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Intramuscular Absorption of Drugs from Oily Solutions in the Rat[1,2]

Taeko Tanaka, Hiroshi Kobayashi, Katsuhiko Okumura, Shozo Muranishi, and Hitoshi Sezaki

Faculty of Pharmaceutical Sciences, Kyoto University[3]

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Oily solutions of various kind of drugs were injected into the hind leg of rats and the intramuscular absorption was investigated by the local clearance method.

The intramuscular absorption of drugs having moderate lipid solubility was more rapid than that of the oily solvent itself and proceeded by the apparent first-order process. Apparent absorption rate constants were affected mainly by injection volume and by the physicochemical properties of drugs and oily solvents. The kinetic results are also consistent with a postulate that the drug was mainly absorbed after being transferred from the oily phase to the aqueous phase, and a fairly good correlationship between partition coefficient and the apparent absorption rate constant was obtained.

In the case of drugs having extremely high partition coefficient, the absorption rates were very slow, for which the solubility of the drugs in the tissue fluid appeared to be a critical factor.

In the previous papers from this laboratory, the intramuscular absorption from aqueous drug solution was investigated from various viewpoints such as the factors governing the absorption of drugs from aqueous injection solutions,[4–6] the effect of water miscible vehicles,[7] and the absorption modifying effect of surfactants.[8]

Drugs, having high lipid solubility and poor water solubility, are commonly used as parenteral preparations in the form of oily solutions, suspensions, and emulsions. Since the absorption characteristics of drugs from these preparations are immediately reflected on their pharmacological effects, it was of interest to study the mechanism of drug absorption from such preparations.

The present study was undertaken to investigate the mechanism of drug absorption from oily parenteral preparations and to contribute toward their formulations.

While previous investigators focused largely on the absorption,[9] the systemic toxicity,[10] local irritation[11] of oily solvents, and their effect on the pharmacological responses and blood levels of drugs,[12,13] the mechanism of absorption from such preparations has not been explored formerly.

1) *a*) This paper constitutes the 7th report in a series of "Biopharmaceutical Studies on the Parenteral Preparations"; *b*) Preceding paper, Part VI: H. Kobayashi, T. Nishimura, K. Okumura, S. Muranishi, and H. Sezaki, *J. Pharm. Sci.*, **63**, 580 (1974).
2) Part of this work was presented at 93th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.
3) Location: *Yoshidashimoadachi-cho, Sakyo-ku, Kyoto.*
4) K. Kakemi, H. Sezaki, K. Okumura, and A. Ashida, *Chem. Pharm. Bull.* (Tokyo), **17**, 1332 (1969).
5) K. Kakemi, H. Sezaki, K. Okumura, C. Takada, and S. Furusawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2058 (1971).
6) K. Kakemi, H. Sezaki, K. Okumura, H. Kobayashi, and S. Furusawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 443 (1972).
7) K. Okumura, H. Sezaki, and K. Kakemi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1607 (1972).
8) H. Kobayashi, T. Nishimura, K. Okumura, S. Muranishi, and H. Sezaki, *J. Pharm. Sci.*, **63**, 580 (1974).
9) R. Deanesly and A.S. Parkes, *J. Physiol.*, **78**, 155 (1933).
10) A.J. Spiegel and M.M. Noseworthy, *J. Pharm. Sci.*, **52**, 917 (1963).
11) W.E. Brown, V.M. Wilder, and P. Schwartz, *J. Lab. Clin. Med.*, **29**, 259 (1944).
12) J. Dekanski and R.N. Chapman, *Brit. J. Pharmacol.*, **8**, 271 (1953).
13) B.H. Tusa and K.E. Avis, *Bull. Parenteral Drug Assoc.*, **26**, 1 (1972).

For this reason, the intramuscular absorption of drugs from various oily solutions, the absorption of oily solvent itself, and relative contribution of the physicochemical properties of drugs and oily solvents were investigated in the rat.

Experimental

Materials——All drugs, isonicotinamide, sulfanilamide, and methyl isonicotinate, were of analytical grade and were obtained commercially. ^{14}C-Testosterone was purchased from Japan Radio Isotope Association (Tokyo, Japan).

Oily Solvents and Surfactant——Diethyl phthalate and tributyrin were obtained commercially and purified by distillation under reduced pressure, 4 mmHg. Methyl oleate, castor oil, mineral oil (*n*-hexadecane), propylene glycol, and Span 80 were obtained commercially and used without further purification. ^{14}C-Methyl oleate was purchased from Japan Radio Isotope Association (Tokyo, Japan).

Animals——Male Wistar albino rats weighing 150—180 g were used in most absorption experiments; rats weighing 180—200 g were used in the study of high injection volume of 25 μl.

Procedure of Absorption Experiments——The absorption experiments were almost identical with those described in the previous paper from this laboratory.[4]

In contrast with the case of aqueous injection solutions, the leak of oily solutions from the site of injection was not negligible. This was minimized by applying the quick adhesive ("Aron Alpha-A" Sankyo Co., Ltd.) to the injection site at the very instant that a needle was drawn out.

Preparation of Injection Solutions——Isonicotinamide (10 mM), sulfanilamide (10 mM), methyl isonicotinate (30 mM, 100 mM), ^{14}C-testosterone (0.01 mM), Oil Red-XO (9 mM, 30 mM), and Sudan Black-B (9 mM, 30 mM) were dissolved in oily solvents.

Oil Red-XO (2.0 mM) and Sudan Black-B (3.3 mM) dissolved in propylene glycol were used.

Determination of Apparent Partition Coefficient——An oily solvent and isotonic NaH_2PO_4–Na_2HPO_4 buffer of pH 7.0 were saturated each other.

Two ml of buffer with 100 μg/ml of drug was added to 2 ml of each oily solvent, maintained at 37°, and shaken well. After equilibration, 0.5 ml of aqueous layer was withdrawn for analysis. Apparent partition coefficient was calculated by the concentrations of a drug in aqueous phase before and after shaking.

In the case of ^{14}C-testosterone, similar method with oily solvents with 0.5 μg/ml of ^{14}C-testosterone was used, and both 0.5 ml of aqueous layer and oily layer were withdrawn for analysis.

Determination of Viscosity——Viscosities were determined at 37° with B-type viscometer (Tokyo Keiki Seisakusho).

Determination of Transfer Rate Constants——The method described previously by Ogata, *et al.*[14] was modified and used.

Thirty ml of oil containing the same concentration of a drug as used in absorption experiment and equal volume of pH 7.0 phosphate buffer were added in a jacketed glass beaker maintained at 37° by circulating water through the jacket. Stirring two layers at 130±5 rpm, samples of 0.5 ml were withdrawn from aqueous layer at fixed time intervals for analysis. From the change of drug concentration, transfer rate constant was calculated.

Determination of Solubility in Muscle Homogenate——The muscle of hind legs of a rat were homogenized with phosphate buffer of pH 7.0. Azo dyes were added to each 10 ml of this homogenate, maintained at 37° for three days with intermittent shaking, and screened through a glass filter (G-2). Seven ml of the filtrate was extracted with 4 ml of chloroform and the organic phase was subjected for spectrophotometric analysis.

Analytical Methods

1) **Isonicotinamide, Sulfanilamide, Methyl Isonicotinate**——a) Absorption Experiments: The removed muscle was homogenized with 30% acetone solution and centrifuged at 3000 rpm for 30 min. The supernatant was determined spectrophotometrically by the same methods as described in the previous papers.[4,7]

b) *In Vitro* Experiments: Sample solutions were diluted with adequate distilled water and determined by the spectrophotometric methods described in the previous papers.[4,7]

2) **^{14}C-Testosterone**——a) Absorption Experiments: The muscle, swollen overnight in 3 ml of 0.5 N NaOH, was dissolved by heating to 90° with vigorous shaking in a glass-stoppered tube for 15 min. After cooling, the sample solutions were diluted to 4.0 ml with distilled water. One ml of 1.5 N HCl was added for neutralization, and extracted with 2 ml of benzene. After centrifugation, 0.5 ml of the organic layer was taken up in 10 ml of scintillation medium,[15] and counted in a Beckman liquid scintillation system LS-232.

14) K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata, and S. Isemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 715 (1972).

15) This scintillation medium was the mixture of toluene (1000 ml), PPO (4 g), and POPOP (0.1 g).

b) *In Vitro* Experiments: In determining the radioactivity of the aqueous solution, 0.5 ml of sample solutions were mixed well with 15 ml of NT-scintillation medium[16] and 1.0 ml of N HCl.

In the case of oily solution, 0.5 ml oily layer was mixed with 10 ml of scintillation medium used in the absorption experiments mentioned elsewhere.

3) **^{14}C-Methyl Oleate**——The radioactivity was determined by the same methods as with ^{14}C-testosterone.

4) **Oil Red-XO**——a) Absorption Experiments: The removed muscle was homogenized and diluted to 15 ml with distilled water. The homogenate was extracted with 8 ml of chloroform and the optical density was determined at 484 mμ.

b) Determination of Solubility: Two ml of chloroform layer was mixed with 4 ml of ethyl alcohol and its optical density was measured at 484 mμ.

5) **Sudan Black-B**——a) Absorption Experiments: The muscle was homogenized and diluted to 10 ml with ethyl alcohol. After centrifugation at 3000 rpm for 30 min, the optical density of the supernatant was determined at 600 mμ.

b) Determination of Solubility: Two ml of chloroform layer was mixed with 4 ml of ethyl alcohol and its optical density was measured at 600 mμ.

Result and Discussion

(1) Time Course of Drug Absorption from Oily Solution

In order to clarify the mechanism of intramuscular absorption of a drug from oily solution, first, the time course of drug clearance from the muscle was studied. Prior to this, it was confirmed by our examination using a dye that the drug solution was injected at the center of the *m. rectus femoris* and that its leak from the site of injection was negligible.

Fig. 1 shows the intramuscular absorption of methylisonicotinate, having relatively high lipid solubility, from diethyl phthalate, tributyrin, and methyl oleate. As is evident from Fig. 1, the absorption rates of methylisonicotinate from oily solutions were slower than

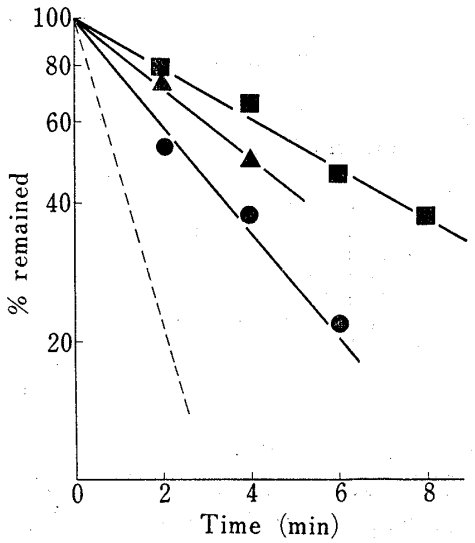

Fig. 1. Absorption Curves of Methylisonicotinate from Oily Solutions

drug concentration: 30 mM
injection volume: 10 μl
——: aqueous solution
—●—: methyl oleate
—▲—: tributyrin
—■—: diethyl phthalate
Each point represents the mean value of at least five experiments.

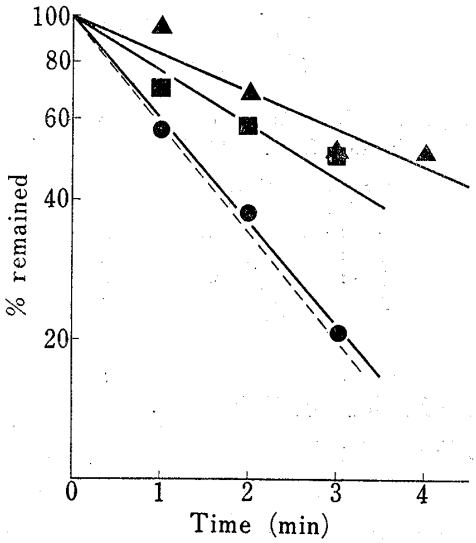

Fig. 2. Absorption Curves of Isonicotinamide from Oily Solutions

drug concentration: 10 mM
injection volume: 10 μl
——: aqueous solution
—●—: methyl oleate
—▲—: tributyrin
—■—: diethyl phthalate
Each point represents the mean value of at least five experiments.

16) NT-scintillation medium was the mixture of toluene (700 ml), nonylphenolpolyethoxyethanol (300 ml), and PPO (4 g).

that from aqueous solution and dependent on the type of oily solvents, although straight lines were obtained in all cases.

The effect of the initial concentration on the intramuscular absorption from oily solution was also examined in the absorption of methyl isonicotinate from diethyl phthalate. In both concentrations of 30 mM and 100 mM, the apparent absorption rate constants were same.

In the previous papers,[4-7] it was reported that the intramuscular absorption of a drug from aqueous solution followed apparent first-order kinetics. Similarly, it seems that the absorption from oily solution is proceeded by the apparent first-order process.

Further examination was made about isonicotinamide and sulfanilamide, having lower lipid solubility than methyl isonicotinate, and ^{14}C-testosterone, having very high lipid solubility and commercially available as oily parenteral preparations. As shown in Fig. 2, Fig. 3, and Fig. 4, the similar results with that of methyl isonicotinate were obtained.

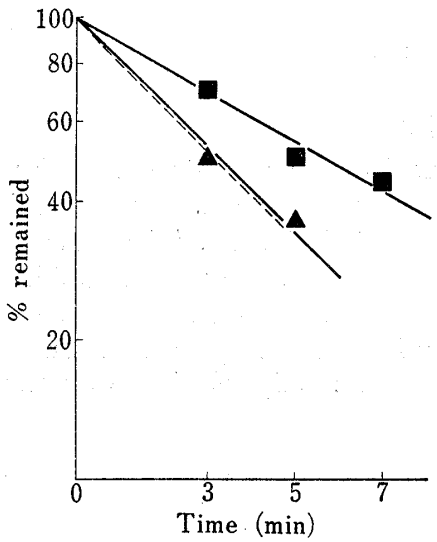

Fig. 3. Absorption Curves of Sulfanilamide from Oily Solutions

drug concentration: 10 mM
injection volume: 10 μl
-------: aqueous solution
—▲—: tributyrin
—■—: diethyl phthalate
Each point represents the mean value of at least five experiments.

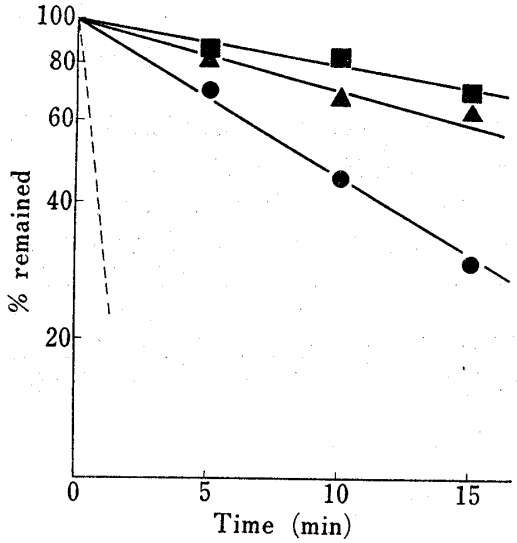

Fig. 4. Absorption Curves of ^{14}C-Testosterone from Oily Solutions

drug concentration: 0.01 mM
injection volume: 10 μl
-------: aqueous solution
—●—: methyl oleate
—▲—: tributyrin
—■—: diethyl phthalate
Each point represents the mean value of at least five experiments.

(2) Effect of Injection Volume

The effect of injection volume on the intramuscular absorption of methyl isonicotinate from diethyl phthalate was investigated as shown in Table I. In the range of injection volume of 5, 10, and 25 μl, the straightness of time courses of drug absorption was retained. In contrast with the case of aqueous solution, however, the apparent absorption rate constant decreased with the increase of injection volume.

From this result, it is suggested that with the increase of injection volume, the dispersion of oily solution in the muscle is reduced and the relative absorption area decreases. This result is in good agreement with the report of Honrath, *et al.*[17]

(3) Contribution of Viscosity

It has been reported previously that the parenteral absorption of drugs from aqueous solution was reduced by water soluble adjuvants and vehicles due to the increase of the viscosity

17) W.L. Honrath, A. Wolff, and A. Meli, *Steroids*, 2, 425 (1963).

Table I. Effect of Injection Volume on the Apparent Absorption Rate Constant

Drug	Solvent	Injection volume (μl)	$k_{obs.}$ (min^{-1})
Methyl isonicotinate[a)]	DP[b)]	5	0.224
		10	0.128
		25	0.085

a) initial concentration: 30 mM
b) DP: diethyl phthalate

Table II. Viscosity of Each Solvent at 37°

Solvent	Viscosity (c.p.)
Buffer[a)]	0.86
Methyl oleate	4.14
Tributyrin	6.50
Diethyl phthalate	7.31

a) isotonic NaH_2PO_4–Na_2HPO_4 buffer of pH 7.0

of solution.[6)] Also in the case of oily solutions, it can be considered that the delayed absorption of drugs is attributed to the viscosity of oily solvents. So the viscosity of each solvent was measured and shown in Table II.

In the range of drugs and oily solvents used in our experiments no correlationship was obtained between the viscosity and the apparent absorption rate constant. Accordingly, the delayed absorption of drugs from oily solution seems to depend more on the other factors than the viscosity of oily solvents.

(4) Relationship between Partition Coefficient and Absorption Rate Constant

The relationship between the clearance of testosterone esters dissolved in ethyl oleate from the muscle and partition coefficient was reported by James, *et al.*[18)]

Table III shows the effect of partition coefficient of drugs between pH 7.0 phosphate buffer and each oily solvent on the apparent absorption rate constant of drugs from oily solution and on the extent of absorption delay.

Except isonicotinamide, the extent of absorption delay increased as partition coefficient increased.

(5) Absorption Model from Oily Solution

The oily solution of a drug injected intramuscularly forms a depot in the muscle. This was confirmed by the microscopic examination of the site taken out of the frozen rat five minutes after injecting the oily solvent with a dye dissolved in it.

It is considered that the drug absorption from the oily depot takes two different routes similarly to the rectal absorption of the drug from oily solution[19)]; 1) a direct absorption of small oil droplets and 2) an absorption by the same mechanism as aqueous solution described previously[4–6)] after being transferred from the oily depot into aqueous phase in the muscle.

However, the oily solvent itself was absorbed so slowly that the contribution of the first route seems to be very little. Therefore, the second route appears to be the main one, in which the absorption rate of a drug is proportional to the amount of the drug in the aqueous phase transferred from the oil phase. So the absorption rate is given by Eq. (3),

18) K.C. James, P.J. Nicholls, and M. Roberts, *J. Pharm. Pharmacol.*, **21**, 24 (1969).
19) K. Kakemi, T. Arita, S. Muranishi, and H. Matsui, *Yakugaku Zasshi*, **86**, 278 (1966).

Table III. Effect of Partition Coefficient on Parenteral Absorption from Oily Solution

Drug	Solvent	Partition[a] coefficient	$k_{obs.}$(min^{-1})	$k_W/k_{obs.}$
Isonicotinamide	buffer[b]		0.553	
	MO[c]	0	0.523	1.06
	TB[d]	0.066	0.193	2.87
	DP[e]	0.112	0.267	2.07
Sulfanilamide	buffer		0.220	
	TB	0.565	0.210	1.05
	DP	1.92	0.124	1.77
Methyl isonicotinate	buffer		0.770	
	MO	4.63	0.263	2.80
	TB	10.5	0.168	4.58
	DP	13.4	0.128	6.01
^{14}C-Testosterone	buffer		0.650	
	MO	229.7	0.080	8.13
	TB	394.7	0.037	17.6
	DP	892.9	0.024	27.1

a) partition coefficient (P) = $\frac{\text{drug concentration in oily solvent}}{\text{drug concentration in pH 7.0 buffer}}$
b) isotonic NaH_2PO_4–Na_2HPO_4 buffer of pH 7.0
c) MO: methyl oleate
d) TB: tributyrin
e) DP: diethyl phthalate

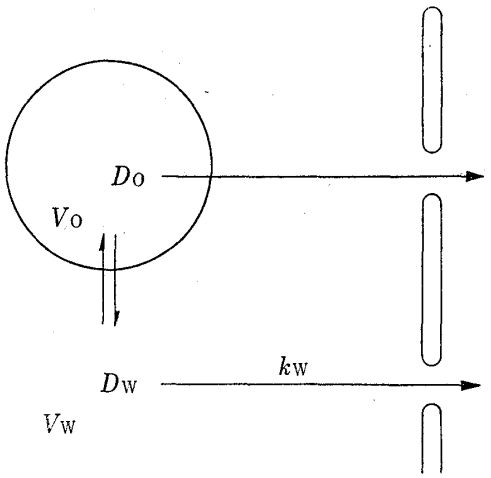

Chart 1. Absorption Model from Oily Solution

V_O, V_W are the volume and D_O, D_W are the amount of a drug in oil depot and water phase, respectively. k_W represents the apparent absorption rate constant from aqueous solution.

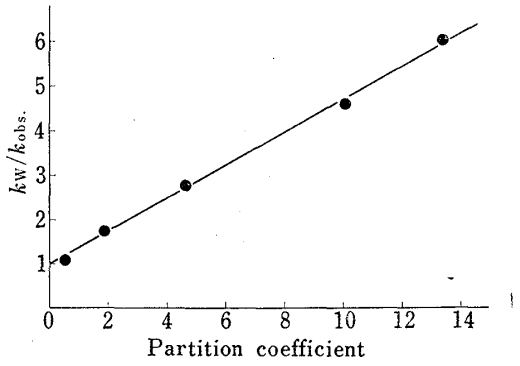

Fig. 5. Relationship between Partition Coefficient and $k_W/k_{obs.}$ of Methyl isonicotinate and Sulfanilamide

$$-\frac{dD}{dt} = -\left(\frac{dD_W}{dt} + \frac{dD_O}{dt}\right) \quad (1)$$

$$\fallingdotseq -\frac{dD_W}{dt} \quad (2)$$

$$= k_W \cdot D_W \quad (3)$$

where D, D_W, D_O, and k_W represent the total amount of the drug in the muscle, the amount of the drug in the aqueous phase, that in the oil phase, and the apparent absorption rate constant from aqueous solution respectively.

If equilibrium is reached very soon, partition coefficient is described by

$$P = \frac{D_O/V_O}{D_W/V_W} \tag{4}$$

where V_O, V_W are the volume of the oil phase and that of the aqueous phase respectively. From Eq. (4),

$$D_W = \frac{a}{a+p} \cdot D \tag{5}$$

where a represents V_W/V_O. Substituting this value for D_W of Eq. (3) gives

$$-\frac{dD}{dt} = k_W \cdot \frac{a}{a+p} \cdot D \tag{6}$$

As shown in Fig. 1—4, the intramuscular absorption of a drug from oily solution is proceeded by the apparent first-order process, so the absorption rate of a drug is given by Eq. (7).

$$-\frac{dD}{dt} = k_{obs.} \cdot D \tag{7}$$

where $k_{obs.}$ is the apparent absorption rate constant of a drug from oily solution.

And Eq. (6) and Eq. (7) give

$$\frac{k_W}{k_{obs.}} = \frac{p}{a} + 1 \tag{8}$$

As shown in Fig. 5, a plot of $k_W/k_{obs.}$ *versus* P gives a straight line about methyl isonicotinate and sulfanilamide. Therefore it seems that this model can be applied to the combinations of drugs and oily solvents whose partition coefficient is in the magnitude of about 1 to 13.

However, the values of isonicotinamide, having very little partition coefficient, and of ^{14}C-testosterone, having greater partition coefficient, deviated remarkably from this straight line. So the absorption mechanism of these drugs can not be explained only by partition coefficient but other factors involving the transfer rate from oil to water must be taken into consideration.

Table IV. Transfer Rate Constant from Oil to Water (k_1) and from Water to Oil (k_2)

Drug	Oil	k_1 (min^{-1})	k_2 (min^{-1})
Isonicotinamide	MO	5.82×10^{-3}	0
	DP	4.36×10^{-3}	4.88×10^{-4}
Sulfanilamide	MO	2.04×10^{-3}	3.92×10^{-3}
	DP	1.65×10^{-3}	7.60×10^{-3}
Methyl isonicotinate	MO	8.93×10^{-4}	1.20×10^{-2}
	DP	2.93×10^{-4}	1.11×10^{-2}
^{14}C-Testosterone	MO	9.10×10^{-5}	2.10×10^{-2}
	DP	1.46×10^{-5}	1.30×10^{-2}

For example, Table IV shows the transfer rate constant of drugs from oil to water obtained by modified Ogata's method,[14] in which V_W/V_O is unity. In the case of isonicotinamide, the smaller transfer rate constant than that expected by partition coefficient was obtained, which may interpret the small absorption rate constant of isonicotinamide from oily solution.

(6) Absorption of Poorly Water Soluble Azo Dyes from Oily Solution

As mentioned above, the intramuscular absorption of drugs from oily solution has been discussed by comparing with that from aqueous solution.

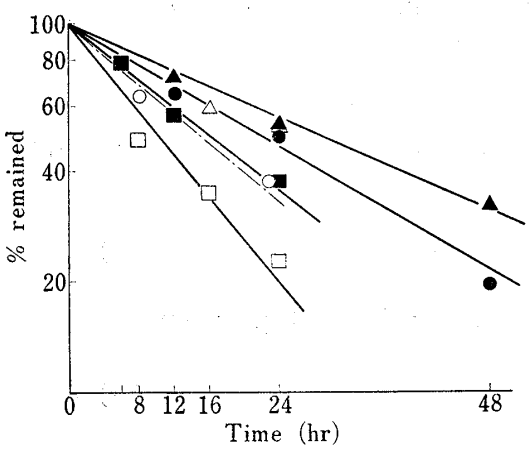

Fig. 6. Absorption Curves of Oil Red-XO from Oily Solutions and Effect of Span 80

drug concentration: 30 mM
injection volume: 10 μl
—●—: methyl oleate
—▲—: tributyrin
—■—: diethyl phthalate
—△—: castor oil
—□—: mineral oil
---○---: methyl oleate with 6% Span 80
Each point represents the mean value of at least five experiments.

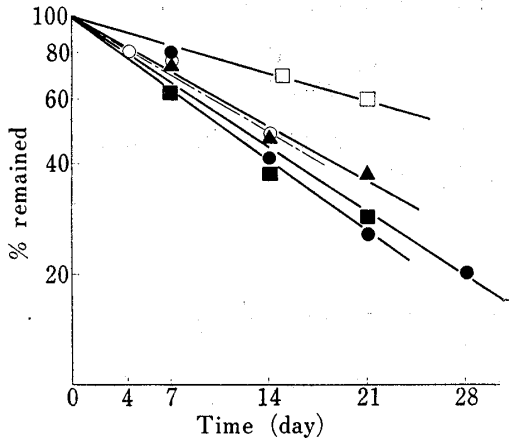

Fig. 7. Absorption Curves of Sudan Black-B from Oily Solutions and Effect of Span 80

Drug concentration was 9 mM (●,▲,■,○) and 30 mM (□).
injection volume: 10 μl
—●—: methyl oleate
—▲—: tributyrin
—■—: diethyl phthalate
---○---: methyl oleate with 6% Span 80
—□—: diethyl phthalate (30 mM)
Each point represents the mean value of at least five experiments.

Furthermore, the absorption of azo dyes, having extremely high lipid solubility and poor water solubility, was examined in investigating the absorption from oily solvents. Fig. 6 shows the time courses of Oil Red-XO absorption from oily solutions.

Though the absorption rates of Oil Red-XO were very low compared with those of other drugs having lower lipophilicity investigated above, straight lines were obtained. Since the apparent absorption rate constant did not alter in the range of 9 mM to 30 mM, it is also considered that Oil Red-XO is absorbed by the apparent first-order process.

About Oil Red-XO, the absorption from castor oil, commonly used as the solvent of the oily parenteral preparations, and mineral oil, of which emulsion has been reported to be very slowly absorbed intramuscularly,[20] was examined. But no remarkable difference from other oily solvents was obtained.

On the other hand, the absorption of Oil Red-XO from methyl oleate was slightly enhanced in the presence of Span 80, a surface active agent. This seems to be due to the accelerated dispersion of vehicle itself, which is to be described below.

In contrast with Oil Red-XO, the absorption rate of Sudan Black-B was lower, and the apparent absorption rate constant was reduced with the increase of initial concentration from 9 mM to 30 mM, and was hardly affected by Span 80 (Fig. 7).

(7) Absorption of Azo Dyes from Propylene Glycol

For the purpose of examining the difference between the absorption rate of Oil Red-XO and that of Sudan Black-B from oily solution, the absorption of these azo dyes dissolved in propylene glycol was put in comparison.

As shown in Fig. 8, Oil Red-XO was more rapidly absorbed than Sudan Black-B from propylene glycol. Since propylene glycol is rapidly absorbed,[6] this difference in the absorption rates seems to be attributable to the difference in the dissolution rates of dyes depositing and remaining in the muscle.

20) J.N. Bollinger, *J. Pharm. Sci.*, **59**, 1084 (1970).

Table V. Solubilities of Oil Red-XO and Sudan Black-B in Muscle Homogenate

Azo Dye	Solubility (mM)
Oil Red-XO	0.0884
Sudan Black-B	0.0175

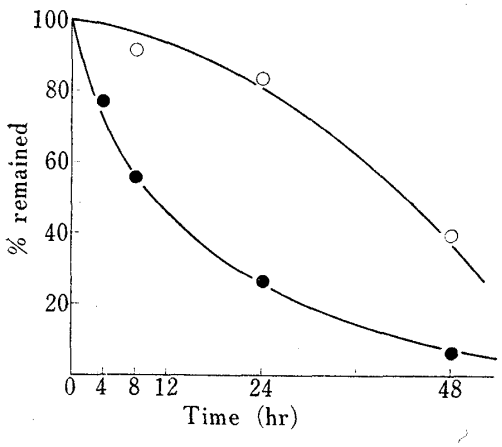

Fig. 8. Absorption Curves of Oil Red-XO and Sudan Black-B from Propylene Glycol

injection volume: 25 μl
—●—: oil Red-XO (2.0 mM)
—○—: Sudan Black-B (3.3 mM)
Each point represents the mean value of at least five experiments.

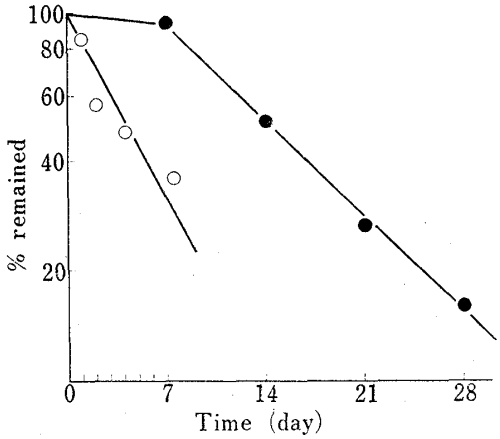

Fig. 9. Absorption Curves of ^{14}C-Methyl Oleate and Effect of Span 80

injection volume: 10 μl
—●—: ^{14}C-methyl oleate
—○—: ^{14}C-methyl oleate with 6% Span 80
Each point represents the mean value of at least five experiments.

In addition, the solubility of Oil Red-XO in muscle homogenate was greater than that of Sudan Black-B as shown in Table V.

From these results, it can be concluded that the difference in the solubility of dyes in the muscle has resulted in the difference between the absorption rates from oily solution. This was supported by the concentration dependence in the absorption of Sudan Black-B.

(8) Absorption of ^{14}C-Methyl Oleate

So far, the intramuscular absorption of a drug from oily solution has been discussed. In the next step, the absorption of oily solvent itself, ^{14}C-methyl oleate, was investigated. As shown in Fig. 9, the absorption of ^{14}C-methyl oleate followed apparent first-order kinetics after a lag time. This lag phase disappeared by the addition of Span 80, which seems to have resulted from the accelerated dispersion of methyl oleate in the muscle.

Furthermore, the muscle, homogenated and applied to thin-layer chromatography one week after an injection of ^{14}C-methyl oleate, retained almost all radio activity as methyl oleate. Also the amount of ^{14}C-methyl oleate observed in the thoracic lymph was negligible. So ^{14}C-methyl oleate is considered to be absorbed into the blood system without hydrolysis.

Anyway, it is evident that its absorption rate is much slower than those of drugs dissolved in it.

As noted above, the intramuscular absorption of drugs from oily solvents seems to depend primarily upon their partition coefficients between the solvent and the tissue fluid and in the case of drugs having extremely large oil-water partition coefficient, to a lesser degree, upon their aqueous solubilities, as well as on the interactions among the vital components such as proteins and mucopolysaccharides.

Kinetical model, examined in relation to experimental data on the rate of absorption from the muscle of drugs having low molecular weight and dissolved in oily solvents, supports the view that when a drug entirely dissolved in an oily solvent is injected to the muscle, the drug is rapidly partitioned between oil and surrounding aqueous tissue phase and absorption occurs mainly *via* the latter phase followed by diffusion through capillaries.

It is also worthy to note that even in the case of methyl oleate, an oily solvent, the drainage through lymph vessels seems to be less important than the clearance through capillary vessels in the absorption from the muscle.