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128. Kiichiro Kakemi, Takaichi Arita, and Shozo Muranishi: Absorption and Excretion of Drugs. XXVI.*1 Effect of Water-Soluble Bases on Rectal Absorption of Sulfonamides.

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As suppository materials, water-soluble bases have been utilized extensively, which include polyethylene glycols and glycero-gelatine. Water-soluble bases are generally incorporated in large amount into suppository, and the elucidation of their influence on the rectal absorption of drug, therefore, is very important. Several papers report that the rectal absorption rate of drugs was considerably affected by the bases used.[1~3] However, the effect of water-soluble bases on the rectal absorption have not been studied systematically and this absorption mechanism has not been clarified.

When the drug is administered to the rectum as the water-soluble base suppository, the suppository is dissolved quickly by rectal secreting fluid, and then the drug is absorbed from this aquoeus solution. The drug absorption from the rectum has been explained by the partition to and the diffusion through the lumen lipoid as described in the previous report.[4]

The present investigation was undertaken to clarify the effect of water-soluble base on the rectal absorption in relation to some physicochemical properties, and to discuss the relationship between the drug absorption and the physicochemical property of water-soluble bases. From the results obtained it is clear that the reduction of drug absorption rate by water-soluble bases is due mainly to the decrease of the partition between the vehicle and the lipoid, and it is found that there is a close relationship between dielectric constant of water-soluble bases and the rectal absorption.

Experimental

Absorption Experiments——Procedure of the absorption experiments have been described previously.[4] As phenol red, which is used for the volume change indicator of recirculation fluid, was absorbed in the presence of polyethylene glycols, this indicator was not employed. Accordingly, the recirculation fluid was collected completely by washing with water after recirculation for one hour, and sulfonamides were determined by regular procedure[4].

The drug solution, which contained 0.5 mmole/L. of sulfonamides and various concentrations of water-soluble bases, was prepared with isotonic buffered solution as described in the previous report.[4]

Refractive Indexes——Various amounts of sulfanilacetamide and polyethylene glycol 4000 (PEG 4000) were dissolved in distilled water and refractive index, n, was measured at 37° using Purfrich refactometer. n^2 was shown in Table I, and molecular weight of PEG 4000 was calculated as 3500. The expriment presents a linear relation between n^2 and mole concentrations of sulfanilacetamide and PEG 4000, indicating that the specific interaction between both does not exist.

Solubilities——Buffered solutions (0.264 M citric acid-0.123 M Na_2HPO_4) of a definite pH with varying concentrations of PEG 4000 were previously prepared, and aliquot portion of the solution was placed in glass-stoppered tubes together with excess quantities of sulfonamides. The tubes were placed in 37° bath and equilibrated by occasionally shaking for 18 hr. Aliquot portions of the supernatant liquid were removed, and determined the solubilities.

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1) C.F. Peterson, C.O. Lee, J.E. Christian: J. Am. Pharm. Assoc., Sci. Ed., **42**, 731 (1953).
2) S. Riegelman, W.J. Crowell: J. Am. Pharm. Assoc., Sci. Ed., **47**, 115, 123, 127 (1958).
3) K. Kakemi, T. Arita, S. Muranishi: Arch. Pract. Pharm., **23**, 39 (1963).
4) K. Kakemi, T. Arita, S. Muranishi: This Bulletin, **13**, 861 (1965)

Table I. Refractive Indexes of Sulfanilacetamide and PEG 4000 in Water

PEG 4000

$M\times10$	0	1	2.5	4	5
n^2	1.7716	1.7816	1.7964	1.8112	1.8208

Sulfanilacetamide

$M\times10$	0	1	2.5	4	5
n^2	1.7716	1.7726	1.7740	1.7757	1.7767

Sulfanilacetamide plus PEG 4000

$M\times10$	Sulfanilacetamide	5	4	2.5	1	0
	PEG 4000	0	1	2.5	4	5
n^2		1.7767	1.7854	1.7989	1.8123	1.8208

Apparent pKa's——The aquoeus solution which contained 0.5 mmole/L. sulfonamides and various concentrations of PEG 4000 were prepared. pKa's of sulfonamides were determined by microtitration method using $N/50$ sodium hydroxide solution at 25°.

Apparent Partition Coefficients——Buffered solutions (0.264M citric acid -0.123M Na_2HPO_4 or 0.1M Na_2CO_3 -0.05M $NaHCO_3$) of a definite pH with varying concentrations of PEG 4000 were previously prepared, and the solutions were shaken with organic solvents to be saturated each other. Sulfonamides were dissolved in 0.5 mmole/L. in the aqueous phase, and 4 ml. portions of the solution were equilibrated with equal volumes of the organic solvent phase. These were kept in a water-bath at 37° with removal for vigorous shaking twenty times in two hours period. The drug content was determined in the aqueous phase, and apparent partition coefficients were calculated. PEG 4000 was practically insoluble in isoamylacetate, benzene and heptane.

Dielectric Constants——The measurement of dielectric constants of water-soluble bases and related compounds was followed the phase compensation using DK-59 type (Yanagimoto Co.). The dielectric constant of D-sorbitol was measured using the aqueous solutions of the various concentrations. Apparent dielectric constant of D-sorbitol was represented by extrapolating the measured value of the solutions.

Analytical Methods——The analytical method of sulfonamides has been described.[4]

Results and Discussion

The Effect of Polyethylene Glycol 4000 on the Rectal Absorption of Sulfonamides

Sulfisoxazole, which is much readily absorbed among sulfonamides, was used in this experiment to determine the effect of polyethylene glycol 4000 (PEG 4000) on the rectal absorption. And the aqueous sulfisoxazole solutions incorporated with the various concentrations of PEG 4000 were recirculated with the same manner as the previous report,[4] and the absorption rate was measured. The effect of PEG 4000 on the absorption rate *vs.* pH profile is shown in Fig. 1. The absorption rates of sulfisoxazole in the absence of PEG 4000 coincide fairly with unionized drug fractions, as described in the previous report,[4] indicating that the unionized form of drug is preferentially absorbed. However, the absorption of unionized form was reduced gradually with the increase of the concentration of PEG 4000, and the absorption rate of ionized form in an alkaline region was not changed. When 60% PEG 4000 was used, the sulfisoxazole absorption rate was not affected by change in pH. Plotting the absorption rates of the unionized sulfisoxazole and of the ionized one against the concentration of PEG 4000, Fig. 2 was obtained. Sulfisoxazole exists almost as unionized or ionized form in the solution, at pH 3.2~3.5 or 10.0~11.0 respectively. The same result was obtained with respect to the absorption of sulfapyridine as shown in Fig. 2.

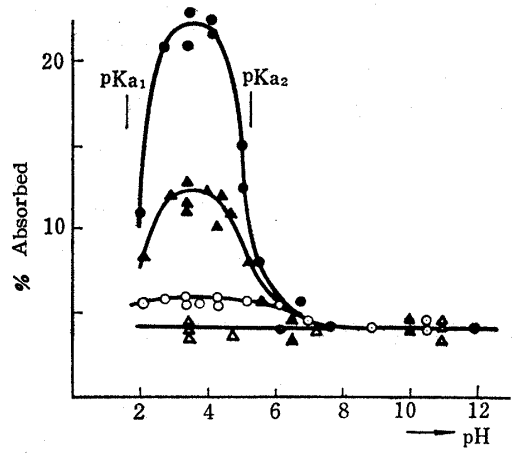

Fig. 1. Effect of PEG 4000 on Rectal Absorption Rate of Sulfisoxazole

●—● PEG 4000 0%
▲—▲ PEG 4000 10%
○—○ PEG 4000 30%
△—△ PEG 4000 60%

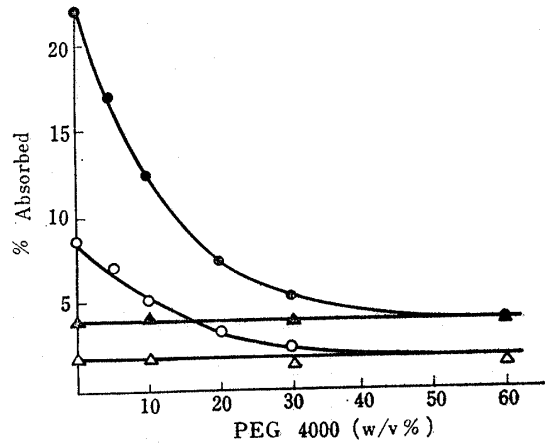

Fig. 2. The Relationship between the Absorption Rate and the Concentration of PEG 4000

Sulfisoxazole ●—● pH 3.2~3.5
▲—▲ pH 10.0~11.0
Sulfapyridine ○—○ pH 5.6~6.1
△—△ pH 11.0~11.6

Interrelation of Sulfonamides and PEG 4000

In order to clarify the cause of the reduction of rectal absorption rate by the addition of PEG 4000, the effect of PEG 4000 on physical property of sulfonamides was investigated.

Possible complex formation by PEG 4000 with many pharmaceuticals (phenol, phenobarbital, salicylic acid and others) were indicated by reports[5,6] of imcompatibilities in polyethylene glycols systems, and if there is possibility of the interaction of sulfonamides with PEG 4000, the drug complex might differ from the free drug itself with respect to its ability to penetrate biologic membranes. However, there is no report about the interaction of sulfonamides and PEG 4000, and therefore to investigate this relation, the refractive index was measured. A specific interaction between sulfonamides and PEG 4000 was not observed as described in Experimental.

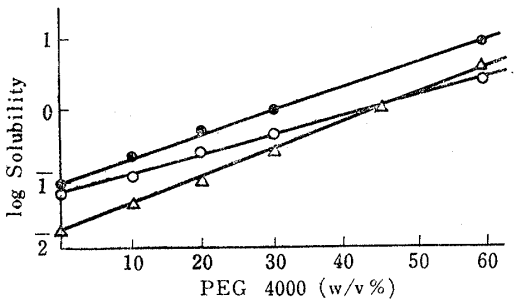

Fig. 3. The Solubility of Sulfonamides in Buffered Solutions Containing Various Concentrations of PEG 4000

●—● Sulfathiazole pH 4.5~4.8
○—○ Sulfapyridine pH 5.6~6.1
△—△ Sulfisoxazole pH 3.2~3.5

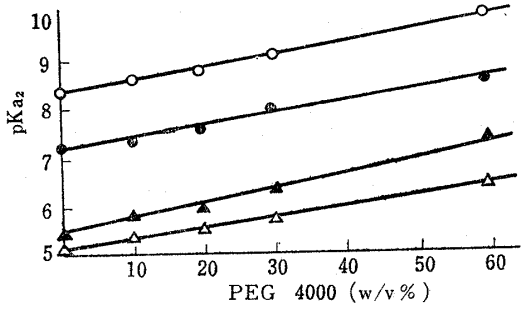

Fig. 4. The Influence of PEG 4000 on the Dissociation Constant of Sulfonamides

●—● Sulfathiazole
○—○ Sulfapyridine
▲—▲ Sulfanilacetamide
△—△ Sulfisoxazole

Furthermore, the solubilities and the ionization constants of sulfonamides in various concentrations of PEG 4000 were determined. Fig. 3 shows the solubility behavior

5) S. W. Goldstein : J. Am. Pharm. Assoc., Pract. Ed., **13**, 250 (1952).
6) T. Higuchi, J. L. Lach : J. Am. Pharm. Assoc., Sci. Ed., **43**, 465 (1954).

of unionized sulfonamides in buffered solutions, indicating a linear relationship between the logarithm of their solubilities and the concentrations of PEG 4000. And the influences of PEG 4000 on depressing the degree of ionization is shown in Fig. 4, where the apparent pKa_2 has been plotted against PEG 4000 concentration. These results show that sulfonamides do not form the complex with PEG 4000, but also these behavior are in agreement with increasing the solubility and depressing the pKa of some weak acids in water-dioxane or water-ethanol mixture reported by Higuchi[7] and Bell.[8] Accordingly, it appears that PEG 4000 influences on the polarity of the sulfonamide solution.

The Effect of PEG 4000 on Organic Solvent : Vehicle Partition of Sulfonamide

PEG 4000 might influence on partition of sulfonamide to rectal membrane lipoid, decreasing the polarity of the fluid, then the apparent partition coefficients were measured at various concentrations of PEG 4000 using isoamyl acetate, benzene and heptane as organic solvents. The aqueous phases in this experiments were the buffered solutions, previously used in the absorption experiments. Fig. 5 shows that apparent partition coefficients of unionized sulfisoxazole are reduced with the increase of the concentrations of PEG 4000, but the change in partition coefficients to every organic solvent was not observed for ionized form, and at the point of 60% concentration of PEG 4000, apparent partition coefficients of unionized and of ionized form were almost same. The similar results were obtained for sulfapyridine, as shown in Fig. 6. A comparison of these curves and the absorption curves (Fig. 2) shows similar patterns in tendency. From the results obtained, it is suggested that the effect of PEG 4000 on the rectal absorption of sulfonamides depends upon depressing the partition to the rectal lipoid.

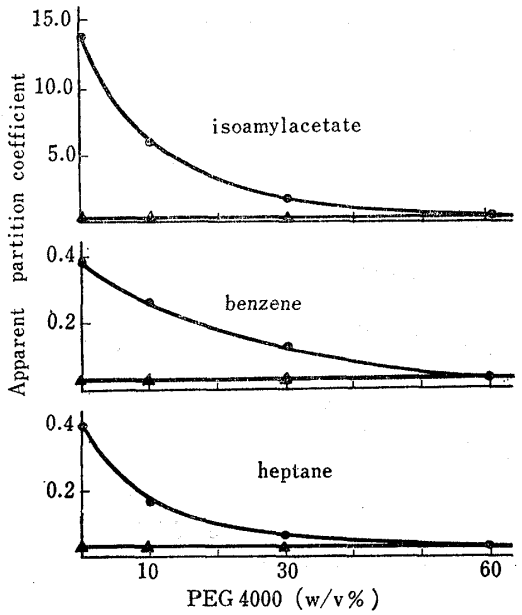

Fig. 5. Influence of PEG 4000 on Apparent Partition Coefficients (organic solvents-vehicle) of Sulfisoxazole

●—● pH 5.6~6.1
▲—▲ pH 11.0~11.6

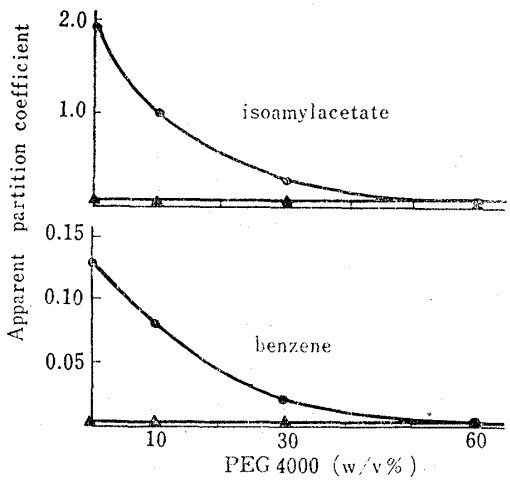

Fig. 6. Influence of PEG 4000 on Apparent Partition Coefficients (organic solvents-vehicle) of Sulfapyridine

●—● pH 5.6~6.1
▲—▲ pH 11.0~11.6

7) T. Higuchi, M. Gupta, L. W. Busse : J. Am. Pharm. Assoc., Sci. Ed., 42, 167 (1953).
8) R. P. Bell, R. R. Robinson : Trans. Faraday Soc., 56, 765 (1961).

The Effect of Various Water-Soluble Bases on the Rectal Absorption of Sulfonamides

As the differences in sulfonamides absorption rate may exist when the various water-soluble bases are incorporated, attempts were made to compare the sulfonamides absorption rates in the presence of polyethylene glycols and their related compounds.

First, the regulation in the effects of water-soluble bases on the absorption was investigated. From the data, the relationship between the absorption rate of unionized sufonamides and the concentration of PEG 4000 could be expressed as follows :

$$\log(A-A_0) = -Kc \cdot C + R$$

where A is the rate of absorption of unionized sulfonamide, A_0 is the rate of absorption of ionizod sulfonamide, C is the concentration of water-soluble base, and Kc and R are constants. From this equation, a plot of the logarithm of $(A-A_0)$ against C shows a straight line, the slope of the line represents Kc, and the Y-intercept represents R. The rate of absorption of ionized sulfonamide is corresponding to the minimum value of the absorption rate of unionized sulfonamide, and these values of sulfisoxazole, sulfaethylthiadiazole and sulfapyridine were respectively 4.0, 0.7, and 2.0%. Fig. 7 shows the effect of various polyethylene glycols on the rectal absorption of sulfisoxazole, where log $(A-A_0)$ has been plotted against C, and each spot represents the mean of three animals. In each polyethylene glycol a good linearity exists among the spots.

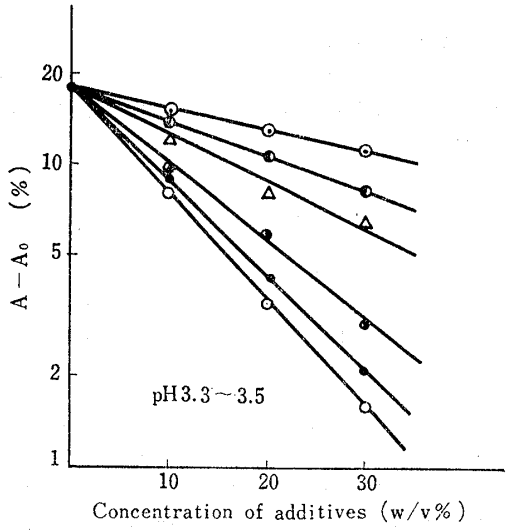

Fig. 7. Effect of Polyethylene Glycols on Rectal Absorption of Unionized Sulfisoxazole

⊙—⊙ Ethylene glycol ◑—◑ PEG 400
◐—◐ Diethylene glycol ●—● PEG 1500
△—△ Triethylene glycol ○—○ PEG 4000
Each spot is expressed as the mean of three animals.

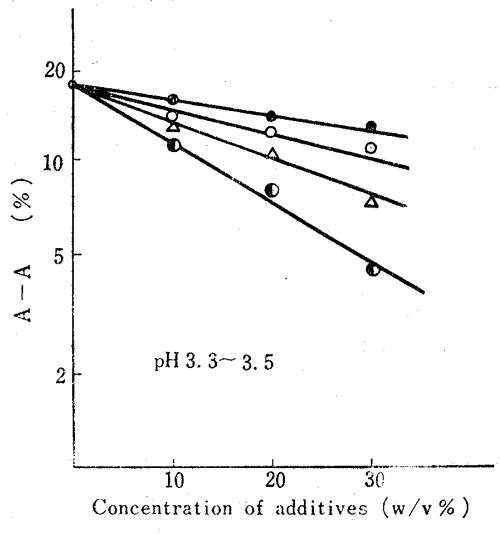

Fig. 8. Effect of the Related Compounds of Polyethylene Glycols on Rectal Absorption of Unionized Sulfisoxazole

●—● D-sorbitol
○—○ Glycerin
△—△ Propylene glycol
◐—◐ Dipropylene glycol

Glycerine, propylene glycol, dipropylene glycol and D-sorbitol were incorporated in the recirculation fluid as the related compounds of polyethylene glycols, and the effect of these compounds on the absorption of sulfisoxazole was studied as shown in Fig. 8. The good linearity exists among the spots in each compound.

Furthermore, the effects of the various water-soluble bases and related compounds on the absorption of sulfaethylthiadiazole and sulfapyridine were studied similarly. The good linearities exist also in both sulfonamides as shown in Figs. 9 and 10.

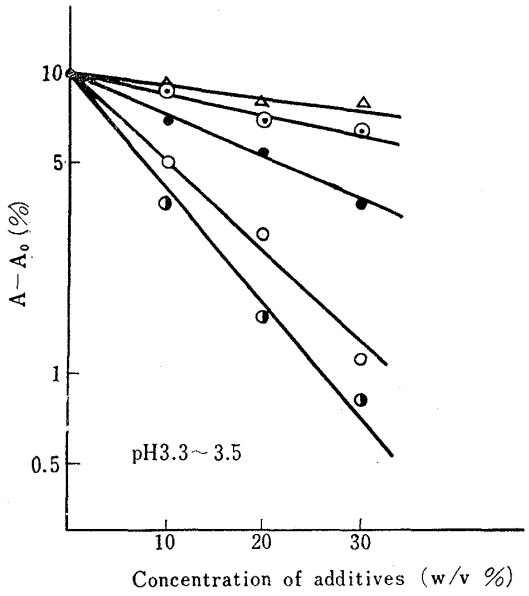

Fig. 9. Effect of Various Water-Soluble Bases on Rectal Absorption of Unionized Sulfaethylthiadiazole

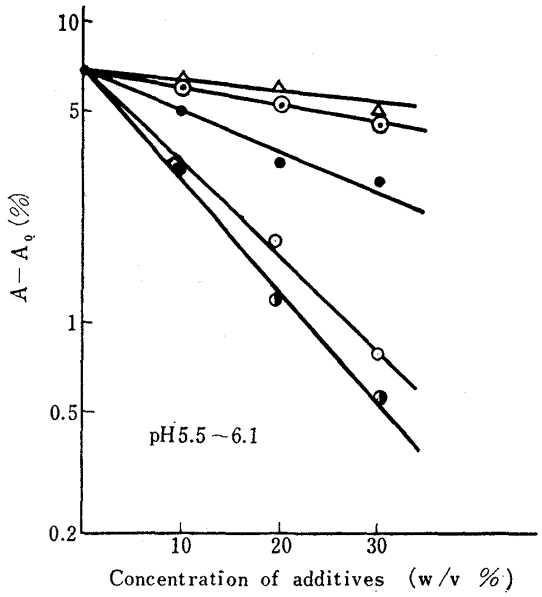

Fig. 10. Effect of Various Water-Soluble Bases on Rectal Absorption of Unionized Sulfapyridine

△—△ D-sorbitol
⊙—⊙ Glycerin
●—● Triethylene glycol
○—○ PEG 1500
◑—◑ PEG 4000

Table II. Kc Values of Sulfonamides

	Sulfisoxazole	Sulfaethylthiadiazole	Sulfapyridine
Ethylene glycol	0.75		
Diethylene glycol	1.21		
Triethylene glycol	1.60	1.42	1.48
PEG 400	2.45		
PEG 1500	3.11	2.95	3.14
PEG 4000	3.50	3.80	3.51
Glycerin	0.78	0.74	0.68
Propylene glycol	1.21		
Dipropylene glycol	1.93		
D-sorbitol	0.52	0.46	0.49

For Figs. 7～10, Y-intercept (R) were depending on the kinds of sulfonamides, but Table II shows that Kc's (the slopes of the lines) present almost the same values among three sulfonamides. Accordingly, it is concluded that Kc is a constant, which depends upon the water-soluble bases or the related compounds, and R is a constant, which depends upon the sulfonamides. From the results obtained, it is clear that the rectal absorption rate of sulfonamides is reduced with the addition of water-soluble bases or related compounds, and the differences exist remarkably in the effect of these various bases on the absorption, but the degree of the effect of a certain water-soluble base is constant regardless of the kinds of sulfonamides. And it is also indicated that the higher the molecular weight of the polyethylene glycols, the larger the effect on rectal absorption of sulfonamides.

The Relationship between the Dielectric Constant of Water-Soluble Bases and the Absorption Rate of Sulfonamides

The relationship between the physical property of water-soluble bases and the effect on the rectal absorption of sulfonamides was investigated. As described in the

previous section, it is suggested that PEG 4000 affects on the partition of drug to the rectal membrane in the absorbing process from the vehicle. The partition of drug between lipoidal phase and aqueous phase might depend mainly upon the polarities of both phases, and since the polarity of aqueous phase is decreasing with the addition of water-soluble base, the partition of drug must be decreased. From these viewpoints, the dielectric constant of water-soluble base was selected as a major factor.

Table III. Dielectric Constants of Various Water-Soluble Bases and Related Compounds

	ε
Ethylene glycol	41.8
Diethylene glycol	31.7
Triethylene glycol	23.7
PEG 400	13.7
PEG 1500	10.8
Glycerin	43.0
Propylene glycol	29.5
Dipropylene glycol	20.5
D-sorbitol	53.5

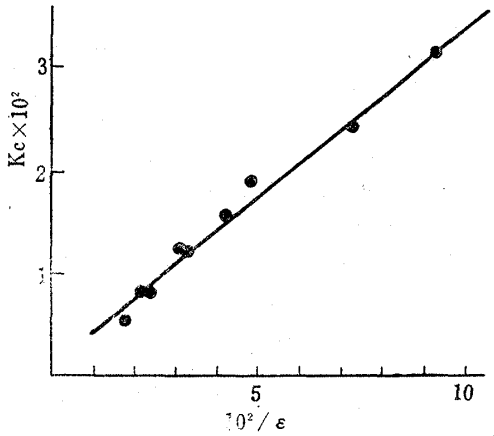

Fig. 11. Relationship between Kc and Reciprocal Dielectric Constant

The dielectric constants of water-soluble bases and related compounds measured at 20° were listed in Table III. These dielectric constants, ε's were plotted against Kc obtained experimentally in sulfisoxazole, indicating that the correlation exists between ε and Kc. And plots of reciprocals of the dielectric constants against Kc's indicated a near-linear relation, as shown in Fig. 11. This shows that the larger the dielectric constant of water-soluble base, the smaller Kc.

From results obtained, it is clear that there is the evident correlation between the dielectric constant of water-soluble bases and the rectal absorption rate of sulfonamides, and the smaller the dielectric constant of water-soluble base, the more the absorption rate is reduced. Therefore, it also appears that the reduction of sulfonamides absorption by incorporating with water-soluble base can be interpreted by the depression of the polarity in the vehicle.

This investigation was supported in part by grants-in-aid from the Smith Kline and French Laboratories Fund.

Summary

The rates of absorption of sulfonamides were measured in the presence of a number of water-soluble bases. The absorption rates was reduced by these bases. This reduction depends mainly upon their decrease of lipid-vehicle partition. The differences existed in their absorption at incorporating the various water-soluble bases, and these differences are related to the dielectric constants of the bases: the larger their dielectric constant, the smaller the reduction of rectal absorption. The results suggest that the drug absorption in the presence of water-soluble bases can be interpreted by the depression of the polarity in the vehicle.

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