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Hideo Yamada, Teruhisa Ichihashi, Fujiko Kogishi, and Ryuichi Yamamoto : Biopharmaceutical Studies on Factors Affecting Rate of Absorption of Drugs. II.*1 Further Investigation of Absorption of Drugs in Micellar Solution.

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The previous paper*1 has reported the relationship between the intestinal absorption rate of salicylamide in polysorbate-80 solution and the concentration of the surfactant. This relationship is shown in the form of Eq. (1),

$$\frac{k}{k_{Df}}=\frac{f_w}{C_{sm}K+f_w} \qquad (1)$$

where k or k_{Df} is the absorption rate constant of the drug in the micellar solution or in the surfactant-free solution, respectively, under the condition described in the previous paper, C_{sm} is the concentration of the surfactant forming the micelle, K is the partition constant of the drug between in the micellar phase and in the aqueous phase and f_w is the volume fraction of the aqueous phase to the total solution. Eq. (1) indicates that the dependence of the ratio, k/k_{Df}, on the concentration of surfactant is mainly governed by the partition constant. In the case of salicylamide, the experimental results well agreed with the calculated values by Eq. (1).

The present paper describes the further investigation of the relationship, shown in Eq. (1), with methylsalicylate and sulfanilamide which have the respective K-value much different from that of salicylamide in the previous study.

Experimental

Determination of the Partition Constants of Methylsalicylate and Sulfanilamide——The method used in determination of the partition constant was essentially the same as that described in the previous report.*1 The assay methods were as follows : For methylsalicylate, to 4 ml. of the outer solution were added 10 ml. of $M/15$ Na_2HPO_4, 4 drops of 2% 4-aminoantipyrine solution and 2 ml. of 1% $K_3[Fe(CN)_6]$. The volume was made up to 20 ml. with distilled water. For sulfanilamide, the outer solution was diluted 20-fold by distilled water and to 10 ml. of this solution were added 3 ml. of N HCl and 4 drops of 0.2% $NaNO_2$. Ten min. later, 4 drops of 10% $NH_4SO_3NH_2$ was added. Five min. later, 4 drops of 0.2% N-(2-dimethylaminoethyl)-1-naphthylamine solution was added. Then, the volume was made up to 20 ml. with distilled water.

The absorbances of these solutions were read on a spectrophotometer (Hitachi Co., Ltd. model EPU-2) at 510 mμ for methylsalicylate and 544 mμ for sulfanilamide.

Determination of the Rate of Absorption from the Rat Small Intestine——The experimental technique employed was essentially the same as that described in the previous paper.*1 Only few variations in method

*1 Part I : H. Yamada, R. Yamamoto : This Bulletin, **13**, 1279 (1965).

*2 Sagisukami, Fukushima-ku, Osaka (山田秀雄，市橋輝久，小岸冨士子，山本隆一).

were as follows: For methylsalicylate, 200 ml. of the test solution which had contained NaCl (0.9%), methylsalicylate (2 m*M*) and polysorbate-80 (0, 0.6, 2 or 5%, respectively) was recirculatingly perfused through the distal part (20 cm.) of ileum. For sulfanilamide, on the other hand, 50 ml. of the test solution which had contained NaCl (0.9%), sulfanilamide (2 m*M*) and polysorbate-80 (0, 2, 5, 10%, respectively) was recirculatingly perfused from duodenum to ileum. The assay methods were essentially the same as described above.

Results and Discussion

The results of equilibrium dialysis are shown in Table I.

Table I. Partition Constant of Methylsalicylate and Sulfanilamide between Micellar Phase and Aqueous Phase

Drug	C_D [a]	C_s [b]	f_w	C_{Dw} [a]	C_{Dw} [a] (mean)	K [c]
Methylsalicylate	1.0	0.05	0.9	(a) 0.13 (b) 0.13	0.13	135
Sulfanilamide	1.0	0.05	0.9	(a) 0.68 (b) 0.70	0.69	11

a) μmole/ml. *b*) g./ml. *c*) ml./g.

Table I shows the partition constant, K, calculated using Eq. (2), which was derived in the preceding study under the condition, $C_{sm} \fallingdotseq C_s$,

$$K = \left(\frac{C_D}{C_{Dw}} - f_w\right) \cdot \frac{1}{C_s} \qquad (2)$$

where C_s is the total surfactant concentration, C_D is the total drug concentration in the dialysing apparatus, and C_{Dw} is the drug concentration in the aqueous phase. The partition constant of methylsalicylate is about four times as large as that of salicylamide in the previous paper. On the other hand, the K-value for sulfanilamide is about one thirds of that for salicylamide.

The ratio of the absorption rate constant from the micellar solution to that from the surfactant-free solution, k/k_{Df}, can be calculated using Eq. (1) under the condition, $C_{sm} \fallingdotseq C_s$. The calculated values are shown in Table II.

Table II. Calculated and Observed Values for k/k_{Df}

C_s [a]	f_w	(k/k_{Df}) calc.		(k/k_{Df}) obs.	
		Methylsalicylate	Sulfanilamide	Methylsalicylate	Sulfanilamide
0	1.00	1.00	1.00	1.00	1.00
0.6	0.99	0.57	—	0.60	—
2	0.96	0.26	0.81	0.30	0.83
5	0.90	0.12	0.62	0.17	0.73
10	0.80	—	0.42	—	0.53

a) % (w/v)

The results of the animal experiments are shown in Fig. 1 and 2.

After the test solution was removed from the intestinal lumen, the intestine was taken out, homogenized and treated with trichloroacetic acid, then the drug contained in the supernatant fluid was assayed in comparison with the standard sample by the same method. The results indicated that the amount of the drug remained on the surface and in the tissue of the intestine was negligible. Furthermore, by the UV

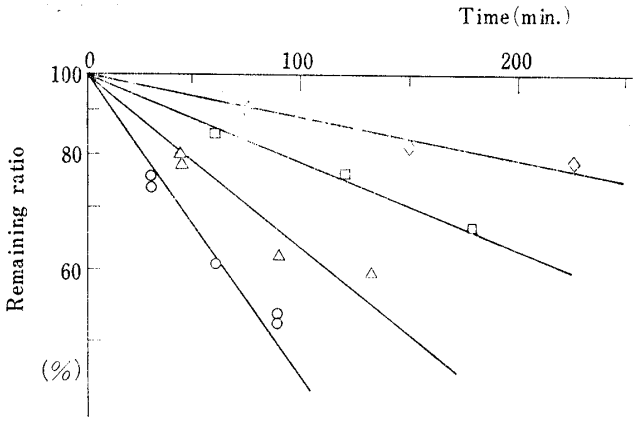

Fig. 1. Logarithmic Plot of Methylsalicylate Remaining in Perfusion Solution Containing Polysorbate-80 in Various Concentration

—○— Surfactant-free solution
—△— 0.6% Polysorbate-80 solution
—□— 2% Polysorbate-80 solution
—◇— 5% Polysorbate-80 solution

Two hundred ml. of the test solution was perfused through the distal part (20 cm.) of ileum of the male rat (weighing 250 to 290 g.).

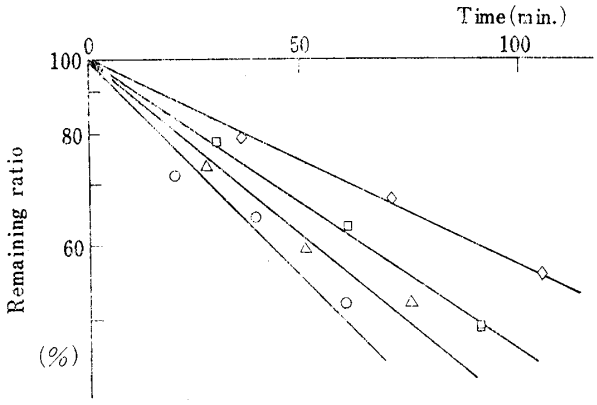

Fig. 2. Logarithmic Plot of Sulfanilamide Remaining in Perfusion Solution Containing Polysorbate-80 in Various Concentration

—○— Surfactant-free solution
—△— 2% Polysorbate-80 solution
—□— 5% Polysorbate-80 solution
—◇— 10% Polysorbate-80 solution

Fifty ml. of the test solution was perfused through duodenum to ileum of the male rat (weighing 250 to 290 g.).

absorption curve, it was confirmed that the decomposition of the drug during the perfusion experiment was negligible under these conditions, so the amount of the drug decreased can be regarded as the amount of the drug absorbed. When the logarithm of residual ratio of the drug in the perfusion solution is plotted against time, a straight line is obtained. From the slope, the absorption rate constant can be obtained by the same method as described in the previous report. The experimentally obtained values of k/k_{Df} are shown in Table II. In Fig. 3, the values of k/k_{Df} for methylsalicylate and sulfanilamide are plotted against the concentration of polysorbate-80. There is a satisfactory agreement between calculated value and observed value of k/k_{Df}.

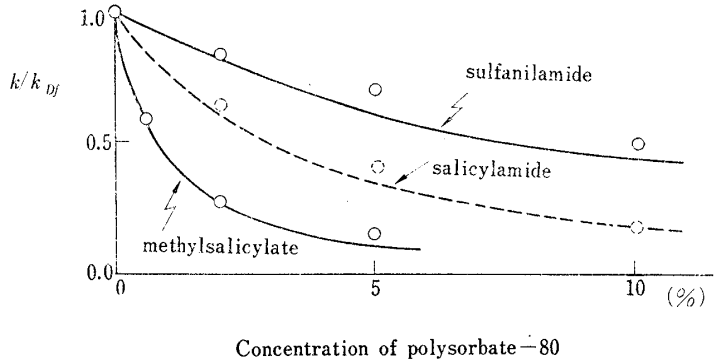

Fig. 3. Relationship between Concentration of Polysorbate-80 and k/k_{Df}

——— Calculated curve
○ Observed value
- - - - - - Calculated curve from the previous paper
○ Observed value from the previous paper

The present results show that the conclusions described in the previous report are right over a wide range of the partition constant.

As for the drug having the extremely large or small partition constant, however, further studies are necessary.

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