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A new buccal absorption model

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Buccal absorption tests indicate that loss of drug from the oral cavity cannot be accounted for solely in terms of passive diffusion into the buccal membrane. A model involving protein-binding is proposed, which satisfactorily explains the observed loss. Studies on two different physical simulations of buccal absorption confirm that the proposed model is consistent with the *in vivo* results.

A simple method of measuring the extent of buccal absorption (Beckett & Triggs, 1967) has led to the development of two models to describe buccal absorption (Beckett, Boyes & Triggs, 1968; Beckett & Moffat, 1970). Our studies of the physico-chemical properties of analgesics have suggested a reassessment of their models.

METHODS

Buccal absorption was measured by a modification of the method of Beckett & Triggs (1967). A solution containing drug (1 mg) in Clark and Lubs 0·2M phosphate buffer (pH 7·2) (25 ml) was circulated round the mouth 60 times/min for a given time, then expelled. The mouth was rinsed with buffer solution (pH 7·2) (10 ml), and the two solutions combined and made up to 100 ml with buffer, then filtered. The drug was extracted from a 5 ml aliquot with 3 × 3 ml ether. After evaporation of solvent, the residue in absolute ethanol (5 ml) was determined spectrophotometrically. This extraction procedure was satisfactory up to a drug concentration of about 6 mg in 25 ml. The minimal period between successive tests, for satisfactory repeat values to be obtained, was about 15 min after a 5 min contact time, and 50 min after a 10 min contact time.

Intra-subject variations are smaller than inter-subject variations (Beckett & Moffat, 1968): a single subject was therefore used in the buccal absorption tests. Each test was performed in duplicate, both solutions being analysed three times; each result is thus the mean of six values. Changes of pH during the test were never more than 0·2 pH units.

Physical simulation

(a) *Interface diffusion system.* The method of Perrin (1967) was modified (Fig. 1). Compartment A (995 ml) represents the oral cavity, and initially contained an appropriate concentration of "drug" (*p*-methylacetanilide was used) in 0·2M Clark and Lubs buffer (pH 7·2). Compartment B (475 ml), representing the buccal membrane, contained 1-octanol, and compartment C (480 ml), representing body fluids, contained 0·2M hydrochloric acid. The use of equimolar solutions in compartments A and C precluded the setting up of an osmotic gradient. Compartment D (100 ml) (which may be taken as representing protein-binding) also contained 1-octanol. Before use the aqueous phases were saturated with 1-octanol, and the 1-octanol with aqueous buffer (pH 7·2).

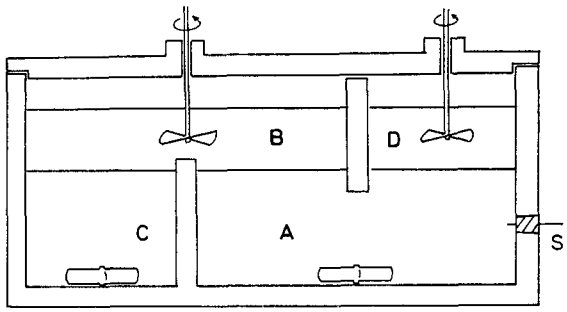

FIG. 1. Interface diffusion system used to simulate buccal absorption. The aqueous layers were stirred magnetically, the 1-octanol layers mechanically. Construction of the box was of 6 mm Perspex, the external dimensions being 24 × 11 × 14·5 cm high.

The test temperature was 22 ± 1°. Samples were withdrawn from and returned to compartment A with a syringe through a butyl rubber plug (S), and were analysed on a Unicam SP.500 spectrophotometer.

(b) *Hydraulic flow system.* The apparatus of Rowe & Morozowich (1969) was modified as shown in Fig. 2. Compartment E (100 ml) represents the oral cavity, and initially contained a solution of "drug" of appropriate concentration: salicylic acid was used, loss of which from E occurred *via* G to a spectrophotometer, whilst E was steadily replenished with water *via* H. Compartment F (100 ml), representing a compartment (such as protein-binding) tending to equilibrium with the oral cavity, initially contained water. The flow-rate of each pump was 35 ml min^{-1}. Spectrophotometric measurements were made on a Unicam SP.800 spectrophotometer, using a flow-through cell.

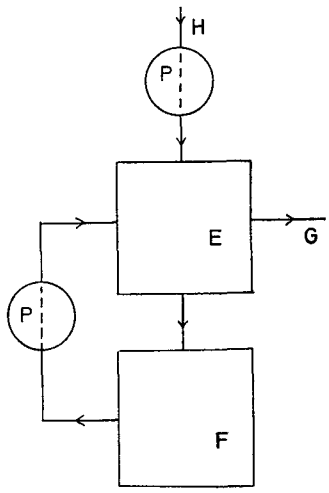

FIG. 2. Hydraulic flow system used to simulate buccal absorption. Peristaltic pumps (P) were used to produce the required flow.

RESULTS AND DISCUSSION

Inspection of the data of Beckett & Moffat (1968, 1970) indicates that the plot of buccal absorption against time is more sharply curved than can be accounted for by their two-compartment model, which invokes only first-order passive diffusion from

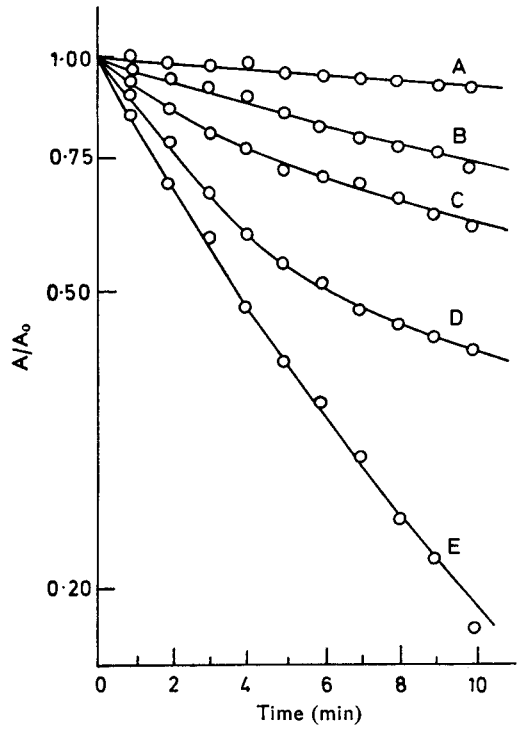

FIG. 3. The buccal absorption of a number of *p*-substituted acetanilides. The substituents are: (A) $-NH_2$; (B) $-OH$; (C) $-H$; (D) Cl; (E) I. A/A_0 is the fraction of drug unabsorbed, corrected for the effect of dilution on diffusion into a membrane (Dearden & Tomlinson, 1971). Over the time scale of a normal buccal experiment (5 min) the effect is small enough to be ignored.

oral cavity to buccal membrane. Inspection of our own results (Fig. 3) confirms that neither this nor a two-compartment model involving reversibility can adequately represent buccal absorption, since such a model must involve equilibrium. Our own and Beckett & Moffat's results show that this does not occur and a model involving at least three compartments must therefore be used.

The curvature of the results in Fig. 3 means either that saturation of the membrane is being approached or that drug is returning to the oral cavity. At the concentration of drug used, the former is unlikely (Beckett & Triggs, 1967), whereas support for the latter viewpoint is given by the observation that *some* drug may be recovered by rinsing the mouth after contact with the drug solution (Beckett, Boyes & Triggs, 1968). It may thus be inferred that the reversible step is between the oral cavity and an adjacent compartment.

In our view, this compartment is probably protein, which binds the drug. Rectilinear correlations between log (protein-binding equilibrium constant) and log (partition coefficient) for a wide variety of drugs have been reported by Penniston, Beckett & others (1969), and these authors point out that in considering the penetration of a molecule to its site of action, not only must passage through membranes be examined, but also adsorption to and desorption from macromolecules. Thus partition of a drug in the mouth may well involve its binding to protein.

Two arguments have been invoked against protein-binding in buccal absorption (Beckett & Triggs, 1967) (although Beckett & Moffat (1971) propose protein-binding

to explain the buccal absorption of some barbiturates)—firstly, that there is lack of stereoselectivity in buccal absorption: however, many proteins are non-stereoselective in any ligand binding (cf. Tucker, Boyes & others, 1970; Hansch, Steward & others, 1968).

Secondly, a rectilinear relation has been claimed between % drug absorbed and concentration, not only for single substances but also for mixtures of up to eight drugs. Examination of the data of Beckett & Triggs (1967), however, suggests that the curvature observed in the above relation is more consistent with some measure of protein-binding.

Three possible models of buccal absorption were therefore considered:

(i) oral cavity $\rightleftharpoons$ membrane $\rightarrow$ body fluids

(ii) oral cavity $\rightleftharpoons$ protein-binding $\rightarrow$ membrane $\rightarrow$ body fluids

(iii) protein-binding $\rightleftharpoons$ oral cavity $\rightarrow$ membrane $\rightarrow$ body fluids.

Model (i) is unlikely, because although reversibility between the oral cavity and the buccal membrane is possible, it cannot occur to any significant extent during absorption of compounds with reasonably high partition coefficients, provided that the membrane is not saturated. For example, Perrin (1967), using a physical model of a membrane comprising aqueous buffer (pH 2)–30% decanol in cyclohexane–aqueous buffer (pH 7·4), has shown that salicylic acid is lost from the acidic buffer solution according to a simple first-order non-reversible process.

Model (ii) (cf. Beckett, Boyes & Triggs, 1968) is tenable only if active transport of the drug by the protein, from the outer surface of the membrane to the lipid bilayer, is involved. Since this generally involves a specific binding mechanism, it is unlikely to be significant in buccal absorption, where many different types of compound are readily absorbed by the buccal membrane. Active transport is also a non-equilibrium process, and it has already been shown that reversibility must be involved in buccal absorption: drug must therefore be returned to free solution, or to a state approxi-

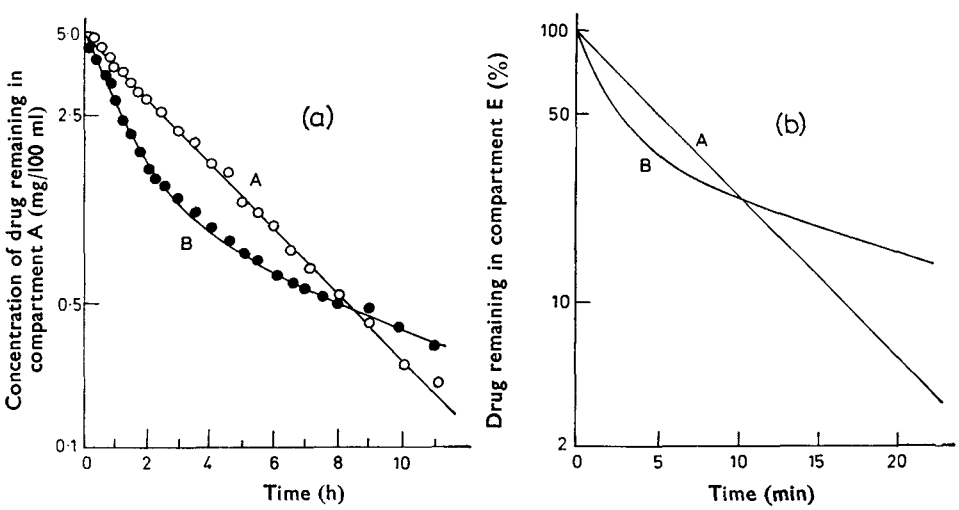

FIG. 4. Simulated buccal absorption using (a) the interface diffusion system; (b) the hydraulic flow system. Curves A are in the absence of, and curves B in the presence of, the compartments representing protein-binding.

mating it, before it can diffuse into the lipid bilayer. Thus model (iii) appears to us to be the best representation of buccal absorption. Other compartments, such as protein-binding *within* the membrane, may exist, but, because they are well-removed from the oral cavity, would influence but little the loss of drug from the oral cavity. Their chief effect would probably be to increase the capacity of the membrane to accept drug from the oral cavity.

Although the protein-binding proposed in model (iii) is not directly involved in buccal absorption, it does serve to concentrate the drug at or near the surface of the buccal membrane, and so increases the rate of absorption.

That our model gives results consistent with the buccal absorption results is shown by the behaviour of the two physical simulators of membrane processes. Fig. 4 shows the results obtained from both simulators. With each, first-order loss of "drug" occurs in the absence of that part of the system representing protein-binding. Inclusion of the "protein-binding" compartment results, in each case, in a more rapid initial loss of "drug", followed by a decrease in the loss rate as "drug" returns to the "oral cavity" from the "protein-binding" compartment. Non-rectilinear plots, similar to those shown in Fig. 3, are thus obtained.

The two physical simulators thus confirm that our proposed model of buccal absorption is entirely consistent with the results of buccal absorption tests.

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