While the models discussed in the present research may not generally explain the complex *in vivo* absorption of drugs, they should contribute significantly to the understanding of baseline behaviors. They, therefore, provide at least a systematic understanding of the simultaneous interaction of the many physicochemical variables in the system, leading often to unexpected results. As future work should show, these models and their elaboration to handle more complex situations should prove very valuable in both experimental design and data analysis of *in vivo* studies.

ADDENDA

It would be instructive to compare the various models (two phase, pseudo two phase, and three phase) under identical source phase pH conditions to answer the following question: How closely, and under what conditions, does the pseudo-two-phase model approximate the true two-phase model (11, 12) where the lipid phase acts as a perfect sink?

Figures 19–21 compare the three models for a homologous series of bases with a pKa of 5 when the pH of the source phase is 3, 5, and 8, respectively. A simplifying assumption in these calculations is very large buffer strength; hence, interfacial pH is equivalent to bulk pH. In all three figures, it is apparent that all models (and the pH-partition theory prediction, based on concentration of the unionized species in the source phase and no aqueous diffusion layers) are equivalent for low partition coefficient solutes. The membrane is overwhelmingly the rate-determining barrier. As the partition coefficient increases, however, the three *diffusional* models show the leveling-off trend. The true three-phase model in Fig. 19 (3/8) levels off at a rate 1% of the true two-phase model value. It is also seen that the pseudo-two-phase model (3/3) does not approximate the true two-phase model (3/sink). When the fraction of base as RN in the source phase increases to 50 and 100% (Figs. 20 and 21), however, the models do converge.

At first glance, then, it would appear that the three-phase model can, in the form of the pseudo-two-phase model, be made to approximate true two-phase conditions whenever an appreciable amount of the solute is in the uncharged form in the source phase and is mainly in the charged form in the receptor phase. However, as the upper solid curve in Fig. 19 indicates, lowering the receptor phase pH from 3 to 1 again equalizes the pseudo- and true two-phase models. It may thus be summarized that the pseudo-two-phase model accurately simulates two-phase conditions simply when there is proportionately more uncharged solute in the source phase than in the receptor phase. This is in concurrence with the results of Ho and Higuchi (23) for buccal absorption of weak acids. Since salivary pH (6.0–7.0) is less than serosal pH (7.4), there is proportionately more uncharged acid in the oral solution; hence, the two-phase model does apply. As stated by Ho and Higuchi (23), this would not be the case for buccal absorption of weak bases.

REFERENCES

(1) L. S. Schanker, D. J. Tocco, B. B. Brodie, and C. A. M. Hogben, *J. Pharmacol. Exp. Ther.*, **123,** 81(1958).

(2) C. A. M. Hogben, D. J. Tocco, B. B. Brodie, and L. S. Schanker, *ibid.*, **125,** 275(1959).

(3) P. A. Shore, B. B. Brodie, and C. A. M. Hogben, *ibid.*, **119,** 361(1957).

(4) L. S. Schanker, P. A. Shore, B. B. Brodie, and C. A. M. Hogben, *ibid.*, **120,** 528(1957).

(5) C. A. M. Hogben, L. S. Schanker, D. J. Tocco, and B. B. Brodie, *ibid.*, **120,** 540(1957).

(6) J. T. Doluisio and J. V. Swintosky, *J. Pharm. Sci.*, **53,** 597 (1964).

(7) J. Perrin, *ibid.*, **56,** 411(1967).

(8) M. A. Augustine and J. Swarbrick, *ibid.*, **59,** 314(1970).

(9) S. A. Howard, M. A. Farvar, A. Suzuki, and W. I. Higuchi, *ibid.*, **58,** 1325(1969).

(10) *Ibid.*, **58,** 1330(1969).

(11) A. Suzuki, W. I. Higuchi, and N. F. H. Ho, *J. Pharm. Sci.*, **59,** 644(1970).

(12) *Ibid.*, **59,** 651(1970).

(13) H. Passow, *J. Theor. Biol.*, **17,** 383(1967).

(14) R. G. Stehle and W. I. Higuchi, *J. Pharm. Sci.*, **56,** 1367 (1967).

(15) D. R. Olander, *AIChE J.*, **6,** 233(1960).

(16) J. R. Senior, *J. Lipid Res.*, **5,** 495(1964).

(17) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, **12,** 421(1964).

(18) A. L. Misra, A. Hunger, and H. Keberle, *J. Pharm. Pharmacol.*, **18,** 531(1966).

(19) E. R. Garrett and P. B. Chemburkar, *J. Pharm. Sci.*, **57,** 944 (1968).

(20) *Ibid.*, **57,** 949(1968).

(21) G. Levy and E. J. Mroszczak, *J. Pharm. Sci.*, **57,** 235(1968).

(22) A. H. Beckett and A. C. Moffat, *J. Pharm. Pharmacol.*, **20,** 239S(1968).

(23) N. F. H. Ho and W. I. Higuchi, *J. Pharm. Sci.*, **60,** 537 (1971).

(24) H. Rosen, A. Leaf, and W. B. Schwartz, *J. Gen. Physiol.*, **48,** 379(1964).

(25) P. Singh, S. J. Desai, D. R. Flanagan, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **57,** 959(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1971, from the *College of Pharmacy, University of Michigan, Ann Arbor, MI 48104*

Accepted for publication July 12, 1972.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

Abstracted from a thesis submitted by R. G. Stehle to the University of Michigan in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported by Grant GM-13368 and Predoctoral Fellowship 1-F1-GM-30,048-05 from the National Institute of General Medical Sciences, U. S. Public Health Service, Bethesda, MD 20014

* Present address: The Upjohn Co., Kalamazoo, MI 49001

▲ To whom inquiries should be directed.