EXPERIMENTAL MODELS FOR BUCCAL AND SUBLINGUAL DRUG ABSORPTION
INCLUDING EPITHELIAL CELL MULTILAYERS AND MONOLAYERS

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Like the skin the oral mucosa is constantly exposed to the environment thus its fundamental property is probably a barrier function. Pathogens and other potentially harmful materials, which may be borne in air, water or food, are excluded by the stratified epithelial cell layers, which seem to be more closely related to skin than to the columnar epithelia of the gastrointestinal tract (Squier and Johnson, 1975). Thus while the barrier properties are important in the resistance of disease they may also compromise potential drug absorption via the buccal or sublingual routes.

Many models for drug absorption have been proposed including partition coefficient, mathematical models and diffusion studies utilising excised tissue and cultured cell monolayers. With particular reference to the buccal route there appear to be few tried and tested models. Consequently some current models under investigation at Reckitt & Colman are reviewed here, and some attempt made to correlate these with each other, with cultured cell systems and, ultimately, with clinical data.

There are many advantages offered by drug delivery via the buccal or sublingual route:

a. Absorbed drug passes directly from the oral cavity into the systemic circulation and thus avoids hepatic first-pass metabolism. This may subsequently give rise to an increase in bioavailability, e.g. with buprenorphine (Bullingham et al., 1981) or reduce inter-patient variation, e.g. with triazolam (Scavone et al, 1986).

b. Labile drugs which would normally be inactivated by gastric acid and digestive enzymes may be delivered by the buccal route such that these processes are avoided. This has been successfully utilised for oxytocin (Anders et al, 1985).

c. During periods of nausea there is often accompanying gastric stasis. Any medication subsequently administered is thus likely to be very slowly and poorly absorbed. Successful treatment via the buccal or sublingual route, which bypasses the G.I. tract, would then be capable of producing relatively rapid and extensive drug absorption.
d. Side-effects and toxicity are potential hazards of any drug treatment. In the event of acute toxicity crises buccally or sublingually administered dosage forms may easily be removed.

Thus while these advantages may appear to make the buccal route very appealing there are also some inherent disadvantages that must be addressed:

a. Taken together the buccal and sublingual mucosae have a surface area of only some 200cm² (Danhof and Breimer, 1978). Obviously this is a fairly insignificant proportion of the 200m² which is generally recognised as an approximate surface area for the intestine.

b. The problem of delivery to such a small area may be circumvented by increasing the exposure time, and this approach has been fairly successful for transdermal medication systems. And while solid buccal and sublingual preparations are not debilitating while they are in position, it is often inconvenient for patients to retain tablets for long periods, especially if eating, drinking or speaking are compromised.

c. Similarly there is an upper limit to tablet size. Garen and Repta (1989) calculated that, for a "hypothetical" drug which displayed a molecular weight of 250, a solubility of 1mM and log P (octanol:water) of 2.5, absorption from a saturated solution would occur at the rate of 1.6 mg cm⁻² day⁻¹. It is clearly not feasible to retain dosage forms in the oral cavity for days on end, thus drugs must be extremely potent to be feasible for administration by these routes.

d. The positioning of any formulation within the buccal cavity is of vital importance to the plasma profiles it subsequently generates. Saliva production, and dissolution of tablet formulations, would appear to be greater in the lower vestibule than the upper, and similarly posterior is greater than anterior (Weatherell et al., 1986). Thus the location of the tablet is a critical factor in choosing dosage forms for rapid onset of action or sustained release.

Thus there are many advantages and disadvantages associated with the buccal and sublingual route of delivery. The barrier properties of the mucosa are an important component of disease resistance. However despite the relative impermeabilities to many substances these routes appear to offer some distinct advantages over oral, percutaneous and nasal routes.

It is not unreasonable to suggest that little is known about drug absorption across the buccal epithelium. In general polar drugs tend to be absorbed by means of leakage through intercellular lateral spaces (the paracellular route). More lipophilic drugs would be expected to partition into the cell membrane then undergo lateral diffusion within the membrane followed by partitioning out of the membrane on the serosal side. By this method these drugs may display depot effects as their rate of partitioning out of the tissue is likely to be inversely proportional to their partition coefficient. So while it is reasonable to assume that buccal absorption will follow these guidelines there appear to be little hard and fast data to substantiate this.