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A REVIEW ON MUCOADHESIVE BILAYER BUCCAL DRUG DELIVERY: A PROMISING APPROACH

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ABSTRACT

The traditional and most common method of drug administration is the per oral administration of drugs but in these case drugs bioavailability is reduced as it is subjected to extensive pre-systemic degradation in the gut wall (or) liver. One of the non-invasive routes known as Buccal route drug delivery which comprises of several advantages such as targeting the specific tissue bypassing the first-pass effect, as well as higher patient compliance and higher bioavailability and have rendered administration route feasible for a variety of drugs. Mucoadhesive delivery is a dosage form which is designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome and the use of mucoadhesive materials which act as hydrophilic macromolecules containing numerous hydrogen bond forming groups helps in the process. The medicines which consist of one or different drugs combined in a single dose for effective treatment of the disease are generally defined by the term Bilayer tablets.

KEYWORDS: Buccal mucosa, Mucoadhesion, Bilayer tablet, Buccal delivery system.

INTRODUCTION

The three distinctive layers of the buccal mucosa are built by the epithelium, basement membrane and connective tissues which represents the oral mucosa. The epithelium lines up the oral cavity. Connective tissues as depicted is supported by the basement membrane.[1]

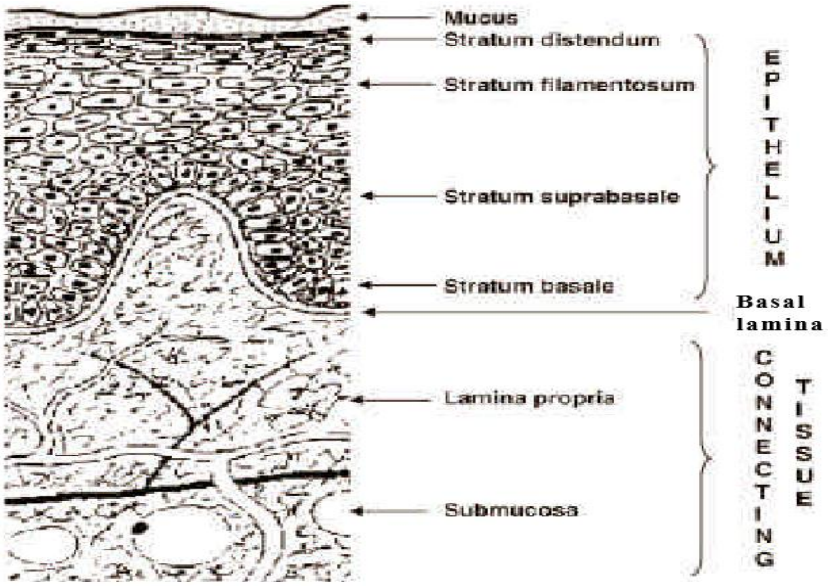

Fig no 1: Anatomy of oral mucosa.

A protective layer for the tissues termed as epithelium beneath is grouped into (I) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips and cheeks and (II) epithelium which is keratinised found in the hard palate and non-flexible regions of the oral cavity.[1]

The cells which originates from the basal cells, mature and change their shape as well as increase in size during their movement toward the surface are known as epithelial cells. In humans, dogs and rabbits thickness of buccal epithelium has been determined to be approximately 500–800mm as per the literature.[2]

Between the connective tissues and the epithelium basement membrane being distinctive layer helps in providing the required adherence between the epithelium and the underlying connective tissues and functions as a mechanical support for the epithelium.[3]

Also stated to as the lamina propria the connective tissues, consist of collagen fibers, a supporting layer of connective tissues, blood vessels and smooth muscles.[3]

Resulting from the external carotid artery is the rich arterial blood supply to oral mucosa. The buccal artery, some terminal branches of the facial artery, the posterior alveolar artery and the infraorbital artery helps in constituting the main sources of blood supply to the lining of the cheek in the buccal cavity.[1,4]

ADVANTAGES OF BUCCAL MUCOSA OVER OTHER TRANS-MUCOSAL DRUG DELIVERY

The permeability of buccal mucosa is relatively less than sublingual mucosa as mucosa of subingual cavity provides rapid absorption and good bioavailability of drugs but it is more suitable for highly permeable drugs with short delivery period and infrequent dosage regimen.

- Rapidly disintegrating tablets and soft gelatin capsules, are the two designs of sublingual dosage forms for mucosa which create a very high drug concentration in the sublingual region before they are systemically absorbed in the buccal mucosa.
- The preferred site for retentive oral transmucosal drug delivery of controlled- and sustained- drug devices is mucosa for buccal. It has an expanse of smooth and relatively immobile mucosa whereas sublingual mucosa lacks it. As it is constantly washed by a considerable amount of saliva drug device placement is difficult on sublingual mucosa.
- Due to its potential irritation and irreversible damage to the ciliary action from chronic application of nasal dosage forms, the nasal cavity is the less attractive route for systemic drug delivery.
- The drug absorption from the nasal cavity site is largely affected from large inter subject and intra subject variations in the mucus.
- Highly susceptible substances to the acidic environment of stomach and cannot be delivered through gastric mucosa are the peptides and proteins.
- Proteins which are characterized with high molecular size and hydrophilic nature is the reason they cannot permeate the intestinal mucosa as easily as they can the buccal tissues.

The ocular, rectal and vaginal mucosae have specific advantages, but poor patient acceptability limits these sites for local drug delivery, rather than systemic administration of drugs.[5, 6,7]

THE DISADVANTAGES ASSOCIATED WITH THIS ROUTE OF DRUG DELIVERY

- Specifically when compared to the sublingual membrane, and a smaller surface area is the low permeability of the buccal membrane.[8,9,10]
- Subsequent dilution of the drug with the continous secretion of saliva (0.5-2l/day.[10]
- The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2, of which ~ 50 cm2 represents non-keratinized tissues, including the buccal membrane.[11,12]

TYPES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Oral mucoadhesive drug delivery system
Ocular mucoadhesive drug delivery system
Vaginal mucoadhesive drug delivery system
Rectal mucoadhesive drug delivery system
Gastrointestinal mucoadhesive drug delivery system

BIOADHESION AND MUCOADHESION

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion.

Leung and Robinson described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used.[13]

THEORIES OF MUCOADHESION

➢ Wetting Theory of Mucoadhesion

The oldest established theory of adhesion is perhaps the wetting theory and to liquid or low-viscosity bioadhesives it is best applied. It describes adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. To have free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface.[14]

➢ Electrostatic Theory of Mucoadhesion

It states that according to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. The outcome is the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.[15]

➢ **Diffusion Theory of Mucoadhesion**

The polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semipermanent bond is best described by diffusion thoery.[16]

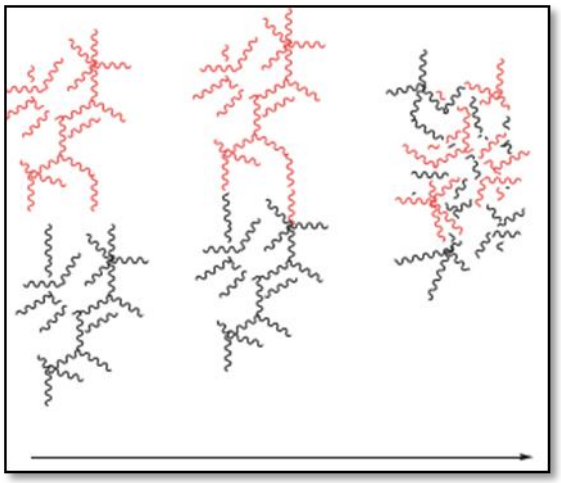

Fig no 2: Diffusion theory.

➢ **Adsorption Theory of Mucoadhesion**

Adsorption theory, illustrates that after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces.[17]

➢ **Fracture Theory of Adhesion**

The force required for the separation of two surfaces after adhesion is understood through this theory. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.[18]

TYPES OF BUCCAL MUCOADHESIVE DOSAGE FORMS

Only a few products are commercially available, although several buccal mucoadhesive dosage forms have been identified.

1. Buccal tablets

The most commonly investigated dosage form for buccal drug delivery to date is still through the tablets. They are represented as small, flat, and oval, with a diameter of approximately 5–8 mm.[19]

Buccal mucoadhesive tablets allow for drinking and speaking without major discomfort unlike conventional tablets. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth.

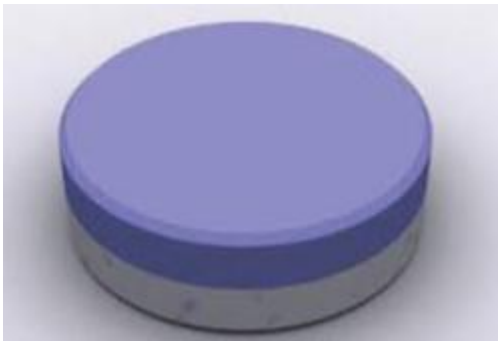

Fig no 3: buccal tablet.

2. Buccal patches

The laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment is known as patches and these buccal patch systems are similar to those used in transdermal drug delivery.

Fig no 4: Buccal patch.

3. Buccal films

The most recently developed dosage form for buccal administration are the buccal films and may be preferred over adhesive tablets buccal films posses greate flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva.

Fig no 5: Buccal film.

4. Buccal gels and ointments

The advantage of easy dispersion throughout the oral mucosa is present in the semisolid dosage forms such as ointments and gels. However, drug dosing from semisolid dosage forms is not as accurate from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations.

A promising dosage form for buccal drug delivery is the Hydrogels and are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion.[20]

BILAYER TABLET

Over the past decade due to immense focus on the marketing of new drug molecules as the combination of these new drug molecules has increased to counter multiple diseases that require different dosage regimens gave momentum that helped in the fabrication of sustained or controlled drug delivery systems.[21,22]

fig no 6: bilayer tablet.

The objective of opting for the controlled, or sustained, delivery systems are the reduction of the dose frequency or increasing the efficacy of the drug.[23]

Advantages

- They are used as an extension of a conventional technology as more useful than it.
- Potential use of single entity feed granules is done with it.
- Separation of incompatible components is achieved.
- Patient compliance is enhanced leading to improved drug regimen efficacy is achieved.
- Patient convenience is improved because fewer daily doses are required compared to traditional delivery system causing a difficulty.
- Maintain physical and chemical stability in it.
- Retain potency and ensure dose accuracy is achieved.[24,25]

General properties of bilayer tablets

Should be free from damages like chips, discolouration and cracks
Should be elegant
Should possess chemical stability
Should possess ability of withstanding mechanical property.[26]

Following are the general steps involved in the preparation of bilayer tablets

Filling of first layer
Compression of first layer
Ejection of upper punch
Filling of second layer
Compressing the second layer
Ejection of prepared bilayer tablet.[27,28]

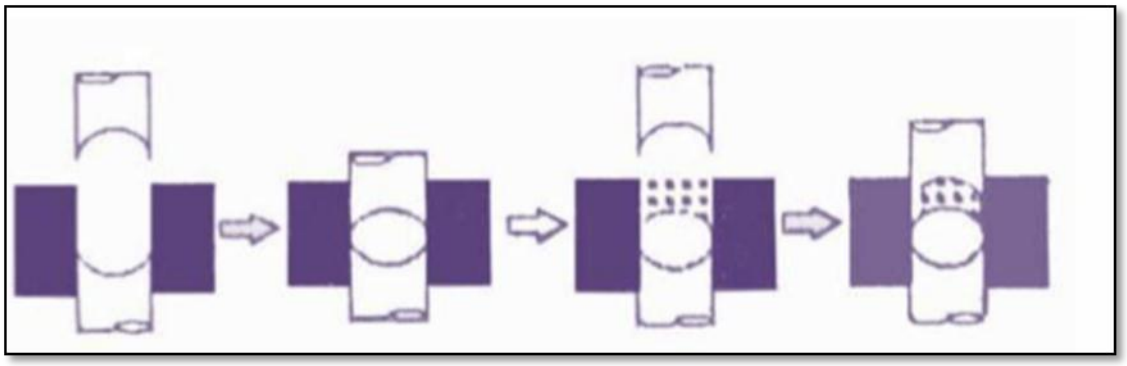

Fig no 7: bilayer tablet preparation steps.

Techniques of bilayer tablets

1. OROS ® push-pull technology

This technology mostly includes two or three layers, among which the first one or two layers contain the active pharmaceutical ingredient and the last one is the push layer. The drug layers are only composed of the drug and a few excipients and are made of poorly soluble material. It could also additionally include a suspending and osmotic agent. A semipermeable layer keeps the tablet core separate from its surroundings.[29,30]

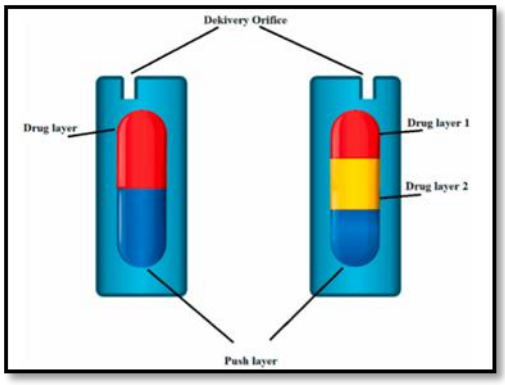

Fig no 8: OROS push pull technology.

2. L-OROS Tm technology

This technology is made by Alza and solves a major problem of solubility. The drug was first developed in the form of lipid soft gel in a dissolved state. It was then covered by a barrier membrane, followed by the osmotic push layer, and after that, the semipermeable membrane was punctured for an exit cavity.[31-33]

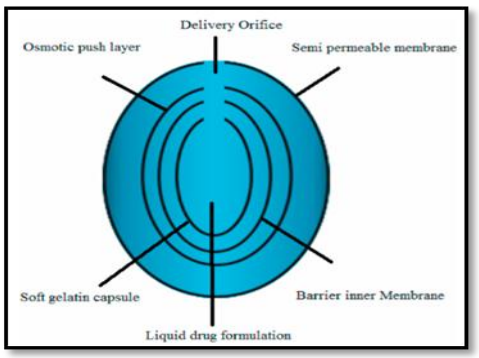

Fig no 9: L-OROS tm technology.

3. DUROS technology (Alza corporation)

The Duros technology relies on the implant technique and acts as a substitute for the transmission of numerous therapeutic substances, which ranges from peptides, proteins, and various other biochemical substances. Also known as "Miniature drug dispensing technology", this system works similarly to a miniature syringe that releases drugs continuously and consistently in a concentrated form for a longer period. In the human body, the therapeutic compounds are protected due to these cylinders, hence, making it resistant to human tissues for a long period. For the annual palliative treatment of advanced prostate cancer, Viadur (leuprolide acetate implant) this technology is employed.[34-36]

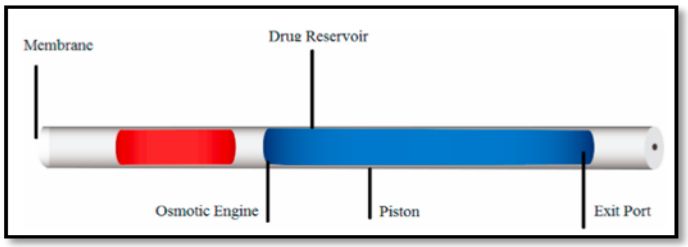

Fig no 10: DUROS.

4. Elan drug technologies' dual release drug delivery system (DUREDAS™ technology)

Dual drug delivery system (DUREDAS) is a technology employed by Elan corporations for two distinct discharge amounts or double discharge from a solo dosage. This technology provides a combination release pattern of drug i.e. immediate or sustained release. This technology produces a tablet through two independent direct compression steps which combine the immediate-release layer with the hydrophilic layer in a single tablet. This generates a complex controlled-hydrophilic matrix that remains compact and gradually absorbs liquid from the gastrointestinal tract (GI tract). The hydrophilic matrix upon absorption of fluid turns in sticky, permeable gel, which acts like obstacles between the dosage and the adjacent fluid, as the gel expands more the surrounding fluid, penetrates the drug, hence, dissolving it.[37.38.39]

5. EN SO TROL technology

An integrated approach is used by the Shire laboratory for the drug delivery system by properly identifying and incorporating the enhancer to get the optimized dosage form in the controlled release system. This approach helps to increase solubility.[40]

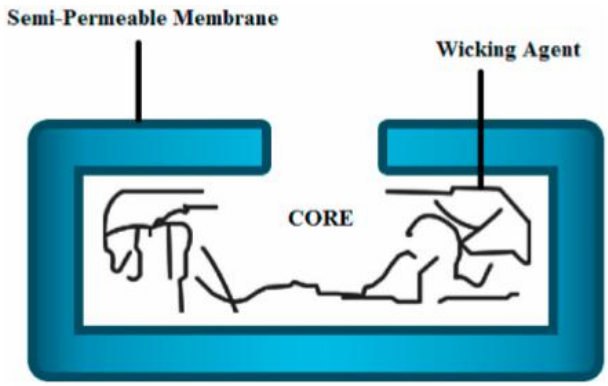

Fig no 11: EN SO TROL TECHNOLOGY.

6. Geminex technology

This technology helps massively in increasing the therapeutic effectiveness of the drugs while also minimizes their side effects. It delivers one or more drugs having different release rates through a single dose. It is extremely beneficial for patients as well as the industry and is largely used by pen west in for cardiovascular diseases, CNS disorders, diabetes, cancer, and central nervous system (CNS) disorders.[41]

7. Programmable oral drug absorption system (PRODAS)

PRODAS, also known as multi particulate drug technology (Elan Corporation), encapsulates mini-tablets of controlled drug release, with size ranging from 1.5 to 4 mm. The technology is a combination of multi- particle and hydrophilic matrix tablet technologies and is used for providing the combined benefits of these drugs in one dose.[42]

PRODAS technology is beneficial in the targeted delivery of the drugs for targeting to GIT. Different release rates of the mini-tablets, such as immediate, delayed, or controlled release, are combined in the form of a single dosage for providing the wanted release rate. The Minitab are sometimes combined with various APIs for forming products with anticipated release patterns.[43]

CHALLENGES IN FABRICATION OF BILAYER TABLET

following are the challenges in preparing bilayer tablets.

Delamination

both the layers should adhere after the process of compression.

Production yields

lower yields are reported in bilayer tablet than in single tablets as the process of dust collection is required which leads to loss.

Cross contamination

cross contamination of layers may also occur if mixing of layers occurs.

Cost

Production of bilayer tablets is expensive as compression steps, stability and interaction is to checked.[44,45]

Evaluation of bilayer tablets

Some of the general test for evaluating bilayer tablets are the following

Hardness
Thickness
Friability
Drug content
Swelling index
Invitro studies

Some test involved in mucoadhesive dosage forms

Mucoadhesive strength test.

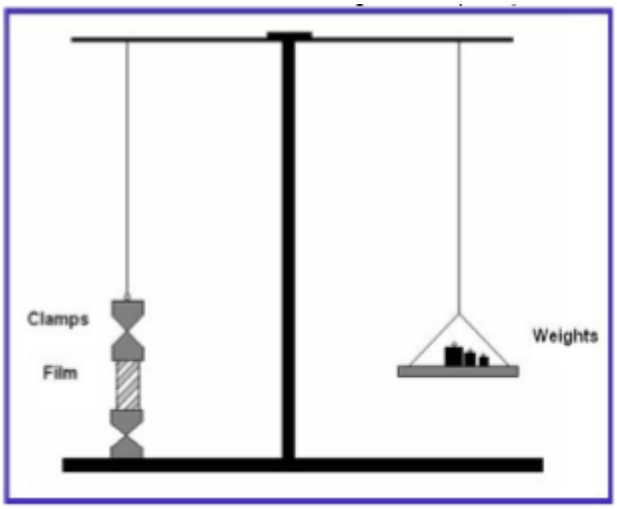

Fig no 12: modified physical balance.

APPLICATIONS

- suitable for sequential release of two drugs in combination and Separating Two Incompatible Substances is done by bilayer tablet.
- Patient Convenience and Compliance is more pronounced.
- The shortcoming of the single layered tablet is improved by beneficial technology known as bilayer tablet
- The loading dose and sustained dose of the same or different drugs are delivered through the bilayer tablets.

- The tablets which are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug is the bilayer tablets.
- The two different drugs having different release profiles are delivered through bilayer tablets.[46]

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