[Chem. Pharm. Bull. 29(3) 834—843 (1981)]

Studies on the Absorption of practically Water-insoluble Drugs following Injection. III.[1] Intramuscular Absorption from Aqueous Nonionic Surfactant Solutions in Rats

Koichiro Hirano,* Teruhisa Ichihashi, and Hideo Yamada

Shionogi Research Laboratories, Shionogi and Co., Ltd., Sagisu 5-12-4, Fukushima-ku, Osaka, 553, Japan

(Received September 5, 1980)

The intramuscular absorption characteristics and kinetics of practically water-insoluble drugs, which were solubilized in water with nonionic surfactants, were studied by the local clearance method in the *m. gastrocnemius* of the intact rat. The solubilized drugs were absorbed approximately according to 1st order kinetics. Their absorption rates were controlled by the distribution coefficient (K, micellar phase/water phase) as well as the injection volume (V_0) and the surfactant concentration (C_{s0}), but depended little on the vehicle viscosity under the present experimental conditions. A model, based on the assumptions that the drug is distributed instantaneously between the micellar and water phases in the depot and that the drug molecules in both phases are transported into the vascular systems by diffusion at different rates, was proposed to account for the kinetic features of the process. It predicted that the plot of the 1st order absorption rate constant (k) against $1/C_{so}$ or $1/K$ would be approximately linear when the injection volume was fixed, the surfactant absorption was very slow, and the contribution of the drug entrapped in micelles to the absorption was much smaller than that of the free drug. The experimental results agreed well with these predictions, except for the systems of very high surfactant concentration. Experimentally, k was inversely proportional to $V_0^{1/3}$ and this was explained reasonably by the model.

Keywords——drug absorption kinetics; intramuscular injection; practically water-insoluble drug; nonionic surfactant; micellar solution; local clearance method; injection volume; surfactant concentration; distribution coefficient; intact rat

We have discussed the intramuscular absorption characteristics and kinetics of practically water-insoluble drugs from water-immiscible oil solutions[2] and aqueous suspensions.[1] Besides these two dosage forms, aqueous solutions of such drugs, which are solubilized with some nonionic surfactants, are also available for administration in laboratory animal experiments. However, less is known about the effect of surfactants on intramuscular or subcutaneous absorption than about their role in absorption from the GI tract[3] or in percutaneous absorption.[4] With reference to the intramuscular absorption of water-soluble drugs, Matsuzawa *et al.*[5] noted the absorption-enhancing effect of nonionic surfactants for a drug with a molecular weight of 2500, while Kobayashi *et al.*[6] reported inhibitory effects on the absorption of drugs (molecular weight, 100—500) which were not distributed in the micellar phase. Except for these investigations, little work has been done on the intramuscular absorption mechanisms and kinetics for practically water-insoluble drugs from aqueous surfactant solutions. The present study was undertaken to clarify such problems.

In this study, the same drugs and method as reported in the previous paper[2] were employed, and nonionic surfactants such as polyoxyethylene hydrogenated castor oil derivatives were used as solubilizers. The effects of initial drug concentration, injection volume, surfactant type or concentration, vehicle viscosity and osmolarity on the drug absorption were examined in detail, in addition to the surfactant absorption. The drug absorption kinetics are discussed on the basis of a possible absorption model.

Experimental

Materials——Azo dyes [*p*-aminoazobenzene (PAAB), *p*-hydroxyazobenzene (PHAB), *o*-aminoazotoluene (OAAT), 1-phenylazo-2-naphthylamine (PANA) and tetrazobenzene-β-naphthol (Sudan III)] and a steroid [2α,3α-epithio-5α-androstan-17β-ol (epitiostanol, ES)] were used as model compounds for practically water-insoluble drugs. They were the same products as reported previously.[2] As nonionic surfactants (solubilizing agents), polyoxyethylene hydrogenated castor oil derivatives (NIKKOL HCO-30, 40, 100 and 160, Nikko Chemicals, Co., Ltd., Tokyo) were adopted for their good solubilizing power. These surfactants were used without further purification. Polyvinyl pyrrolidone (PVP K-90, Tokyo Kasei Kogyo, Co., Ltd., Tokyo) was also used to examine the effect of vehicle viscosity. All other chemicals were of analytical or reagent grade.

Preparation of Test Solutions——A given amount of a test drug was first dissolved in the desired amount of a surfactant under mild heating (below 50°), then this mixture was dissolved in distilled water. To each preparation, 0.9% (w/v) NaCl was added. For all the test solutions used here, neither change in visible absorption spectrum nor precipitation was observed during the experimental period. For the intramuscular absorption study of HCO-40, its solution containing no drug was used.

Procedure of Absorption Experiment——Male Wistar albino rats weighing 240—280 g were used in all absorption experiments. The local clearance method in the *m. gastrocnemius* of the intact rat described in our previous paper[2] was employed for the present absorption study. Unless otherwise mentioned, 50 μl of a test solution was injected. *In vitro* incubation of all the test drugs in the surfactant solution used here with freshly removed muscle tissues demonstrated that the metabolic changes at the injection site were negligible and hence the absorption experiment adopted here reflected the true absorption characteristics of the systems of interest.

Viscosity——The viscosity of a test solution was measured at 37° according to the method reported previously.[2]

Distribution Coefficient between Micellar and Water Phases——The distribution coefficient (K) of the drug between the micellar and the surrounding water phases is defined by[7]

$$K = \frac{D_m/C_{sm}}{D_f/f_w} \qquad \text{(Eq. 1)}$$

where D_m and D_f, C_{sm}, and f_w represent the amounts (mg) of the drug in the micellar and water phases, the concentration (mg/ml) of the surfactant forming the micelles, and the volume fraction of the water phase, respectively. When C_{sm} is approximated to the total surfactant concentration (C_s), Eq. 1 can be rearranged to

$$C_{DW} = C_D/(KC_s + f_w) \qquad \text{(Eq. 2)}$$

where C_{DW} and C_D are the drug concentrations in the water phase and in the whole system, respectively.[3b] C_{DW} was determined by equilibrium dialysis against variable C_D at fixed C_S. The distribution coefficient (K) was calculated from the slope of the C_{DW} *versus* C_D plot using the f_w value obtained below.

(i) Measurement of C_{DW}: Fifty milliliters of the drug-surfactant aqueous solution (containing 0.9% NaCl) was transferred into a cellophane bag 28.6 mm in diameter (membrane pore size, 28 Å) and dialyzed against 50 ml of 0.9% NaCl aqueous solution at 37° for 22—29 hr. The drug concentration in the outer solution was analyzed for the determination of C_{DW}.

(ii) Measurement of f_w: By using the equation $\eta_{rel} = 1 + 2.5\phi + 14.1\phi^2$, which gives the relationship between the relative viscosity (η_{rel}) and the volume fraction (ϕ) of colloidal particles,[8] ϕ was calculated first. Next, the value of f_w was calculated from $f_w = 1 - \phi$. The value of ϕ/C_s depended only a little upon C_s in the range of 2—20% (w/v) for the surfactants used here.

The value of K determined above was independent of C_D and was in good agreement with that estimated from the solubilization data.

Analytical Method——(i) Absorption Experiment: The remaining amounts of PAAB, PHAB, OAAT, PANA, Sudan III and ES in the injection site were determined as described previously.[2] The determination for HCO-40 was done by the method of Favretto and Tunis,[9] which was partly modified in the following manner. To the removed muscles 5 ml of EtOH was added, then the muscles were homogenized with a high speed blender (Ultra-turrax, Janke and Kunkel K.G., Ger.) under cooling in an ice-water bath. Five milliliters of water was used to wash the blender and added to the homogenate. Next, 10 ml of water, 6 g of NaCl and 20 ml of 1,2-dichloroethane (DCE) were added, then the mixture was mechanically shaken for 30 min. After centrifugation at 2500 rpm for 10 min, 3 ml of the DCE layer was withdrawn and the solvent was evaporated off. Next, 6 ml of water, 2.4 g of NaCl and 3 ml of DCE were added to the residue. The same extraction procedure was repeated, then 1 ml of the DCE layer was diluted adequately with DCE. Ten milliliters of this DCE solution was shaken well with 10 ml of water, 5 ml of 1.84% (w/v) sodium picrate in 0.1 N NaOH and 5 ml of 56.6% (w/v) $NaNO_3$ in 0.1 N NaOH and centrifuged at 2500 rpm for 10 min. The surfactant–sodium picrate complex, which was transferred into the DCE layer, was analyzed spectrophoto-

metrically. Optical density was read at 372 and 500 nm with a Hitachi EPS-3T recording spectrophotometer (Hitachi Co., Ltd., Tokyo) and the difference between them was adopted for this analysis.

(ii) Equilibrium Dialysis: For the determination of the distribution coefficient of the test drug, the concentration of the drug in the dialysate (outer solution) was analyzed according to the method reported previously.[2)]

Results

Absorption Time Course of a Solubilized Drug and the Effect of Initial Drug Concentration

Figure 1 shows an absorption time course of PHAB in 10% (w/v) HCO-40 from the *m. gastrocnemius* in intact rats. The percentage of the drug remaining in the injection site was plotted against time on a linear (A) or log (B) scale. The good linear relationship of the semilogarithmic plot (B) indicated that PHAB might be absorbed according to 1st order kinetics. To confirm this, the effect of initial PHAB concentration (C_0) on its absorption was examined at a fixed surfactant concentration (10% HCO-40). Figure 2 shows the results of this examination on a semilogarithmic scale. The good linear absorption time profiles with the same slope suggested that such a profile of PHAB depended little on its initial concentration.

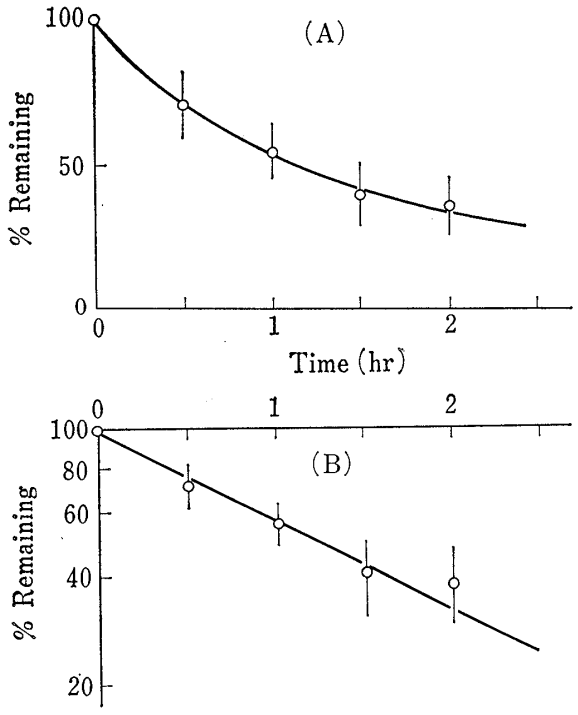

Fig. 1. Linear (A) and Semilogarithmic (B) Plots of the Time Course of PHAB Remaining in the Muscle

Each data point represents the mean of 4 or 5 experiments and the vertical bar shows the standard deviation. PHAB, 0.5 mg/ml; HCO-40, 10% (w/v); injection volume (V_0), 0.05 ml.

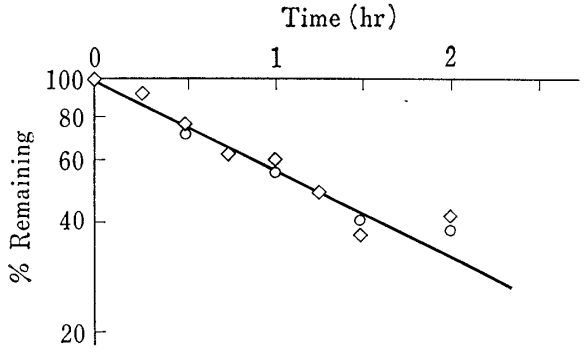

Fig. 2. Effect of Initial PHAB Concentration (C_0) on Its Intramuscular Absorption from 10% HCO-40

Key (C_0): -◇-, 5 mg/ml; -○-, 0.5 mg/ml. Injection volume (V_0): 0.05 ml. Each data point represents the mean of 4 or 5 experiments.

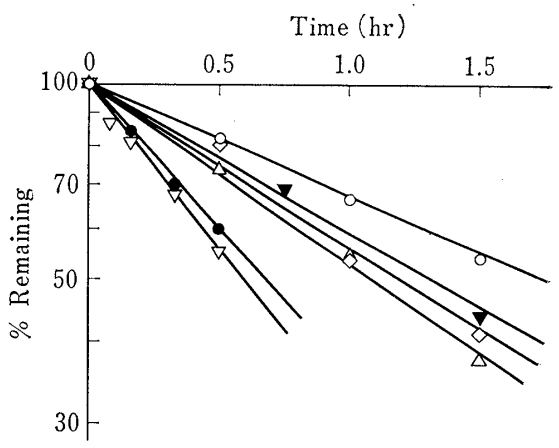

Fig. 3. Effect of Injection Volume (V_0) on the Intramuscular Absorption of PHAB from 10% HCO-40

Key (V_0): -○-, 100 μl; -▼-, 75 μl; -◇-, 50 μl; -△-, 25 μl; -●-, 10 μl; -▽-, 5 μl. C_0: 1 mg/ml (25—100 μl) and 5 mg/ml (5—10 μl). Each data point represents the mean of 4 or 5 experiments.

Since this was also true for other model compounds tested, it seemed reasonable to conclude that the intramuscular absorption of practically water-insoluble drugs from micellar solutions proceeds approximately according to a 1st order rate process.

Effect of Injection Volume

In the intramuscular absorption from water-immiscible oil solutions[2] and aqueous suspensions,[1] the effect of injection volume was not negligible. Figure 3 shows this effect on the absorption of PHAB in 10% HCO-40. The semilogarithmic plot for each injection volume (V_0) was nearly linear but its slope increased with a decrease in V_0. Whether this phenomenon was caused by the variation in the total amount of the surfactant injected or in the ratio of the surface area of the depot to its volume is discussed later.

Effect of Surfactant Concentration

The concentration of HCO-40 greatly affected the absorption rate of the model compounds tested here. As can be seen from Table I, the 1st order absorption rate constant decreased with increasing surfactant concentration. An increase in the surfactant concentration results in an increase in vehicle viscosity and a decrease in the drug concentration in the non-micellar phase of the depot. Which of the two has the greater effect on the decrease in the absorption rate is discussed later.

Table I. List of the First Order Absorption Rate Constants (k) and Distribution Coefficients (K) between Micellar and Water Phases for Six Test Compounds

Compound	k (hr^{-1})[a] Concentration of HCO-40, % (w/v)			K (ml/mg)[b]
	5	10	20	
PAAB	1.397(0.197)	0.695 (0.033)	0.614 (0.066)	2.7
PHAB	1.183(0.093)	0.512 (0.051)	0.351 (0.050)	5.3
ES		0.392 (0.099)	0.277 (0.040)	10.4[c]
OAAT	0.819(0.041)	0.456 (0.029)	0.341 (0.020)	15.7
PANA	0.402(0.044)	0.231 (0.013)	0.196 (0.023)	257.0
Sudan III	0.112(0.004)	0.0526(0.0082)	0.0514(0.0023)	—[d]

a) First order absorption rate constant at $C_0=0.5$ or 5 mg/ml and $V_0=0.05$ ml: the rate constant was estimated by the least-squares method and is given together with the standard error in parentheses.
b) Distribution coefficient (micellar phase/water phase) at 37°.
c) Calculated from solubility data in 20% (w/v) HCO-40 and saline.
d) Not determined but estimated to be exceedingly large.

Comparison of Absorption Rate among Different Solubilized Compounds

Table I compares the absorption rates of different model compounds solubilized in HCO-40 aqueous solution. At a fixed surfactant concentration, the compounds having smaller distribution coefficients (K, micellar phase/water phase) appeared to be absorbed more quickly. Accordingly, the distribution coefficient was expected to be a very important factor controlling the drug absorption rate from the systems in question.

Effect of Vehicle Viscosity and Osmolarity

First, the effect of the vehicle viscosity on the absorption of PAAB solubilized in HCO-40 aqueous solution was investigated, by using two vehicles of 5% (w/v) HCO-40 with and without 2.6% (w/v) PVP K-90 (with relative viscosities of 9.7 and 1.4, respectively). Figure 4 shows that there was no significant difference between the absorption time profiles from these two vehicles. Since the distribution coefficients (K) of the systems were approximately equal to each other (2.7—2.9), we concluded that the effect of the vehicle viscosity was not significant under the present experimental conditions (η_{rel} below at least 9.7).

Second, the effect of the vehicle osmotic pressure on the drug absorption was studied. Kakemi *et al.*[10] noted a more delayed absorption from more hypotonic solutions for the in-

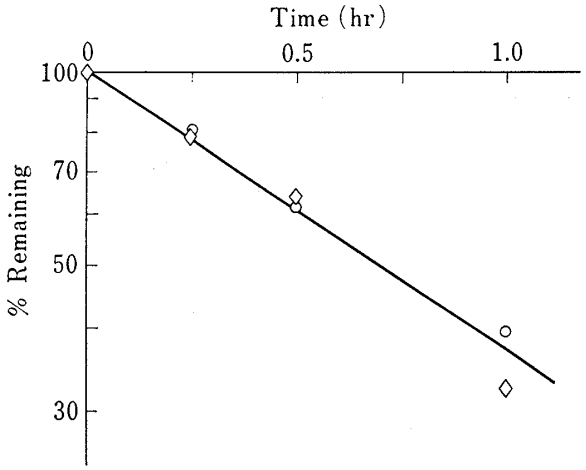

Fig. 4. Effect of Viscosity of the Vehicle on PAAB Intramuscular Absorption from 5% HCO-40

Key (η_{rel}): -○-, 9.7; -◇-, 1.4. C_0, 0.5 mg/ml; V_0, 0.05 ml. Each data point shows the mean of 4 or 5 experiments.

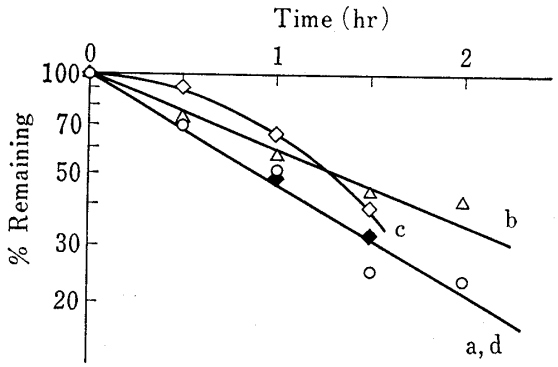

Fig. 5. Effect of Osmotic Pressure on the Intramuscular Absorption of PHAB from 10% HCO-40

Key: -○- (a), 0% NaCl (hypotonic); -△- (b), 0.9% NaCl; -◇- (c), 1.8% NaCl (hypertonic); -◆- (d), 4.5% NaCl (hypertonic). C_0, 0.5 mg/ml; V_0, 0.05 ml. Each data point shows the mean of 4 experiments.

tramuscular absorption of some water-soluble drugs, while Sidell[11] reported opposite results for that of atropine. The contribution of this factor to the absorption thus appears to be very complicated. Figure 5 compares the absorption time courses of PHAB from four vehicles having different osmolarities. However, this effect was not marked, and no clear relationship between the vehicle osmolarity and the drug absorption rate could be found in the present study. Possibly, this may be attributed to the faster exchange of electrolytes between the injected solution and the body fluid, compared with the absorption of the drug component.

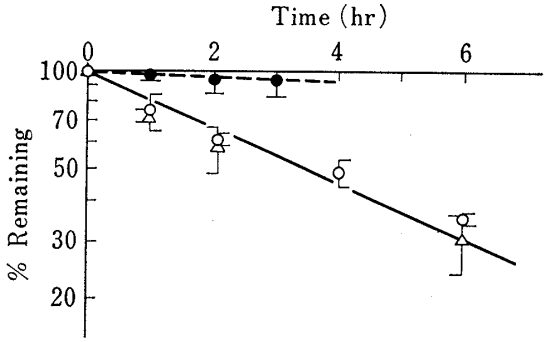

Fig. 6. Disappearance Curves of HCO-40 from the Injection Site in Intact and Postmortem Rats

Key: -○-, HCO-40, 20% (intact); -△-, HCO-40, 10% (intact); ---●---, HCO-40, 20% (postmortem). V_0: 0.05 ml. Each data point represents the mean of 4—6 experiments.

Absorption of Surfactant

Kobayashi *et al.*[6c] reported that polysorbate 80, a typical nonionic surfactant, slowly disappeared from the intramuscular region in anesthetized rats. In our present study, HCO-40 was mainly used as a model surfactant; its absorption time profiles are given in Fig. 6. The absorption experiments in intact rats showed nearly monoexponential disappearance curves (solid line) which depended little upon the surfactant concentration under the conditions tested.

For comparison, the time course of percent recovery of the same surfactant from the injection site in postmortem rats at 37° was followed and is shown in this figure by closed circles and a dotted line. This demonstrated recovery of nearly 100% of the dose even 3 hr after the injection. Accordingly, we concluded that the disappearance observed in the absorption experiments in intact rats was probably not caused by metabolic changes in the muscle but mainly by transport into the vascular systems.

Comparison of Absorption Rates from Various Surfactant Solutions

To gain more detailed information on the drug absorption from micellar systems, the intramuscular absorption of PAAB, PHAB and OAAT from different surfactant solutions

Table II. Comparison of Absorption Rate Constants (k) with Distribution Coefficients (K) and Viscosities (η_{rel})

Compound[a]	SAA[b]	k (hr^{-1})[c]	K (ml/mg)[d]	η_{rel}[e]
PAAB	HCO-30	0.523(0.024)	3.5	1.90
	HCO-40	0.695(0.033)	2.7	2.29
	HCO-100	1.497(0.178)	1.8	4.39
	HCO-160	1.611(0.167)	1.4	9.56
PHAB	HCO-30	0.482(0.049)	7.5	1.90
	HCO-40	0.512(0.051)	5.3	2.29
	HCO-100	1.242(0.084)	4.2	4.39
	HCO-160	1.083(0.132)	3.2	9.56
OAAT	HCO-30	0.439(0.027)	20.7	1.90
	HCO-40	0.456(0.029)	15.7	2.29
	HCO-100	0.751(0.079)	9.2	4.39
	HCO-160	0.879(0.069)	8.6	9.56

a) Concentration (C_0), 0.5 mg/ml.
b) Concentration (C_{s0}) of surfactant (SAA), 10% (w/v).
c) First order absorption rate constant: this was estimated by the least-squares method and is given together with the standard error in parentheses.
d) Distribution coefficient (micellar phase/water phase) determined by equilibrium dialysis at 37°.
e) Relative viscosity of 10% SAA solution at 37°.

(HCO-30, 40, 100 and 160) was examined. The semilogarithmic plot of the percent of the drug unabsorbed *versus* time for these solutions gave good straight lines with different slopes. The 1st order absorption rate constants (k) obtained from this plot are summarized in Table II with the distribution coefficients (K) and the relative viscosities (η) of the vehicles. This table shows that the k value of each test drug increased with decrease in the K value. An increase in η_{rel} lowers the diffusibility of the drug component and commonly results in a decrease in the rate of absorption, but the present results showed the opposite tendency. This finding also indicated that drug absorption from these systems was affected little by the vehicle viscosity.

Discussion

Absorption Kinetics of Solubilized Drugs

The experimental results suggested that the intramuscular absorption of practically water-insoluble drugs solubilized in water with some nonionic surfactants depended mainly on the distribution coefficient (K) between the micellar and the surrounding water phases, which determined the concentration of the free drug in the depot, and little on the vehicle viscosity. A system with a smaller K value gave a faster drug absorption rate. These findings lead to the absorption model illustrated in Fig. 7. In this figure, D_f and D_m represent the amount of the drug in the water phase and that in the micellar phase of the depot, respectively. The parameters k_f and k_m are related to the diffusibility of the free and micelle-entrapped drug, respectively. The assumption that k_m is considerably smaller than k_f can explain qualitatively the experimental results mentioned above.

Assuming that the diffusion of the drug, free and micelle-entrapped, in phase II is rate-limiting in the drug absorption process, we can express the change in the remaining amount (D) of the drug in the injection site with time as follows:

$$-dD/dt = -(dD_f/dt) - (dD_m/dt) \quad \text{(Eq. 3)}$$

The first term in the right-hand side of Eq. 3 can be represented as:

$$-dD_f/dt = k_f A D_f / V_w \quad \text{(Eq. 4)}$$

where A and V_w are the surface area (=effective diffusion area) of the depot and the volume

of the water phase (non-micellar phase) in it, respectively. The second term, which is the change in the amount of the drug in the micellar phase of the depot with time, can be written as follows:

$$-\mathrm{d}D_\mathrm{m}/\mathrm{d}t = -B(D_\mathrm{m}/S_\mathrm{m})(\mathrm{d}S_\mathrm{m}/\mathrm{d}t) \qquad \text{(Eq. 5)}$$

where B is defined as a parameter which corrects for the difficulty of the collapse of the micelles solubilizing the drug during their diffusion in phase II, and ranges from 0 to 1. The case of $B=1$ means that no collapse of such micelles occurs before they reach the blood or lymph stream. S_m represents the amount of the surfactant which forms micelles in the depot and is approximately equal to its total amount (S) for surfactant concentrations much higher than the critical micelle concentration. Figure 6 indicates that the kinetics for the absorption of the surfactant (HCO-40) approximate to those of a 1st order rate process under the present conditions. Thus, we can introduce a rate constant $k_\mathrm{s}A/V$,

$$-\mathrm{d}S_\mathrm{m}/\mathrm{d}t = -\mathrm{d}S/\mathrm{d}t = (k_\mathrm{s}A/V)S \qquad \text{(Eq, 6)}$$

where V is the volume of the depot. Substitution of Eq. 6 for $\mathrm{d}S_\mathrm{m}/\mathrm{d}t$ in Eq. 5 yields

$$-\mathrm{d}D_\mathrm{m}/\mathrm{d}t = (k_\mathrm{s}AB/V)D_\mathrm{m} \qquad \text{(Eq. 7)}$$

By using Eqs. 4 and 7, Eq. 3 can be rewritten as follows:

$$-\mathrm{d}D/\mathrm{d}t = (k_\mathrm{f}AD_\mathrm{f}/V_\mathrm{w}) + (k_\mathrm{m}AD_\mathrm{m}/V) \qquad \text{(Eq. 8)}$$

where $k_\mathrm{m}=Bk_\mathrm{s}$.

Assuming that the distribution equilibrium defined by Eq. 1 may be established at any time in the depot,

$$D_\mathrm{f} = V_\mathrm{w}D_\mathrm{m}/KS_\mathrm{m} \qquad \text{(Eq. 9)}$$

When $D_\mathrm{m} \gg D_\mathrm{f}$ (this may be true for practically water-insoluble but oil-soluble drugs), D_m can be approximated to D. Further, S_m can be approximated to S for high surfactant concentration, as explained above. Substitution of Eq. 9 for D_f in Eq. 8 and employment of the above two approximations yield the following equation:

$$-\frac{\mathrm{d}D}{\mathrm{d}t} = A\left(\frac{k_\mathrm{f}}{KS}+\frac{k_\mathrm{m}}{V}\right)D \qquad \text{(Eq. 10)}$$

From Eq. 6

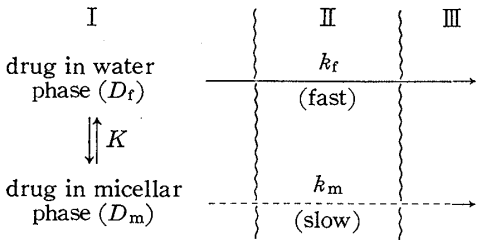

Fig. 7. Model for the Intramuscular Absorption of Drugs Solubilized in Micellar Solution

I : depot formed after injection of micellar solution.
II : intercellular space of muscle fiber or connective tissue, vascular membrane, *etc.*
III : blood or lymph.

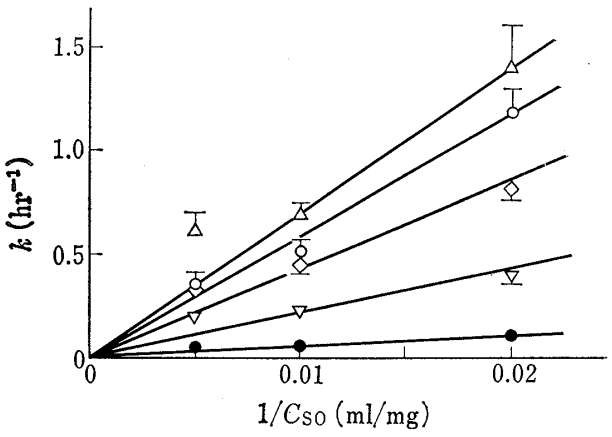

Fig. 8. Relation between Absorption Rate Constant (k) and HCO-40 Concentration (C_{s_0})

Key: -△-, PAAB; -○-, PHAB; -◇-, OAAT; -▽-, PANA; -●-, Sudan III. C_0, 0.5 mg/ml; V_0, 0.05 ml. This figure was constructed by using the data shown in Table I. The vertical bar shows the standard error.

$$S = S_0 e^{-k_s' t} \qquad \text{(Eq. 11)}$$

were S_0 represents S at $t=0$ and $k_s' = k_s A/V$. Substitution of Eq. 11 for S in Eq. 10 and subsequent rearrangement yield the following equation:

$$-\frac{dD}{D} = \frac{Ak_f}{KS_0} e^{k_s' t} dt + \frac{Ak_m}{V} dt \qquad \text{(Eq. 12)}$$

When the terms Ak_f and Ak_m/V are regarded as constant, Eq. 12 can be integrated as follows:

$$-\ln \frac{D}{D_0} = \frac{Ak_f}{KS_0 k_s'} (e^{k_s' t} - 1) + \frac{Ak_m}{V} t \qquad \text{(Eq. 13)}$$

where D_0 represents D at $t=0$, that is, the dose.

By using a three-term Maclaurin expansion for $e^{k_s' t}$, the term $e^{k_s' t} - 1$ in Eq. 13 can be written as follows:

$$e^{k_s' t} - 1 = k_s' t + \frac{(k_s' t)^2}{2} + \frac{(k_s' t)^3}{6} \qquad \text{(Eq. 14)}$$

It should be noted that the relative error introduced by neglecting the second and third terms in the right-hand side of Eq. 14, estimated from the experimental value of 0.175 hr^{-1} for k_s' (obtained from Fig. 6), does not exceed 20% during the first 2 hr. Therefore, the approximation $e^{k_s' t} - 1 \fallingdotseq k_s' t$ is considered reasonable when the absorption period is not too long. Thus, the following approximate equations for describing the drug absorption rate process from micellar solutions can be finally derived:

$$\ln (D/D_0) = -kt \qquad \text{(Eq. 15)}$$

$$k = \frac{Ak_f}{KS_0} + \frac{Ak_m}{V} \qquad \text{(Eq. 16)}$$

These equations correspond to 1st order kinetics and are consistent with the experimental results mentioned above. Introduction of the initial surfactant concentration (C_{s0}) and the injection volume (V_0) instead of S_0 in Eq. 16 yields

$$k = \frac{Ak_f}{V_0 K C_{s0}} + \frac{Ak_m}{V} \qquad \text{(Eq. 17)}$$

This equation shows the relationship between the absorption rate constant (k) and C_{s0}, K or V_0. Accordingly, if the validity for each relationship shown by this equation is confirmed experimentally, Eq. 17 may be generally applicable for many systems other than the model systems presented here. The experimental validity is discussed below.

Relation between Absorption Rate Constant (k) and Surfactant Concentration (C_{s0})

Equation 17 means that a plot of k against $1/C_{s0}$ should give a straight line for a given drug-surfactant system at a constant injection volume if k_m is independent of C_{s0} or exceedingly small. To confirm this, the data shown in Table I were plotted in Fig. 8. For each test compound, linear extrapolation of the data points at C_{s0} less than 100 mg/ml gives an intercept on the k-axis at a point near zero. This suggests that k_m ($=Bk_s$) in Eq. 17 is close to zero under such C_{s0}. However, with a higher C_{s0} than this, k_m seems to be more significant, and its contribution to k may no longer be negligible. In this case, the drug molecule may be partly transported into the vascular systems by surfactant aggregates such as micelles. The upward deviation for each test compound near $C_{s0}=200$ mg/ml from the straight line with the zero intercept seems to support this speculation. Therefore, we can conclude that Eq. 17 is consistent with the experimental results on the relation between k and C_{s0}, and that k_m is sufficiently small to neglect, except for systems of very high surfactant concentration.

Relation between Absorption Rate Constant (k) and Distribution Coefficient (K)

The distribution coefficient (K) of the drug between the micellar and water phases varies

considerably depending upon the surfactant type used in the preparation. Equation 17 means that k is inversely proportional to K when the drug, surfactant concentration (C_{s0}) and injection volume (V_0) are fixed, and if the value of k_m is small enough to neglect and k_f depends little on the surfactant type. Figure 9 shows plots of k *versus* $1/K$ using the data for the three test compounds in Table II. Although the experimental values are slightly scattered (the slight modification of k_f by the surfactant may be one of the causes for this scattering), it appears that these plots tend to be linear with a near-zero intercept. Thus we can conclude that Eq. 17 is also consistent with the experimental results on the relation between k and K. The slope of the linear relationship in Fig. 9 decreases in the order of OAAT, PHAB and PAAB. This difference in the slope is expected to be caused by the difference in k_f in Eq. 17.

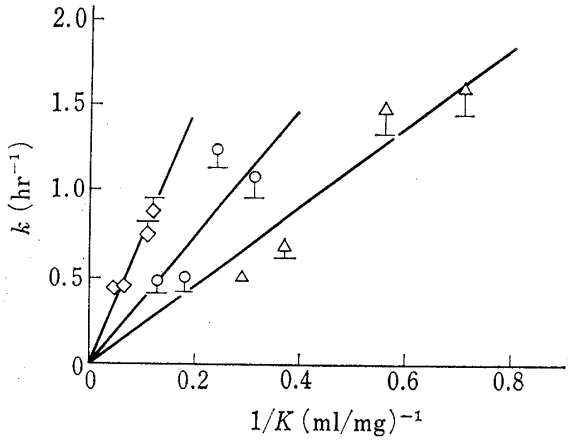

Fig. 9. Relation between Absorption Rate Constant (k) and Distribution Coefficient (K)

Key: -△-, PAAB; -○-, PHAB; -◇-, OAAT. C_0, 0.5 mg/ml; V_0, 0.05 ml; C_{s0}, 10%. This figure was constructed by using the data shown in Table II. The vertical bar shows the standard error.

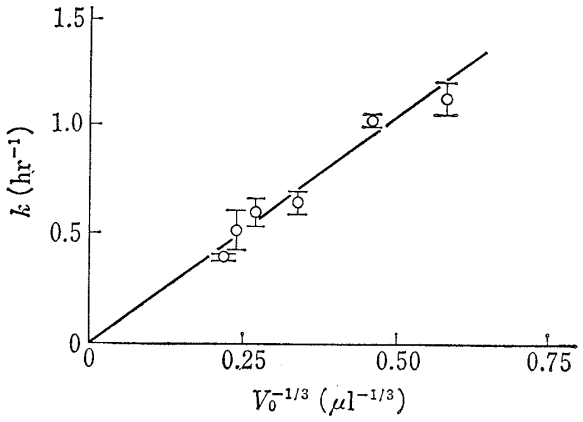

Fig. 10. Relation between Absorption Rate Constant (k) and Injection Volume (V_0)

PHAB; C_0, 1 or 5 mg/ml; C_{s0}, 10%. The k value was estimated by the least-squares method from the data in Fig. 3 and is plotted togenther with the standard error (vertical bar).

Relation between Absorption Rate Constant (k) and Injection Volume (V_0)

For systems in which the surfactant concentration (C_{s0}) is not too high, Eq. 17 can be approximated to

$$k = \left(\frac{A}{V_0}\right)\frac{k_f}{KC_{s0}} \qquad \text{(Eq. 18)}$$

When only the injection volume is changed, Eq. 18 can be rearranged to the following form:

$$k = k'(A/V_0) \qquad \text{(Eq. 19)}$$

where k' is a constant. It can be shown mathematically that A/V_0 is inversely proportional to the cube root of V_0 when the depot retains the same dimensions despite alteration in V_0. For this case,

$$k = k'' V_0^{-1/3} \qquad \text{(Eq. 20)}$$

where k'' is a constant. Figure 10 shows a plot of k'' against $V_0^{-1/3}$ using the data obtained from Fig. 3. The good linear relationship of this plot suggests that the relationship described by Eq. 20 is almost applicable to the systems of interest. Accordingly, the effect of the injection volume (V_0) on the absorption rate constant (k) can be explained reasonably by the term A/V_0 in Eq. 18, like that for the intramuscular drug absorption from water-immiscible oil solutions.[2]

The above discussions lead to the final conclusion that Eqs. 15 and 17 are broadly consistent with the experimental results. These equations should be generally applicable for drug-surfactant systems other than those presented here. Previous investigators have ob-

served that the presence of a low concentration of nonionic surfactants caused a pronounced decrease in the intramuscular absorption rates of water-soluble, micelle-free drugs, and concluded that it was mainly due to the effect of the surfactant on the extracellular space and the connective tissue permeability.[6] Our present results could be reasonably explained in physicochemical terms. This, however, does not imply that such a surfactant effect is not involved. It was probably not detected because it may have been similar in extent in all the systems tested in view of the high surfactant concentrations (5—20%). This effect should also be considered in addition to physicochemical factors when applying the present results to other systems.

Acknowledgement The authors are indebted to Mrs. A. Yumoto for her skillful technical assistance and also to Prof. J. Watanabe, Nagoya City University, for helpful discussions. The authors also wish to thank Prof. M. Nakagaki, Kyoto University, for his valuable suggestions on the manuscript.

References and Notes

1) Part II: K. Hirano, T. Ichihashi, and H. Yamada, *Chem. Pharm. Bull.*, **29**, 817 (1981).
2) K. Hirano, T. Ichihashi, and H. Yamada, *Chem. Pharm. Bull.*, **29**, 519 (1981).
3) *a*) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.*, **13**, 976 (1965); *b*) H. Yamada and R. Yamamoto, *ibid.*, **13**, 1279 (1965); *c*) M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **59**, 579 (1970); *d*) C.J. Kreutler and W. Davis, *ibid.*, **59**, 1835 (1970); *e*) J.H. Collett, R. Withington, and B. Cox, *J. Pharm. Pharmacol.*, **26**, 34 (1974).
4) *a*) C.W. Whitworth and E.R. Carter, *J. Pharm. Sci.*, **58**, 1285 (1969); *b*) M. Mezei and K.J. Ryan, *ibid.*, **61**, 1329 (1972).
5) T. Matsuzawa, H. Fujisawa, K. Aoki, and H. Mima, *Chem. Pharm. Bull.*, **17**, 999 (1969).
6) *a*) H. Kobayashi, T. Nishimura, K. Okumura, S. Muranishi, and H. Sezaki, *J. Pharm. Sci.*, **63**, 580 (1974); *b*) H. Kobayashi, Tso-chin Peng, A. Kagayama, K. Okumura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.*, **23**, 42 (1975); *c*) H. Kobayashi, Tso-chin Peng, M. Fujikawa, S. Muranishi, and H. Sezaki, *ibid.*, **24**, 2383 (1976); *d*) H. Kobayashi, Tso-chin Peng, R. Kawamura, S. Muranishi, and H. Sezaki, *ibid.*, **25**, 569 (1977); *e*) H. Kobayashi, Tso-chin Peng, R. Kawamura, S. Muranishi, and H. Sezaki, *ibid.*, **25**, 1547 (1977).
7) T. Nakagawa, *Ann. Repts. Shionogi Research Lab.*, **8**, 31 (1958).
8) E. Guth and R. Simha, Kolloid-Z., **74**, 147 (1936). Quoted by A.E. Alexander and P. Johnson, "Colloid Science," Vol. I, Oxford Univ. Press, London and New York, 1949, p. 360.
9) L. Favretto and F. Tunis, *Analyst*, **101**, 198 (1976).
10) K. Kakemi, H. Sezaki, K. Okumura, C. Takada, and S. Furusawa, *Chem. Pharm. Bull.*, **19**, 2058 (1971).
11) F.R. Sidell, *Clin, Pharmacol. Ther.*, **16**, 711 (1975).