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BUCCAL DRUG DELIVERY SYSTEMS

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Buccal administration offers certain unique advantages for the drugs which cannot be easily or efficiently administered by oral or intravenous route. However, transbucccal delivery receiived relatively little attention and few well-controlled studies of buccal mucosa permeability have been conducted. The oral mucosa provides a protective covering for the underlying tissue, being as a barrier for microorganisms and toxins. This article extensively reviews the histology of buccal mucosa, permeation studies (both invitro and in vivo) of buccal drug delivery system, their development and various types of techniques and devices available for the delivery of drugs through buccal mucosa.

NATURE OF THE ORAL MUCOSA :

STRUCTURE

Oral Mucosa is made up of stratified squamous epithelium and a connective tissue lamina propria containing variable amounts of fibers and cells in an aqueous ground substance. Oral epithelium may be

keratinized, para-keratinized or non-keratinized, while epidermis is Invariably keratinized various appendages are situated in, or below the lamina-propria. These comprises hair follicles and sweat glands in skin, teeth, the ducts of salivary glands, and occasionally, sebaceous glands in oral mucosa. These structures communicate with the exterior and interrupt the otherwise intact surface, providing a route for substance unable to penetrate the epithelium proper ; they, thus forms shunts or parallel diffusion pathways. In skin such shunts represents only 0.1% of the total surface area and are unlikely to contribute significantly to steady-state diffusion[1] . They are even less extent in the oral mucosa (with the important exception of teeth) so, that they are unlikely to affect the permeability of this tissue.

It is generally accepted that the connective tissue of the skin or oral mucosa is not an effective barrier against the penetration of polar substances, although it may tend to limit diffusion of non-polar molecules[2] and of macromolecules[3], while a rapid absorption of drugs from the oral cavity has been ascribed to the rich vascular supply of the oral mucosa[4], it would seem that blood supply, unless it is drastically reduced, is not normally a significant factor[2].

Although the basal lamina of epidermis and oral epithelium may limit the passage of certain particles such as immune complexes[5], there is considerable evidence that the only real barrier to percutaneous diffusion is the stratum corneum of the epidermis[1,2]. The absence of keratinized layer in many areas of the human oral cavity has been interpreted as evidence for greater permeability of oral mucosa than that of skin[6,7].

The intercellular route through epidermis and oral epithelium, certainly in the deeper cell layers, is essentially an aqueous channel. Although intercellular space is only a minor component of the tissue volume-value as low as 1% having been quoted for epidermis[1,2] it may nevertheless provide the pathway by which electrolytes and lipid-in soluble substances traverse the tissue[2] provided that they can overcome the intercellular barrier in the superficial layers. Kaaber,(1974)[8] found that the non-keratinized oral epithelium was more permeable to water than that of keratinized oral epithelium and attributed this to the presence of a higher concentration of osmotically active particles in the keratinized cells exerting a flow - regulating effect on the water. Scheuplein, et al (1972)[1] similarly argues that the major site of resistance to diffusion is the keratin itself which restricts the passage of both polar and non-polar substances.

This can be summarized as, there is an intercellular barrier in the superficial layer of both keratinized and non-keratinized oral epithelia that can limit the penetration of substances traversing the tissue by this route

- that is, predominantly polar molecules and electrolytes. Substances with a preferential lipid solubility are more likely to pass along membranes and there may be limited by the formation of a keratin layer -as is water which passes across the cells.

PERMEABILITY OF THE ORAL MUCOSA :

The presence of stratified squamous epithelium prevents the permeation of potentially dangerous substance, resembling the surface of the skin rather than the simple columnar epithelium that lines the Gastro-intestinal tract. At the same time oral mucosa shares with the gut by the ability to maintain a moist surface, one of the characteristics of any mucous membrane; this so far as permeability is concerned, is both a strength and weakness for, while components of saliva may contribute to barrier function, the accompanying hydration may increase permeability. Despite assumptions to the contrary, the oral mucosa is not a highly permeable tissue and is closer to skin than to the gut in its permeability characteristics. Nevertheless as a route for drug administration, it offers advantages over both the percutaneous and gastrointestinal (oral) pathways, and this alone justifies a study of mucosal permeability in addition, its barrier properties are an important component of resistance to disease.

Squier C.A. (1984)[9] in an attempt to characterize the permeability barrier of the oral mucosa, he has treated small pieces of keratinized and non-keratinized oral epithelia and epidermis with specific enzymes. These enzymes were selected for their effect on carbohydrate - protein, carbohydrate - lipid compounds and phospholipids. The effect of enzyme treatment was monitored by exposing the digested tissue to horse radish peroxidase. Electron microscopic examination of tissue treated with phospholipase revealed considerable damage to membrane structures but not to the integrity of the permeability barrier. Hyaluronidase and neuraminidase caused less structural damage but did not impart barrier function, this was only seen after treatment with chondroitinase ABC. This enzyme may degrade certain amount of polar molecules thought to be necessary to stabilize the neutral lipid bilayer of the intercellular barrier and thus disrupt its barrier properties (penetration enhancers act in this way-discussed in the latter section).

Non-keratinized oral epithelium possesses an homologous population of granules which amy also be associated with formation of a barrier in the superficial layer of the tissue[10]. Yuji Kurosaki et al. (1991)[11] has seen the regional permeability of oral mucosa to salicylic acid which was investigated in-vivoly in hamster along with histological variations

especially the degree of keratinization; Histological sections from six various (i.e.) sub-lingual mucosa, buccal mucosa, dorsum of tongue, ventral surface of the tongue, labial mucosa, and cheek pouch mucosa, were prepared to access the degree of keratinization. The area under the plasma concentration-time curve of salicylic acid following the administration of salicylic acid to the oral mucosa with a film dosage form and the thickness of stratum corneum of each side were in inverse proportion to each other, suggesting that the stratum corneum layer represents the principle barrier to drug absorption. They suggested that, drug absorption through epithelia might be restricted by atleast two significant barriers. One is an enzyme barrier for drugs that are highly metabolized during absorption process[12&13], the other one is a physio-chemical barrier for all drugs diffusing through the tissue.

Substances can traverse cells by endocytosis (sometimes called pinocytosis), by active transport and by diffusion movement through the intercellular spaces and the influences of the basement membrane are also relevant. Endocytosis, a large number of different cell types are capable of taking up solid particles (Phagocytosis), or fluids (Pinocytosis) from their external environment by engulfing the material in membranous vesicles. The processes, referred to in general as endocytosis[14], afford a means of transporting materials across the cell-membrane of transferring material across the whole cell. While cells of the oral epithelium and epidermis are capable of taking up materials by endocytosis, particularly in the basal and prickle layers[16&17] it does not seem a likely transport mechanism across an entire stratified epithelium[17].

Active transport across the membrane can be supported by the evidence of transport of some sugars, and amino acids across intestinal epithelia[18] and for certain ions across frog skin[19] but it is unlikely that this process is involved in the movement of molecules and ions across skin or oral mucosa[8].

Depending on physical or chemical properties of the penetrant, diffusion across biological membranes which take place through a lipid phase or along aqueous channels. Fick's law operates here. There are considerable evidences that most substances passing across skin and oral mucosa move by simple diffusion and obey fick's law[2&20], although stratified squamous epithelia are structurally more complex than the simple membrane considered.

Intercellular movement, although epithelia consists of closely apposed cells, intercellular space is sufficient to allow the diffusion of some molecules and ions.Substances moving along this route will not traverse the plasma membranes of the cell but, may encounter tightly apposed

regions of adjacent cell membranes that effectively block the intercellular pathway. On the basis of how effective these barriers are; Epithelia are classified as "tight" or "leaky"[19] In oral epithelium it seems that tight junctions are rare[21] and are not the major inter-cellular barrier. The intact basal lamina has some restrictive effect, probably limiting the passage of substances with a molecular weight above 70,000[22] .

FACTORS AFFECTING ORAL TRANSMUCOSAL PENETRATION :

The single most important factor determining the extent to which any substance will cross oral mucosa is the physical and chemical nature of that substance. In general, molecule penetrate more readily than ions, small molecules more readily than large molecules, and volatile substances and gases most readily of all[23]. Experimental results, however do not follow such generalizations, possibly because of variations in method; dextrans with a molecular weight upto 70,000 will cross non-keratinized rabbit mucosa in vitro[24] while in vivo, the protein horse-radish peroxidase (Mol. wt., approximately 40,000) does not[16]. A factor governing the ionic compounds is their degree of ionization at any particular pH (their pKa value), while the property of undissociated molecule that most influences penetration is its relative solubility, or partition coefficient in non-polar (lipid) and polar (aqueous) solvents. Substance that dissolve readily in both types of solvents pass most rapidly across the oral mucosa, but optimum passage is demonstrated by substances with a slight preferential lipid solubility[25&26], probably reflecting the lipid-aqueous nature of the multiple cell membrane that the drug must traverse.

Beckett A.H. & Moffat, B.C. (1970)[27], has studied a simple model for the buccal absorption of some carboxylic acids. The rate constants determined gave a positive correlation with the logarithms of previously determined n-Heptane : 0.1 N hydrochloric acid partition coefficients. Reze M. Tavakoli-Saberin and Kenneth L. Audus, (1989)[28] have found out that the permeation of propranolol and atenolol (increases) as pH increases. He also proved that the transepithelial flux of selected beta-adrenergic antagonists (Propranolol, alprenolol, metoprolol, pindolol and atenolol) depends on time, temperature and pH.

The type of solvent or vehicle in which a substance is applied has a significant role in determining the rate of penetration. One effect of solvents is a direct action on the tissue surface; the hydration of the surface layers of the epidermis when water is the solvent, or such as occurs after occluding the surface with a dressing, greatly enhances penetration[29]. As the surface layers of the oral epithelium tend to be

hydrated by saliva, this may account for its greater permeability when compared with dry skin.

Minako Tanaka and Norio Yanagibashi et al. (1980)[30] has seen the effect of different types of ointment base on salicylic acid absorption at the mucous membrane of the oral cavity. clear differences in absorption was found between emulsion base, water soluble base and oleaginous base.

Bremecker K.D. et al. (1983)[31] has seen the novel mucosal adhesive ointment which is based partly on neutralized polymethacrylic acid methyl ester. They also found the new system of the mucosal adhesive ointment which is not limited to the incorporation of retinoin (Vitamin A acid) as the active agent; Combined with other drugs the system could be applied to all types of mucosal membranes. They found this new ointment vehicle and preparation were found to be pleasant for the patients to use rather than the conventional one causing irritation to the mucous membrane.

Rhandhawa M.A. et al.(1986)[32] has noticed the new investigational antidepressant drug's buccal absorption at pH 5-9, which can be considered as an in-vivo model of passive drug transfer through a lipid membrane. Medifoxamine, the new investigational antidepressant drug, whose maximum absorption occurred at pH 8, which is close to its PKa 8.5. There are differences in penetration of any given type of the substances to the physiological state of the tissue surface being considered. Human skin is less permeable than that of many experimental animals', including rabbit, guinea-pig and rat[2&33] and this also seems to be true for the oral mucosa[34]. Oral mucosa is more permeable than skin[6,7], there appears to be little supporting evidence such as for the penetration of the water and certain ions is concerned, kaaber (1974)[8] has shown that the permeability of human oral mucosa is very similar to that of hydrated skin surface. The only conflicting evidence is that tumors are more readily induced in skin than in oral mucosa by the application of topical carcinogens; this difference may be directly attributable to certain salivary constituents contributing to the barrier function of the mucosa, or simply to the washing effect of the secretion[35&36].

Michel M. Veillard et al. (1987)[37] has given the data that hamster's cheek pouch of 40 micrometer epithelial thickness having a permeability coefficient for water about 2 times (1.95times) as that of human skin and also dog frenulum (150 micrometer thickness) having a permeability coefficient for water about 4.5 times as that of human skin. They have also given for butanol permeability coefficient, that also varies for hamster's cheek pouch and dog frenulum to that of human skin.

As far as the other regions of the oral mucosa are concerned, it has been suggested that drug absorption through the sub-lingual mucosa is more effective than through buccal mucosa would tend to increase permeability to most substances. Kaaber (1974)[8] has compared the permeability of the human palatal and buccal mucosa. Whereas both tissues, like epidermis of the skin[38], were relatively impermeable to electrolytes. The non-keratinized buccal epithelium was almost twice as permeable as the keratinized -palatal epithelium to water. Yuji Kurosaki et al. (1991)[11] has compared the permeability of the hamster's sublingual, buccal, dorsum of tongue, ventral surface of tongue and labial mucosa. According to kaaber (1974)[8] the electrolyte and water follow different pathways in traversing the oral mucosa, and so encounter different barriers.

It is clear that permeability will depend on the state of the surface; breaks in the epithelial covering and pathological conditions affecting its cohesion and maintenance or turn over will all tend to alter permeability. Pathological conditions (disease state of oral mucosa) and breaks in the epithelial covering (with the aid of permeation/penetration enhancers) will be discussed in the latter section.

EFFECT OF PERMEATION ENHANCERS IN ORAL TRANSMUCOSAL ABSORPTION:

Bruce J. Aungst and Nancy J. Rogers, (1989)[39] has shown the oral transmucosal delivery is useful for peptide and protein drugs because the oral bioavailability of these drugs is usually negligible and there is a need for alternatives to injections. Transmucosal delivery is especially germane for drugs that are administered chronically and by the patient himself. Insulin typifies these attributes, and transmucosal insulin by the nasal and rectal route has shown promising results in initial clinical trials[40,41&42].

One of the problems confronting transmucosal delivery of proteins and peptides is that bioavailability may be low because of metabolism at the absorption site or because of poor membrane permeability. Therefore, there exists a need for methods to improve transmucosal bioavailability by inhibiting metabolism or by increasing membrane permeability. A further advantage of transmucosal delivery, in contrast to oral route of administration is that the effects of absorption promotors can be localized to a small area. The major efforts of scientists to improve transmucosal absorption are addressed to the use of substances acting as absorption promoters, otherwise called absorption enhancers or penetration enhancers. Absorption enhancers can be divided in many different classes : a first classification is between the chemical and

physical enhancers. Generally speaking, chemical enhancers act by destructing the mucosa, very often in the irreversible way. Physical enhancers have the effect to slow the mucosal clearance generally forming a gel. This latter effect is reversible as the clearance is impaired for a limited period of time, until the gel is cleared. Among chemical enhancers, chelating agents, fatty acids, bile acid salts, and other surfactants, fusidic acid, carboxylic acid (Ascorbic acids, amino acids) play an important role, pH and osmolarity can also play an important role.

It is well known that surfactants interact with not only drug molecules but also with biological membranes and that consequently they may alter the drug absorption[43&44]. However, there is little information concerning the influence of surfactants on the oral mucosal absorption. Seigel & Gordon, (1985)[45] reported that ionic surfactants such as SLS and CPC increased the permeability of non-keratinized oral mucosa to several substances. Polysorbate-80, a non-ionic surfactant did not show any marked effect. Yuji Kurosaki et al. (1988)[46] has seen the effect of surfactants on the absorption of salicylic acid from keratinized oral mucosa, which was investigated by hamster's cheek pouch method in vivo at pH 3,4 and 7. Four surfactants, SLS, CPC, PS-80 and sodium tauro-cholate were examined as adjuvants.

Bruce J. Aungst & Nancy J. Rogers, (1989)[39] have evaluated the effects of various classes of transmucosal and transdermal absorption enhancers on buccal insulin absorption in rats. Insulin absorption was estimated from the cummulative response of plasma glucose concentrations and by comparison to an i.m. dose/response curve. In the absorption with enhancer, buccal insulin was less than 4 per cent as effective as i.m. insulin. All steroidal detergents examined as absorption promoters markedly improved the buccal insulin absorption using aqueous vehicles containing 5% adjuvant where, concentrations greater than 1% were required. The non-ionic surfactant laureth - 9, was also an effective absorption promoter and was effective at lower concentrations. Ester non-ionic surfactants has no effects. The effect of pH was evaluated for sodium fusidate and laureth-9 vehicles. Other effective absorption promoters includes SLS, sodium laurate (at pH 8.9), palmitoyl carnitine and a lauric acid/propylene glycol vehicle. With the most effective absorption promoting vehicles, buccal insulin was 1/4th to 1/3rd as effective as intra muscular insulin.

Yuji Kurosaki et al. (1989a)[47] has found out the enhancing effect of azone on the permeability of Keratinized oral mucosa, he has investigated in vitro and in vivoly[48] The in vitro permeability of hamster cheek pouch to salicylic acid (model compound) was approximately 4.4

times higher than that of the abdominal skin's, and the stratum corneum of the cheek pouch isolated by the trypsin treatment, showed the similar permeability to the full-thickness preparation of the cheek pouch, and the magnitude of the enhancement was identical. The direct action of azone during the pre-treatment on the stratum corneum, a major barrier for drug-permeation, was clarified. In in_vivo studies, it has been found that, azone -pretreated cheek pouch was approximately 2.7 times greater than the non-treated one.

In relation to the mucosal function, the regional differences may effect the permeability of the drugs. Keratinized oral mucosa is found in regions which are particularly susceptible to the stresses and strains resulting from masticatory activity; gingiva, dorsum of tongue, hard palate and transitional zone of lips which are keratinized in human mouth[49] Recently reported that the ionic surfactants increase the permeability of keratinized oral-mucosa to salicylic acid[46]. Azone is a smooth, oily, hydrophobic liquid, which has been reported to be capable of enhancing the percutaneous penetration of a variety of compounds[50].

Sodium glycocholate increased insulin absorption after nasal, rectal and buccal administration[51]. An adhesive patch containing a core of 10% sodium glycocholate in cocoa butter has been administered buccally to dogs, but, the percentage of insulin absorbed was only about 0.5% relative to i.m.[52]. Structure/effect studies of non-ionic surfactants as absorption promoters for nasal[53], Rectal[54] and transdermal[55] have also tried as buccal absorption promoters[39]. They also found the effect of steroidal detergents, fusidic acid as sodium fusidate which is having pKa of 5.7[56], the efficacy of buccal insulin to i.m., it apparently primarily involves in the para-cellular in this way it is similar to EDTA, which also had little effect on buccal insulin absorption[51]. Hyaluronidase and chondroitinase effect were studied[9], because there were indications that these enzymes could digest the materials packed in the inter cellular spaces of the buccal epithelium. In the presence of this agent very little insulin was absorbed[39].

Propylene glycol vehicles containing decyl methyl-sulfoxide or lauric acid also allow good skin penetration rates for low molecular weight drugs[55], these improves buccal insulin absorption slightly at 5% adjuvant concentrations, and at 10% concentration lauric acid was quite effective. Seation T.A. et al (1976)[57] has found the influence of penetration enhancers on buccal absorption of peptide drugs. They found that 0.075% w/v SLS was included as an adjuvant, there was a small, but significant, increase in the rate of diffusion, and the total quantity of drug absorbed was promoted by 65%. Jie Zhang et al, (1991)[58] has studied the transbuccal delivery of insulin using tauro-cholic acid as a

permeation enhancer. They, have used the buccal mucosa for depot action

Small unilamelar vesicles-insulin, where insulin entrapped using a combination of lipids comprising egg lecithin - cholesterol-steryl amine (7:2:1) administered via buccal route. Ethanol induces the structural and functional alterations of epidermal qrowth factor-receptor in buccal mucosa[59] .

EFFECT OF DISEASE STATES ORAL TRANSMUCOSAL PERMEABILITY:

There is no virtually, experimental evidence of alterations of oral mucosal permeability in disease states, though much can be inferred from studies on strain in which physical stripping of surface layers and various inflammatory conditions have been shown substantially to increase permeability to various drugs and tracer molecules[6&23] Erosion (thinning) of oral mucosa may be brought about the damage to the upper cell layers, or lay imbalance between the rates of cell-division, cell maturation and desquamation. In erosive and vesicular lesions therefore, such as, some forms of lichen planus, pemphigus, viral infections and allergic reactions, the basal and prickle-cell layers may be all that remain; the major permeability barrier between the superficial cells may thus be destroyed and a more permeable tissue will result. Overly ulcerated mucosa would clearly be permeable to exogenous substances, but, the fibrin clot, which act as a partial barrier, and the outward flow of the inflammatory exudate may tend to limit the entry of many substances.

Subepithelial inflammation, will also cause increase epithelial permeability. The effect of associated hyperaemia in increasing uptake of topically applied drugs by more rapid clearance from the site may have been over-emphasized. Mucosae often produces hyper plastic changes characterized by acanthosis and hyperkeratosis, for e.g. "White lesions" of the oral mucosa. Little is known as the pathogenesis of lesions, but both the nature and severity of the inflammatory response appear to play a part[60]. In hyper plastic lesions, accelerated cell division and accelerated passage of cells to the surface often occur[61] and this may not allow sufficient time for the normal barriers (layers) to be formed, with consequent increase in permeability. Increase in thickness of epithelium is often associated with less complete maturation of the surface cells, and such tissue, despite its greater depth, may not necessarily be less permeable[1] .

An interesting situation is found in oral infections with the fungus 'candida albicaus'. Hyphae grow on the surface of the mucosa and normally invade only the superficial layers of the epithelium[62], though

toxic substance persumably penetrate completely and estabilsh an inflammatory response. The limit of organismal penetration is at the level of the epithelial barrier, perhaps antagonists, such as serum antibodies, can permeate the epithelium only upto this level. By contrast, when cultured oral mucosa is infected with these organisms, penetration in all cell layers occurs[63].

STUDIES ON THE DEVELOPMENT OF MATHEMATICAL AND PHYSICAL MODELS OF BUCCAL ABSORPTION:

Beckett, Boyes & Triggs (1968)[64] studied the kinetics of buccal absorption of amphetamines using an analogue computer. The results indicated that kinetic constants may be useful to assign numerical values to the relative partitioning properties of drugs into the oral mucosa. Data from Beckett & Moffat's[65,66&67] 5 min. cummulative absorptions showed the most important criteria for the rapid absorption of drugs which should have large partition coefficient. So, Beckett & Moffat, used 10 acids, with previously determined pKa values and partition coefficients to test this hypothesis, from solution pH 4.0 using a single subject. These rate constants gave a positive correlation with the logarithm of previously determined n-Heptane : 0.1 N hydrochloric acid partition coefficient. They have suggested useful compartmental model for the buccal absorption of some carboxylic acids to be :

Drug buffer solution _____ Drug in buccal mucosa
mouth (A)

The following mathematical equations were used to describe the transfer:

$$-\frac{dA}{dt} = K_1 \frac{RA}{V}$$

$$\frac{dB}{dt} = K_1 \frac{RA}{V}$$

Where A & B = Percentage of drug in the respective compartment
K = rate constant governing the transfer of Unionized drug molecules between Compartments (ml/min)
R = Fraction of drug unionized at any time 't'
V = volume of the buffer in the oral cavity at time' t'

Schurmann. W. & P. (1978)[68] has seen the buccal absorption characteristics and physio-chemical properties of the beta-adrenoceptor blocking agents. Propranolol and atenolol have been investigated to evaluate their permeation properties across bilogical liquid membranes. The dissociation constants, solublites of free base, and n-heptane partition coefficients lipophilic than atenolol, both drugs being bases with similar pKa. Buccal absorption was studied under conditions of varying drug concentrations, contact time, and pH and controlled through the use of non-absorbable marker. A new compartmental diffusional model that includes membrane storage and a hypothetical "aqueous-pH buffering surface system" allowed a more exhaustive interpretation to be made. A method for the estimation of intrinsic pH and buffer capacity of postulated surface system from drug pH absorption data and partition coefficient alone is described. With human oral mucosa the intrinsic pH was near 6.7 and the buffering capacity of the system (expressed as the ratio pH/ pH effective) about 2.86. The in vivo partition coefficient of unionized propranolol relative to the mucous membrane could be calculated for the pseudo-steady state of absorption (i.e.) the partition equilibrium between mouth content and membrane to be approximately 776; this value is of the same order as the in vitro partition coefficient for the erythrocyte/plasma system.

Beckett and Moffat (1969,1970)' reported on a number of experiments on buccal absorption which can be summarized as follows:

[i] Buccal absorption of phenyl acetic acids,

(a) A linear relationship between the percentage absorption and alkyl chain length.

(b) In p-Halogeno acids, absorption increases with the atomic weight of the halogen atom.

(c) An oxygen atom between the alkyl group and the ring is equivalent to reducing the chain length by one methylene group.

(d) Absorption of methyl substituted acids is greater than that of unsaturated acids.

[ii] Partition coefficient of amines, acids and their absorption,

(a) Linear relationship between alkyl chain length and the log of the partition coefficient of the amines and acids.

(b) Linear relationship between log partition coefficient and the percentage buccal absorption.

[iii] Partition coefficient of carboxylic acids and their buccal absorption rate constants.

The rate constant of buccal absorption of acids from a pH 4 buffer solution gave positive correlations with the log of the n-heptane : 0.1.N HCL partition coefficient. Similar results were also obtained with studies on steroids.

Beckett and Moffat, assumed a simple passive diffusion to account for the loss of the drug from the oral cavity. Dearden and Tomlinson (1971a)[108] proposed a model involving protein binding which more satisfactorily explains the observed loss. Studies on two different physical simulations of this three compartment model confirmed that the proposed model was consistent with the in vivo results. The essence of the proposed model was as follows :

Protein binding --- oral cavity --Membrane -- Body fluids

Ho and Higuchi (1971)[69] gave a quantitative interpretation of the in vivo- buccal absorption of n-alkanoic acids (beckett and Moffat, 1969) by the physical model approach to the quantitative and mechanistic interpretation of in vivo- buccal absorption of drugs. They also calculated as self consistent, bio-physically meaningful factor (2.33) for the buccal lipoidal membrane-aqueous incremental partition constant for a methylene group. Exceptionally good agreement of the absorption rate buffer pH profiles between the experimental results and theory was found.

Vora et al. (1972)[70], used a two phase compartment model to quantitatively analyse the buccal absorption data of para-n-alkyl phenyl acetic acids and toluic acids reported by Beckett and moffat The incremental partition constant of a methylene group for the para-n-alkyl phenyl acetic acids was found to be 2.22 in agreement with Ho and Higuchi"s Model.

The diffusion model described by Vora et al was a two compartment model. The first compartment (mucosal side) consisted of the bulk aqueous solution phases and a diffusion larger of thickness "LI" which was in relies with a homogenous lipid phase compartment of thickness "L2". It was assumed that there was a perfect sink on the serosal side after the lipid phase and that only non-ionized species transfer occurs across the lipid membrane.

The equations describing steadystate first order rate of buccal absorption are as follows :

$$K_u = B_1 . f(T)$$

Where,

$$B_1 = \frac{AP_{W,1}}{V}$$

$$f(T)=\frac{1}{(1+\frac{K_a}{[H^+]})T+1}$$

$$T=\frac{P_{W,1}}{P_{O,2}}$$

Here, K, being the absorption rate constant; B, a constant with units time descriptive of the permeability coefficient of the drug in water phase Pw, 1. The surface area A, and the volume of the drug solution V; f (T) a dimensionless parameter with limits 0 < f (T) <I; the diffusion efficiency coefficient, T is the ratio of the permeability coefficient of the drug in the aqueous solution layer pw, I and the lipoidal membrane Po, 2; Ka and [H+] are the dissociation constant and hydrogen ion concentration respectively. The incremental change in the lipid aqueous partition coefficient from one compound to the molecular modified compound within a given series may generally be expressed by,

$$n=\frac{k_{i+1}}{K_i}=\frac{P_{O,2,i+1}}{P_{O,2,i}}=\frac{T_i}{T_{i+1}}$$

Wagner and Sedman (1973)[71] proposed two different models to explain all the buccal absorption data given by Beckett and Moffat and others.

METHODS OF STUDY OF ORAL MUCOSAL ABSORPTION:

[A] IN VIVO METHODS :

Methods for studying the permeability of intact mucosa comprise those techniques that exploit the viological response of the organism locally or systemically and those that involved direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simplest studies of mucosal permeability utilized the systemic pharmacological produced by cardiovascular stimulants, such as nitroglycerine, after application to the oral mucosa[4].

This approach has also need used locally to access the penetration of anaesthetic by recording changes in the sensation of the mucosa such as pain, tingling or pressure[20], while in the skin effects such as reddening or blanding have been taken to indicate percutaneous absorption of

vasoactive agents[29]. Although, these methods can be applied to human subjects and involve little or no mechanical interference with the mucosa, the recognition of the systemic or local responses may be highly subjective and, consequently reliable quantity of data can seldom be obtained in these way. Other similar methods have involved the histological demonstration of increased capillary permeability after topical application of histamine in gingiva[72], the change in the epidermal mitotic activity after topical application of mitotic inhibitors such as glucocorticosteroids[29], the inhibition of bacterial growth by punch-biopsies of corium taken after application of antimicrobial agents to the epidermal surface[29] and the immunological response of sensitized animals to the topical application of antigen to the mucosa[73&74]. While some of this techniques offer considerable sensitivity in detecting small amounts of penetrant.

Radioactive isotopes offer the means of levelling almost any penetrant, and provide great sensitivity. Moreover, after application to the mucosal surface an isotope can be monitored systemically in blood or urine[75&5] or locally by autoradiography[76&22]. Fluorescent compounds offer a sensitivity comparable to that of radio-isotopes but, the type of compound that can be tested is limited; their penetration into mucosa after topical application has been recorded by fluorescence microscopy[77&36]. Sacchard iron oxide[78],throstrast and lanthanum[79] have been used to study the permeability of the epithelium of the gingival crevice, while Gavin[79] and McDougall[80&81] used a protein tracer, horse-radish per-oxidase. Similarly the permeability of keratinized and non-keratinized oral epithelium has been studied using horse radish peroxidase[16] and lanthanum[82]

One of the simplest direct measures of penetration through the oral mucosa is the so called "buccal absorption" test, in which the uptake of compound is derived from the difference between its concentration in a solution before and after rinsing around the mouth and expelling it[83]. However, the buccal absorption test cannot provide information as to the relative permeability of different regions of the oral cavity for there is no reason where absorption may have taken place. Kaaber (1974)[8] has described a gravimetric method for measuring the uptake or loss of water, sodium and potassium ions using small filter paper discs applied to the mucosal surface, the ionic concentrations being determined by flame photometry. Michel M. Veiland et al. (1987)[37] has developed in vivo perfusion model in dogs for the purpose of investigating epithelial permeability and potential methods of permeability enhancement. Such perfusion apparatus has considerable constraints in terms of not disrupting the normal tissue and supra-tissue environment but, yet being

able to be used in a fully awake animal. They also assessed "Hamster cheek pouch" as a potential model for buccal absorption.

Jie Zhang et al (1991)[58], has established a reliable, practical, economical in vivo screening test for evaluating the permeability of fentanyl citrate in oral transmucosal fentanyl citrate and to use data generated by the model for formulation development work. A cell was designed that attaches to the exposed buccal mucosal surface of an an aesthetized dog. Oral transmucosal fentanyl citrate solutions were placed into the cell and the change in fentanyl citrate concentration, over time was determined by analysis of aliquots removed at selected intervals and from this results the apparent permeability coefficient (p) at any given time interval was calculated.

Renu Gambhir (1991)[84], has established a simple and efficient non-invasive in vivo method of studying the buccal absorption of drugs through the buccal mucosa of the hamsters (Golden syrian). Sustained release morphine tablets were utilized as the model system to validate this method.

[B] IN VITRO METHODS :

In vitro methods enable anatomically well defined areas of mucosa to be studied under controlled conditions, usually by clamping between diffusion cells (usually used for transdermal and other membrane permeation studies). Provided that the specimen is securely held so as to prevent leakage around the edge of the tissue, a known concentration of the penetrant under study can be introduced into one cell and the rate at which it appears in the second cell is determined. If necessary, the temperature can be controlled by circulating water from a thermostat, the fluid in the chambers being agitated to prevent stagnation and continually replaced to maintain an adequate concentration gradient across the tissue. Radio isotope have been used in such systems to measure the movement of water[85] and dextrans[24] across the oral mucosa. The great disadvantage of the diffusion chamber is that considerable mechanical manifestation of the tissue is required and, as in any in vitro system, the tissue is removed from systemic influences and placed in a highly artificial environment; the extrapolation of results obtained under these circumstances at the in vivo situation requires caution. Despite the variety of techniques used to study permeability, no one method can identify the optimum mucosal region for penetration of a given compound, the pathway of entry and the kinetics of penetration of that compound; at best only two of these factors may be determined in any one experiment, and most results have provided only crude information as to whether penetration has or has not occurred.

The draw backs of the above mentioned experiments can be overcome to some extent by conducting the permeation studies across an in vitro buccal epithelium model suggested by Reza M et al. (1989)[28]. This model consisted of primary cultures of hamster pouch buccal epithelium grown on collagen-coated polycarbonate filters. They proved that utility of primary cultures of hamster buccal epithelium in vitro model and in characterizing Physico-chemical factors affecting drug delivery by the buccal route. Seaton T.A. et al (1976)[57], has suggested that de-keratinized skin (i.e. dermis which has been exposed by stripping away the stratum corneum) provides excellent correlation with freshly excised buccal mucosa[86].

Consequently an in-vitro model, comprising dekeratinized, hairless mouse skin was utilized to determine the potential buccal absorption of a water soluble, tripeptide assessed. E Quadros S.J. cassidy, (1991)[87], has done the in vitro study of Buprenorphine to determine its buccal flux. Nagai Tsunej & Ryoji koinshi, (1937)[88] has shown a apparatus similar to that of tablet dissolution apparatus for determining the mucosal adhesive dosage form of lidocaine.

Smart et al., (1984)[89] has developed an in vitro-system to investigate the adhesiveness of various materials to mucus. The results obtained showed good agreement with the further in-vestigations found that these materials become adhesive on hydration. Chain length and presence of ionizable groups in the molecule, were found to be the determinate factors. The physical nature of the gel and the location at which the mucoadhesive materials hydrated, were of less importance. Peppas et al., (1986) also developed a new method of evaluation of bio adhesive property of buccal films. Michel M. Veillard et al., (1987)[37] has told the importance of this bio-adhesive patches, such as, development of Sustained release bioadhesive patch to demonstrate the principle of localization of a peptide delivery system in a selected region of part of a day, under varying conditions of food and beverage intake, and the bio-compatible with the underlying tissue.

Reinhold Anders & Hans P. Meikle, (1989)[90] has developed & evaluated the adhesive patches for buccal administration, consisting of two poly-laminates of an impermeable backing layer and a hydrocolloid polymers and subsequent drying. The integrity of the laminate is based on adhesive bonds between the hydrocolloid layer and an agarose layer grafted to one side of the backing membrane. After mucosal contact, firm adhesion to the mucosal surface is established by interactions of the smooth polymer and the buccal mucus layer. The duration of mucosal adhesive in vivo is affected by the type of polymer used, its viscosity grade, polymer load per patch, and the drying procedure for preparation.

A wide range of drug release rates can be achieved by varying these parameters. Drug release rates are controlled by polymer dissolution kinetics. As a consequence, adhesive mucosal dosage forms were suggested for oral delivery, including adhesive tablets[91&92], adhesive gels,[93,94,95&96] and adhesive patches[93,94,97&98].

2.8 BUCCAL ADHESIVE DOSAGE FORMS :

Adhesive buccal tablets are positioned high up between the upper lip and gum. The tablet softens and adhere to the gum and is retained in position until dissolution is complete. After a short time the presence of tablet is reported to be no longer noticeable to the patient. The tablet should not be moved about the mouth once in position as this causes more rapid drug release. The position of successive tablets can be alternated on either side of the mouth; Patients wearing dentures may place the tablet in any comfortable position between the lip and gum.

Usually buccal tablets, dissolve or erode slowly over a period of 15 to 30 mins., for effective absorption. It is important that excepients do not cause/stimulate salivation as this cause a larger fraction of drug to be swallowed rather than absorbed.

Novel buccal dosage forms consists mainly of sustained release systems for buccal delivery, these are intended to release the drug in defined period of time. The different formulations for buccal sustained release can be grouped into two categories,

[a] Adhesive systems e.g. Mucoadhesive gel-matrices and self adhesive films

[b] Chewing gums

The latest developments have been applied to the treatment of angina pectoris and cancer pain as well as the cure of smoking.

For Angina pectoris, Nitroglycerine and isosorbide dinitrate via buccal route - first choice of treatment and prophylaxis (Abrams; 1985, Vlay and cotn; 1985, Adrams, 1987; Parker, 1987). Buccal nitroglycerine tablet (suscard) is based on a hydrophilic matrix that gels in contact with moisture. The gelling starts when the small tablet is placed between the mucous membrane helps to keep the tablet from moving when the patient is talking/eating. After the initial rapid release of nitroglycerine the remainder is released by controlled diffusion over a period of 4 to 5 hr.,[99]. Similarly verapimil and Nifedipine also formulated in buccal dosage form[100&101]. Morphine buccal administration was currently investigated to avoid the first pass effect and also compared with the I.M. Morphine[102]. Nicotine chewing gum (Nicorette), where nicotine bound to an ion exchange resin and incorporated into a gum base[103].

At present much effort is focused on the problems of absorption of high M.wt., Compounds such as peptide and proteins, because the oral bio-availability is poor. Iso-prenalin, oxytocin, Ethisterone, chymotrypsin etc., are some of the drug administered by this route. Generally salicylic acid is used as the model compound to know the permeability characteristics of buccal-mucosa. Buccal insulin delivery system was deviced and under research to enhance the permeation of insulin absorption[1]. Buccal absorption of medifoxamine[39], has deviced and studied. Novel mucosal-adhesive ointment was formulated for retinoin (Vitamin A acid) for the treatment of lichen planus[96], which is based partly on neutralized poly methacrylic acid methyl ester. Here both the vehicle and preparation were found to be pleasant for the patients to use.

Salicylic acid was formulated using different ointment base such as emulsion base, water-soluble base and oleaginous base[30]. Laminated muco-adhesive patches for buccal drug delivery, the polymers used were hydroxy ethyl cellulose, hydroxyl propyl cellulose, poly vinyl pyrrolidone and poly vinyl alcohol[90]. In another, in vitro investigation of mucosa-adhesive materials for use of controlled drug delivery was sodium alginate, sodiumcarboxy methyl cellulose, and hydroxy propyl methyl cellulose, gelatin, pectin and polyvinyl pyrrolidone, 44000 (PVP), acacia, carbopol 934, PEG 600, Tragacanth B.P., hydroxy propyl cellulose and Gantran[89]. Oral mucosal adhesive tablets, for the administration of insulin, and for the treatment of aphthous stomatitis, has been developed[2].

Tsuneji Nagai & Ryoji Konishi, (1987)[88] also developed a muco-dosage form using hydroxy propyl cellulose, carbopol and 'lidocaine' of a model drug for the treatment of toothache by the application of the system to the human gingiva.[104], also formulated a lignocaine patch for dental analgesia safety and early pharmacology, here, impermeable backing membrane (poly urethane) which ensured that diffusional release of lignocaine from the patch was unidirectional[105].Tsuneji Nagai & Ryoji Konishi, (1987)[88] have formulated an adhesive gingival plaster which contains 50 mcg of prostaglandin F (PG F) for the facilitation of both movement. Two adhesive buccal tablet are currently available in the UK(suscard buccal, Pharmax, and buccastern, Reckitt & Colman) ; Drugs administered by the buccal routes also includes, buprenorphine[87], prochlorperazine(Buccastem) and Nifeidipine(Adalat,Bayer) and also fentanyl citrate[58]. Anaesthetic, steroids and antibiotics are also administered through this form which stimulate thyrotropin and prolactin and also a peptide[106].

Nalbupine (Hussain et al., 1986)[107] and Naltrexone also given as bucco-dosage form so as to have a higher % of bioavailability and to circumvent the first pass effect. Ishida et al, (1991, 1982a, 1982b)[52,93&94], used a freeze dried mixture of Hydroxy propyl cellulose and carbopol 934 to prepare mucosal adhesive tablets and obtain excellent results.

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