of the product to which it is added. Lactose DC, starch, microcrystalline starch is commonly used as diluent for its high aqueous solubility, its flavouring characteristics and physico-mechanical properties.[10]

d) Plasticizers

Depending upon nature of the polymer and the type of solvent used in solvent casting method, suitable plasticizer is selected. It forms one of the vital ingredients in the preparation of buccal patch. Mechanical properties and percentage elongation can be enhanced by the addition of suitable plasticizer. It imparts strength to the polymer, thereby enhancing the better polymer flow. It helps to improve the flexibility of patch as well as reduces its brittleness and reduce glass transition temperature of polymer. Plasticizers are usually used in the concentration range of 0-20% and must be volatile in nature. Inappropriate use of plasticizer often leads to film cracking, splitting and peeling of strip. The absorption rates of certain drugs were seen to be affected by use of certain plasticizer. Commonly used plasticizers: PG, glycerol, PEG, phthalates, citrates and castor oil.[2]

e) Sweeteners

Sweeteners are salient part of pharmaceutical dosage form that is intended to be disintegrated or dissolved in the oral cavity. Paediatric population prefers sweet taste in the formulation for better patient compliance. Natural as well as artificial sweeteners improve the palatability of the formulation. They are used in concentration range of 26%. Sorbitol, mannitol and isomalt can be used in combination which provides good mouth feel and cooling sensation. In diabetic population as well as diet conscious patients, the use of natural sweetener is restricted, which increased the popularity of artificial sweeteners.

a. Natural sweeteners - glucose, ribose, mannitol, xylose, fructose, mannose, galactose, sucrose and sorbitol.

b. Synthetic sweeteners - Aspartame, sucralose, neotame and cyclamate.[10]

f)Surfactants

Surfactants are used as solubilizing, dispesing and wetting agent. It allows the patch to be dissolved within seconds and release the active pharmaceutical agent instantly. It is mainly added to improve the solubility of poorly soluble drugs. Commonly used surfactants - Tweens, benzalkonium chloride and benzethonium chloride, Polaxamer 407.

g)Flavoring agent

Flavouring agents are used to mask the undesirable taste of the formulations. They are either added alone or in combination. Natural or artificial flavors are

incorporated into the buccal patch depending upon the drug to be incorporated in the formulation. The amount of flavor depends on the flavor type and strength. Commonly used flavors - Artificial vanilla, peppermint oil, cinnamon oil, chocolate, menthol and fruit flavors.

METHODS FOR THE PREPARATION OF BUCCAL PATCH

- Solvent casting method
- Hot melt extrusion method
- Direct milling

a)Solvent casting method

In this technique, buccal patches were prepared by first mixing the mucoadhesive polymer and solvent with constant stirring allowing the polymer to swell. To this, the required quantity of plasticizer (propylene glycol, glycerin or dibutyl phthalate) is added with constant stirring. Finally measured amount of drug is incorporated into small volume of solvent and then into the polymer solution and mixed well. The prepared solution was casted into the glass petri plate and covered with the inverted funnel, whose end was plugged with the cotton wool to allow the controlled evaporation of solvent and is kept aside in desiccators until evaluation studies.[2,4]

Advantages

- It forms better uniform thickness patches
- The patch is more flexible and has better physical properties.

Disadvantages

- Polymer must be soluble in volatile solvents or water.
- A viscous stable solution must be formed to create a patch.

b)Hot melt extrusion

In this technique, the mixture containing drug, polymer and excipients are extruded under high temperature to form uniform mass which is then casted to form a smooth patch. This is a solvent free technique. The major drawback of this method is that thermolabile substances cannot be incorporated due to use of high temperature during extrusion.

Advantages of hot melt extrusion:

- Solvent or water is not used.
- Bioavailability of drug is improved.
- Lesser processing steps.
- The compressibility properties of drug is not necessary.

c)Direct milling

There is no use of any solvent in direct milling. The drug and excipients are mixed by direct milling or kneading then this mixture is rolled on a release liner to get desired thickness. After this, the backing material is laminated. Solvent free process is preferred because there is no possibility of solvent related health issues.[2,4,11]

EVALUATION OF BUCCAL PATCH

The buccal patches were evaluated using the following methods.

1) Organoleptic evaluation

The formulated buccal patches were evaluated for organoleptic characteristics like color, odor and shape.[12]

2) Folding endurance

Folding endurance was determined by repeatedly folding the patch at the same place till it breaks. The number of times it can be folded without breaking gives the value of folding endurance[12][13]

3) Thickness

The thickness of the patch was measured using calibrated Verniercaliper at different spots of the patch. The mean thickness was calculated [13][14]

4) Weight variation

Weight variation was determined by individually weighing 10 randomly selected patches and average weight was calculated. Weight of each patch was measured using digital weighing balance. The S.D of weight was computed from the mean value [11,14] AV (Acceptance Value)= $| M-\bar{X} | +ks$. Where M is the reference value

$\bar{X}$ is the mean of the estimated contents of units tested, k is the acceptability constant

s is the sample standard deviation

5) Surface pH

The pH meter was calibrated using buffer of pH 4.0 and 7.0 before measurement.

The patches to be tested was moistened with phosphate buffer pH 6.8 in a petridish and kept for 30 sec. The pH of the formulation was noted after bringing the electrode of pH meter in contact with the surface and allowed to equilibrate for 1 min.[11,15]

6) Percentage elongation

% elongation was calculated by dividing the extension at the point of rupture by initial length of the specimen and multiplying by hundred[14].

% elongation = Increase in lengthOriginal length*100

7) Tensile strength

Tensile strength was determined using a Texture Analyzer. It is the maximum stress applied to a point at which patch breaks and is measured by dividing applied load at rupture by the cross-sectional area which is given by the equation10.

Tensile strength =load at breakagestrip thickness*strip width

8) Drug content uniformity

Drug content uniformity was determined by assay of 3 dosage units individually. The patch was transferred into a graduated flask, dissolved in100 ml methanol and the flask was shaken continuously. The solution was filtered after suitable dilutions with methanol and the absorbance was measured at 245nm using UV spectrophotometer. The drug content was calculated.[17]

9) Percentage moisture loss

Accurately weighed three patches of area 2 cmx2 cm and kept in desiccators for 3 consecutive days, patches were removed and reweighed. The % moisture loss was calculated using the formula[14]

% moisture loss =Initial weight − Final weightInitial weight*100

10) Ex vivo mucoadhesion time

The ex vivo mucoadhesion (residence) time was determined using a locally modified USP disintegration apparatus. The disintegration medium used was 800 ml of simulated saliva fluid, pH 6.8, maintained at 37 ºC. A segment of goat buccal mucosa, with 3 cm in length and 1 cm in width, was glued to the surface of a glass plate of similar dimensions, and vertically attached to the apparatus. The mucoadhesive patch was hydrated from one side with 2 ml of simulated saliva fluid (pH 6.8) and the hydrated surface was then brought in contact with the buccal mucosa. The glass slab was vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch was completely immersed in simulated saliva at the lowest point and was out of the solution at the highest point. The time of complete erosion or detachment of the patch from

the mucosal surface was recorded as ex vivo mucoadhesion time[16]

11)In vitro dissolution study

The dissolution study of the patch was carried out using modified type 5 dissolution apparatus at37°C±0.5°C using 300ml of simulated saliva (pH 6.8) as dissolution media.The agitation speed of paddle was 50 rpm. At predetermined time intervals, 5ml of sample was withdrawn and replaced with fresh medium. The sample was filtered through Whatmann filter paper and analyzed by UV spectrophotometer at 245 nm.[18]

CONCLUSION

The present review concludes that the buccal film is the most accurate and acceptable dosage form, which bypasses the hepatic first pass effect and shows good bioavailability. This is the most promising and innovative technology, which is useful to all the age groups, specifically pediatric, geriatric patients and also to the patients with swallowing difficulties. Buccal films can replace the conventional dosage forms, including fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured with low cost. This technology This technology provides a good tool for maintenance of drug therapeutic value.

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