intestinal motility (and gastric pH) may have a corresponding effect on dissolution rate limited drug absorption. It is possible, therefore, that 2 types of tablet formulations of a given drug may show pronounced dissolution rate differences in one kind of population or clinical environment, but not in another. However, it must be emphasized that the conclusions concerning these *in vivo* implications are clearly preliminary and require confirmation in a large population sample containing significant numbers of consistently rapid and slow absorbers.

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Received June 12, 1967.
Accepted for publication August 8, 1967.

Diffusional Model for Transport Rate Studies Across Membranes

Sir:

There has been much in the literature in recent years concerning the so-called "three-phase" model of drug absorption. Absorption studies in this area have concentrated mainly on the passive or diffusional transport of drugs. Most models currently proposed are kinetic outgrowths of the original Brodie-Shore-Hogben pH-partition thesis. In recent communications to this journal authors (1, 2) have proposed equations based on first-order kinetics, which give the amount of drug in each of the three phases *versus* time.

The importance of diffusion in drug absorption has been recognized (3). However, no strictly diffusional model of drug absorption has been proposed for the three-phase multicomponent diffusion problem that can physically describe, for example, pH effects.

The authors in these laboratories are exploring general diffusional models for gastrointestinal absorption of ionizing and nonionizing drugs. A proposed steady-state model, shown in Fig. 1 for the case of a weak base, RN, which can become protonated to give RNH^+, allows for intestinal and blood buffers. It is assumed here also that only the uncharged drug species can diffuse in the lipid phase. An important feature of this model is the inclusion of aqueous diffusional barriers on each side of the lipoidal membrane.

Preliminary results (Fig. 2) obtained for the steady-state case *via* computer correlate the combined effects of varying pKa and the partition coefficient (KLH). The units of G, the transport rate, are mmoles cm.$^{-2}$ sec.$^{-1}$. TH1 and TH3, the effective aqueous diffusion layer thicknesses on the left and right side of the membrane, respectively, are taken as equal for these calculations. TH2 is the effective thickness of the lipid phase. For low to moderate agitation conditions, TH1 should be around 50 to 200 μ (4). The authors would estimate TH2 to be effective somewhere between tens of microns to few millimeters.

In Fig. 2 most noticeable is the fact that steady-state transport rates are linear with increasing partition coefficients only up to a certain point

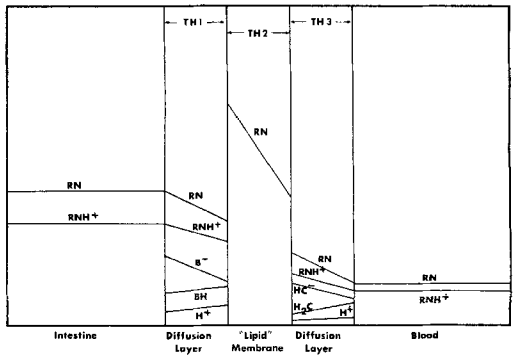

Fig. 1—The steady-state diffusional model for the transport of a weak amine drug, RN, *across the intestinal barrier. Concentration profiles are schematically given for all species:* RNH^+ *= protonated drug;* BH *and* B^- *= the buffer molecule and its anion in the intestinal fluids;* H^+ *= hydrogen ion;* H_2C *and* HC^- *= carbonic acid and bicarbonate in the blood.* TH1, TH2, *and* TH3 *are the diffusion layer thicknesses in the three phases.*

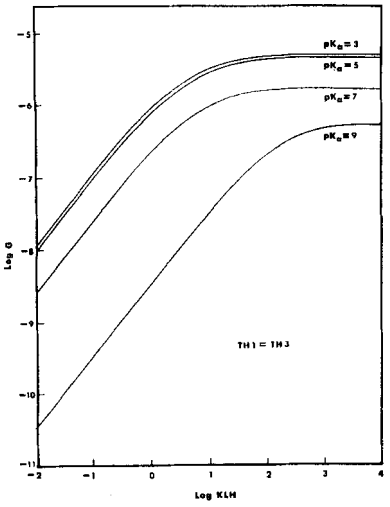

Fig. 2—The results of drug transport rate computations for the steady-state model for basic drugs of various pKa's. G, the transport rate, is in mmoles cm.$^{-2}$ sec.$^{-1}$. All diffusion coefficients are assumed to be D = 1×10^{-5} *cm.^{2} sec.$^{-1}$. Intestinal pH = 6.5. The total drug concentration,* (RN) + (RNH^+), = 10^{-2} M. *The total buffer concentration,* (B^-) + (HB), = 10^{-2} M. *Total serum carbonate,* (H_2CO_3) + (HCO_3^-), = 2.6×10^{-2} M. TH1 *and* TH3 *were taken to be* 10^{-2} *cm., while* TH2 *was taken as* 10^{-1} *cm.*

(KLH ~1), beyond which the aqueous diffusion layers give a limiting effect. Experimental data given by Hogben *et al.* (3) indicate that this leveling off effect does occur in rat intestine absorption studies. Hogben and his associates indicated in the same paper that the observed pattern of intestinal absorption demonstrated the crucial importance of drug diffusion to the intestinal wall when absorption conditions (high partition coefficient, drug present mostly in uncharged form) were otherwise favorable. We feel that this phenomenon should also be observed in *in vitro* absorption studies. The collodion-phospholipid membranes used by Misra *et al.* (5) averaged 20 μ in thickness. In this case the aqueous diffusion layers (50 to 200 μ) would probably be greater than the thickness of the membrane by the order of magnitude of 2.5 to 10. The diffusional leveling off effect, if a 20-μ membrane were to be inserted in the above model, would occur at partition coefficient values of about 10^{-2}. If the diffusion coefficient of the drug in the lipid is less than that in these calculations, the leveling off would occur at correspondingly larger KLH values.

The data curves (Fig. 2) are quite close at low pKa values until the pKa of the drug approaches the intestinal pH, at which point they become increasingly separated with increasing pKa. The linearity of *G* with increasing partition coefficient for a base with a pKa of 9 is seen to extend over a much wider range than for weak bases having lower pKa values. This indicates that, due to the lower amount of the uncharged species present per amount of charged species, the diffusion process is still dependent on the permeability of the lipid layer at partition coefficients in the neighborhood of unity.

An expression for the nonionizing drug case, under the same conditions as above, fits point-for-point the pKa = 3 curve in Fig. 2. Further work is underway concerning the case of weak acids in the intestine. Due to the generality of the model, additional factors such as micellar transport and complexation can be considered. Further studies should also treat the nonsteady-state case and the heterogeneous nature of the lipid barrier.

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Received May 1, 1967.
Accepted for publication July 18, 1967.

This investigation is supported by fellowship 1-F1-GM-30, 048-02 and by grant GM-13368 from the National Institute of General Medical Sciences, U. S. Public Health Service, Bethesda, Md.