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Mechanism of Intestinal Absorption of Drugs from Oil in Water Emulsions. II. Absorption from Oily Solutions[1]

Kiichiro Kakemi (the late), Hitoshi Sezaki, Shozo Muranishi, Hiroyasu Ogata and Kumiko Giga

Faculty of Pharmaceutical Sciences, Kyoto University[2]

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Drug absorption from oily solutions was investigated by the rat large intestine using *in situ* recirculation technique. Three model drugs (acetanilide, sulfapyridine, and salicylamide) and three different kinds of oil (isopropyl palmitate, ethyl laurate, and diethyl phthalate) were chosen for absorption studies.

It was found that in oily solution, drug absorption through the large intestinal membrane usually took place after being liberated from oil into the secreting fluid.

In the absorption of a drug having oil/water partition coefficient of less than one, apparent enhancement in the absorption was observed. This was attributed to the small volume of secreting fluid (aqueous phase) and the local concentration build-up of a drug at the absorptive surface.

Some comparisons have been made with the absorptive behavior of drugs from oil in water emulsions.

In a previous report[1] a mechanism of the intestinal absorption of drugs from oil in water emulsions was presented. This report is concerned with another situation; absorption from oily solution, an extreme case of oil: water volume ratio ($\phi=\infty$), and with its effect on the drug absorption process. Understanding of such influence of oil on the intestinal absorptive membrane of drugs is basic to the elucidation of the mechanism of drug transfer in emulsion system.

Recently a well-defined method for measuring the intestinal absorption from oily solutions was presented.[3] In this communication, this technique has been applied to the investigation of the influence of various oils employed in the previous report of this series upon the absorption of drugs from the rat large intestine.

As will be seen, some comparisons have been made with the absorptive behavior of drug from oil in water emulsions.

Experimental

Materials——Isopropyl palmitate, ethyl laurate, diethyl phthalate were the same as those described in the previous paper.[1] All other chemicals used were reagent grade quality.

Analytical Methods——The same procedure as for the determination of sulfapyridine and salicylamide was employed.[1]

Apparent Partition Coefficient——Five ml of aqueous solution containing predetermined concentrations of drug was added to five ml of oil. This two-phase system was shaken on a shaker at 37° until the drug was equilibrated between the two phases. The aqueous phase was then separated from the oil phase and the drug concentration within the aqueous phase determined. The initial concentration of drug, minus the concentration of drug found in the aqueous phase at equilibrium, represents the concentration of drug in oil. This is devided by the equilibrium concentration of drug in the aqueous phase is the apparent oil/water partition coefficient (K). The values used in this paper were same as shown by Table III in the previous paper.[1]

1) Part I: K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata and S. Isemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 708 (1972).
2) Location: *Yoshidahimoadachi-cho, Sakyo-ku, Kyoto.*
3) K. Kakemi, T. Arita, S. Muranishi and H. Matsui, *Yakugaku Zasshi*, **86**, 278 (1966).

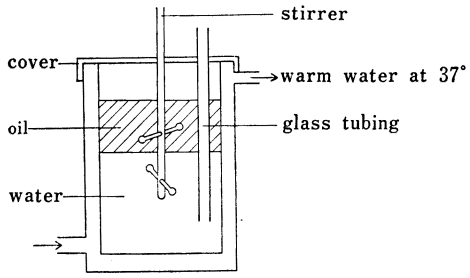

Fig. 1. Schematic Diagram Showing The Apparatus Used for The Transfer Experiments

Transfer of Drug from Oil Phase to Aqueous Phase——Fig. 1 is a shematic diagram of the experimental apparatus used in the transfer experiment. Thirty ml of water was added in a glass beaker and 20 ml of oil containing predertermined concentration of drug was carefully added on top of the aqueous layer. Stirring was achieved by means of two glass paddle wheels about 1.5 cm in diameter. The two wheels were adjusted so that one wheel was in oil layer and the other in aqueous layer. Stirring speed was 130±5 rpm, by which the interface was only slightly disturbed and both layers were stirred well. High reproducibility was obtained at these situations. Samples of 0.5 ml were withdrawn from aqueous layer through a glass tubing at 30, 90, and 180 min. The beaker was covered with aluminium foil to prevent evaporation.

Absorption Experiment——The drug absorption from oil solution was determined according to the procedure described previously.[1,3] After 60 minute recirculation of 20 ml of oil containing drug through the large intestine, the recirculated oil was collected as completely as possible by washing out the intestinal contents with 50 ml of the same kind of oil containing no drug (A solution). The intestinal contents was further washed out with 2.5% sodium carbonate solution (pH 11), and the washings was completely collected in a volumetric flask to make 50 ml (B solution). Absorption was calculated from A and B solutions as the loss from the amount of drug in the initial recirculating solution.

Effect of Oil on Absorptive Membrane——Direct effect of oil on the absorptive membrane was investigated by a pretreatment procedure. Twenty ml of oil containing no drug was recirculated through the large intestine for one hour at 37°. After removing the oil completely by washing out with physiological saline, 20 ml of aqueous solution containing a drug was recirculated for one hour, and the absorption of drug from aqueous solution was determined and compared with control experiment.

Result and Discussion

This study was devised to evaluate the effects of oil upon the intestinal transport of drug from oil to absorptive membrane. Two model drugs and three different oils were chosen for the absorption studies because oil in water emulsions of these systems have been evaluated in an earlier report,[3] convenient oil-water partition coefficients, oil and water solubilities, chemical stability, ease of assay of drugs, and general compatibility were available.

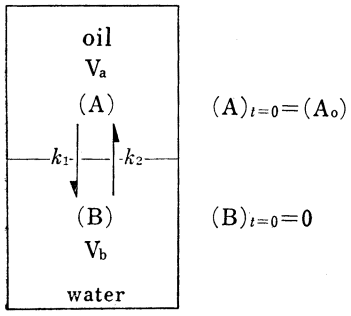

Fig. 2. Schematic Model of Drug Transfer between Oil and Water

V_a, V_b are the volumes and (A), (B) are the concentration of drugs at any instant in oil and water phases, respectively. (A_o) is the initial concentration present in oil phase at time $t=0$. The symbols k_1 and k_2 represent the rate constants for drug transfer from oil to water and from water to oil, respectively.

Transfer from Oil Solution

As described in the previous paper,[1] transfer from oil to aqueous phase is one of the rate-limiting steps in absorption when drug is mainly distributed in oil initially. Fig. 2 shows schematic model of such drug transfer, in which k_1 and k_2 are the first order transfer rate constants, and A and B represent the concentration of a drug in oil and in aqueous layer with their respective volume V_a and V_b.

The differential equation describing the kinetics of transfer for the system is given by

$$V_b\frac{dB}{dt} = V_a k_1 A - V_b k_2 B \qquad \text{Eq. (1)}$$

Mass balance consideration for the total system gives

$$V_a A_0 = V_a A + V_b B \qquad \text{Eq. (2)}$$

From equilibrium condition, Eq. (1) gives

$$V_a k_1 A_e - V_b k_2 B_e = 0 \qquad \text{Eq. (3)}$$

where A_e and B_e are the equilibrium concentration in oil and aqueous phase, respectively.
From Eq. (3)

$$k_2 = \frac{V_a A_e}{V_b B_e} k_1 = \frac{V_a}{V_b} K k_1 \qquad \text{Eq. (4)}$$

and Eq. (5) is given by inserting Eqs. (2) and (4) into Eq. (1) using the initial conditions, $A=A_0$, $B=0$.

$$V_b \frac{dB}{dt} = k_1 \{V_a A_0 - (V_b + V_a K)B\} \qquad \text{Eq. (5)}$$

By integration

$$\ln\left\{\frac{V_a A_0}{V_a A_0 - B(V_b + V_a K)}\right\} = (1+\phi K) k_1 t \qquad \text{Eq. (6)}$$

From Eq. (2)

$$A_0 = A_e + \frac{V_b}{V_a} B_e \qquad \text{Eq. (7)}$$

A_e is given by Eq. (8)

$$A_e = K B_e \qquad \text{Eq. (8)}$$

Subsituting this value for A_e of Eq. (7) gives

$$A_0 = \left(K + \frac{V_b}{V_a}\right) B_e \qquad \text{Eq. (9)}$$

And substituting this value into Eq. (6) yields

$$\ln\left(\frac{B_e}{B_e - B}\right) = (1+\phi K) k_1 t \qquad \text{Eq. (10)}$$

A plot of log $[B_e/(B_e-B)]$ against "t" will give a straight line of slope $(1/2.303)(1+\phi K)k_1$ and the rate constant k_1, inversely proportional to K, may be obtained from the value of the slope and k_2 may then be obtained from Eq. (4). The transfer of salicylamide and sulfapyridine are shown in Fig. 3 and their rate constants are given in Table I.

TABLE I. Transfer Rate Constants from Oil to Water (k_1) and from Water to Oil (k_2)

Drug	Oil	K	k_1 (min^{-1})	k_2 (min^{-1})
Salicylamide	IPP	2.37	5.55×10^{-3}	4.38×10^{-3}
	EL	5.56	3.27×10^{-3}	6.06×10^{-3}
	DP	32.2	7.85×10^{-4}	8.45×10^{-3}
Sulfapyridine	EL	0.25	7.83×10^{-3}	6.53×10^{-4}
	DP	9.97	1.18×10^{-3}	6.02×10^{-3}

Effect of Oil on the Absorptive Membrane

Fig. 4 shows the effect of oils on the absorptive membrane. By the pretreatment with oils on absorptive membrane, absorption rates were suppressed in all cases. As shown in the figure, absorption of rate of salicylamide was suppressed to 73% of the control value by the pretreatment with diethyl phthalate.

Salicyamide is mainly absorbed by a passive transport mechanism.

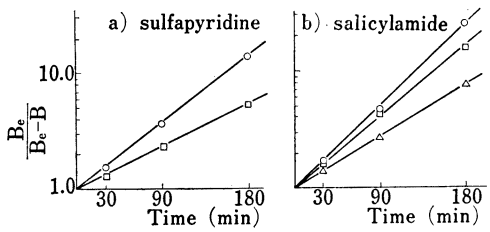

Fig. 3. Plot for The Determination of Transfer Rate Constant from Oil to Water Phases

oil phase: —○—, DP; —□—, EL; --△—: IPP

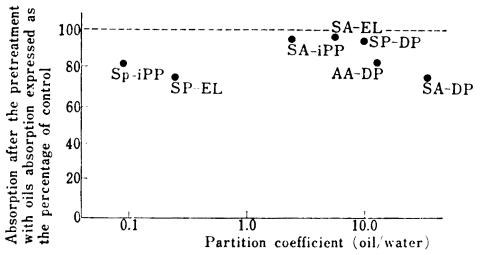

Fig. 4. Effect of Oil Pretreatment on Drug Absorption

Recent report,[4] however, revealed that salicylamide was absorbed by an active-like transport mechanism consisted of glucuronide conjugation in the intestinal membrane. It seems possible for diethyl phthalate to inhibit such active-like mechanism of salicylamide transport. However, absorption of sulfapyridine and acetanilide, which were absorbed by passive transport, were also suppressed by the pretreatment with the oils. This indicates that the suppression of absorption by oils is due to some other non-specific reasons.

Since it was unable to remove oils completely from large intestinal lumen after oil pretreatment, absorption experiments had to be done with leaving very small amount of oil in the lumen. As shown in Fig. 4, suppression of drug absorption by oils seems more or less related to the drug partitioning behavior to oils. In the absorption of drugs having partition coefficient of more than 10 or less than 0.5, absorption rates after oil pretreatment were suppressed to 70 to 80% of the control values. On the other hand, drugs with the partition coefficients of 0.5 to 10, absorption rates were almost equal to the control values. It is difficult to draw a general correlation between degree of suppression from this profile. However, it seems reasonable that suppression is due to oils left in the lumen.

In the case of drugs having partition coefficient of more than 10, drugs dissolve partially in the oil left in the lumen, thus reducing availability of drugs. On the other hand, in the case of drugs having partition coefficient of less than 0.5, oils left on the surface of the absorptive membrane interfere drug access to membrane owing to their poor "familiarity." Further investigations are necessary to clarify such effect of oils on the absorptive membrane.

Absorption from Oil Solutions

In a previously published report from this laboratory[3] concerning the rectal absorption of drugs from oil solutions, it was found that drug absorption from oil generally took two different routes; the one through the rectal membrane after being liberated from oil into the secreting fluid and the other a direct absorption from oil through the membrane. It was also proved that the former was a major route in which drug transfer from oil to secreting fluid is a dominant factor.

As shown in Fig. 5, similar patterns were obtained in the absorption of salicylamide and sulfapyridine from three kinds of oil solutions.

It is worthy to note that in the absorption of sulfapyridine from oil with partition coefficient of less than one, higher absorption was observed from oil solution in comparison with that from aqueous solution. As indicated in Table I, drugs transfer faster from oil to aqueous phase as partition coefficient becomes smaller. Furthermore, since volume of the secreting fluid is very small in this part of the intestine, apparent rate constant of absorption from the secreting fluid becomes very large by the reason described in the previous paper.[1] In spite of small volume of secreting fluid, large amount of drug having K value of less than one is

4) W.H. Barr and S. Riegelman, *J. Pharm. Sci.*, **59**, 164 (1970).

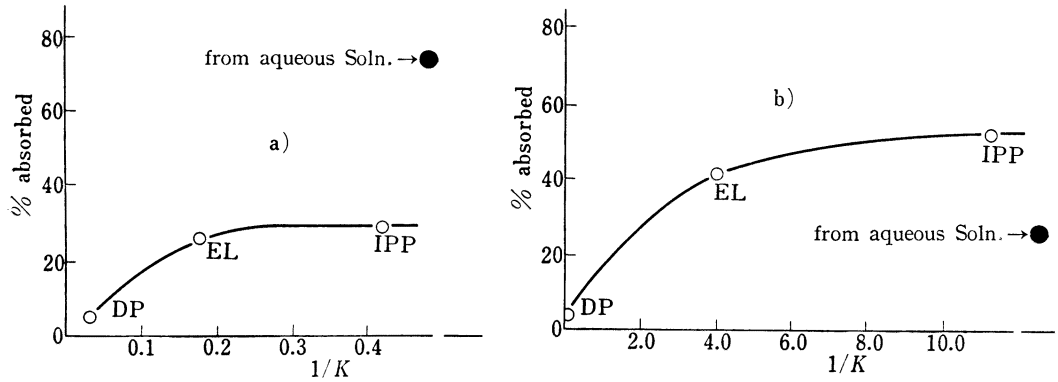

Fig. 5. Plot of Drug Absorption from Oily Solution *vs.* Reciprocal Partition Coefficient
a) salicylamide *b*) sulfapyridine

transferred from oil to the fluid, resulting in the build-up of local concentration of the drug. Combinations of these factors seem to favor absorption of drug from oil solution. These results should be generally important to the eventual understanding of the role of oil phase and phase volumes on the intestinal absorption of drugs and other physiologically important substances from emulsions.

Comparative Considerations of Absorption from Emulsions and from Oil Solutions

As described above, a drug distributed between immiscible oil and water is transported in accordance with such factors as the amount of the drug in both phases (M_o and M_w), trasfer rate constants (k_1 and k_2), apparent absorption rate constant (k'), partition coefficient (K), volume of phases (V_o and V_w), and the area of interface through which drug is transported (S). In an emulsion system, total surface area of oil droplets is extremely large. Assuming an emulsion with identical droplets of 5 μ in diameter, total surface area of oil droplets, S, is given by

$$S = \frac{6V}{R} = 1.2 \times 10^4 V \ (\mathrm{cm}^2)$$

where V and R are the total volume of oil droplets and the diameter of an oil droplet, respectively. From this relation, apparent transfer rate constant, represented by kS, is extremely large. If aqueous phase satisfies perfect sink consition, drugs in oil droplets will transfer to aqueous phase quite rapidly as denoted by Ghanem, *et al.*[5] The systems used in our experiments, however, do not satisfy this condition and aqueous phase can accomodate a limited amount of drugs. Therefore, in spite of extremely large apparent transfer rate constant, apparent transfer rate is dependent on the amount of a drug in aqeous phase which is mainly governed by partition coefficient, K.

In an oil solution, interfacial area between oil and secreted fluid of large intestine becomes much smaller and apparent transfer rate constant (kS) is not so large. As shown in the previous report, apparent absorption rate constant is inversely proportional to the volume of aqueous phase. Apparent absorption rate constant, however, increases with decreasing volume of oily phase in emulsion. An extreme case of this is the case of oily solutions. As a small quantity of secreting fluid of large intestine corresponds to aqueous phase of an emulsion, apparent absorption rate constant will increase about 100 times in comparison with that of aqueous solution.

5) A. Ghanem, W. Higuchi and A.P. Simonelli, *J. Pharm. Sci.*, **58**, 165 (1969).

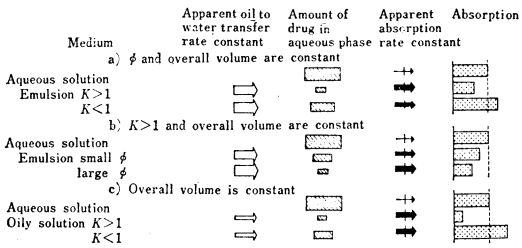

Fig. 6. Schematic Relation between Absorption and various Factors affecting the Absorption from Aqueous Solution, Emulsion, and from Oily Solutions

The width of arrows, the area of squares and the length of bars represent the relative rate constant, the relative amount of drugs in aqueous phase, and the relative magnitude of absorption, respectively

On the basis of foregoing considerations, degree of apparent absorption rate in various systems in comparison with aqueous solution can be presented diagrammatically in Fig. 6. In (a) and $K>1$, apparent absorption rate is decreased in spite of large transfer rate constant as the amount of drug in aqueous phase becomes very small. Conversely, in the case of $K<1$, amount of drug in aqueous phase is almost equal to that of aqueous phase and apparent absorption rate constant becomes large and the absorption rate increases.

In (b), apparent absorption rate constant increases as oil: water volume ratio (ϕ) increases, but amount of drug in aqueous phase gradually decreases as ϕ becomes large. Therefore, apparent absorption rate is not so slow as is supposed from the amount of drug in aqueous phase. Generally, apparent absorption rate has a tendency to decrease as ϕ increases.

In (c), though apparent absorption rate constant is very large in the case of $K>1$, amount of drug in the secreting fluid is very small. Therefore, apparent absorption rate is decreased. On the other hand, in the case of $K<1$, amount of drug in secreted fluid is comparatively large and apparent absorption rate becomes extremely large.