DRUG DELIVERY VIA THE BUCCAL MUCOSAL ROUTE.:AN OVERVIEW

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ABSTRACT: The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combinations of polymers, absorption enhancers.This review on buccal tablets gives the information about buccal mucosa structure, its permeability, theories of muco-adhesion, formulation and method of manufacture of buccal tablets and various evaluation methods for buccal tablets.

KEYWORDS:- Bioadhesion, buccal drug delivery, permeation enhancers, mucoadhesive polymers

I. INTRODUCTION

Among the delivery routes, the oral route is the most acceptable route for drug administration because it is more natural and less invasive than other traditional routes, such as i.v. and i.m. injections (1, 2). The mucosal layer lines a number of regions of the body including the GIT, urogenital tract, airways, ear, nose and eye. These represent potential sites for attachment of any bioadhesive system (3).

Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug. The mucoadhesive drug delivery system includes the following:

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1. Buccal drug delivery systems
2. Sublingual drug delivery systems
3. Rectal drug delivery systems
4. Vaginal drug delivery system
5. Ocular drug delivery systems
6. Nasal drug delivery systems

Even though the rectal, vaginal, ocular, mucosa offer certain advantages, the poor patient acceptability associated with these sites render them reserved for local application rather than systemic drug administration. Drug delivery through the membranes of the oral cavity can be subdivided as follows:

Buccal delivery: the drug administration through the lining of the cheek to the systemic circulation.

Sublingual delivery: the administration of drug via membranes of the floor of the mouth or the underside of the tongue to the systemic circulation.

Local delivery: By administration to the affected mucosal tissues [4].

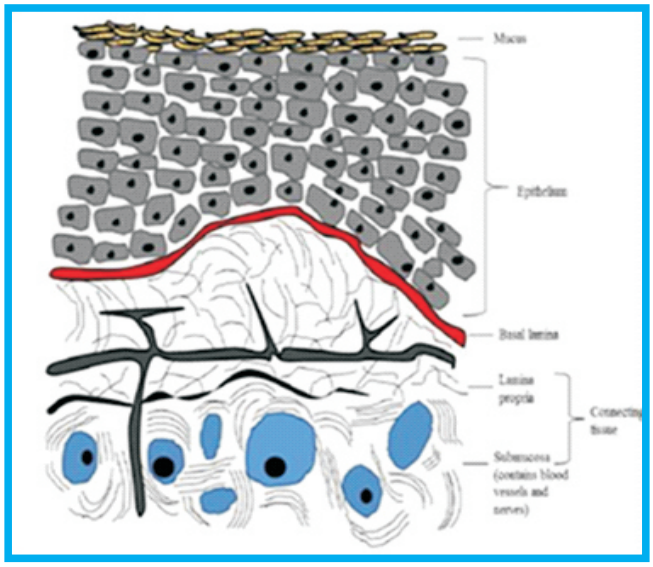
Buccal drug delivery can be defined as the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation [4]. Absorption of drugs was noted as early as 1847 by Sobrero via the mucous membranes of the oral cavity. The presence of nitroglycer-ine and systemic studies of oral cavity absorption were first reported by Walton in 1935 & 1944[5].

Table 1: Advantages of buccal drug delivery systems.

1. Drug is easily administered and extinction of therapy in emergency can be facilitated.
2. Drug release for prolonged period of time.
3. In unconscious and trauma patient's drug can be administered.
4. Drugs bypass first pass metabolism so increases bioavailability.
5. Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
6. Drug absorption by the passive diffusion.
7. Flexibility in physical state, shape, size and surface.
8. Maximized absorption rate due to close contact with the absorbing membrane.

Oral mucosa:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides.



Novel buccal dosage forms:

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

Buccalmucoadhesive tablets: Buccalmucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of HPC and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

Patches and Films: Buccal patches

consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required shape. A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of HPC and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hrs even when it is challenged with fluids.

Semisolid Preparations (Ointments and Gels): Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems - "orabase"- consists of finely ground pectin, gelatin and NaCMC dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 mins.

Powders: HPC and beclomethasone in powder form when sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution isseen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hrs[23].

BIOADHESION [27-29]:

'Bioadhesive' is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time. Bioadhesive are classified into three types.

Bioadhesion between biological layers without involvement of artificial materials. Cell diffusion and cell aggregation are good examples. Bioadhesion can be represented by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials. Adhesion of artificial substances to biological substrate such as adhesion of polymer to skin or other soft tissue.

Mechanism of bioadhesion [30-32, 29]:

For bioadhesion to occur, three stages are involved:An intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive. Penetration of the bio-adhesive into the tissue takes place. Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle.

The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

THEORIES OF MUCOADHESION

Several theories have been developed in the formation of bioadhesive bonds and are based on the formation of mechanical bonds, while others focus on chemical interactions [4].

The electronic theory:

This assumes that bioadhesive material and the glycol-protein mucin network have different electronic structures. Formation of a charged double layer at the interface of the mucus and the polymer due to the electron transfer results in attraction in the interface region and contributes to the inter diffusion of the two surfaces.

The adsorption theory:

This is the most widely accepted theory

of bioadhesion. Based on this theory, the bioadhesive bonds formed between an adhesive substrate and intestinal mucosa is due to Van-der Waals' interactions, hydrogen bonds, and related forces.

The wetting theory:

Describes the ability of bioadhesive polymer to spread over a biological surfaces to develop intimate contact with the corresponding substrate for bond formation. This theory is used predominantly in liquid adhesives.

The diffusion theory:

This theory is based on the formation of semi permanent adhesive bonds due to the interpenetration and entanglement of bioadhesive polymer chains and mucus polymer chain .The depth of penetration of polymer chains increase with the bond strength. The bioadhesive polymers and mucus should have similar chemical structures for the forma-tion of strongest bioadhesive bond. For the diffusion to occur, it is important to have good solubility of one component in the other.

The fracture theory:

States that, the force required for the detachment of polymers from the mucus depends on the strength of the adhesive bond. This is the most useful theory for studying bioadhesion strength through tensile experiments. The maximum tensile stress produced during detachment is the ratio of maximum force of detachment and the total surface area involved in the adhesive interaction.

FORMULATION AND PREPARATION OF BUCCAL TABLETS

The mucoadhesivebilayeredbuccal tablets consist of drug-releasing polymer layer and a backing layer of ethyl cellulose, which allow unidirectional release of the drug. They are prepared by the direct compression method involving two steps. In the first step, the drug-polymer mixture is to be prepared by homogeneously mixing the drug with mucoadhesive polymers. The other excipients present in the formulation like the diluents, permeation enhancers, organoleptic agents etc are to be added to the above mixture in a glass mortar and triturated to achieve a homogeneous blend. The lubricant is now mixed to the blend and compressed within the die cavity of single-stroke multi station tablet machine [11] or single punch tablet compression machine.The upper punch should then be removed and backing layer material, ethyl cellulose to be added over it and finally compressed at a constant compression force [12]

EVALUATION OF BUCCAL TABLETS

The buccal tablets are to be evaluated for the following studies after preparation:

PHYSICOCHEMICALCHARACTERISATION

Weight variation: The weight of the tablets prepared is routinely measured to help ensure that a tablet contains the proper amount of drug. Composite samples of the tablets are to be taken and weighed throughout the compression process. The tablets should pass the weight variation limits provided by United States Pharmacopoeia or National Formulary[21].

Thickness:

The thickness of prepared tablets can be measured by are Vernier calipers or a Screw-guage[18].

Hardness:

The hardness test of tablets is performed

by placing the tablet in between the two anvils, force is then applied and the crushing strength that just causes the tablet to break is recorded. Several devices operating in this manner to test the tablet hardness are: The Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester etc [21].

Friability:

The laboratory friability tester known as the Roche friabilator can be used to test the friability of tablets where the tablets are subjected to abrasion and shock by utilizing a revolving plastic chamber [21].

Drug content:

The drug content was determined by dissolving the tablets in ethyl alcohol, the drug residue obtained after filtration is to be diluted in a pH 6.8 phosphate buffer and analyzed by a U.V. Spectrophotometer [11].

Stability studies:

Stability studies are performed by placing the tablets in an amber colored bottle by wrapping them in an aluminium foil. The tablets are to be stored at 40oC, 75±5% RH for 3 months. Every month the tablets should be taken out and tested for physical characteristics, bioadhesion strength and in-vitro drug release. Stability study data obtained is to be compared with that obtained at zero time at ambient temperature. The results are analyzed with statistical correlation [20].

IN-VITRO STUDIES

Surface pH study: The surface pH study for buccal tablets has to be done to investigate the possibility of any side-effect in vivo. An acidic or alkaline pH may irritate the buccal mucosa, so the surface pH of tablet should be almost neutral. The tablets are allowed to swell by placing them in an agar plate for 2hr. The surface pH was measured by using a pH digital meter placed on the core surface of the swollen tablet [12]. Bottenberg et.al used a combined glass electrode for the study. In this method the tablet was allowed to swell by placing it in contact with 1mL of distilled water (pH 6.5±0.05) for 2hrs at room tempera-ture. The pH was determined by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1minute [23].

Swelling study:

At first the buccal tablets are weighed individually (W 1) and then the tablets are placed in an agar gel plates 1% or 2% in a Petri-dish with the core (drug-polymer layer) facing the gel surface, incubated at 37±1°C for up to 6 hrs. At regular intervals of time, the swollen tablets are removed from Petri-dish; the excess water is removed with the help of a filter paper and weighed again (W 2). The Swelling Index (SI) can be calculated using the formula [11].

SI= ×100

In-vitro drug permeation study:

Can be performed using Keshary-chien type glass diffusion cell at 37±0.2 °C. The fresh pig buccal mucosa (buccal membrane closely resembles the human buccal membrane in terms of structure and permeability) is to be mounted between donor and receptor compartments, the buccal tablet is placed with the core facing the mucosa and the compart-ments are clamped together. The donor compartment is to be filled with 1mL of phosphate buffer pH 6.8 and receptor compartment with phosphate buffer pH 7.4, hydrodynamics between compartments is maintained with a magnetic bead at a uniform slow speed. The samples at pre-determined intervals of time are analyzed with

the help of a U.V Spectro-photometer [11].

In-vitro drug release study:

The USP dissolution apparatus is used for the drug release study. It can be either a rotating paddle type, where backing layer of buccal tablet is to be attached to a glass disk with cyano-acrylate glue and the disk is placed at the bottom of the apparatus6 or rotating basket type [12]. The dissolution study is to be performed by suitable amount of phosphate buffer pH 6.8, samples at pre-determined time intervals are taken out and replaced with fresh buffer medium. The samples are filtered and suitable dilution is made and analyzed by an U.V Spectrophotometer [13].

EX-VIVO STUDIES

Ex-vivo mucoadhesive strength:

The mucoadhesion strength of buccal tablets can be determined by using a modified balance method. The apparatus constitutes of a two pan balance which has been modified by replacing one pan of the apparatus with a Teflon assembly on which the tablet is stuck. This pan is in turn lowered on to the other Teflon assembly over which the model buccal mucosa has to be tied. Fresh sheep buccal mucosa or fresh porcine buccal mucosa within 2hrs of slaughter can be used as a model membrane for the study. The mucosa is to be stored in phosphate buffer (pH 7.4) at room temperature before use. The mucosal membrane is to be excised by removing the underlying connective and adipose tissues and then equilibrated in 0.2 molar phosphate buffers, pH 6.8, at 37±1°C for 30 min. The tablet is to be stocked to the Teflon arm using cyano-acrylate adhesive and lowered onto the mucosa under a constant weight of 5g for a total contact period of 5 min. The Mucoadhesion strength is assessed in terms of weight (g) required to detach the tablet from the membrane[14].

Ex-vivo mucoadhesion time:

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.

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