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Validity of the steady-state assumption in in vitro liposomal absorption enhancement modeling: the free solute mechanism as an example

K.D. Ertel and J.T. Carstensen

University of Wisconsin School of Pharmacy, Madison, WI 53706 (U.S.A.)

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Since the early seventies, liposomes have received considerable attention as drug delivery systems owing to their structural diversity and their inherent ability to entrap solutes. Much of the interest in liposomes has centered on their use as parenteral and oral drug delivery systems; however, several recent studies have looked at topical liposomes as a cutaneous delivery system for steroids (Mezei and Gulasekharam, 1980, 1982) and have demonstrated the (apparent) ability of liposomes to yield increased concentrations of steroid in the skin while decreasing systemic absorption and side effects.

The mechanism(s) whereby liposomes (apparently) produce an enhanced absorption of drug into the skin is not known. Ganesan et al. (1984) recently published the results of a study which looked at the ability of liposomes to influence the percutaneous absorption of glucose, hydrocortisone, and progesterone. Based on the data obtained from in vitro absorption studies and from in vitro liposomal leakage studies, Ganesan et al. presented three possible mechanisms by which liposomes could enhance the percutaneous absorption of a compound. In the case of glucose, which was found to leak relatively slowly from liposomes, a free solute mechanism was proposed in which liposomal leakage of the compound was the rate-limiting step for absorption. Progesterone leakage from the liposomes was found to be imperceptible; thus, a direct transfer mechanism for absorption was proposed. Hydrocortisone leakage occurred very slowly (but was measurable), leading to the proposal of a combination mechanism wherein direct transfer was responsible for 99% of the absorption of the drug.

To develop these ideas further, Ganesan et al. presented mathematical models for each of the proposed absorption mechanisms. In the derivation of these models, they assumed that the release of solute from the liposomes is described by:

$$J_{lip} = 4\pi a^2 n P_{bl}(C^* - C_b) \quad (1)$$

and that the flux of free solute across the mem-

Correspondence: J.T. Carstensen, University of Wisconsin Center of Health Sciences, School of Pharmacy, 425 North Charter Street, Madison, WI 53706, U.S.A.

brane into the sink of the receiver compartment is described by:

$$J_s = AP_sC_b \quad (2)$$

where the variables are as defined in the cited work. In order to obtain a final equation from which the effective permeability coefficient (P_e) could be easily determined, they further assumed that the system was at steady-state, i.e. that $J_{lip} = J_s$ during the experimental time period of 60 h used in their study.

We feel that although these models provide insight into the process of liposomal absorption enhancement, some care must be exercised in their application since, as is apparent from Eqns. 1 and 2, the validity of the steady-state assumption will be dependent on the relative magnitudes of the lipid bilayer and skin permeability coefficients. To demonstrate this, a computer simulation of the free solute mechanism has been developed which calculates the various fluxes and solute concentrations of the in vitro system as a function of time. In developing the simulation, we have assumed that the liposomes are monodisperse and that the release of solute is described by Eqn. 1; however, sink conditions were not assumed for the receiver phase, hence Eqn. 2 is replaced by:

$$J_s = AP_s(C_b - C_r) \quad (3)$$

where C_r is the solute concentration in the receiver phase. Furthermore, to keep the model as simple as possible, we have assumed that the liposomes do not penetrate the skin.

When the lipid bilayer and skin permeability coefficients do not differ by more than 2 or 3 orders of magnitude, the assumption of steady-state is certainly valid. As the difference between the permeability coefficients increases, however, the validity of the assumption becomes questionable. If, for example, the permeability coefficients for glucose reported by Ganesan et al. are used in the simulation program ($P_s = 14 \times 10^{-7}$ cm/h, $P_{bl} = 6.2 \times 10^{-9}$ cm/h), the flux values reported in Table 1 are obtained. While steady-state does not exist during the initial part of the experiment, the flux values do become reasonably close during the latter part, and hence, the steady-state assumption is valid. The assumption will not hold, however, for permeability coefficients that differ by much more than this. For example, if P_s is taken to be 5×10^{-4} cm/h and P_{bl} is taken to be 4×10^{-9} cm/h, the flux values in Table 2 are obtained. The assumption of steady-state clearly does not hold during the experimental time period used by Ganesan et al. for these permeability coefficient values.

TABLE 1

SIMULATED LIPID BILAYER AND SKIN FLUXES FOR GLUCOSE

Time (h)	J_{lip} (g/h) [a]	J_s (g/h)
10	3.479×10^{-9}	4.011×10^{-10}
20	3.470×10^{-9}	5.826×10^{-10}
30	3.462×10^{-9}	7.524×10^{-10}
40	3.453×10^{-9}	9.112×10^{-10}
50	3.444×10^{-9}	1.060×10^{-9}
60	3.436×10^{-9}	1.199×10^{-9}
70	3.428×10^{-9}	1.329×10^{-9}
80	3.419×10^{-9}	1.450×10^{-9}
90	3.411×10^{-9}	1.563×10^{-9}
100	3.403×10^{-9}	1.669×10^{-9}

[a] These units are consistent with those used by Ganesan et al. (1984).

In addition to generating flux values, the above simulation can also be used to generate plots of receiver phase solute concentration (C_r) versus time. Such a plot has been generated using the data for glucose reported by Ganesan et al., and is

TABLE 2

SIMULATED LIPID BILAYER AND SKIN FLUXES CALCULATED FOR $P_{bl} = 4 \times 10^{-9}$ cm/h AND $P_s = 5 \times 10^{-4}$ cm/h

Time (h)	J_{lip} (g/h)	J_s (g/h)
10	2.246×10^{-9}	9.435×10^{-11}
20	2.243×10^{-9}	1.399×10^{-11}
30	2.239×10^{-9}	1.843×10^{-10}
40	2.235×10^{-9}	2.277×10^{-10}
50	2.232×10^{-9}	2.700×10^{-10}
60	2.228×10^{-9}	3.114×10^{-10}
70	2.225×10^{-9}	3.517×10^{-10}
80	2.221×10^{-9}	3.517×10^{-10}
90	2.218×10^{-9}	4.296×10^{-10}
100	2.214×10^{-9}	4.671×10^{-10}

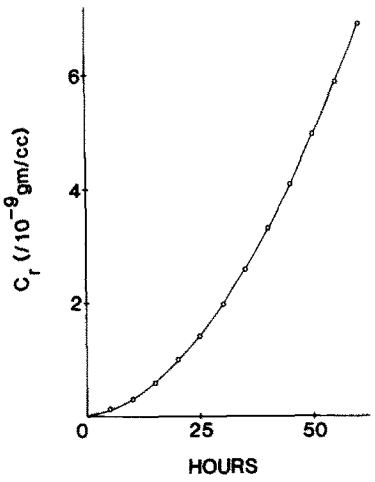

Fig. 1. Plot of receiver phase glucose concentration versus time generated by the simulation program.

shown in Fig. 1. From this plot, a lag time for the appearance of glucose in the receiver can be estimated to be about 30 h, a value which is in good agreement with the experimental lag time observed by Ganesan et al. However, it must be emphasized that in cases where the steady-state assumption does not apply, such agreement does not exist.

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