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A REVIEW ON ORAL MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Despite of tremendous advancement in drug delivery the oral route of drug administration is the most important method of administration of drug for systemic effect. The parenteral route is not routinely used for self administration of medication. It has been known for centuries that buccal and sublingual administration of drug solute is rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa. The oral mucosa has rich blood supply and it is relatively permeable. The permeability of the buccal mucosa is 4- 1000 time greater then that of skin. the administration of drugs by the buccal route has several advantage over per oral administration such as QWICK ACTION, avoid of first pass metabolism , drug is not subject to acidic environment of the stomach and also the improved patient compliance particularly with pediatric & geriatric patient. It is the objective of this article to review the oral mucosal drug delivery by discussing briefly the structural feature of mucosa as drug delivery such as buccoadheshive film & tablet, medicated chew gum, fast dissolving tablet, film & capsule etc.

INTRODUCTION: A drug can be administered via a many different routs to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self–administration of medication.

It is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there.

It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by there doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by paediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

It has been known for centuries that buccal and sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal juglar vein, and braciocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens.

Structural Features of Oral Mucosa: The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. The oral mucosa is composed of an outermost layer of stratified squamous epithelium, below this lays a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. Three different types of oral mucosa can be identified. i. e. masticatory, lining and specialized mucosa. The masticatory mucosa covers the gingival and hard palate. It comprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissue and as such is able to

withstand the abrasion and shearing forces of the masticatory process. The lining mucosa covers all other areas except the dorsal surface of the toung.

The regional differences in morphology result in different permeability characteristics that have considerable influence on the design and siting of the drug delivery. The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. The blood flow through a tissue is important for achieving good drug absorption. The external carotid artery is the main source of blood supply to the oral tissues. It branches into maxillary, lingual and the facial artery. Blood from the capillary beds is collected by three principle veins that flow into the internal jugular vein. Even during disease, blood flow through human oral mucosa is believed to be sufficiently fast as not to be rate-limiting in drug absorption.

Because they oral mucosa is a highly vascular tissue the two main factors that influence drug absorption from the mouth are the permeability of the oral mucosa to the drug and the physicochemical characteristics (molecular weight, degree of ionization, lipid solubility) of the drug that is presented at the site of absorption.

Advantage and Limitation: The administration of drugs by the buccal route has several advantages over per oral administration such as; [1, 8]

- The drug is not subjected to destructive acidic environment of the stomach.
- Therapeutic serum concentration of the drug can be achieved more rapidly.
- The drug enters the general circulation without first passing through the liver.
- 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.
- Delivery can also be terminated relatively easily if required.

For some drugs a considerable barrier contribution arises as a result of presystemic metabolism. The enzymatic activity of the buccal mucosa is relatively low, and drug inactivation is neither rapid nor extensive. Nevertheless, enzymes existing in the oral cavity could degrade some drugs, particularly peptide or protein drugs. Co- administration of enzyme inhibitors such as aprotinin, bestatin, puromycin and bile salts reduces the activity of proteolytic enzymes, altering the conformation of the peptide drug or forming micelles, and/or rendering the drug less accessible to enzymatic degradation. The main obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. The mucin film may act as a barrier, although unless the drug binds specifically with the mucin or are large molecules, the diffusion through the mucus is not a rate limiting step. Rapid removals of

conventional delivery system, primarily through copious salivary flow are also clear impediments to successful use of this route. Bioadhesive polymer can overcome the removal issue.

Oral Mucosal Dosage Forms: Various drug delivery systems are their which uses the oral mucosa as a drug delivery site such as – fast dissolving tablets, orodissolving films, fast caps, buccoadheshive film and tablets, chewing gums etc.

(a) Fast Dissolving Tablet (FDT): Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. They also impart unique product differentiation thus enabling use as line extension for existing commercial products. FDTs can be prepared by various techniques like direct compression, sublimation, melt granulation, moulding, volatilization and freeze drying. Some of patented technologies are zydis, orasolve, durasolv, flash dose, wowtab, flash tab etc. some drugs which are poorly water soluble and have a variable bioavailability and bio-inequivalence related to its poor water solubility. The solubility of drug was increased by various methods to make a fast dissolving tablet like solid dispersion technique, by cogranulation with beta – cyclodextrin.

Because fast dissolving systems dissolves or disintegrate in patient's mouth, thus the active constitute come in contest with the taste buds and hence taste masking of the drugs become critical to patient compliance. Taste masking can be done by various methods like addition of sweeteners, or by mass extrusion technique using eudragit E100. Recently various comparative studies were done between fast dissolving and conventional formulations. In an acceptance survey of FDT in allergic patients it is observed that if given the choice 93 % would choose FDT formulations

(b) Fast Dissolving Films: However, the fear of taking solid tablets and the risk of choking for certain patient population still exist despite their short dissolution/disintegration time. Recent development in novel drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration. One such approach is rapidly dissolving film. It consists of a very thin oral strip, which releases the active ingredient immediately after uptake into the oral cavity. Rapid film combines all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability)**.**

The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and dissolves to release the medication for oromucosal absorption. One or a combination of the following processes can be hot melt extrusion, solid dispersion extrusion, rolling, semisolid casting, and solvent casting. Spence S.H. et al disclosed orally consumable films that include pullulan as a water soluble film forming agent. A film is also developed that may deliver rotavirus vaccine to infants in improvised

area. Mashru R. C. et al also developed a fast dissolving film of salbutamol sulphate using PVA as a polymer. A taste masked film was developed by Renuka Sharma et al. using Eudragit EPO and HPMC. Various patents are also assigned for water soluble films for oral administration.

(c) Fast Caps. A new type of fast dissolving drug delivery system based on gelatine capsules was developed. In contrast to conventional hard capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of the capsule shell. The advantage of these fast disintegrating capsules are high drug loading, possible solid and liquid filling, no compression of coated taste-masked or extended release drug particles/pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging.

(d) Buccoadheshive Film and Tablets: Recent years have seen an increasing interest in the development of novel muco- adhesive buccal dosage forms. These are useful for the systemic delivery of drugs as well as for local targeting of drug to a particular region of the body. Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparations due to their susceptibility to "dose dumping phenomena ". Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once- a- day dose treatment.

(e) Medicated Chewing Gums: Medicated chewing gum is an attractive alternative for drug delivery system with several advantage including convenience for administration, individually controlled release of active substance and effective buccal drug administration for the treatment of local oral disease and systemic action. Mainly chewing gum is used to promising controlled release drug delivery system.

Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness and freshening of breath. A hydrophobic gum was used for the formulation of chewing gum. A new chewing gum device in the form of a three layer tablet (3Tab gum) has been also developed. In vitro release study of chewing gum requires special apparatus and instrumental setting.

Marketed Products: Table 1 shows some of the example of marketed product which utilizes the oral mucosa as a site for systemic action.

Table 1: Marketed products

BRAND NAME	COMPNY	DOSAGE FORM
Zofran	Galaxo smithkline	Rapid film
Pepcid RPD	Merk frosst	MDT*
Clarin raditab		MDT*
Nicotinell	Novartis	Chewing gum

*MDT – mouth dissolving tablet

CONCLUSION: Beside delivery drug to the body, a drug delivery system with a aim to improve patient compliance and convenience are more important. Now days there is huge work going in developing to novel dosage form to satisfy increased patient demand of more convenient dosage forms. These dosage

forms are expected to become more popular oral mucosal delivery offers a convenient way of dosing medication, not only to special population group with swallowing difficulties, but also to general population. They also provide opportunity for the product line extension in the market place and extension of patent term of innovator.

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