Short communication

Kinetics of Passive Transport in Water/Membrane/Water System. A Mathematical Description

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Passive transport across the lipid region of the membrane is considered to be one of the main mechanisms by which many solutes, especially xenobiotics, enter the cell (Stein 1981). Although the problem of mathematical description of the process has been intensively treated, it continues to be a subject of controversy. Some approaches do not take into account the solute accumulation in the membrane (Stein 1981), while others consider only equal volumes of individual phases (Kubinyi 1976; van de Waterbeemd et al. 1978; Hyde and Lord 1979; Cooper et al. 1981; Aarons et al. 1982). However, apparently any of the approximations mentioned above does not fully correspond to the real situation. In this communication usefully simplified equations for general description of the time course of solute accumulation in both aqueous compartments as well as in the membrane are presented.

The kinetics of the solute partitioning in a 3-compartment system (Fig. 1) can be described by a set of linear differential equations (1)—(3) using the real assumption of practically instantaneous homogeneous concentration in the bulks of individual phases, owing to their small volumes (Baláž et al. 1984) or to appropriate stirring:

$$-dc_1/dt = (Al_1/V_1)c_1 - (Al_2/V_1)c_2 \quad (1)$$

$$-dc_2/dt = -(Al_1/V_2)c_1 + (2Al_2/V_2)c_2 - (Al_1/V_2)c_3 \quad (2)$$

$$-dc_3/dt = -(Al_2/V_3)c_2 + (Al_1/V_3)c_3 \quad (3)$$

where c_i and t stand for concentration in the i-th compartment and time, respectively (for other symbols, see Fig. 1). The water-to-lipid transport rate parameter l_1 and the lipid-to-water transport rate parameter l_2 characterize transport across interfaces (i. e. diffusion through the diffusion layers on both sides of the interface, and partitioning on the interface) which is assumed to be the only rate limiting step. As far as model interfaces "immiscible organic solvent/water" are considered, the parameters l_1 and l_2 are related to the partition coefficient $P = l_1/l_2$ as:

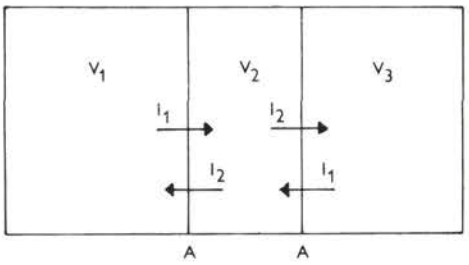

Fig. 1. Layout of the water/membrane/water system. V — volumes, A — interfacial areas, l_1 — the water-to-lipid transport rate parameter, l_2 — the lipid-to-water transport rate parameter. Solute added to the 1st compartment at time $t = 0$.

$$l_1 = aP/(bP + 1) \tag{4}$$
$$l_2 = a/(bP + 1) \tag{5}$$

The values of empirical constants a, b depend only on the model system in use even in the case of non-homologous series including ionic pairs and partially ionized compounds (using the apparent partition coefficient; van de Waterbeemd et al. 1981).

Using the procedure of *Wolf et al. (1977)*, the following solution is obtained from (1)—(3) combined with (4) and (5):

$$c_i/c_0 = a_{1i} \exp(-s_1 t) + a_{2i} \exp(-s_2 t) + a_{3i}, \quad i = 1, 2, 3 \tag{6}$$

where
$$s_1 = aA(X + Y)/2(bP + 1),$$
$$s_2 = aA(X - Y)/2(bP + 1),$$
$$a_{11} = (P^2/V_1^2 - P^2/V_1V_3 + PY/V_1)/[Y(X + Y)],$$
$$a_{21} = (P^2/V_1V_3 - P^2/V_1^2 + PY/V_1)/[Y(X - Y)],$$
$$a_{31} = a_{33} = V_1/(V_1 + PV_2 + V_3),$$
$$a_{12} = [2P^2/V_2V_3 - P(X + Y)/V_2]/[Y(X + Y)],$$
$$a_{22} = [P(X - Y)/V_2 - 2P^2/V_2V_3]/[Y(X - Y)],$$
$$a_{32} = PV_1/(V_1 + PV_2 + V_3),$$
$$a_{13} = 2P/V_2V_3Y(X + Y),$$
$$a_{23} = -2P/V_2V_3Y(X - Y),$$
$$X = P/V_1 + 2/V_2 + P/V_3,$$
$$Y = [P^2(V_1 - V_3)^2/V_1^2V_3^2 + 4/V_2^2]^{0.5},$$

and c_0 is the initial concentration in the 1st compartment. Equation (6) can often be approximated using $X = 2/V_2 + P/V_3$ and $Y = (P^2/V_3^2 + 4/V_2^2)^{0.5}$ because of $V_1 \gg V_2 \sim V_3$ in real 3-compartment biosystems (e. g. suspensions of liposomes, bacteria or isolated cells). Another simplification is possible for various absorption simulators ($V_1 = V_3$): $X = 2P/V_1 + 2V_2$ and $Y = 2/V_2$. Equation (6) describes the

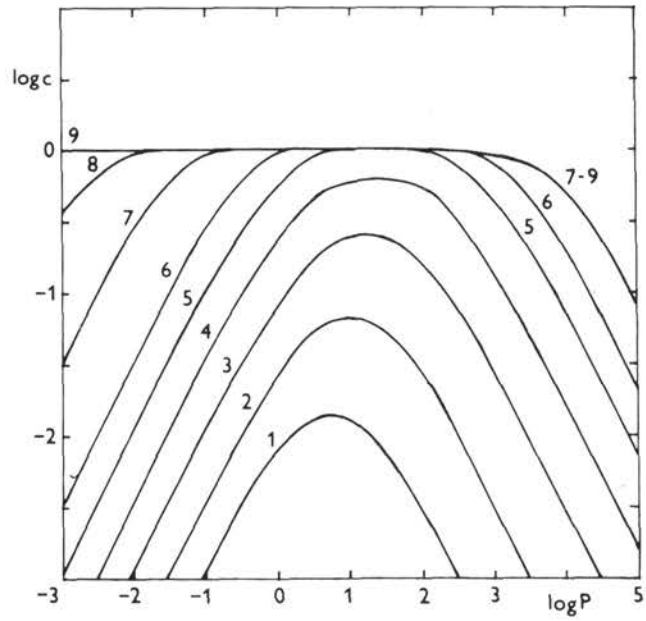

Fig. 2. Concentration vs. partition coefficient profile for the 3rd compartment. $V_2/V_1/V_3 = 1/10{,}000-/100$; $At/V_1 = 0.001$ (1), 0.003 (2), 0.01 (3), 0.03 (4), 0.1 (5), 0.3 (6), 3 (7), 30 (8), 300 or ∞ (9) in dm h^{-1}; $a = 0.245$ dm h^{-1}, $b = 0.286$ (Baláž and Šturdík 1984).

motion of molecules due to concentration gradients alone. Influence of membrane potential on transport of charged molecules requires additional correction.

The validity of the system of equations presented may easily be tested by applying experimental data concerning the relationship between the biological activity and lipophilicity of a given compound. Biological activity might monitor the solute concentration in the receptor surroundings, provided that all of the compounds tested have the same affinity constants as it is often the case within a homologous series. The data are usually expressed as double logarithmic plots "biological activity after a constant time of application vs. the partition coefficient". The relevant plots of equation (6) for the 3rd compartment are given in Fig. 2. The resulting curves are of bilinear shape or are composed of three linear parts connected by curved portions. The occurrence in *in vivo* situations of both types is well documented (Kubinyi 1976; Baláž and Šturdík 1984). This fact might indicate the ability of equation (6) to describe the time course of the solute concentration in the individual phases of simple biosystems.

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Received December 9, 1983 / Accepted July 27, 1984