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A REVIEW ON CONTROLLED RELEASE BUCCOADHESIVE BILAYERED TABLET OF PROCHLORPERAZINE MALEATE

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ABSTRACT

The oral mucosa can be divided into two general regions, the outer vestibule and the oral cavity. The vestibule is bounded on the outside by the lips and cheeks and on the inside by the upper and lower dental arches. Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. Although the target of many bioadhesive delivery systems may be a soft tissue cell layer (i.e. epithelial cells), the actual adhesive bond may form with either the cell layer, a mucous layer or a combination of the two. The mucoadhesive power of a polymer is affected by the nature of polymer and also by the nature of surrounding medium.

KEY WORDS: Tablet, bioadhesion,mucoadhesive, prochlorperazine maleate

1. INTRODUCTION:

Drugs can be absorbed from the oral cavity through the oral mucosa either by sublingual or buccal route[1]. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that may be associated with oral route of administration[3].In general, rapid absorption from these routes is observed because of the thin mucus membrane and rich blood supply. After absorption, drug is transported through the deep lingual vein or facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism[1, 2].

1.1 ORAL MUCOSA AS A SITE OF DRUG ABSORPTION[1, 4]:

The oral mucosa can be divided into two general regions, the outer vestibule and the oral cavity. The vestibule is bounded on the outside by the lips and cheeks and on the inside by the upper and lower dental arches. The oral cavity is situated within the dental arches framed on the top by the hard and soft palates and on the bottom by the tongue and floor of the mouth. The oral mucosa consists of an outermost layer of stratified squamous epithelium, below which lies a basement membrane, and below this, in turn, a lamina propria and submucosa.

The oral mucosa can be distinguished according to five major regions in the oral cavity[6]:

- The floor of the mouth (sublingual region)
- The buccal mucosa (cheeks)
- The gum (ginigiva)
- The palatal mucosa
- The inner side of the lips.

The presence of saliva in the mouth is important to drug absorption for two main reasons[6]:

- Drug permeation across moist (mucus) membranes occurs much more readily than across nonmucus membranes. For example compare to drug absorption across the gastrointestinal tract and skin.
- Drugs are commonly administered to the mouth in the clinical trials in a solid form. The drug must therefore first dissolve in saliva before it can be absorbed across the oral mucosa. That is, the drug cannot be absorbed directly from a tablet.

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1.2 FACTORS INFLUENCING DRUG ABSORPTION FROM THE ORAL CAVITY[4, 6]:

As the oral mucosa is a highly vascular tissue, the main factors that influence drug absorption from the mouth are:

a) The permeability of the oral mucosa to the drug.

b) Physicochemical characteristics of the drug and

c) Miscellaneous factors

a) Permeability of the oral mucosa to drugs [1, 4, 6]:
Permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicated by a wide range in this reported values, there are considerable differences in permeability between different regions of the oral cavity. In general, permeability of the oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal. This is based on the relative thickness and degree of keratinization of these tissues.

2. The keratin layer is an effective barrier to penetration of human skin by water soluble substances. The permeability barriers of the oral mucosa are supposed to reside within the superficial layers of the epithelium. It has been shown that for some compounds the barrier to penetration is not the upper one third of the epithelium. Alfano and his coworkers studied the penetration of endotoxins through non-keratinized oral mucosa. The results indicated that the basement membrane is a rate limiting barrier to permeation[1].

3. Some workers have suggested that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called "Membrane Coating Granules" (MCGs). The barriers exist in the intermediate cell layers of many stratified epithelia and are of 100-300 nm in diameter.

4. Other factors which may affect the permeability of molecules include exogenous substances placed in the mouth for their local effects, such as mouthwashes and toothpastes, which contain surfactants and nutritional deficiencies.

b) Physicochemical characteristics of the drug[6]: The various physicochemical characters that play an important role in absorption of drug from the oral cavity are considered below:

i) Molecular weight: Molecules penetrate the oral mucosa more rapidly than ions and smaller molecules more rapidly than larger molecules. In case of hydrophilic substances, the rate of absorption appears to be rapid for small molecules (molecular weight less than 75-100 Da), but permeability falls off rapidly as the molecular size increases.

ii) Degree of ionization: The average pH of saliva is 6.4. Because the un-ionized form of a drug is the lipid-soluble-diffusible form, the pK_a of the drug plays an important role in its absorption. Adequate absorption through the oral mucosa occurs if the pK_a is greater than 2 for an acid or less than 10 for a base.

iii) Lipid solubility:A common way of assessing the lipid solubility of a drug is to measure

its oil-water partition coefficient. Partition coefficient between 40-2000 is necessary for optimal drug absorption. If the partition co-efficient exceeds 2000, solubility in the saliva is insufficient to provide the concentration gradient necessary for drug absorption. That is in addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids for absorption.

iv) pH of the saliva: The saliva pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentration increases leading to and increase in the pH[6]. Absorption is maximum at the un-ionized form of drug in pH of saliva.

c) Miscellaneous:

i) Binding to oral mucosa:

Systemic availability of drugs that bind to oral mucosa is poor.

ii) Storage Compartment:

A storage compartment in the buccal mucosa appears to exist which is responsible for the slow absorption of drugs.

iii) Thickness of oral epithelium:

Sublingual absorption is faster than buccal since the epithelium of former region is thinner and immersed in a larger volume of saliva.

1.4 BIOADHESION AND MUCOADHESION [1,3,4,7]:

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In the case of bioadhesive drug delivery systems, it is a bond formed between polymers and soft tissues. If the bond is formed between mucus and polymer, it is described as mucoadhesion.

1.5 FACTORS AFFECTING MUCOADHESION[1, 4, 8]:

The mucoadhesive power of a polymer is affected by the nature of polymer and also by the nature of surrounding medium.

a) Polymer Related Factors:

i) Molecular weight: For the successful mucoadhesion, the molecular weight of polymer should be at least 100000. For example, polyethylene glycol (PEG), with a molecular weight of 20000 has a little adhesive character, where as PEG-200000 has improved and a PEG-400000 has superior adhesive properties. Thus mucoadhesiveness improves with increasing molecular weight for linear polymers.

ii) Concentration: There is an optimum concentration of a mucoadhesive polymer to produce maximum mucoadhesion. In highly concentrated systems, the adhesive strength drops significantly, because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

iii) Chain flexibility: This factor is important in case of interpenetration and entanglement. As water soluble polymers become cross linked, mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces mucoadhesive strength.

b) Environment – Related Factors:

i) pH: pH can influence the charge on the surface of mucus as well as of certain ionisablemucoadhesive polymers. Some studies have shown that the pH of the medium is important for the degree of hydration of crosslinkedpolyacrylic acid, showing consistently increased hydration from pH 4 through pH 7 and then a decrease as alkalinity and ionic strength increases.

ii)Contact Time: Contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. Moreover, mucoadhesive strength increases as the initial contact time increases.

iii)Swelling: Swelling depends on the polymer concentration, ionic strength, as well as presence of water. During the dynamic process of mucoadhesion, maximum mucoadhesion occurs with optimum water content. Over-hydration results in the formation of a wet slippery mucilage without adhesion.

1.6 MUCOADHESIVE POLYMERS [1, 5,6,7,8]:

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymers should possess optional polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.

1. The polymer and its degradation products should be nontoxic and nonabsorbable in the gastrointestinal tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and offer non hindrance to its release.
6. The polymer must not decompose on storage or during shelf-life of the dosage form.
7. The cost of polymer should not be high.

Table 1: Mucoadhesive polymers with their mucoadhesive property[5]

Sr.No	Polymer	Mucoadhesive property
1	Carbopol 934	+++
2	Carboxymethylcellulose	+++
3	Polycarbophil	+++
4	Tragacanth	+++
5	Sodium alginate	+++
6	Hydroxyethyl cellulose	+++

7	Hydroxypropyl methylcellulose	+++
8	Gum karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
11	Polyethylene glycol	+
12	Hydroxypropyl cellulose	+

Note: +++ excellent, ++ fair, +poor

1.7 ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS[1, 4, 5, 6, 13]:

Drugs administration via oral mucosa offers several advantages

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose related side effects.
7. Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
8. Drugs which show poor bioavailability via the oral route can be administered conveniently.
9. It offers a passive system of drug absorption and does not require any activation.
10. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
11. Systemic absorption is rapid.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
13. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

1.8 LIMITATION OF BUCCAL DRUG ADMINISTRATION[1, 4, 5, 6, 13]:

Drug administration via buccal mucosa has certain limitations.

Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour; can not be administered by this route.

1. Drugs, which are unstable at buccalpHcan not be administered by this route.
2. Only drugs with small dose requirements can be administered.
3. Drugs may swallow with saliva and loses the advantages of buccal route.
4. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
5. Eating and drinking may become restricted.
6. Swallowing of the formulation by the patient may be possible.
7. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

1.9 CONCLUSION:

Buccal route offers several advantages such as rapid absorption, high blood level and ease of administration and termination of therapy. Hence in the present work Buccoadhesivebilayered tablets of Prochlorperazine maleate were prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolonged period of time.Prochlorperazine maleate is an anti-emetic drug. It is under goes extensive first pass metabolism resulting in an oral bioavailability of 0 to 16 % and it shows variable absorption from GIT.

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