

Mechanism of the Intestinal Absorption of Drugs from Oil in Water Emulsions. IV.¹⁾ Absorption from Emulsions containing the Higher Concentration of Emulsifier

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Mechanism of the absorption of drugs from oil in water emulsions to which emulsifier was added at higher concentration was studied in rat large intestine, using *in situ* recirculation technique. Synthesized esters of fatty acids, tri-*n*-butyrin and ethyl laurate as oil and polysorbate-80 as emulsifier were chosen. Two model drugs, vitamin A acetate (VAA) and phenylbutazone (PB) were chosen for absorption studies.

VAA was distributed into oily, and micellar phases, not into aqueous phase. Oil/micelle partition coefficient of VAA was determined using ultrafiltration method. PB was distributed into oily and micellar phases, and a few into aqueous phase in spite of its nearly complete ionization at neutral pH.

In the absorption of VAA, amount of the drug in micellar phase was a critical factor for absorption as VAA was absorbed mainly *via* micellar phase. VAA was released from micelles adsorbed on mucosal layer and was absorbed, and this process was interfered with oil droplets adsorbed on mucosal layer. In the absorption of PB, amount of the drug in aqueous phase was a critical factor for the absorption as PB was absorbed mainly *via* aqueous phase. Absorption process of PB was not interfered with oil droplets adsorbed on mucosal layer.

In the previous papers,^{3,4)} the mechanism and the factors affecting the intestinal absorption of drugs from oil in water emulsion system were presented, in which emulsifier, polysorbate 80 (PS-80), was kept at low concentration, 0.1 w/v %, to avoid complexity of the system. In the system, drugs were distributed into oily and aqueous phases, and negligibly into micellar phase.

This study dealt with emulsion system containing more than 0.1% of PS-80, in which drugs might be distributed also into micellar phase. Bikhazi and Higuchi⁵⁾ had studied transfer of steroids in emulsion system and speculated drug absorption model. Absorption of fats from the intestine had been studied, and related with distribution of solutes between oil droplets and micelles by many authors.⁶⁻⁸⁾ But in past decade, mechanism of absorption of drugs distributed in emulsion system having higher concentration of emulsifier had not been clarified in detail. In this paper, using vitamin A acetate (VAA) and phenylbutazone (PB) as model drugs, mechanism and factors affecting the intestinal absorption from the emulsion system in which drugs were distributed into three phases, oily, micellar, and aqueous phases, have been investigated.

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Experimental

Materials—Ethyl laurate was purified by redistillation under reduced pressure. Tri-*n*-butyrin (E. Merk Ag Darmstadt), VAA and PS-80 (Tokyo Kasei Kogyo Co., Ltd.). Other chemicals used were of reagent grade quality.

Preparation of Emulsion—In the case of VAA, the drug was dissolved in isotonic phosphate buffer solution (pH 7.4) of PS-80. To this solution freshly prepared for each experiment, tri-*n*-butyrin was added as oily phase, and 100 ml of the mixture was emulsified by sonication (Kubota Ultrasonic Generator KMS-200: output voltage; 120) for 20 minutes. The emulsions obtained were placed at 37° for 2 hours before absorption experiments. In the case of PB, the drug was dissolved in isotonic phosphate buffer solution (pH 6.0) of PS-80, and ethyl laurate was added to the solution. The mixture was emulsified according to the procedure described above. Physical stabilities of the emulsions were well maintained during absorption experiments.

Analytical Methods—VAA: Emulsions were diluted to 5 times by volume with pH 7.4 isotonic phosphate buffer. To 25 ml of the diluted emulsion, 10 ml of benzene and 10 g of sodium chloride were added, and the mixture was shaken mechanically for 20 minutes, centrifuged, and concentration of VAA in organic layer was determined according to Moton-Stubbs Oster's correction method.⁹⁾

$$\text{Corrected absorbance} = 7 \times A_{331 \text{ m}\mu} - 2.800 \times A_{316 \text{ m}\mu} - 4.200 \times A_{341 \text{ m}\mu}$$

where *A* denotes the absorbance at the respective wave length.

PB: Extraction of PB from emulsions was followed by the same procedure previously reported.⁹⁾ To 3 ml of the solution in which drug was extracted, 1 ml of conc. hydrochloric acid and 8 ml of *n*-heptane were added, and the mixture was shaken for 20 minutes, and centrifuged. To 6 ml of the organic layer, 4 ml of 0.1 N sodium hydroxide was added, and the mixture was shaken for 20 minutes, and centrifuged. Absorbance at 265 mμ of aqueous layer was determined.

PS-80: Determined by the modified method of Brown, *et al.*¹⁰⁾ Twenty five ml of ammonium cobalt thiocyanate solution (15 g of cobalt nitrate and 100 g of ammonium thiocyanate in 500 ml of water) was added to 2 ml of sample solution, and the mixture was vigorously shaken for 1 minute. After 5 minutes standing, 15 ml of chloroform was added to the solution and the mixture was shaken for 20 minutes. Optical density of the separated organic layer was determined at 318.5 mμ.

Interaction of PS-80 and PB—Equilibrium dialysis was carried out at 37° using Visking cellulose tubings, 24/32 inches in diameter, which were boiled and washed repeatedly before experiments. After incubation for more than 48 hours, concentrations of PB in the external and the inner side were determined.

Absorption Experiments—a) Complete Collection Method: The procedure was described in previous paper.³⁾

b) Sampling Method: When PS-80 was added to recirculating fluid at more than 1.0%, volume of the fluid was not changed during animal experiment. So, disappearance of drug in the fluid was determined by measuring the concentration of drug in the samples taken out from the fluid at appropriate time intervals.

Determination of Solubilized Oil Concentration—Emulsions having various oil concentrations were prepared by the procedure described above, and were placed at 37° for 2 hours. Measuring the turbidity visually, upper limits of concentration of oil solubilized with defined concentration of PS-80 were determined.

Results

Distribution of VAA in Emulsion System

As reported by Kakemi, *et al.*¹¹⁾ VAA was hardly dissolved in water. It is thought that VAA will be distributed into oily and micellar phases in emulsion system respectively, not into aqueous phase. To know distribution profile of VAA in emulsion system, it is necessary to separate two phases, oily and micellar phases. Borgström¹²⁾ obtained each phase concentrations of drug by equilibrium dialysis using Millipore Filter. Feldman, *et al.*¹³⁾ applied emulsions to gel columns, and measured distribution of lipid solutes into the two phases. Goldberg, *et al.*¹⁴⁾ reported more speedy and easier separation method, ultrafiltration with

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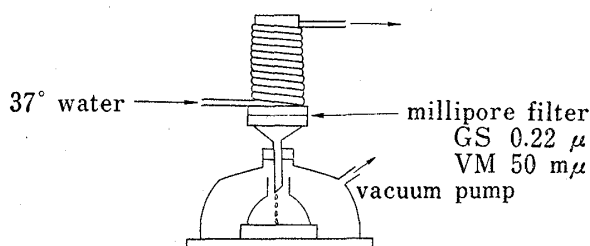


Fig. 1. Apparatus used for Filtration of Emulsion

TABLE I. Adsorption of VAA with Filter through Filtration

Conc. of PS-80 (% w/v)	% adsorbed of VAA ^{a)} Conc. of VAA	
	40 γ/ml	80 γ/ml
0.25	24.0	29.7
0.50	16.7	17.2
1.00	10.3	7.9

a) through VM filter

millipore filter. Within these methods, modified Goldberg, *et al.*'s method was applied in our experiments for the merits discussed above.

Fig. 1 shows a schematic diagram of the experimental apparatus used for ultrafiltration of emulsions. Emulsions stored at 37° beforehand were filtrated under reduced pressure (4–5 mmHg). The rate of filtration depended on concentrations of oil and PS-80 in emulsion respectively, and the higher the concentration of oil and/or PS-80 was, the slower the filtration rate became. In the case of the emulsion having considerably high concentration of oil and/or PS-80, it took long time to obtain the filtrates, and the filtrates were exposed to the condition under reduced pressure for long time and condensed. So, the filtrates did not show exact concentration of VAA in micellar phase. To obtain filtrates for short time, modified filtration method with two steps was presented. The first step was coarse filtration with Millipore Filter GS (0.22 μ pore diameter), and the second step was re-filtration of the filtrate obtained by the first step with Millipore Filter VM (50 mμ pore diameter). With this modification, clear filtrates were obtained more rapidly and easily. In spite of the improvement, compositions of emulsion from which clear filtrates could be obtained by this method, were restricted to the ranges, less than 2% of PS-80 and less than 1.5% of oil.

As shown in Table I, VAA was adsorbed from micellar solution to Millipore Filter during filtration, dependently on PS-80 concentration and independently on VAA concentration. It seems that VAA was entrapped in micelles perfectly, and therefore, adsorption of VAA might be dependent on adsorption of PS-80 micelles. Therefore, to know degree of adsorption of VAA through filtration, concentration of PS-80 before filtration had to be known.

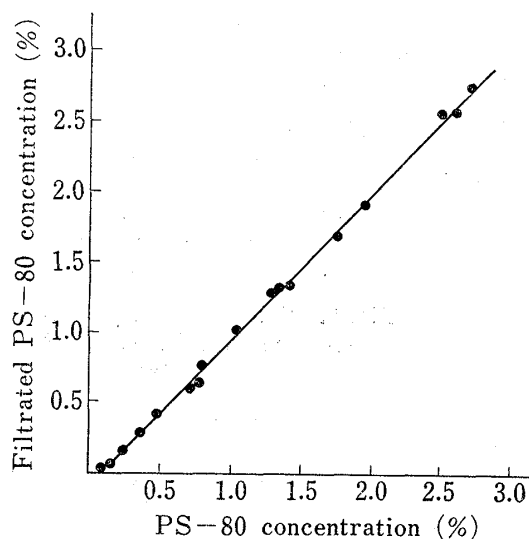


Fig. 2. Filtration of Polysorbate 80 through Millipore Filter

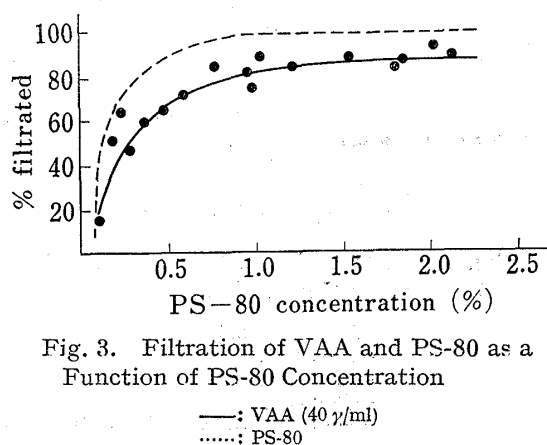


Fig. 3. Filtration of VAA and PS-80 as a Function of PS-80 Concentration

—: VAA (40 γ/ml)
: PS-80

Fig. 2 shows relation of PS-80 concentration before and after filtration. As shown in Fig. 2, saturated amount of PS-80 adsorbed was so small that relation between the two showed linearity.

Fig. 3 represents the relation of PS-80 concentration before filtration and adsorption of VAA, where, broken line shows the case of adsorption of PS-80. Percent of VAA adsorbed did not agree with that of PS-80, and the former was less than the latter. It seems that this difference might be due to decomposition or penetration to the filter during filtration. Applying these relation, corrected amount of VAA in micellar phase could be determined. Namely, emulsions were filtrated under reduced pressure using Millipore Filter GS and VM successively, and concentrations of VAA and PS-80 in filtrates were determined. From Fig. 2, concentration of PS-80 before filtration, and applying this to Fig. 3, percent of VAA filtrated was obtained. By correcting concentration of VAA in filtrate with percent of VAA filtrated, true amount of VAA in micellar phase could be determined. Amount of VAA in oily phase could also be determined by subtracting amount of VAA in micellar phase from total amount of VAA.

Fig. 4 shows apparent distribution of VAA into micellar phase in emulsions having various oil concentrations. From these data, how to calculate true oil/micelle partition coefficient of VAA will be considered below. If VAA is distributed between oily and micellar phases following simple partition law, oil/micelle partition coefficient of VAA (K) is represented by the following equation

$$K = \frac{M_o}{M_m \phi} \quad (1)$$

where M_o , M_m and ϕ represent amount of VAA in oily phase, amount of VAA in micellar phase, and oil/micelle volume ratio, respectively. To obtain K , ϕ has to be decided at first. Yamada, *et al.*¹⁵⁾ had reported micelle/water partition coefficients of drugs by application of Shinoda and Hutchinson's pseudo-phase separation model.¹⁶⁾ According to their report, volume fraction of aqueous phase (f_w) in PS-80-0.9% sodium chloride solution (pH 6.5) at 37° had been shown by the following equation

$$f_w = 1 - 2.0C_s \quad (2)$$

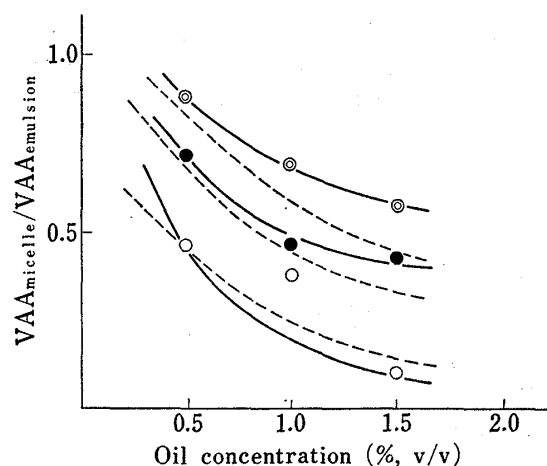


Fig. 4. Distribution of VAA to Oil and Micelle in O/W Emulsion

PS-80 concentration
 —○—: 1.5%
 —●—: 1.0%
 —○—: 0.5%
: calculated curve (see text)

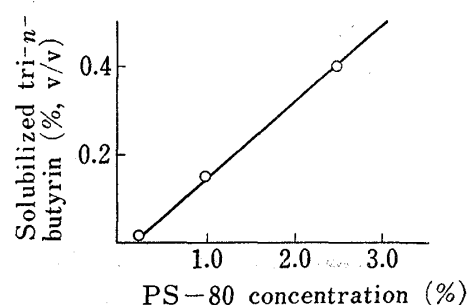


Fig. 5. Solubilization of Tri-*n*-butyrin with PS-80 at 37°

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where C_s represents concentration of PS-80 (g/ml). Also in our report, by substituting the equation, volume of micellar phase could be obtained. Volume of oily phase will be almost equal to the volume of added oil, when concentration of PS-80 is low and solubilization of oil is negligible. But when the concentration of PS-80 is high and solubilized amount of oil is not negligible, volume of oily phase will not agree to the volume of added oil.

Fig. 5 represents solubilization of tri-*n*-butyrin with PS-80. As shown in the figure, solubilization of oil was not negligible for our experiments. Volume of oily phase was obtained by correction with solubilized oil volume. Substituting M_0 and M_m into eq. 1, oil/micelle partition coefficients of VAA were calculated in each emulsions. Values of K did not show dependency on concentrations of oil and PS-80. Average K was obtained as follows.

$$K = 0.0252 \pm 0.0098$$

Ratio of amount of VAA in micellar phase (M_m) to total amount of VAA (M) is represented by the following equation.

$$\frac{M_m}{M} = \frac{1}{K\phi + 1} \quad (3)$$

Substituting average K into eq. 3, theoretical values of M_m/M against oil concentration were obtained, and shown with broken line in Fig. 4. In spite of many assumptions involved in these calculations, close agreements between observed and calculated values were obtained as shown in Fig. 4. These results will be supported that distribution of VAA between oily and micellar phases may follow simple partition law as presumed.

Absorption of VAA from Emulsion System

Fig. 6 shows VAA absorption from emulsions having various oil concentrations. In the figure, broken line represents region of solubilized transparent solution, and solid line that of emulsion. In emulsion system, the higher the oil concentrations were, the less VAA was absorbed.

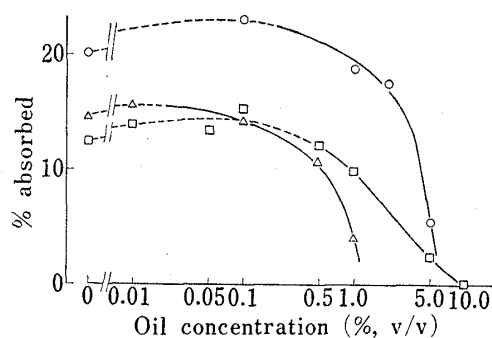


Fig. 6. VAA Absorption from Emulsion with Various Oil and PS-80 Concentrations, obtained by Complete Collection Method

PS-80 concentration
 —△—: 0.25%
 —○—: 1.0 %
 —□—: 2.5 %

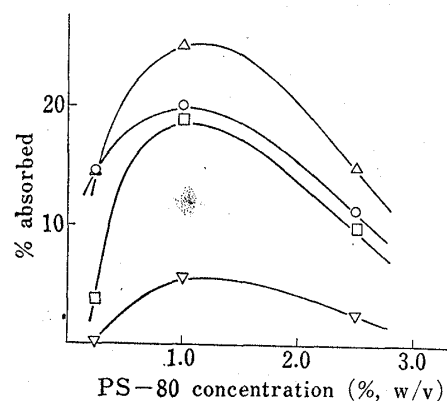


Fig. 7. Effect of PS-80 Concentration on VAA Absorption from O/W Emulsion, obtained by Complete Collection Method

oil concentration
 —○—: 0 % (v/v)
 —△—: 0.1%
 —□—: 1.0%
 —▽—: 5.0%

Fig. 7 represents the effect of PS-80 concentration on VAA absorption from emulsion system. Absorption rate of VAA from PS-80 solution, where oil concentration was zero, were dependent on concentration of PS-80 as shown already by Kakemi, *et al.*¹¹⁾ Furthermore, absorption rates from emulsions were also dependent on concentration of PS-80 in any oil concentrations. It seems reasonable to assume that VAA was absorbed dominantly from

micellar phase, and that absorption rates of VAA from emulsion system were controlled by amounts of VAA in micellar phase just as absorption rate was controlled by amount of drugs in aqueous phase in the case of the system reported previously.^{3,4)} Furthermore, in the case of 0.1% of oil concentration, oil was perfectly solubilized by more than 1.0% of PS-80, and VAA absorption rates were enhanced in comparison with that oil was not added. The reason of the enhancement of absorption was not clarified. The relation of the absorption rate and amount of VAA distributed in micellar phase was studied more detail in emulsions having comparatively low oil concentration and was shown in Fig. 8. A_e/A_a represents the ratio of absorption rate from emulsion to that from aqueous solution containing PS-80.

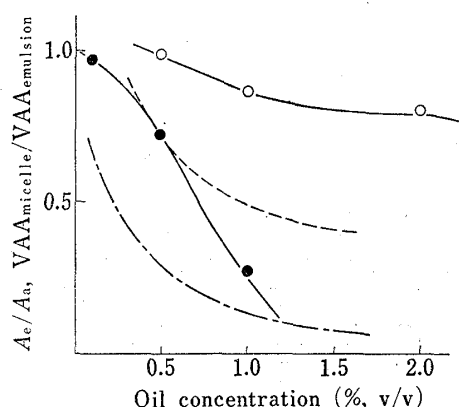


Fig. 8. Comparison of VAA Absorption with Its Distribution to Micellar Phase in Emulsion System

—○— PS-80: 1.0 % } absorption
 —●— PS-80: 0.25 % }
 — — — PS-80: 1.0 % } distribution
 ····· PS-80: 0.25 % }

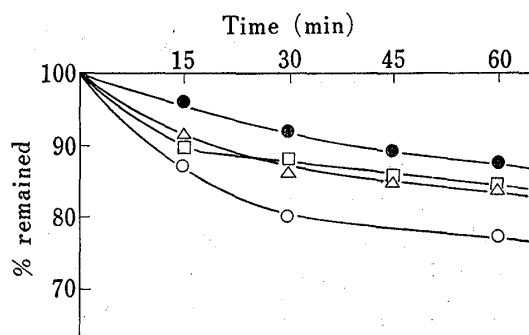


Fig. 9. Disappearance of VAA from Perfusing Emulsion, obtained by Sampling Method

oil concentration
 —○—: 0 %
 —△—: 1.0%
 —□—: 5.0%
 —●—: 10.0%
 PS-80 concentration: 1.0%

As can be seen from the figure, two characteristics are found. The one is that the rates of absorption were much faster than that estimated from the amount of VAA distributed into micellar phase. This phenomenon is similar one as shown previously.³⁾ It seems that VAA transfers from oily phase to micellar phase rapidly, being controlled by oil/micelle partition coefficient, and is then absorbed from micellar phase. The other is that in emulsions with 0.25% of PS-80, absorption rates were slower than that estimated from the amount of VAA distributed into micellar phase in considerably high concentration of oil. This phenomenon is different from the case previously reported.³⁾ It suggests that there is some specific inhibition factors in absorption of VAA from emulsions with high oil concentration.

Fig. 9 shows time course of VAA disappearance from perfusing emulsions. In this experiments, sampling method was applied. In spite of VAA absorption not being detectable from emulsions having more than 10% of oil concentration by complete collection method, VAA disappeared nearly 10% for one hour from the perfusate. It seems that disappearance of VAA from the perfusate observed by sampling method may be due to adsorption of VAA on mucosal layer of the large intestine. To substantiate the above remarks in emulsions with various oil concentrations, up to 50%, two different disappearance curves of VAA from the perfusates were obtained by sampling method and complete collection method respectively, as shown in Fig. 10.

As drug left on mucosal layer of the intestine was removed by complete collection method, loss of VAA from the perfusate will correspond to true absorption, and on the other hand, disappearance of VAA observed by sampling method will contain adsorption of VAA on mucosal layer. So, subtracting the former from the latter will correspond to un-absorbed VAA left on mucosal layer in the large intestine. Since the difference of the both was not

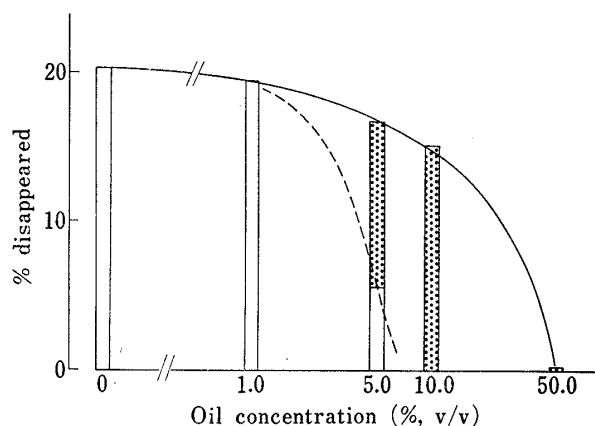


Fig. 10. Relation of Apparent Disappearance and Absorption of VAA to Oil Concentration of Perfusing Emulsion

— : apparent disappearance
 : adsorption
 : absorption

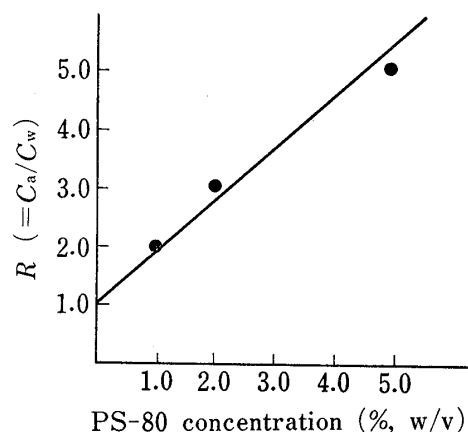


Fig. 11. Interaction of Phenylbutazone and Polysorbate 80 in Aqueous Solution at 37°, pH 6.0

observed in micellar solution, VAA in micellar phase seems not to be left on mucosal layer. Consequently, VAA left on mucosal layer seems to be due to the adsorption of oil droplets in which VAA was dissolved. From the fact that absorption rate of VAA was more suppressed with the increase of oil concentration than that estimated from amount of VAA in micellar phase, inhibition of VAA absorption may be related to adsorption of oil droplets on mucosal layer in the large intestine.

Distribution of PB in Emulsion System

In spite of almost complete ionization at pH 6.0, ethyl laurate/water partition coefficient of PB was extremely large, 167.8 at 37°, and PB was also distributed much into micellar phase following simple partition law as shown in Fig. 11.

Bean, *et al.*¹⁷⁾ reported that in emulsion system concentration of drug non-interacting with emulsifier in aqueous phase was related to oil/water volume ratio (ϕ') by the expression

$$C_w = C \frac{\phi' + 1}{K'\phi' + R} \quad (4)$$

where C_w , C , K' and R represent concentration of free drug in aqueous phase, overall concentration, oil/water partition coefficient of drug, and the ratio of total to free drug in aqueous phase (C_a/C_w), respectively.

Converting C_w into M_w , eq. 4 is given

$$M_w = M \frac{1}{K'\phi' + R} \quad (5)$$

where M_w and M represent amount of free drug in aqueous phase, and overall amount of drug, respectively.

From Fig. 11, at 1.0% of PS-80

$$R = \frac{C_a}{C_w} = 1.93$$

Substituting R and K' into eq. 5 gives

$$M_w = M \frac{1}{167.8\phi' + 1.93} \quad (6)$$

and at 0.1% of PS-80

17) H.S. Bean, G.H. Konning, and S.A. Malcolm, *J. Pharm. Pharmacol.*, **21**, Suppl. 173S (1969).

$$R = 1.0$$

$$M_w = M \frac{1}{167.8\phi' + 1} \quad (7)$$

Fig. 6 and 7 give theoretical relation of amount of free drug in aqueous phase and oil/water volume ratio at 1.0% and that at 0.1% of PS-80, respectively.

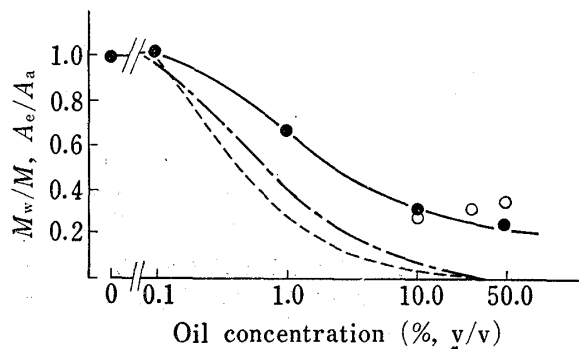


Fig. 12. Absorption of Phenylbutazone from EL Emulsion ($K'=167.8$) as a Function of Oil Concentration, Obtained by Complete Collection Method

0.1% PS-80
○ : A_e/A_a
----- : M_w/M
1.0% PS-80
● : A_e/A_a
----- : M_w/M

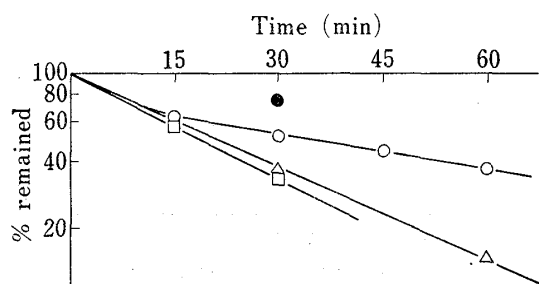


Fig. 13. Disappearance of Phenylbutazone from Perfusing Emulsion, obtained by Sampling Method

○ : disappearance from 10% EL emulsion
● : absorption from 10% EL emulsion
△ : absorption from aqueous solution
□ : absorption from PS-80 solution
PS-80 concentration : 1.0% (w/v)

Absorption of PB from Emulsion System

Fig. 12 represents absorption rates of PB from emulsion with various oil concentrations. In the figure, broken and chain-like lines show M_w/M calculated from eq. 6 and 7, respectively. Absorption rates were also decreased with the increase of oil concentration as in the case of VAA, but absorption rate was much faster than that estimated from M_w/M even in 50% of oil concentration. These results are the same as reported previously,³⁾ and suggest that PB also may transfer from oily and micellar phase to aqueous phase rapidly, being controlled by oil/water and micellar/water partition coefficients, and may be absorbed. In Fig. 12, it is also seen that absorption rate of PB did not depend on PS-80 concentration. It seems that owing to large oil/water partition coefficient of PB, fraction of drug distributed into micellar phase became comparatively small.

Fig. 13 shows time course of disappearance of PB from perfusing emulsion observed by sampling method. In the figure, drug left on mucosal layer of the large intestine was also detectable as the case of VAA. This will be probably due to adsorption of oil droplets and micelles in which drug was dissolved. But in this case, as described above, absorption rate of PB was not suppressed less than that estimated from amount of drug in aqueous phase. So, adsorption of oil droplets on mucosal layer might not play a role as the inhibitor of absorption of PB from emulsion system.

Discussion

It was proved that VAA was distributed into oily and micellar phases following simple partition law, and was absorbed from micellar phase predominantly. If the relation was applicable to all regions of oil concentration used in experiments, ratios of A_e/A_a had to become larger than those estimated from ratios of M_m/M in all emulsions. But absorption rates of VAA from emulsions became slower than those estimated from ratios of M_m/M in emulsions having comparatively high concentration of oil, and VAA was not absorbed at

all at more than 10% of oil. These interesting phenomena were not detectable in the case of PB. The difference between the two drugs, VAA and PB, seems probably to be due to the difference of absorption mechanisms. Namely, in the case of VAA, adsorption of PS-80 micelles on mucosal layer in which VAA was entrapped was the first step of VAA absorption. In this step, micelles may compete for adsorption on mucosal layer at same sites with oil droplets as surfaces of oil droplets and micelles are composed with same PS-80 molecules. So, adsorption of micelles on mucosal layer will be decreased with the increase of oil concentration when PS-80 concentration is kept constant, and consequently absorption rate will be suppressed less than that estimated from M_m/M . On the other hand, in the case of PB which was not absorbed from micellar phase but from aqueous phase, it seems reasonable to assume that adsorption of oil droplets on mucosal layer will not work as inhibitor for the drug absorption because adsorption of oil droplets and absorption of the drug are completely independent phenomena each other. So, rate of absorption of PB may be controlled only by the amount of drug distributed into aqueous phase just as that reported previously.³⁾

The relations are represented by the scheme in Fig. 14. a) shows the case of PB absorbed from aqueous phase, and b) shows the case of VAA absorbed from micellar phase. Drugs will be distributed, in generally, among aqueous, micellar, and oily phases following simple partition law. In the case of a), drug in aqueous phase may be absorbed without interaction with micelles or oil droplets. On the other hand, in b), as micelles of PS-80 are competing their binding sites with oil droplets on mucosal layer, absorption rate of the drug will depend not only on the amount of drug in micellar phase, but also on the degree of absorption of micelles on mucosal layer. Adsorption of micelles on mucosal layer is controlled by oil concentration at constant concentration of PS-80.

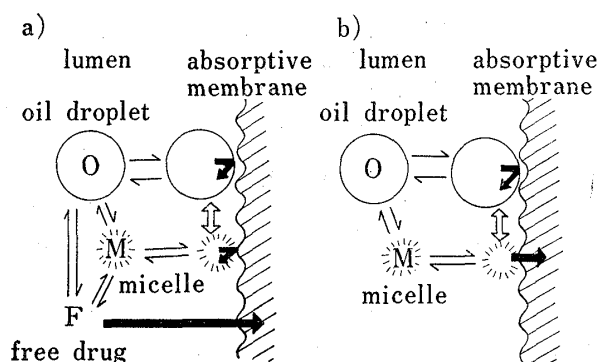


Fig. 14. Schematic Relation between Absorption and Mode of Drug Distribution in O/W Emulsion

O, M and F represent drug in oil droplets, in micelles and in aqueous phase, respectively. $A \rightleftharpoons B$ and $A \rightleftharpoons B$ represent equilibrium state and competitive state between A and B, respectively.