Transmucosal drug delivery: advantages

INTRODUCTION:

Among the various routes of the drug delivery, oral route is mostly favored by the patients and preferred by the clinicians. However, peroral (Jain. et. al., 2003) administrations of drugs have disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI, which thus prohibits oral administration of certain classess of drugs.

A rapid onset of pharmacological effect is often preferred from drugs, especially in the treatment of the acute disorders. Onset of action can be achieved effectively by parenteral administration , but this method may not be convenient to the patient forevsrenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. Solid dosage forms such as tablets are generally the first choice for drug administration because of the relative ease of both production and usage. Whereas, for acute disorders, the time to onset of action for a conventional oral tablet is in general not acceptable; this is usually attributable to gastric emptying causing a high variability in lag time phase between drug administration and onset of intestinal absorption [Christer Nystrom. et. al., 2003].

Oro-mucosal delivery, especially that utilizing the buccal and sublingual mucosa as absorption site, is a promising drug delivery route which promotes rapid absorption and high bioavailability, with subsequent almost immediate onset of pharmacological effect. Mainly these advantages were due to the result of highly vascularized oral mucosa through which drugs

enter the systemic circulation directly, by passing the gastrointestinal tract and the first pass effect in the liver [Moffat, A. C. et. al., 1971].

There are several aims to deliver the drug molecule into systemic circulation through oral mucosa. These include: to increase patient compliance, improve drug bioavailability, decrease pulsed entry and control drug appearance in the systemic circulation and reduce the side effects and ineffectiveness associated with other routes of drug administration. Consequently the aims of the pharmaceutical scientist working in this area are to manufacture efficient, effective and economical delivery systems which optimize the systemic delivery of drugs via oral mucosal membranes.

These aims require a detailed understanding of:

- Problems and restrictions of the oral cavity as a site for delivering to systemic circulation.
- The main role of saliva in the distribution and clearance of drug in the oral cavity;
- The pathways, mechanisms, and barriers to drug permeation;
- A mechanistic view into how permeation enhancers increase membrane permeability

[Rathbone, M. J. et. al., 1993].

We refer particularly to the use of the term buccal being interchangeable with the term oral, for example, the buccal cavity and oral cavity. Therefore for the sake of clarity some commom terms will be defined and the terms that should become redundant identified. Oral cavity – the area of the mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth,

oral cavity mucosa – the membrane that line the oral cavity which include the buccal mucosa, sublingual, the gums (gingivae), the palatal mucosa and the labial mucosa; buccal membrane – the membrane that lines the cheek inside the mouth; sublingual administration – systemic administration of drugs via the membranes that line the floor of the mouth and ventral surface of the tongue; buccal administration – systemic and local administration through the buccal membrane.

Oral mucosal drug delivery system:

A delivery system mainly designed to systemically or locally delivery of drugs through the oral cavity membranes.

Buccal drug delivery system:

A delivery system designed to deliver drugs systemically or locally through the buccal mucosa (Michael J. Rathbone. et. al., 1993).

Sublingual mucosa as a site for drug delivery:

The sublingual mucosa is relatively permeable, gives rapid absorption and acceptable bioavailabilities of many drugs, and is accessible, convenient and generally well accepted. (Harris, D. et. al., 1992). The Sublingual route is considerably the most widely studied of all these routes. Sublingual dosage forms are of two different dosage forms, those composed of rapidly disintegrating tablets, and also those consisting of soft gelatin capsules filled with liquid drug; such delivery systems create a very high drug concentration in the Sublingual region before they are systemically absorbed across the mucosa. Local delivery of drug moiety to tissues of the oral cavity has a number of applications, including the treatment of tooth aches, periedontal

disease, bacterial and fungal infections, apthous and dental stomatitis, and in facililitating tooth movement with prostaglandins. The Sublingual region lacks expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Due to the rich blood supply and the high permeability, the sublingual route is capable of producing a rapid onset of action making it suitable for drugs with short drug delivery period requirements with infrequent dosing regimen. (Amir H. Shojaei. Et. at., 1998).

ALTERNATIVE ROUTES:

The gastrointestinal [GI] tract is the major route for drug entry into the systemic circulation. Though, for some drug moieties this route presents problems. The GI tract is a hostile environment; it contains enzymes, a varying range of pH conditions and varies in its composition, e. g., food. In addition the membranes of the GI tract contain enzymes, while the blood that drains the gastrointestinal tract [GI] goes directly into the liver. Therefore the drugs which are susceptible to acid hydrolysis, extensive metabolism are readily degraded in the liver may exhibit poor bioavailability when administered through this route. In an attempt, to avoid these problems alternative routes of drug administration are required. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs.

Systemic delivery of drugs through mucosal membranes presents a possible solution to the problems of hepatic and gastrointestinal metabolism associated with oral delivery and the health risks associated with the parenteral route.

The major limitations of mucosal drug delivery are

(a) Due to low permeability of the mucosal membranes and relatively small surface area available for absorption resulting in low flux through the tissues and

(b) Due to the Poor retention of the drug or delivery system at the site of absorption resulting in short contact times. These problems may be overcome by rational drug delivery system design as transdermal drug delivery attests.

Initially the drug molecules are impermeable through skin, though, the following extensive investigation and development of new concepts to introduce new technologies, approaches, strategies, it was recognized that this barriers could be overcome and the skin became an alternative site for drug delivery.

The rectal route suffers from changeable patient acceptance and depending upon the site of absorption of the drug may be subjected to hepatic first-pass metabolism. Buccal and sublingual mucosa are not connected with many of these disadvantages. As a result the oral cavity is selected to be a viable site for the systemic delivery of pharmacologically active compounds.

ADVANTAGES OF TRANSMUCOSAL ROUTE:

i) Oral mucosa is a region has a rich blood supply

ii) Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein into the systemic circulation.

iii) To circumvent the first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the type of drug, a better enzymatic flora for drug absorption.

iv)The mucosal lining of the oral cavity is generally more permeable to drugs than the skin, but in contrast has a much smaller surface area available for absorption.

v) Though, the area of the buccal membrane is sufficiently large to allow a delivery system which is to be placed at different sites on the same region of the oral cavity on different situations which may be advantageous if the drug, delivery systems or other excipients reversibly damage or irritate the mucosa.

vi) There is good convenience to the membranes that line the oral cavity which makes application painless and without discomfort, precise dosage form localization possible and facilities ease of removal without significant associated pain and discomfort.

vii) Patients could feasibly control the period of administration or terminate delivery in cases of emergencies.

viii) The oral mucosal route has in the past exhibited better patient compliance than either the vaginal or rectal route of drug administration thus it would be anticipated that novel buccal or sublingual dosage forms would be well accepted by patients.

ix) There are some therapeutic reasons why the oral cavity is preferred to be a useful route for drug delivery, for example , for those patients nil-by-

mouth, if either nausea or vomiting is a problem, if the patient is unconscious, in patients with an upper gastrointestinal tract disease or surgery which effects oral drug absorption, or in patient group which have difficulty swallowing peroral medications , e. g., the very young and the elderly .

x) The Sterile techniques are not required during manufacture or administration of the dosage forms, the oral cavity contains teeth upon which drug delivery systems can be physically attached using dental adhesives.

xi) The oral mucosa is having low enzyme activity and enzymatic degradation is relatively slow, hence from the point of drug inactivation, considered the oral mucosal route would be preferred to that of the nasal or rectal routes.

LIMITATIONS:

The oral cavity:

1. The surface area available for absorption in the oral cavity is relatively small(total surface area of oral cavity membranes – 170cm2).
2. The oral cavity is a composite environment for drug delivery as there are many mutually dependent and self-governing factors which reduce the absorbable concentration at the site of absorption.
3. The tongue is extremely innervated area and any delivery system administered to the oral cavity is likely to be explored by this organ which may affect release rates or retention times.

4. The involuntary swallowing of saliva results in a major part of the dissolved or released drug being removed from the site of absorption.
5. Only the drugs with small dose requirements can be able to be administered through this route.