[Chem. Pharm. Bull. 23(4) 716—724 (1975)]

UDC 615.31.015.14.011.4.014

Mechanism of the Intestinal Absorption of Drugs from Oil in Water Emulsions. V.[1] Enhanced Absorption of Methyl Orange Adsorbed at Oil/Water Interface in Emulsions

Hiroyasu Ogata,[2a] Kiichiro Kakemi (the late), Akiyuki Furuya, Michiko Fujii, Shozo Muranishi, and Hitoshi Sezaki[2]

Faculty of Pharmaceutical Sciences, Kyoto University[2]

(Received May 8, 1974)

Absorption of drug which is adsorbed at oil-water interface in emulsion was studied in rat large intestine using *in situ* recirculation technique. Methyl orange (MO) which was chosen as a model drug, was adsorbed at oil-water interface by the coexistence with emulsifiers. Its physico-chemical states were varied with oil concentrations. MO was absorbed well more than ten times from emulsion system compared with that from aqueous solution. Enhancement of MO absorption was interrelated with the adsorption of MO at oil-water interface. Furthermore it was found that not only quantity but also quality of MO adsorption at oil-water interface affected on the absorption rate of MO. Critical oil concentration which showed maximum absorption rate, depended on the length of the absorption site and the degree of adsorption of oil droplets on mucosal membrane was also rate-determining factor for MO absorption from emulsion system.

One of the characteristics of emulsion system is the presence of an extreamly wide interface between immiscible two phases. Heman-Ackah, *et al.*[3] studied that biological activity of phenol was enhanced in emulsion more than that speculated from concentration of phenol in aqueous phase, due to the adsorption of phenol at oil-water interface on which microorganism was also adsorbed. It has been also pointed out that on the surface of fat droplets, fat was hydrolyzed to fatty acid by lipase.[4–6] But studies on the absorption of drugs adsorbed at oil-water interface had been reported scarcely. The purpose of this paper is to investigate the effect of adsorption of drug at oil-water interface on absorption of the drug, methyl orange (MO) as a model drug. Polysorbate 80 (PS-80) and HCO-60, nonionic surfactants, were employed as emulsifiers, and their concentration in emulsion system was kept low, 0.1% w/v, to make MO interact with emulsifiers in aqueous phase as little as possible.

Experimental

Material——MO[7] and ethyl laurate[8] were same as those described in previous papers. HCO-60 (polyoxyethylene derivatives of hydrogenated castor oil) was obtained from Nikko Chemicals Co., Ltd. PS-80 from Tokyo Kasei Co., Ltd. Other chemicals used were of reagent grade quality.

1) Part IV: H. Ogata, K. Kakemi, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 707 (1975).
2) Location: *Yoshidashimoadachi-cho, Sakyo-ku, Kyoto*, to whom inquires should be directed; *a*) Present address: *National Institute of Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo.*
3) S.M. Heman-Ackah, and G.H. Konning, *J. Pharm. Pharmacol.*, **19**, Suppl. 189S (1967).
4) J.R. Senior, *J. Lipid Res.*, **5**, 495 (1964).
5) J.W. Lagocki, N.D. Boyd, J.H. Law, and F.J. Kezdy, *J. Am. Chem. Soc.*, **92**, 2923 (1970).
6) R.G.H. Morgan, J. Barrowman, H. Filipik-Wender, and B. Borgström, *Biochim. Biophys. Acta*, **167**, 355 (1968).
7) K. Kakemi, H. Sezaki, H. Ogata, and C. Nagai, *Chem. Pharm. Bull.* (Tokyo), **20**, 1053 (1972).
8) K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata, and S. Isemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 708 (1972).

Preparation of Emulsion——Concentration of emulsifiers was kept at 0.1%. Amount of MO added was decided so as aqueous phase concentration of MO to be maintained constant in various oil concentrations. The other procedures were same as described previously.[8]

Analytical Methods——MO: To five ml of sample of MO which was diluted by phosphate buffer (pH 7.4), 6 ml of isoamyl aloohol and 2.5 g of sodium chloride were added, and shaken for 20 minutes. After centrifuged, three ml of the separated organic layer was mixed with 1 ml of ethanol containing 4% v/v of hydrochloric acid. The mixture was centrifuged, and the optical density of the clear supernatant was read at 525 mμ.

PS-80 and HCO-60: The procedure was same as described previously.[1]

Interaction of MO with Emulsifiers in Aqueous Solution——The procedure was same as described previously.[1]

Adsorption of MO at Oil-Water Interface in Emulsion System——Modified equilibrium dialysis was applied for the experiments. Into inner side of cellulose tubing, 10 ml of emulsion and into outer side, 30 ml of aqueous solution of MO were added respectively. After incubation for 30 minutes at 37°, concentration of MO in outer side became higher in comparison with that at initial time, fresh solution with higher concentration of MO into outer side, and fresh same emulsion into inner side were added, and incubated for 30 minutes. When concentration of MO in outer side conversely became lower, fresh solufti on which had lower concentration of MO was added and the same procedure above mentioned was followed. These procedures were repeated untill concentration of outer solution did not change after incubation for 30 minutes. Its concentration thus obtained was concentration of free MO in emulsion. Subtracting amounts of free MO in aqueous phase (outer side) from total amounts of MO in emulsion (inner side), sum of amounts of MO adsorbed at oil-water interface and of MO interacting with emulsifiers in aqueous phase was obtained. The latter was calculated from the relation of interaction of MO and emulsifiers in aqueous solution. From the result, it became clear that amount of MO adsorbed at oil-water interface was negligible in the emulsion whose oil/water volume ratio, ϕ, was 1/999. Though the surface area of oil droplets was not able to be obtained directly, it seemed reasonable that amounts of MO adsorbed per oil volume were approximately substituted for the amounts of MO adsorbed per surface area, as the surface area of oil droplets is thought to be in proportion to oil volume.[9]

Absorption Experiments——a) *In Situ* Large Intestinal Loop Method: The procedure was described in previous paper.[7] Disappearance of MO from the lumen was obtained for 2 hours.

b) *In Situ* Large Intestinal Recirculation Method: Experiments were done at four absorption sites, large intestine (15—17 cm), rectum (4—5 cm), rectum and descending colon (8—9 cm from the anus), and ascending colon (4—5 cm from the caecum), respectively. The procedure of absorption experiments was described in previous paper.[8] Aqueous phase volume of emulsion was kept constant as 18 ml. Total concentration of MO in emulsion was controlled to be 10, 150, and 300 γ/ml in aqueous phase, respectively. The recirculating fluid was collected completely by washing out with fresh phosphate buffer, pH 7.4, after 2 hours recirculation, and the amount of MO in collected fluid was determined.

Adsorption of MO from Emulsion System *in Vitro*——Experiments were done at two sites, large intestine and rectum, respectively. The everted sac of the lumen in which any solution was not put was incubated in the emulsion at 37° for 2 hours. Disappearance of MO in the emulsion was thought to be the adsorpton of MO onto mucosal membrane. The relation of percent adsorbed of MO and aqueous phase volume of emulsion was calculated by following equation which was obtained by modification of Nogami, *et al.*'s equation[10]

$$\frac{\log X_1}{\log X_2} = \frac{V_2}{V_1} \qquad (1)$$

where X_1 and X_2 represent percent of drug remained in emulsions whose aqueous phase volume are V_1 and V_2, respectively.

Results and Discussion

Interaction of MO and Emulsifiers in Aqueous Solution

Interaction of drugs and surfactants has been reported by many authors, and according to their reports, unionized form of drugs was predominantly entrapped in micellar phase formed with nonionic surfactants. While, Hurwitz, *et al.*[11] DeLuca, *et al.*[12] and Taziri[13]

9) K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata, and K. Giga, *Chem. Pharm. Bull.* (Tokyo), **20**, 715 (1972).
10) H. Nogami, H. Hanano, and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 389 (1968).
11) A.R. Hurwitz, P.P. DeLuca, and H.B. Kostenbauder, *J. Pharm. Sci.*, **52**, 893 (1963).
12) P.P. DeLuca and H.B. Kostenbauder, *J. Pharm. Sci.*, **49**, 430 (1960).
13) H. Taziri, *Kogyo Kagaku Zasshi*, **65**, 174 (1962).

showed that ionized forms of drugs having a large hydrophobic group in its molecule were also interacted with nonionic surfactants. As MO is present almost anionic form in neutral aqueous solution, its pK_a being 3.46,[14] and furthermore has a hydrophobic group in its molecule, it seems probable that interaction of MO with nonionic surfactants exists.

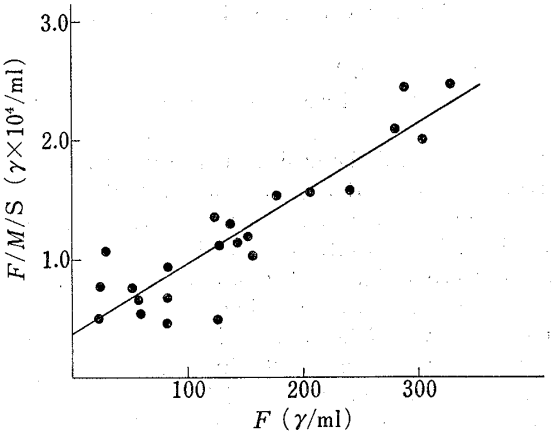

Fig. 1. Interaction of Methyl Orange and Polysorbate 80 in Aqueous Solution at 37°

F, S, and M represent concentration of free MO, that of surfactant, and that of MO in micelle, respectively.

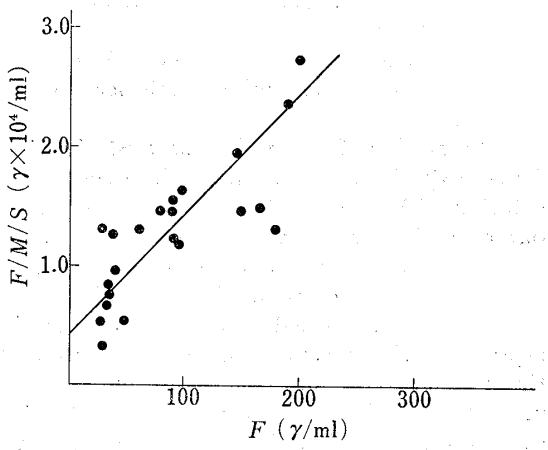

Fig. 2. Interaction of Methyl Orange and HCO-60 in Aqueous Solution at 37°

F, S, and M represent concentration of free MO, that of surfactant, and that of MO in micelle, respectively.

Interaction of MO and emulsifiers, PS-80 and HCO-60, were studied by equilibrium dialysis. MO was interacted with both emulsifiers, and their interaction manners showed the saturation phenomenon for the amount of MO interacted with emulsifiers. As shown in Fig. 1 and 2, MO and emulsifiers interacted according to the adsorption isotherms of Langmuir type for the most part. In these experiments, correction for Donnan equilibrium was not applied as its effect was thought to be negligible. The type of interaction was different from the general type that drugs are distributed between micellar and aqueous phases following by simple partition law.

Table I. Interactions of Non-ionic Surfactants with Methyl Orange

Constant[a]	Non-ionic Surfactant	
	PS-80	HCO-60
α	0.0159 ml/γ	0.0263 ml/γ
β	0.0170 γ/g	0.0102 γ/g

a) $M/S=\alpha\beta F/(1+\alpha F)$
M: concentration of MO in micelle
S: concentration of surfactant
F: concentration of free MO
α,β: constant

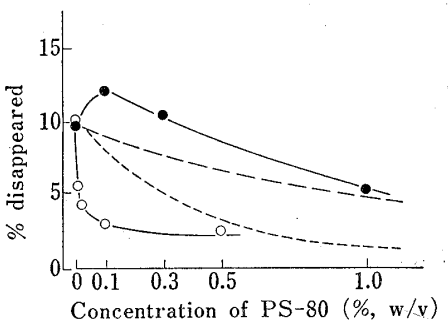

Fig. 3. Effect of Polysorbate 80 on Disappearance of Methyl Orange in Aqueous Solution from the Large Intestinal Lumen *in Situ*

methyl orange concentration
—○— : 60 γ/ml —●— : 300 γ/ml
Dotted lines represent the calculated lines on the basis that only non-interacting form of MO with PS-80 is absorbable.
methyl orange concentration
------: 60 γ/ml ———: 300 γ/ml

14) I.M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930).

Table I shows parameters for Langmuir type interaction of MO and PS-80 or HCO-60, where α and β represent the adsorption constant and saturated amount of MO adsorbed, respectively. As shown in Table I, HCO-60 was interacted with MO stronger than PS-80 was, but its adsorption capacity for MO was smaller than that of PS-80.

Absorption of MO from PS-80 Solution

Fig. 3 shows the effect of PS-80 on MO disappearance from large intestinal loop *in situ*. When initial concentration of MO was 300 γ/ml, disappearance rate of MO showed maximum at 0.1% of PS-80, and decreased following to the speculated line at more than 0.1% of PS-80. Acceleration of MO disappearance seemed to be due to the same reason shown by Kaneda, *et al.*[15] On the other hand, when initial concentration of MO was 60 γ/ml, disappearance rate of MO at 0.01% of PS-80 was suppressed to one half of that added no PS-80. As critical micelle concentration of PS-80 is about 0.01%, suppression of disappearance of MO seems not to be attributable to the interaction of MO and PS-80 in aqueous solution. As shown previously,[7] two routes were found in MO disappearance from the large intestinal lumen. The one is passive transport process, and the other is enzymatic decomposition process on mucosal layer. The latter is dependent on the concentration of MO, and is inhibited completely by 0.01% of PS-80. From these facts, it seems that disappearance of MO is suppressed by inhibition of the enzymatic decomposition process at less than 0.01% of PS-80, and also suppressed by the interaction of MO and PS-80 in aqueous solution at more than 0.01% of PS-80.

Distribution of MO in Emulsion System

It has been reported that MO was distributed into *n*-octanol in *n*-octanol–water system[16] and also was oriented at benzene–water interface.[17] In our experiment, ethyl laurate–water system, MO was not distributed into the organic layer, and also was not oriented at oil–water interface. Ethyl laurate-water partition coefficient of MO at 37° showed zero. Nevertheless, in the PS-80–ethyl laurate–water system, it was observed that concentration of MO in aqueous phase was decreased, but MO was not detected at all in oily phase, and recovery of MO from

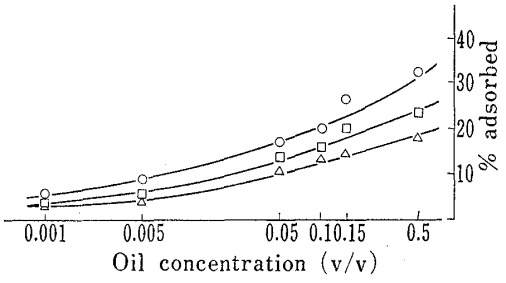

Fig. 4. Adsorption of Methyl Orange at the Oil: Water Interface in Emulsion System using Polysorbate 80 as Emulsifier

polysorbate 80 concentration : 0.1% (w/v)
methyl orange concentration
—○— : 10 γ/ml
—□— : 150 γ/ml
—△— : 300 γ/ml

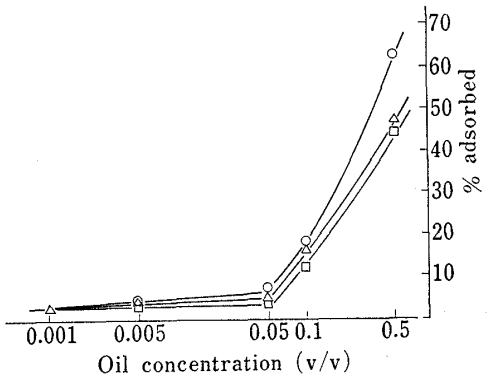

Fig. 5. Adsorption of Methyl Orange at the Oil: Water Interface in Emulsion System using HCO-60 as Emulsifier

HCO-60 concentration: 0.1% (w/v)
methyl orange concentration
—○— : 10 γ/ml
—□— : 150 γ/ml
—△— : 300 γ/ml

15) A. Kaneda, K. Nishimura, S. Murashnii, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **22**, 523 (1974).
16) H. Terada and T. Inaki, Abstracts of Papers, the 19st Annual Meeting of Phermaceutical Soceity of Japan, Fukuoka, April, 1971, p. 542.
17) C.W. Gibby and C.C. Addison, *J. Chem. Soc.*, **1930**, 119.

the system was complete. From these results, it seems that MO is adsorbed at oil-water interface in the presence of emulsifier.

Fig. 4 and 5 represent adsorption of MO at oil–water interface of emulsion systems having various oil concentrations at 37°. These data were obtained by modified equilibrium dialysis. Concentration of MO in aqueous phase was controlled to be constant in order to compare the degree of absorption among emulsions having various oil concentrations. As shown in Fig. 4 and 5, adsorption was increased with increase of oil concentrations. This is probably due to the increase of the total area of oil–water interface with increase of oil concentrations. Manners of adsorption with MO were different between the two emulsifiers. In the case of HCO-60, adsorption of MO was increased in proportion to the increase of total interface area. On the other hand, in the case of PS-80, adsorption did not show same tendency as the case of HCO-60. Adsorption of MO in the case of PS-80 was larger at comparatively small concentration of oil, 0.5—5%, but adsorption of MO was smaller at higher oil concentration, 15—50%, in comparison with the case of HCO-60. Since MO was not adsorbed for itself at oil–water interface, but adsorbed by the coexistence with emulsifiers as described above, it seems that adsorption of MO at oil–water interface will be affected by the state of emulsifiers at oil–water interface, and also by the state of interaction of emulsifiers and MO at the interface.

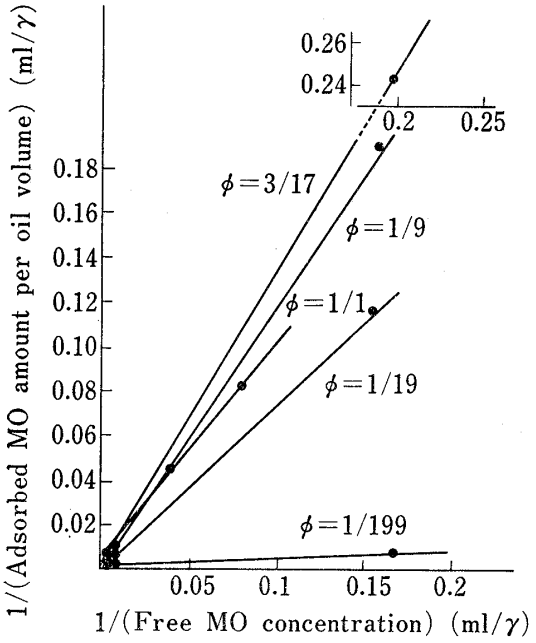

Fig. 6. Langmuir Plots of Methyl Orange Adsorptionat Oil: Water Interface in Emulsion System using Polysorbate 80 as Emulsifier

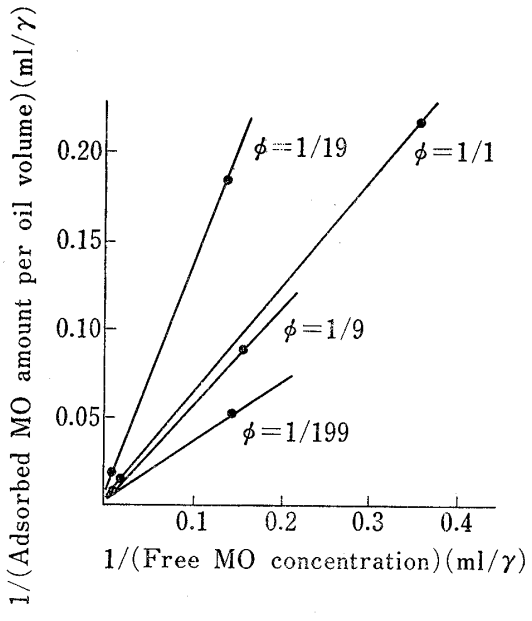

Fig. 7. Langmuir Plots of Methyl Orange Adsorption at Oil: Water Interface in Emulsion System using HCO-60 as Emulsifier

Fig. 6 and 7 show Langmuir isotherm adsorption of MO at oil–water interface in emulsion system. As shown in the figures, MO adsorbed at the interface might follow with Langmuir iso-therm adsorption, but the states of adsorption were varied with oil concentrations of emulsions. The variation could be found in adsorption constants rather than in saturated amount of adsorption. If the states of oil–water interface were not varied with oil concentrations, all points must fall on a same straight line independently on oil concentrations.

Absorption of MO from Emulsion System

In the study of absorption of MO from emulsion system, volume of aqueous phase must be maintained constant to compare absorption rates among the emulsions having various

oil concentrations, as described previously,[8] since MO was not distributed into oilyphase at all. So, constant aqueous phase volume procedure mentioned previously[8] was applied to this study.

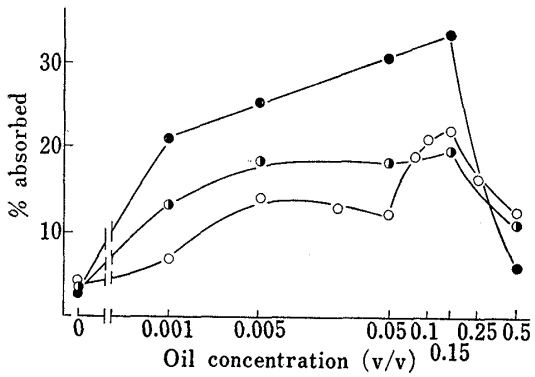

Fig. 8. Methyl Orange Absorption from Emulsion System using Polysorbate 80 as Emulsifier

Polysorbate 80 concentration: 0.1% (w/v)
methyl orange concentration
—●— : 10 γ/ml
—◑— : 150 γ/ml
—○— : 300 γ/ml

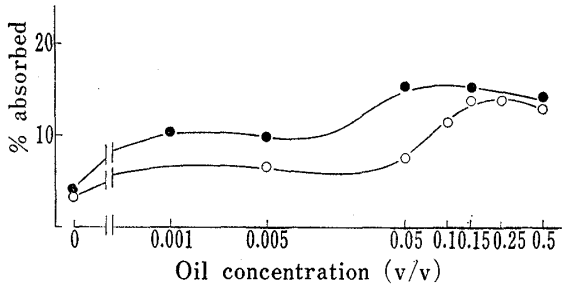

Fig. 9. Methyl Orange Absorption from Emulsion System using HCO-60 as Emulsifier

HCO-60 concentration: 0.1% (w/v)
methyl orange concentration
—●— : 10 γ/ml
—○— : 300 γ/ml

Fig. 8 and 9 show the absorption rates of MO from emulsions whose emulsifiers were PS-80 and HCO-60, respectively. Concentration of emulsifiers was kept low, 0.1% w/v, to make MO interact with emulsifier in aqueous phase as little as possible. In micellar solution, MO was absorbed merely 2—3% for 2 hours in recirculation experiment. On the other hand, in emulsion system, MO was absorbed considerably well even from the emulsion whose oil concentration was 0.001% v/v. Absorption rates from emulsions showed the dependency on MO concentration, which was not detectable in micellar solution, and also showed the dependency on oil concentration. These phenomena were found in both emulsifiers. In our previous paper,[7] it was suggested that enzymatic reduction on mucosal surface, one of the routes of MO elimination from the large intestine, was not accelerated in emulsion system. So, the enhancement of MO absorption may probably be attributed to the acceleration of passive transport of MO from the lumen. The enhancement of MO absorption from emulsion system was very noticeable phenomenon which have not ever been reported. From these observations, it seemed reasonable to assume that adsorption of MO at oil–water interface would be a main factor for enhancement of MO absorption. To confirm the speculation, interrelation between adsorption and absorption of MO was plotted in Fig. 10.

In the both emulsion systems, a definite relation between the two was hold in emulsions having a certain oil concentration, but common relation was not hold for every emulsions just same as the case of the adsorption shown in Fig 6 and 7. These relations showed that even if same amount of MO was adsorbed in emulsions having various oil concentrations, absorption rates from the emulsions were not the same. This phemomenon seems probably to be attributable to physico-chemical states of MO at oil-water interface which were dependent on oil concentration as shown in Fig. 6 and 7. In Fig. 6 and 7, adsorption constants rather than saturated amount of MO adsorbed were varied largely with oil concentrations, and those complex phenomena of MO at the interface seem reasonably to be affecting on absorption rate of MO. It is very interesting phenomenon that not only quantity, apparent amount of MO adsorbed, but quality, physico-chemical state of MO, should affect on the absorption rate of MO in emulsion system.

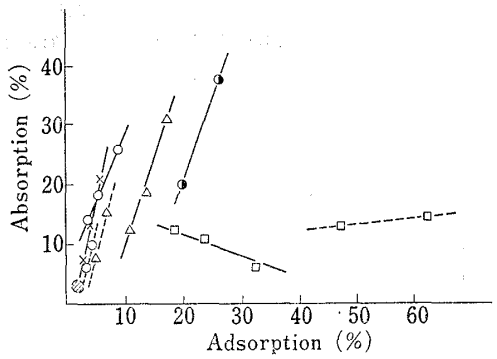

Fig. 10. Correlation of Absorption and Adsorption at Oil : Water Interface in Emulsion System

emulsifier
——: Polysorbate 80
----: HCO-60

oil volume fraction
◍ : 0
× : 0.001
○ : 0.005
△ : 0.05
◑ : 0.15
□ : 0.5

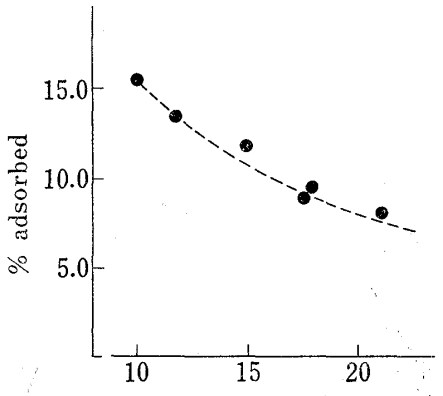

Fig. 11. Effect of Volume of Emulsion on Methyl Orange Adsorption to Large Intestinal Mucosa *in Vitro*

Dotted line represents theoretical values calculated by equation(1) using X_1=84.3, V_1=10.0.

Therefore the enhancement of absorption of MO was reduced in emulsions having more than 15% of oil concentration. As the reduction of absorption enhancement was the phenomenon depended on oil concentration, not on concentration of MO ,or not on degree or amount of MO adsorbed at oil-water interface, reduction seems to be due to the interaction of emulsion system and absorptive membrane, not to that of MO and absorptive membrane. It is presumed that absorption rate of MO may depend on the degree of contact of oil droplets to the absorptive membrane. With increasing oil concentration, degree of adsorption of MO at oil-water interface will increase, but conversely degree of contact of oil droplets to absorptive membrane will decrease. As a result of the balance of the two above mentioned factors, apparent absorption rate of MO will be determined. Equilibrium of the two factors will be maintained at 15% of oil concentration, and the degree of adsorption of MO at oil-water interface will be rate-determining factor at less than 15% of oil concentration, and at more than 15% of oil concentration the degree of contact of oil droplets to absorptive membrane will become rate-determining factor.

Adsorption of MO onto mucosal membrane in emulsion system *in vitro* was studied to substaniate the above remarks. Adsorption may be affected by aqueous phase volume like absorption[8] even if concentration of MO in aqueous phase were controlled constantly.

Fig. 11 shows the effect of aqueous phase volume on adsorption of MO in emulsion, ϕ=3/17. Adsorption was decreased with increase of aqueous phase volume as shown in Fig. 11. From the results, it became clear that volume of aqueous phase must be maintained constant to compare the adsorption among emulsions having various oil concentrations.

Fig. 12 shows adsorption of MO onto mucosal membrane of whole large intestine *in vitro* in emulsion system. In emulsion system having comparatively low oil concentration, adsorption seemed to be same as the case of micellar solution, but adsorption was reduced with the increase of oil concentration at more than 15% of oil concentration. It seems conclusive that percent of adsorption of oil droplets on the surface of mucosal membrane would be reduced with the increase of oil concentration, and as the result, apparent adsorption of MO also was reduced. It was also shown in Fig. 12 that critical oil concentration, at which adsorption of MO showed the maximum, depended on the length of the sites used for the experiments. Therefore critical oil concentration per length of adsorption sites is almost same whether adsorption sites might be large intestine or rectum. It is also noticeable that absorption rate of MO from micellar solution was much less than that from emulsion system in spite of

the same degree of adsorption in micellar solution and emulsion at less than 10% of oil concentration. From the result, specific physico-chemical properties of MO at oil-water interface should also be pointed out.

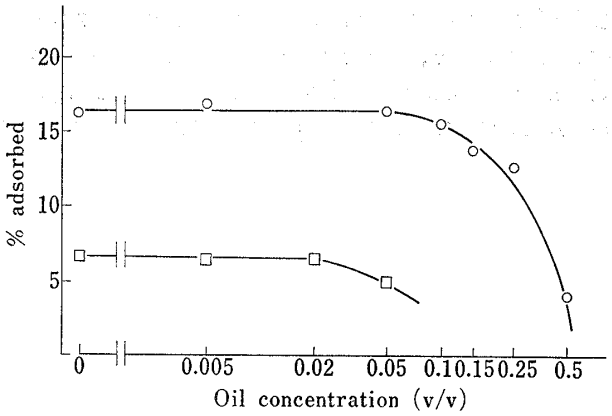

Fig. 12. Effect of Sites and Their Lengths on Methyl Orange Uptake from Emulsion System *in Vitro*

—○— : large intestine (15—17 cm)
—□— : rectum (4—5 cm)

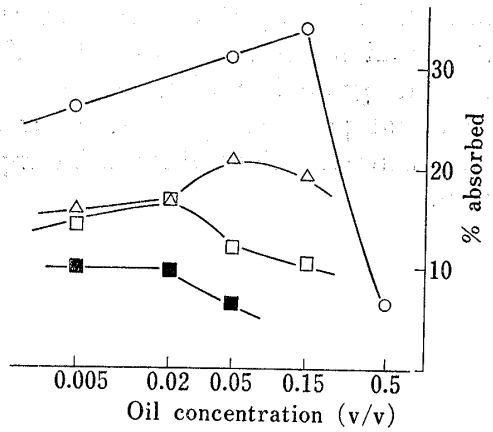

Fig. 13. Effect of Absorptive Sites and Their Lengths on Methyl Orange Absorption from Emulsion System

—○— : large intestine (15—17 cm)
—△— : descending colon+rectum (8—9 cm)
—□— : rectum (4—5 cm)
—■— : ascending colon (4—5 cm)

Fig. 13 shows the effect of absorption sites and their length on MO absorption from emulsion system. Critical oil concentration also depended on the length of the absorptive sites. Critical oil concentration per length of the absorptive sites became almost same among four different absorptive sites. These situations were entirely same as that of adsorption. These results also seems to resemble well to the case of absorption from PS-80 solution.[15,18] On their papers, drugs were transferred with micelles on surface of mucosal membrane, and released. Degree of adsorption of micelles on the surface dominantly affected on the absorption rates of drugs. In emulsion system, it is reasonable to conclude that MO was transferred with oil droplets to the mucosal membrane, released, and absorbed. It may also pointed out that role and behavior of micelles and oil droplets have many similarities as carrier of drug to absorptive membrane, but oil droplets also have the specific role for the enhancement of absorption of drug, not observed in micelles.

The summary of our observations about MO absorption is shown below. 1) MO is interacted with nonionic emulsifier in water, and absorption of MO is not enhanced but reduced. 2) MO is adsorbed onto oil droplets, probably by the interaction with emulsifier situated on oil droplets, and absorption of MO is enhanced well. 3) Enhancement of MO absorption has an interrelation with adsorption of MO onto oil droplets, and the absorption rate of MO is affected by not only quality but also quantity of MO adsorption. 4) Oil droplets, on which MO is situated, must contact with absorptive membrane for the absorption of MO from emulsion system. It is proposed that physico-chemical properties of MO adsorbed at oil-water interface might be less stable than that in aqueous solution or in micellar phase, and affinity of MO to absorptive membrane might be highly increased. However the "activated" state of MO at oil-water interface must be clarified by further experiments.

In past, Engel, *et al.* studied absorption of heparin[19,20] and insulin[21] from the emulsion

18) K. Kakemi, H. Sezaki, S. Muranishi, and A. Kaneda, *Chem. Pharm. Bull.* (Tokyo), **18**, 1563 (1970).
19) R.H. Engel and M.J. Fahrenbach, *Proc. Soc. Exptl. Biol. Med.*, **129**, 772 (1968).
20) R.H. Engel and S.J. Riggi, *J. Pharm. Sci.*, **58**, 1372 (1969).
21) R.H. Engel, S.J. Riggi, and M.J. Fahrenbach, *Nature*, **291**, 856 (1968).

system, and showed interesting results that absorption of those drugs from emulsion were far enhanced in comparison with that from aqueous solution. They also showed that the absorption rates depended on oil concentrations and the rate showed maximum in relation to oil concentration. The apparent situations seem to be resemble very well to the situations of MO. Recently it was also reported that griseofulvin was enhanced its absorption when it was administered with emulsion.[22] It is not clear now whether the absorption rates of these drugs are increased by the common factor. However, the new characteristics of emulsion that poor-absorptive drugs are improved their intestinal absorption when drugs are administered with emulsion will compel us to re-evaluate emulsion as pharmaceutical preparation.

22) P.J. Carrigan and T.R. Bates, *J. Pharm. Sci.*, **62**, 1476 (1973).