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Review Article

A review: Buccal buccoadhesive drug delivery system

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ABSTRACT

Bioadhesive drug delivery system utilizes the property bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. It has a rich blood supply that drains directly into the jugular vein, thus by passing the liver and sparing the drug from first pass metabolism. Ease of drug delivery even in unconscious patients those who are permitted nothing by mouth. The development of mucoadhesive buccal films has increased dramatically over the past decade because it is a promising delivery alternative to various therapeutic classes including peptides, vaccines and nanoparticles. The "film casting process" involves casting of aqueous solutions and/or organic solvents to yield films suitable for this administration route. Over the last decade, hot-melt extrusion has been explored as an alternative manufacturing process and has yielded promising results. Characterization of critical properties such as the mucoadhesive strength, drug content uniformity, and permeation rate represent the major research areas in the design of buccal films. The objective of this article is to review buccal drug delivery of patches (films) by discussing buccal mucosa and characterization of mucoadhesive buccal patch**.**

Key words: Buccal drug delivery, Mucoadhesion, Buccal patch, Oral mucosa

INTRODUCTION

Buccal administration of drugs provides a convenient route of administration for both systemic and local drugs actions [1]. Over the last two decades mucoadhesion has become of interest for its potential for localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation an intimate contact with the absorption site (e.g. buccal cavity) [2]. Recently various Mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offers greater flexibility and comfort than adhesive tablets. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides direct access to the systemic circulation through the jugular vein by passing the hepatic first pass metabolism leading to high bioavailability [3] .

The term bioadhesion is typically used to describe the adhesion between polymer either synthetic or natural to soft tissue. In instances when bond is formed between mucus membrane and polymer the term mucoadhesion is used. Mucus membrane is one, in which the goblet cells are present for the secretion of mucus which is composed of glycoprotein mucin. Buccal mucosa presents a relatively smooth and immobile surface for the placement of Mucoadhesive dosage form. The amount of drug that can be incorporated is limited by the size limitation of the buccal dosage form. In general, a drug with a daily requirement of 25 mg or less is suitable for buccal delivery. Drug with short half-life, requiring sustained or controlled release showing poor aqueous solubility and which is sensitive to enzymatic degradation, may be successfully delivered across the buccal mucosa. Buccal delivery system is found to be the most promising because buccal mucosa itself provides a protecting covering for the underlying tissues acting as a physical barrier against toxins and microorganism [4-5]. Buccal delivery system provides easy administration thereby increasing patient compliance. Drug is easily administered and extinction of therapy in emergency can be facilitated. It can be administered in unconscious and trauma patients .Large contact surface of the

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oral cavity contributes to rapid and extensive drug absorption. Because of the high permeability and the rich blood supply transport via the sublingual route results in a rapid onset of action.

Propranolol hydrochloride is widely used beta blocker in the treatment of hypertensive, Angina pectoris and cardiac arrthymia. When administered orally frequent dosing is needed due to short biological half life ($t^{1/2}$-3.5 hrs) drug undergoes high hepatic first pass metabolism thus bioavailability is reduced to 15-23%. Buccal route bypass the hepatic first-pass effect the dose of propranolol hydrochloride could be reduced when it is formulated as a buccal patch. The physiochemical properties of propranolol hydrochloride such as short half-life (3-5hrs) and low molecular weight (295.81) make it a suitable candidate for administration by the buccal route [6-7].

ADVANTAGES [8-12]

- Patient may control the period of administration and terminate delivery in case of emergencies.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance.
- Easy & painless to administered.
- There is greater flexibility in physical state, shape, size & surface.
- It is passive system for drug absorption so there is no any requirement of any activation.
- For patient suffering from nausea or vomiting or in the state of unconsciousness.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.

LIMITATION [8-12]

- Drugs that are unstable at buccal pH cannot be administered.
- Buccal membrane has low permeability mostly when compared to the sublingual membrane.
- Drugs which have a bitter taste or unpleasant taste or irritate the mucosa cannot be administered through this route.
- Drug with the small dose can only be administered.
- Only those drugs which are absorbed by passive diffusion can only be administered by this route.
- There is restriction on eating and drinking.
- The flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
- Only drug with small dose is applicable.

ENVIRONMENT OF BUCCAL MUCOSA [13-14]

Role of Saliva:

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Role of Mucus:

- Made up of proteins and carbohydrates
- Cell-cell adhesion
- Lubrication
- Bioadhesion of Mucoadhesive drug delivery systems

DRUG DELIVERY WITHIN THE ORAL MUCOSAL CAVITY [15-16]

1) *Sublingual delivery:* This is systemic delivery of drug by the mucosal membranes lining the floor of the mouth, administration of drug via sublingual mucosa (membrane of the ventral surface of the tongue and floor of the mouth) to the systemic circulation. The sublingual mucosa is relatively permeable gives rapid absorption and acceptable bioavailability of many drugs and is convenient, accessible and generally well accepted. The sublingual route is by far the most widely studied of these routes.

2) *Buccal delivery:* Drug is administered through the mucosal membranes lining the cheeks (buccal mucosa). The buccal mucosa is considerably less permeable than that sublingual area, and is generally not able to provide rapid absorption and good bioavailability seen with sublingual administration.

3) *Local delivery:* Drug delivery into the oral cavity for the treatment of conditions of oral cavity principally ulcers fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time. The preferred site for retentive oral transmucosal delivery systems for sustained and controlled-release delivery devices is the buccal mucosa, mainly because of differences in permeability characteristics between the two regions.

BUCCAL PATCHES ARE OF TWO TYPES [17]

(a)*In matrix type*-The drug is homogeneously dispersed in hydrophilic or lipophilic polymer matrix and the medicated polymer is then moulded into medicated disc with a defined surface area.
(b)*In 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 in the mouth and to prevent drug loss.

COMPOSITION
Active ingredient:

- Polymer (adhesive layer): hydroxymethylcellulose, Eudragit®RS100, Eudragit®RL100 and Carbopol 934. And other Mucoadhesive polymer [18].
- Solvents: Methanol, Dichloromethane
- Sweetening agent; Sucralose, Aspartame, Mannitol, etc
- Flavouring agent: Menthol, Vanillin, Clove Oil, etc.
- Backing layer: Ethyl Cellulose, etc
- Penetration enhancer:
- Plasticizer: PEG-.100,400, Propylene Glycol, etc

METHOD OF PREPARATION OF BUCCAL PATCH [19-20]

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 protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of desired size and geometry.
2. *Direct milling*: In direct milling, 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 mixing process resultant material is rolled on a release liner until 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 two processes solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.
3. *Solid dispersion extrusion*:
In this immiscible component are extrude with drug and then solid dispersions are prepared. Finally, the solid dispersions are shaped in to films by means of dies.
4. *Semisolid casting*: In the semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (cellulose acetate phthalate, cellulose acetate butyrate) which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally, the gel mass is casted in to films or ribbons using heat controlled drums. Thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble forming polymer should be 1:4.
5. *Rolling Method*: In this rolling method solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers and cut in to desired shapes and sizes.
6. *Hot melt extrusion*: In this method, firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally, the melt is shaped in to films by dies. There are certain benefits of hot melt extrusion, fewer operation units, better content uniformity and an anhydrous process.

EVALUATION OF PATCHES [21-22]

Weight variation- The three disks of 1cm^2 was cut and weight individually on electronic balance for weight variation test and the average weights were calculated. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.
Thickness- Thickness of the patch was measured by using vernier callipers with atleast count 0. 001mm.The thickness uniformity was measured at five different points and average reading was taken.
Folding endurance- The folding endurance was determined for the patch by repeatedly folding the patch at the same place till it breaks. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.
Drug content uniformity- Drug content uniformity determined by dissolving 1cm^2 patch in (5% of methanol contained)100 ml of phosphate buffer pH6.8 then it was shacked for 24 hrs at room temperature. The solution was filter through what man filter paper no.42 and analysed at 290nm using a UV spectrophotometer.
Swelling index- Swelling index of buccal patches were determined by weighed individually (designated as W1) and placed separately in 2% agar gel plates, 19 incubated at 37 ^{0}C±1 ^{0}C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed (W2)

and the swelling index (SI) were calculated using the following formula:

SI= (W2-W1)/W1× 100.

Surface pH study-A combined glass electrode may used for this purpose. Each patch 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 and the pH was noted by bringing the electrode into contact with the surface of the patch and allowing it to equilibrate for 1 minute.

In vitro drug release- The US Pharmacopeia XXIII rotating paddle method used to study drug release from the buccal patches 200 mL of phosphate buffer (pH 6.8) used as the dissolution medium, at 37.0 ± 0.5^{0}C and a rotation speed of paddle was 50 rpm. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel 24 Samples (5 mL) were withdrawn at half-hour intervals and replaced with fresh medium. The samples were filtered through 0.45-µm Whatman filter paper and analyzed.

Ex-vivo mucoadhesion time: The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa. 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.

CONCLUSION

Adhesion of bioadhesive drug delivery devices to mucosal membranes leads to an increasing drug concentration gradient at the absorption site and improves the 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 requirement and minimize the 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. Presently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally in efficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. The need for safe and effective buccal permeation and absorption enhancers is a crucial component for the prospective future in the area of buccal drug delivery system.

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CONFLICT OF INTEREST

The authors have no conflicts of interest with regards to the content of this review article.

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