J. Pharm. Pharmac., 1970, **22**, 15–19 *Received June* 2, 1969

Kinetics of buccal absorption of some carboxylic acids and the correlation of the rate constants and n-heptane:aqueous phase partition coefficients

A. H. BECKETT AND A. C. MOFFAT*

*Department of Pharmacy, Chelsea College (University of London), Manresa Road, London, S.W.*3, *U.K.*

A simple model for the buccal absorption of some carboxylic acids is proposed. This model has been used, in conjunction with an analogue computer, to determine the rate constants of buccal absorption of ten acids from solutions of pH 4·0 using a single subject. These rate constants gave a positive correlation with the logarithms of previously determined n-neptane:0·1N hydrochloric acid partition coefficients (correlation coefficient 0·89).

Beckett, Boyes & Triggs (1968) studied the kinetics of buccal absorption of amphetamines using an analogue computer. Their results indicated that kinetic constants may be useful in assigning numerical values to the relative partitioning properties of drugs into the oral mucosa. Data from previous studies (Beckett & Moffat, 1968, 1969a,b), of 5 min cumulative absorptions, showed the most important criteria for the rapid absorption of drugs to be that the drugs should be in their unionized forms and that these forms should have large partition coefficients. The rate constants of absorption should therefore show a similar dependence on these two physico-chemical features. Ten acids, with previously determined pK_a values and partition coefficients (Beckett & Moffat, 1969b), were therefore used to test this hypothesis.

EXPERIMENTAL AND RESULTS

Buccal absorption

The method previously described (Beckett & Moffat, 1968) was used with the following modifications. Drug solution (25 ml McIlvaine citric acid-phosphate buffer, pH 4·00) containing 1 mg of drug was introduced into the subject's mouth for 1, 2, 3 . . . 10 min intervals. The waiting period between each test was 30 min for tests taking 1 to 5 min, increasing to 50 min for the 10 min test.

A typical result is shown in Fig. 1 where the points represent the experimentally determined absorptions of *o*-toluic acid. There was little transfer of acid from the buccal mucosa back to the oral cavity after a test, even when a buffer solution of pH 9·09 was used for 5 min as a mouthwash.

* Present address: Institute for Lipid Research, Baylor College of Medicine, Texas Medical Center, Houston, Texas, 77025, U.S.A.

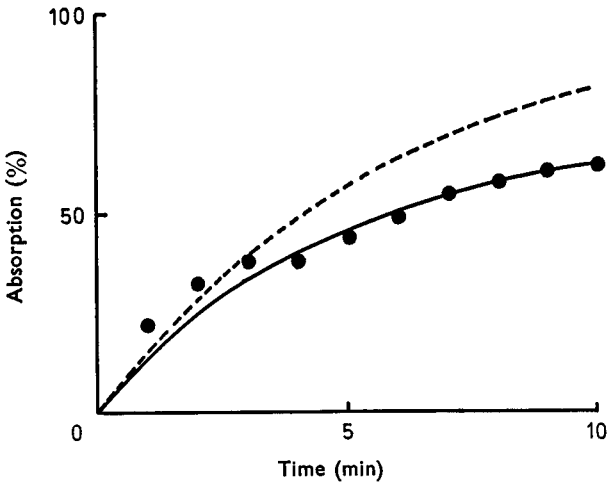

FIG. 1. Buccal absorption of *o*-toluic acid at pH 4·0. The points show the experimental results, the solid line the computer calculation and the dotted line the computer calculation ignoring the changes of pH and volume of the buffer solution.

Mathematical treatment

Apparatus. A TR–20R Analogue computer (Electronics Associates Ltd.) was used.

Method. Inspection of the above results suggested the simplest useful compartmental model for the buccal absorption of some carboxylic acids to be:

$$\underset{\text{(A)}}{\text{Drug buffer solution in mouth}} \xrightarrow{K_1} \underset{\text{(B)}}{\text{Drug in buccal mucosa}}$$

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 and B = percentage of drug in the respective compartments
K_1 = rate constant governing the transfer of unionized drug molecules between compartments (ml min^{-1})
R = fraction of drug unionized at any time t
V = volume of buffer solution in the oral cavity at any time t.

To compensate for the increase in pH and volume of the buffer solution, and associated decrease in the value of R/V during the course of the experiments, a variable diode function generator was used in the computer program (Fig. 2). Although the recorded changes of R/V were for individual tests, by simulating their values with time an approximation of their values over the whole 10 min test period can be made for each drug, e.g. Fig. 3.

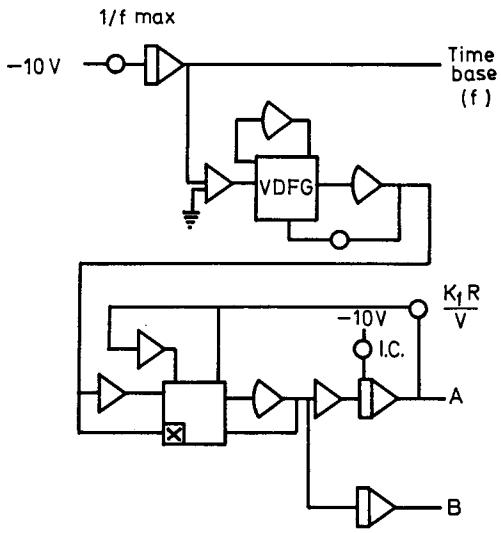

FIG. 2. Analogue computer program for the study of the kinetics of buccal absorption of some carboxylic acids.

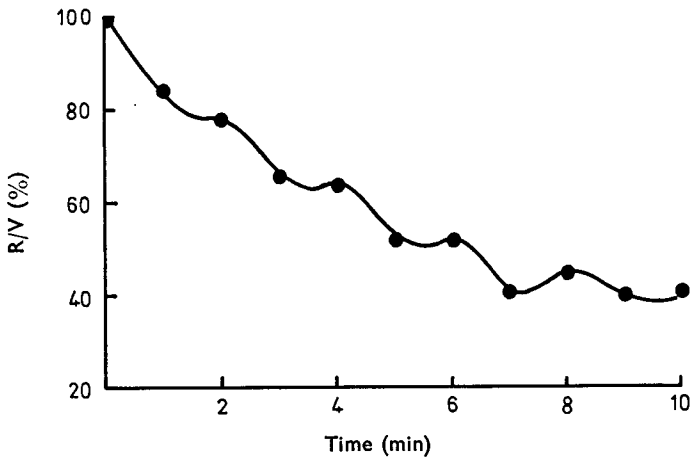

FIG. 3. Change in the fraction of unionized molecules/volume (R/V) with time during the buccal absorption test using *o*-toluic acid. The points show the experimental results, the line the variable diode function generator simulation.

The computer solutions for the absorptions of each acid were obtained by programming the variable diode function generator for each acid and by systematically altering the potentiometer representing K_1 R/V until good agreement was obtained between the computer calculations for the amount of drug absorbed and the experimental data. Since R/V values were known at the start of the test, K_1 could be calculated from the potentiometer setting.

The values of the kinetic parameters for the buccal absorption of each 'drug' are summarized in Table 1.

Table 1. *Physico-chemical constants and kinetic parameters for the buccal absorption of some carboxylic acids by one subject*

Acid	pKa at 37°[1]	At start of test: Buffer pH	At start of test: Volume (V_1) (ml)	At start of test: R_1/V_1	At start of test: $\frac{K_1R}{V}$	K_1 (ml min^{-1})	n-Heptane: 0·1N HCl partition coefficient (ml$^{1/2}$μg$^{-1/2}$)[1]
Benzoic	4·21	4·00	25·0	0·0248	0·16	6·5	0·11
o-Toluic	3·92	4·00	25·0	0·0182	0·17	9·3	0·25
m-Toluic	4·24	4·00	25·0	0·0254	0·225	8·9	0·31
p-Toluic	4·33	4·00	25·0	0·0272	0·26	9·6	0·23
2,4-Dimethylbenzoic	4·28	4·00	25·0	0·0227	0·245	10·6	0·88
2,5-Dimethylbenzoic	4·05	4·00	25·0	0·0212	0·27	12·7	0·63
3,5-Dimethylbenzoic	4·31	4·00	25·0	0·0268	0·26	9·7	0·68
o-Chlorophenylacetic	4·07[2]	4·00	25·0	0·0216	0·11	5·1	0·03
m-Chlorophenylacetic	4·14[2]	4·00	25·0	0·0232	0·13	5·6	0·11
p-Chlorophenylacetic	4·19[2]	4·00	25·0	0·0243	0·15	6·2	0·06

[1] From Beckett & Moffat (1969b).
[2] At 25°.

DISCUSSION

A linear relation between absorption and time was not obtained after plotting the results on semi-log paper. This indicated that the absorption was apparently not a simple first order process. However, there was little return of the acid to the oral cavity after a test. Also, the increase in pH and volume of the buffer solution during a test diminished the concentration of unionized drug and its subsequent absorption. Thus, it was considered that a good approximation of the results could be obtained using a two compartmental model which incorporated volume and pH changes but a first order process.

The model is the simplest that could be devised for a system such as this. It may not be the correct one since other compartments, e.g., the blood, may need to be considered. However, good fits to the experimental points were obtained, e.g., Fig. 1. The proposed computer model is therefore a good mathematical approximation of the biological system. The necessity of including the generated function (R/V) with time is clearly seen by comparing the experimental buccal absorption data, the computer model simulation and a first order curve having the same K_1 value for *o*-toluic acid (Fig. 1). The first order curve is very much above that of the computer curve and buccal absorption data. Beckett & others (1968) used a three compartmental model for the buccal absorption of some amphetamines involving four rate constants, one of which did not exist until certain levels in other compartments had been reached. They also assumed that the volumes of the compartments did not change appreciably. Thus it is possible that by using the much simpler, more logical model now proposed, a good fit could have been obtained. It is not possible to put this to the test, since the authors had not measured volume or pH changes.

The rates of absorption of the acids studied are directly proportional to the fraction of acid in the unionized form as shown by the good fit of the experimental data to the computer simulation. This explains why buccal absorption-pH curves rise so steeply as they move from ionized to unionized molecules (see Beckett & Triggs, 1967; Beckett & Moffat, 1968, 1969a). The different rate constants for absorption of the acids are due solely to the different abilities of the unionized forms to penetrate the buccal muscosa. Plotting the rate constants for the different acids against the

logarithms of their n-heptane:0·1N hydrochloric acid partition coefficients gives a straight line (Fig. 4) (correlation coefficient 0·89), viz.

$$K_1 = 4{\cdot}42 \log K + 11{\cdot}4$$

Where K_1 = rate constant (ml min^{-1})

K = partition coefficient ($ml^{1/2}\,\mu g^{-1/2}$)

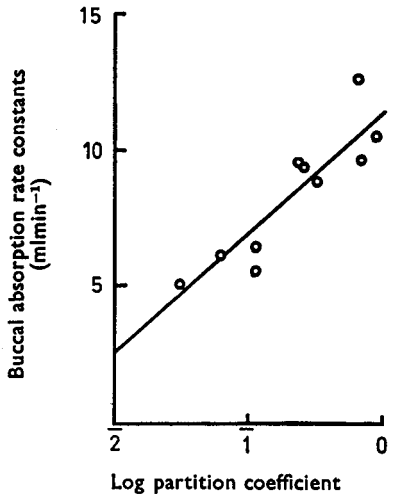

FIG. 4. Correlation of n-heptane:0·1N hydrochloric acid partition coefficients of some carboxylic acids with their rates of buccal absorption (correlation coefficient 0·89).

Although the relation is empirical it shows that n-heptane has similar properties to the lipid membrane of the buccal mucosa with respect to absorptions of the acids used in these experiments, which is in agreement with our previous findings concerning the good positive correlations of n-heptane:aqueous phase partition coefficients with buccal absorption data using acids and amines at 1 and 10% levels of unionization.

Acknowledgements

The authors wish to thank P.G.J. for participating in the trials.

One of us (A.C.M.) also thanks the Science Research Council for a research studentship.

REFERENCES

BECKETT, A. H., BOYES, R. N. & TRIGGS, E. J. (1968). *J. Pharm. Pharmac.*, **20**, 92–97.

BECKETT, A. H. & MOFFAT, A. C. (1968). *Ibid.*, **20**, *Suppl.*, 239S–247S.

BECKETT, A. H. & MOFFAT, A. C. (1969a). *Ibid.*, **21**, *Suppl.*, 139S–143S

BECKETT, A. H. & MOFFAT, A. C. (1969b). *Ibid.*, **21**, *Suppl.*, 144S–150S

BECKETT, A. H. and TRIGGS, E. J. (1967). *Ibid.*, **19**, *Suppl.*, 31S–41S.