Effect of Vehicles on Percutaneous Absorption. IV. Error and Addenda: Effect of Vehicles on Percutaneous Absorption I—III

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Corrections for misprints and erroneous descriptions are given with some complementary explanations.

Keywords—percutaneous absorption; salicylic acid; drug diffusion; trans-epidermal water loss; partition coefficient; non-diffusional resistance; simulation

Many misprints and erroneous descriptions are found in the above-titled papers. Some of them are rather trivial, but some are quite serious and invalidate the argument delivered therein. Necessary corrections are given below. Each pair of parentheses contains four terms, page number, line number, error, and correction in this order.

In Part I

(1765; 22; have; has), (1765; 25; Gemmel; Gemmell), (1765; 27; than petrolatum; than from petrolatum), (1765; 30; for SA; of SA), (1765; 32; technique; techniques), (1766; 1; were; was), (1766; 5; may controlled; may be controlled), (1766; 12; authors; authors), (1766; 12; disorderliness; disorderliness), (1766; 21; used are in; used are summerized in), (1766; 40; Intervals; intervals), (1767; 10; as a ratio; as the ratio), (1767; 4; 2000 mg to; 2000 mg and 1 to 6 hr, respectively, to), (1767; 30; \( P = C \) (dry epidermis)/C(vehicle); \( P = C \) (dry epidermis)/C(vehicle), and the concentration of SA in the epidermis was calculated on the basis of the dry epidermis), (1767; 28; 37° and the; 37°, the), (1767; 34—35; The charged... of the cup.; The amount of agar gel was adjusted to position the top of gel at the height of the brim of cup.), (1768; 6; on the grounds of; on the basis of), (1769; 2; supported; supported), (1769; 10—11; volume of the drug; the volume of drug), (1769; 11; decrease; decreased), (1769; 12; may increase by; may be increased by), (1769; 12; but IPB could not explain by; but the low Q value of IPB cannot be explained by), (1769; 14; which have an abnormally; which has an abnormally), (1769; 15; may attributes to; may be attributed to), (1769; 16; possesses; possess), (1769; 16; estimated; inferred), (1769; 25—27; but the ... obtained.; but the homologes with a higher solubility or a larger partition coefficient show generally a lower absorption.), (1769; 30; solubility; solubilities), (1769; 32; are; between SA and vehicle must be), (1769; 33; play a role; act), (1771; 3; possessed; possesses), (1771; 3; may have promoted; may promote), (1772; 28; acceralated; accelerated), (1772; 28—29; when in ... 2000 mg.; when the vehicle was in contact with the skin, and the discharged TEWL values were increased markedly when the sample amount was increased from 25 to 2000 mg.), (1772; 29;

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alterating; alternative), (1772; 32; tenadancy; tendency), (1772; 33; reach; reached), (1773; 6; with increase; with an increase in).

**In Part II**

(1774; 10; model of; model if), (1774; 13; interface.; interface are known.), (1774; 19; coefficient; coefficients), (1774; 31; Notation; Notations), (1775; 3; and (2); and (3)), (1775; 22; I = ; t = ), (1775; 23; Where I; where t), (1776; 6; subtract; subtract), (1777; 7; shows the; show the), (1777; 15; but longer; but the longer), (1777; 31; existence; existence of non-diffusional resistance,), (1777; 33; honey; horny).

**In Part III**

For “honey layer” and “separation number” read “honey layer” and “division number”, respectively.

(1779; 10; the proportionality; good agreements), (1779; 11; sufficient; found), (1779; 11; an unknown; a hitherto unknown), (1779; 14—15; by an ... the cell.; by the wettability of the cell by the vehicle.), (1779; 18 and 20; P_0; P_a), (1779; 21; Due to; Owing to), (1779; 22; skin, drug; skin by which drug), (1779; 25—27; In simulation ... another value.; (exclude)), (1779; 28; reported; report), (1779; 28; coefficient; coefficients), (1779; 29; simulated values of; results of simulation for), (1779; 31; comparable; corresponding), (1779; 32; simulated values.; simulation results.), (1780; 2; A volume; The volume), (1780; 4; P=C(saline)/C(skin); P=C(skin)/C(saline)), (1780; 6; (IV) Diffusion; (IV) Apparent Diffusion), (1780; 15; Fortran program; Fortran program), (1780; 16; simulated ... computer.; obtained by the simulation technique.), (1781; Table II foot note; \( \Delta x = 0.0033, X/\Delta x = 10508, \) as \( P_e = 1.0; (\Delta x)_{so} = 3.333 \times 10^{-4}, X_{W/\Delta x}_{so} = 33145, \) by eq. (11).), (1781; Table III 3rd column; Layer number, original value; Division number, those shown in Table II), (1781; Table III 4th column; eq. (4); eq. (11)), (1781; 1; (III) Diffusion; (III) Apparent Diffusion), (1781; 2; Diffusion; Apparent diffusion), (1781; 2; of the intact; in the intact), (1781; 3; diffusional resistance; resistance), (1782; 4; depends mainly upon; is mainly due to), (1781—1782; Section (IV); Transport ... Table II.; (be replaced by [A] described later)), (1782; 24; Number of ... and; Number and), (1782; 25; (y); (y or o)), (1782; 25; (N) of the; (N)), (1782; 26; drug ...), the smaller; as shown in Eq.(11) or (14). The larger the division number and the smaller, (1782; 27; \( \alpha, \beta, \gamma, \delta \) ... case.; \( \alpha, \beta, \gamma, \delta \), the more accurate the calculation result.), (1782; 27; N and; N or), (1782; 29—35; The ... values.; (be replaced by [B] described later)), (1782; 39—41; calculated ... with; \( Q \) values calculated on assuming \( X = 0 \) (see Fig. 4). The experimental values are situated closely to), (1782; 43—45; the skin ... surface.; the non-diffusional resistance \( X \) is localized at the honey layer.), (1783; 1; only and; only, and), (1783; 1; decrease with vehicle; decreased with an increase in vehicle), (1783; 2; increase (see Fig. 5).; (see Fig. 5).), (1783; 2; agreed sufficiently with; fall on or near), (1783; 3; separated; deviate), (1783; 5; of an ... and the; of the wettability of the), (1783; 6; cell.; cell by the vehicle.), (1783; 6; than that ... curve.; than the theoretical.), (1780; Fig. 1; 25 ml; 20 ml).

[A]: (IV) Simulation

As pointed out in Part II, \( \alpha \) and \( \beta \) must satisfy the conditions \( \alpha/\beta = D_a/D_b \), \( \alpha < 0.5 \), and \( \beta < 0.5 \). Unless otherwise stated(cf. the third column of Table III), Equations (2) and (3) were used.

\[
\frac{D_a}{D_{\text{water}}} = \alpha/0.2 \\
\frac{D_{\text{striped skin}}}{D_{\text{water}}} = \beta/0.2
\]

If there are no non-diffusional resistances at the vehicle-skin and skin-blood interfaces, \( y \) and \( \delta \) can be calculated by

\[
\frac{1}{r} = \frac{1}{2\alpha(P_e/P_a)} + \frac{1}{2\beta} \\
\delta = 2\beta
\]
which are easily derived from Eqs. (19), (22), and (23) in Part II with paying attention to that \( P_s \) was defined in Part II as the partition coefficient between vehicle and skin (the latter being the reference phase), for which (partition coefficient between vehicle and water)/(that between stripped skin and water) = \( P_s/P_s \) (under the definitions in Part III) may be substituted. Calculations using Eqs. (4) and (5), however, did not show the agreement between \( Q(\text{calcld}) \) and \( Q(\text{exp}) \) for any vehicle applied on intact skin. The existence of non-diffusional resistance \( X \) or \( Y \) or both had to be assumed for the agreement.

In the presence of \( X \) and \( Y \), \( \gamma \) and \( \delta \) are given by

\[
\frac{1}{\gamma} = \frac{1}{2a(P_a/P_b)} + \frac{1}{2\beta} + \frac{D_o}{\beta} \frac{X}{dx}
\]

\[
\frac{1}{\delta} = \frac{1}{2\beta} + \frac{D_o}{\beta} \frac{Y}{dx}
\]

which are derived from Eqs. (19), (24), and (25) in Part II. Their numerical values must be determined empirically, because we have no \( a \) \emph{priori} knowledge about the nature of \( X \) and \( Y \) except that \( X \) changes from vehicle to vehicle whereas \( Y \) is independent of the kinds of vehicles unless a considerable amount of vehicle constituent penetrates to the skin-blood interface. The authors tried first to determine the \( \gamma \) value of water vehicle on assuming \( Y = 0 \) \( i.e. \), \( \delta = 2\beta \). By trial-and-error method, the \( \gamma \) value was repeatedly adjusted until \( Q(\text{calcld}) \) agreed well with \( Q(\text{exp}) \); \( cf. \) the bottom line of Table II. At the calculation of \( Q(\text{calcld}) \), the number of imaginary layers of water vehicle (division number) was taken as 60, and that of skin as 6. These numbers will be denoted hereafter with \( N_o \) and \( M_o \), respectively.

The effective thickness of the skin, \( b_o \), was taken as 0.2 mm in considering that the dermis contains the capillaries.

The \( \gamma \) value (120 \( \times 10^{-6} \)) finally attained was used to determine \( X_w \) by a modification of Eq. (6).

\[
\frac{1}{\gamma_w} = \frac{1}{2a_w(P_{a_w}/P_b)} + \frac{1}{2\beta} + \frac{D_o}{\beta} \frac{X_w}{(dx)_w}
\]

The subscripts \( w \) and \( N_o \) stand for water and the division number.

The \( X \) values for the other vehicles were estimated in the following way. The \( F \) value obtained by TEWL experiments is a measure of the easiness for the migration of water across the skin surface treated with a vehicle, and may serve also as a similar for the migration of SA. Thus, \( X \) was assumed to be inversely proportional to \( F \).

\[
X = \frac{F_w}{F} X_w
\]

If a division number \( N \) other than \( N_o \) is used,

\[
(dx)_w = (dx)_w \times \frac{N_o}{N}
\]

must be satisfied. Inserting (9) and (10) into (6), one gets

\[
\frac{1}{\gamma} = \frac{1}{2a(P_a/P_b)} + \frac{1}{2\beta} + \frac{D_o}{\beta} \frac{X_w}{(dx)_w} \frac{F_w}{F} \frac{N}{N_o}
\]

This equation is applicable to any vehicle with any division number, and has been used to calculate the \( \gamma \) values listed in Table II and III. Good agreements between \( Q(\text{calcld}) \) and \( Q(\text{exp}) \) shown in Table II and Fig. 3 suggest that the non-diffusional resistance at the skin-blood interface is not large if any.

Eq. (11) can be rewritten as follows,

\[
\frac{1}{\gamma} = \frac{1}{2a(P_a/P_b)} + \frac{1}{2\beta} + \frac{X}{(dx)_w} \frac{N}{FN_0}
\]

where
\[ X' = \frac{D_bF_wX_w}{\beta} \]  \hspace{1cm} (13)

By using \( \gamma_w = 126 \times 10^{-6} \), \( \alpha = 0.2 \), \( P_w = 1 \), \( P_b = 3.51 \), \( \beta = 0.0072 \), \( N_o = N = 60 \), \( F_w = F = 1.37 \), and \( D_b = 171.3 \times 10^{-5} \text{ cm}^2/\text{hr} \), \( X_w/(\Delta x)_{N_o} = 33145 \) and \( X'/(\Delta x)_{N_o} = 10808 \) (dimensionless) were obtained from Eqs. (11) and (12).

With respect to several vehicles for which pertinent data of \( Q(\text{exp.}) \) were available, \( Q(\text{calc.}) \) has been represented as a function of time measured from the drug administration. As seen in Fig. 3 of Part I, the agreement between both \( Q \)'s is satisfactory.

Some persons may want to know what happens if the calculation is made on assuming \( X = 0 \) and \( Y \neq 0 \). This question is answered by the following examination. For non-zero \( Y \), the equation

\[ \frac{1}{\delta} = \frac{1}{2\beta} + \frac{D_b}{\beta} \frac{Y}{(\Delta x)_{N_o}} \frac{N}{N_0} \]  \hspace{1cm} (14)

applies. A \( Y \)-value, with which good agreement was found between \( Q(\text{calc.}) \) and \( Q(\text{exp.}) \) for water vehicle at 4 hr after the administration, could be obtained by trial-and-error method. However, for other vehicles and even for water at other times, \( Q(\text{calc.}) \) obtained with this \( Y \) value did not agree with \( Q(\text{exp.}) \). [B]: Table III shows that the calculated \( Q \) values changed only little with an increased division number or decreased transport coefficients. This implies that the original division number \( (N_o) \) was sufficiently large and that the transport coefficients (given in Table II) were sufficiently small.