UDC 615.412-011 : 615.778.25[612.38]

134. Keiji Sekiguchi and Noboru Obi : Studies on Absorption of Eutectic Mixture. I. A Comparison of the Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man.*2

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The absorption of a drug is influenced by several factors, such as the physical form of the preparation, site of application, and the presence of other active ingredients. In oral administration of a powdered medicine, it is assumed that the rate of absorption is largely dependent upon its rate of solution which is a function of particle size. Reinhold, *et al.*[1] found that patients receiving microcrystalline suspension of sulfadiazine showed significantly higher concentrations in serum and larger excretion in urine during the first 6 hours than those who received the ordinary form. Similar investigation concerning the absorption and excretion of acetylsalicylic acid was reported by Nogami and Kato.[2] They concluded that the finer the crystals were, the better therapeutic effect could be expected.

A eutectic mixture is composed of microscopically fine crystals of each component, mixed very intimately. If a eutectic mixture is composed of a slightly soluble drug and an inactive, easily soluble compound, it will be disintegrated by water or intestinal fluid into finely divided particles of the former. As this suspension has much greater surface area, the rate of solution will be improved and the drug will be readily absorbed.

In the present work, an attempt was made to obtain eutectic mixtures containing sulfathiazole as one component by thermal analysis and the difference in the rate of absorption and excretion was examined between ordinary sulfathiazole and sulfathiazole-urea eutectic mixture, which was selected as a suitable one to test the idea mentioned above.

Experimental and Results

Thermal Analysis——Thermal analysis was carried out on six kinds of two-componental system. One component was sulfathiazole and the second component was urea, *l*-ascorbic acid, acetamide, nicotinic acid, or succinimide. The phase diagrams thus obtained are shown in Figs. 1~6. These

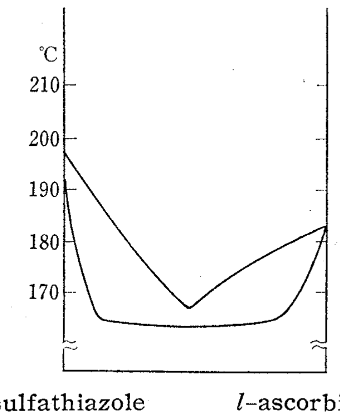

Fig. 1. Sulfathiazole and *l*-Ascorbic acid

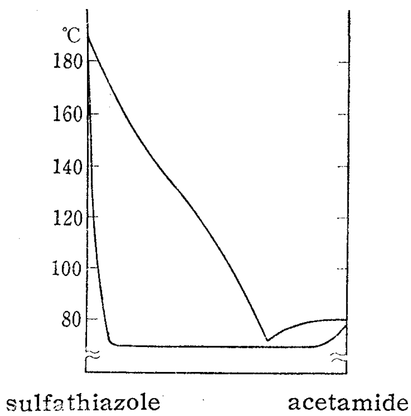

Fig. 2. Sulfathiazole and Acetamide

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*2 A part of this paper was presented at the Hokkaido Local Meeting of the Pharmaceutical Society of Japan, June, 1959.

1) J. Reinhold, F. Phillips, H. Flippin : Am. J. Med. Sci., **210**, 141 (1945).
2) H. Nogami, Y. Kato : Yakuzaigaku, **15**, 152 (1955).

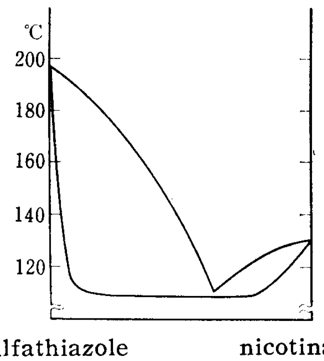

Fig. 3. Sulfathiazole and Nicotinamide

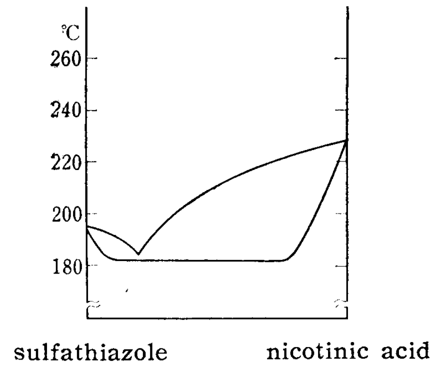

Fig. 4. Sulfathiazole and Nicotinic acid

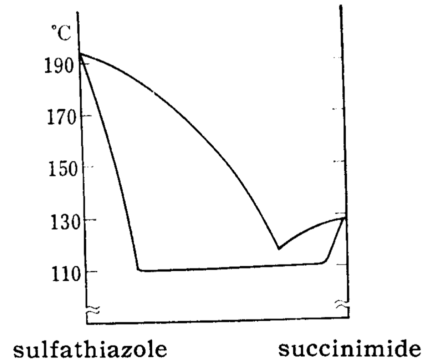

Fig. 5. Sulfathiazole and Succinimide

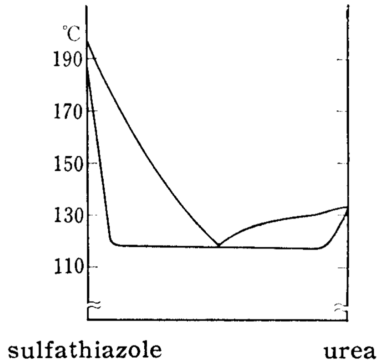

Fig. 6. Sulfathiazole and Urea

results indicate that all of the soluble compounds used form eutectic mixtures with sulfathiazole. In the system of sulfathiazole and urea, the eutectic mixture is composed of 52% of sulfathiazole and 48% of urea by weight and melts at 112°.

Preparation of Eutectic Mixture of Sulfathiazole and Urea——Sulfathiazole and urea were weighed in a platinum crucible in the desired proportion of the composition of eutectic mixture. They were mixed thoroughly and carefully heated just above the eutectic point using an electric furnace. The melted mixture was cooled rapidly in an ice-bath under vigorous stirring until solidification. The white mass thus obtained was very hard and was crushed in a mortor with a pestle. As shown in Photo. 1, crystals of sulfathiazole and urea in eutectic mixture of sulfathiazole and urea are very fine and uniform in size (1~2 μ). When the granules of eutectic mixture of sulfathiazole and urea are shaken with water, a suspension of microcrystalline sulfathiazole is formed (Photo. 2). Photo. 3 is a photomicrogram of sulfathiazole particles in this suspension. For absorption study, the particle size of ordinary sulfathiazole and eutectic mixture of sulfathiazole and urea were adjusted to between 50 and 100 mesh by sieving.

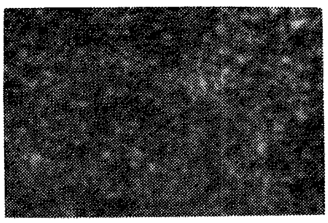

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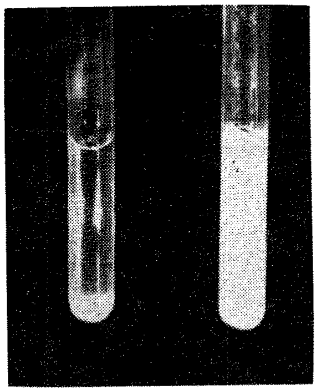
Photo. 1. Eutectic Mixture of Sulfathiazole and Urea



(A) (B)

Photo. 2. Suspension is not formed from ordinary sulfathiazole (A) but easily formed from a eutectic mixture (B)

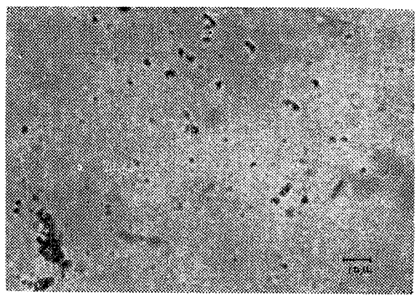
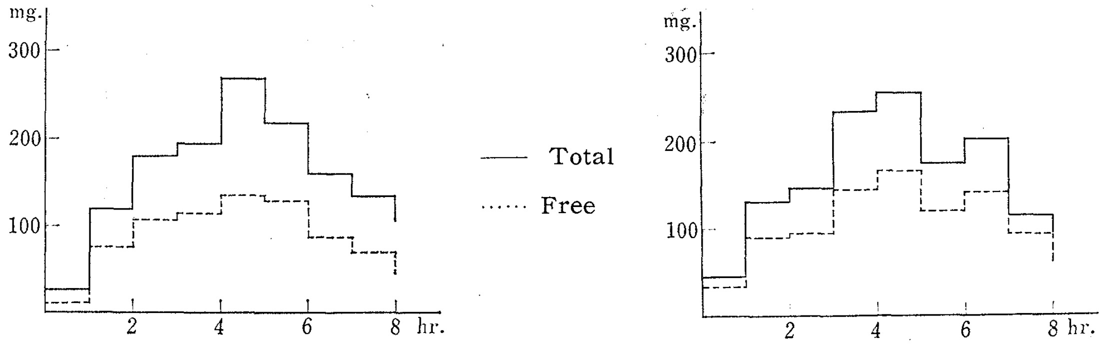


Photo. 3. Sulfathiazole suspension prepared from Eutectic Mixture

Effect of Urea in Simple Mixture of Ordinary Sulfathiazole and Urea on the Absorption and Excretion of Sulfathiazole——To examine the effect of urea on absorption and excretion of sulfathiazole, comparison of ordinary sulfathiazole and a simple mixture of sulfathiazole and urea was made. Two adult human subjects were each given an oral dose of 2.0 g. of ordinary sulfathiazole. Blood and urine specimens were taken at certain intervals, and free and total sulfathiazole were determined by the modified Bratton-Marshall method with Tsuda's coupling reagent,[3] using Hitachi Photoelectric Spectrophotometer, Type EPU-II, at 550 mμ. Nine days later, the experiment was repeated on the same subjects with a simple mixture of sulfathiazole and urea containing 2.0 g. of each. The results shown in Fig. 7 indicate that the absorption of sulfathiazole is not affected by the presence of urea.



(A) Average Amount excreted in Urine after Ingestion of Ordinary Sulfathiazole

(B) Average Amount excreted in Urine after Ingestion of Simple Mixture of Ordinary Sulfathiazole and Urea

Fig. 7.

Comparison of the Absorption of Ordinary Sulfathiazole and Eutectic Mixture——Two g. of sulfathiazole and equivalent dose of eutectic mixture of sulfathiazole and urea were alternately administered by mouth to a healthy adult, 6 times in turn. In the first experiment, blood and urine specimens were taken at every one hour after dosage, and in the other experiments, only urine was collected at the same time intervals. All specimens were analyzed colorimetrically for free and total sulfathiazole. Results of the analyses on blood and urine are shown in Tables I to III, and in Figs. 8~11. Data in Table I and Figs. 8 and 9 indicate a correlation between sulfathiazole concentration in blood and its quantity excreted in urine. The correlation coefficient for total sulfathiazole calculated is 0.88 and this is highly significant. Accordingly, the difference of absorption between ordinary sulfathiazole and eutectic mixture of sulfathiazole and urea can be estimated by the amount of sulfathiazole excreted in urine. Tables II and III, and Fig. 11 show the trends of free and total sulfathiazole excreted in urine following ingestion of eutectic mixture of sulfathiazole. Statistical treatment[4] of the two excretion curves of free and total sulfathiazole indicates

Table I. Concentration of Sulfathiazole in Blood and its Amount excreted in Urine after Ingestion of Eutectic Mixture and Ordinary Sulfathiazole

Time after ingestion (hr.)	Eutectic mixture				Ordinary sulfathiazole			
	Concn. in blood (mg. %)		Amt. excreted in urine (mg.)		Concn. in blood (mg. %)		Amt. excreted in urine (mg.)	
	total	free	total	free	total	free	total	free
1	1.9	1.8	38	31	1.3	1.2	19	12
2	4.0	3.4	153	111	2.0	1.8	87	68
3	5.0	4.6	197	136	2.6	2.3	132	95
4	3.7	3.2	173	121	3.0	2.5	142	102
5	3.4	2.8	137	90	3.2	2.6	177	114
6	2.4	2.0	121	79	3.2	2.5	160	97
7	2.0	1.4	126	70	2.6	2.0	119	63
8	1.6	1.4	92	49	2.2	1.5	98	50

3) A. Bratton, E. Marshall, *et al.* : J. Biol. Chem., **128**, 537 (1939); K. Tsuda : Yakugaku Zasshi, **62**, 362 (1942).
4) M. Masuyama : J. Meteorol. Soc. Japan, **21**, 385 (1943).

Table II. Amount of Sulfathiazole (mg.) excreted in Urine after Ingestion of Eutectic Mixture

No. of ingestion \ Time after ingestion (hr.)		1	2	3	4	5	6	7	8
1	total	38	153	197	173	137	121	126	92
	free	31	111	136	121	90	79	70	49
2	total	26	92	122	179	166	159	126	91
	free	20	69	94	126	136	120	89	58
3	total	69	163	190	179	152	119	105	91
	free	52	114	135	118	91	82	61	51
4	total	44	146	158	137	162	183	127	111
	free	27	106	129	119	104	111	80	68
5	total	25	107	160	134	135	125	103	72
	free	20	88	112	103	104	96	81	53
6	total	65	160	180	165	137	128	118	102
	free	48	112	126	113	103	85	69	58
mean	total	45	137	168	161	148	139	118	93
	free	33	100	122	117	105	96	75	56

Table III. Amount of Sulfathiazole (mg.) excreted in Urine after Ingestion of Ordinary Sulfathiazole

No. of ingestion \ Time after ingestion (hr.)		1	2	3	4	5	6	7	8
1	total	19	87	132	142	177	160	119	98
	free	12	68	95	102	114	97	63	50
2	total	18	85	131	139	118	101	77	60
	free	13	65	89	92	81	65	47	37
3	total	12	45	116	137	148	161	114	99
	free	9	33	90	96	100	104	88	58
4	total	17	77	141	166	184	125	119	93
	free	12	64	100	110	145	94	76	63
5	total	17	74	96	116	78	95	81	68
	free	13	52	68	74	60	65	48	38
6	total	14	75	132	120	128	128	147	76
	free	10	62	92	87	89	76	88	47
mean	total	16	74	125	137	139	128	110	82
	free	12	57	89	94	98	84	68	49

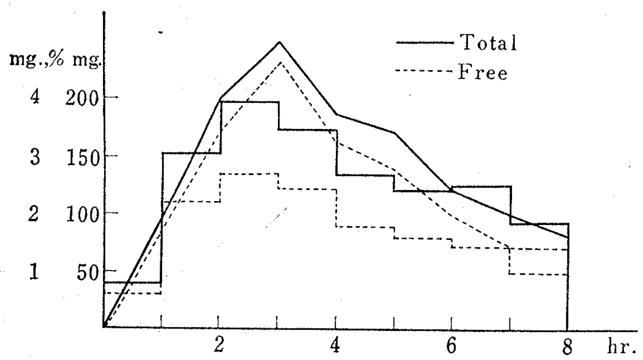


Fig. 8. Concentration in Blood (curve) and Amount excreted in Urine (histogram) after Ingestion of Eutectic Mixture

that the difference is significant for the first 4 hr., although the rate of fall after 5 hr. is about the same for both preparations. Therefore, it may be said that a eutectic mixture produces higher blood levels than ordinary sulfathiazole and the rate of absorption is greater during the initial period.

Solubility of Sulfathiazole in the Presence of Urea——Solutions of various concentrations of urea in simulated gastric juice were prepared.[5] These were stirred with excess sulfathiazole in a

5) Simulated gastric juice : 5 g. of saccharated pepsin and 10 cc. of HCl (d=1.18) are dissolved in distilled water to make 1000 cc.

TABLE IV. Statistical Treatment of the Difference between the Two Curves (in Fig. 11) for the First Four Hours

$$F_0=\frac{(M+N-k-1)\times M\times N}{k(M+N)}\sum_{\alpha=1}^{m}\sum_{\beta=1}^{n}\varphi_{\alpha\beta}(\bar{x}_\alpha-\bar{y}_\alpha)(\bar{x}_\beta-\bar{y}_\beta)$$

M No. of ingestion of eutectic mixture =6
N No. of ingestion of ordinary sulfathiazole =6
k No. of determination of sulfathiazole in each ingestion =4
x Amount excreted after ingestion of eutectic mixture
y Amount excreted after ingestion of ordinary sulfathiazole
α, β Time after ingestion $(m, n=4)$
$\varphi_{\alpha\beta}$ cofactor/determinant $\phi_{\alpha\beta}$

$$\phi_{\alpha\beta}=\sum_{i=1}^{M}(x_{i\alpha}-\bar{x}_\alpha)(x_{i\alpha}-\bar{x}_\beta)+\sum_{i=1}^{N}(y_{i\alpha}-\bar{y}_\alpha)(y_{i\beta}-\bar{y}_\beta)$$

$$\bar{x}_\alpha=\sum_{i=1}^{M}x_{i\alpha}/M \qquad \bar{y}_\alpha=\sum_{i=1}^{N}y_{i\alpha}/N$$

A) Total

$\phi_{\alpha\beta}$

$\beta \backslash \alpha$	1	2	3	4
1	1822	2596	1710	711
2	2596	5608	4054	672
3	1710	4054	5182	1475
4	711	672	1475	3713

Cofactor $\times 10^{-10}$

$\beta \backslash \alpha$	1	2	3	4
1	+4.0374	−2.2032	+0.5613	−0.5974
2	−2.2032	+2.1202	−1.0627	+0.4603
3	+0.5613	−1.0627	+1.1738	−0.3815
4	−0.5964	+0.4603	−0.3815	+0.7676

$(\bar{x}_\alpha-\bar{y}_\alpha)(\bar{x}_\beta-\bar{y}_\beta)$

$\beta \backslash \alpha$	1	2	3	4
1	841	1827	1247	696
2	1827	3969	2709	1512
3	1247	2709	1849	1032
4	696	1512	1032	576

$$\text{determinant } \phi_{\alpha\beta}=\begin{vmatrix}\phi_{11} & \phi_{12} & \phi_{13} & \phi_{14}\\ \phi_{21} & \phi_{22} & \phi_{23} & \phi_{24}\\ \phi_{31} & \phi_{32} & \phi_{33} & \phi_{34}\\ \phi_{41} & \phi_{42} & \phi_{43} & \phi_{44}\end{vmatrix}=2.1718\times10^{13}$$

$\varphi_{\alpha\beta}$ $\times 10^4$

$\beta \backslash \alpha$	1	2	3	4
1	+18.591	−10.145	+ 2.585	− 2.731
2	−10.145	+ 9.763	− 4.893	+ 2.119
3	+ 2.585	− 4.893	+ 5.405	− 1.757
4	− 2.751	+ 2.119	− 1.757	+ 3.534

$$\sum_{\alpha=1}^{4}\sum_{\beta=1}^{4}\varphi_{\alpha\beta}(\bar{x}_\alpha-\bar{y}_\alpha)(\bar{x}_\beta-\bar{y}_\beta)=0.554$$

$$F_0=\frac{(6+6-4-1)}{4\times(6+6)}\times 0.554=4.33$$

$P_r\{F>F_0\}<0.05$

$n_1=k \quad =4$

$n_2=M+N-k-1=7$

B) Free

$\phi_{\alpha\beta}$

$\beta \backslash \alpha$	1	2	3	4
1	979	1012	581	−10
2	1012	2462	1653	112
3	581	1653	1922	580
4	−10	112	580	1091

Cofactor $\times 10^{-7}$

$\beta \backslash \alpha$	1	2	3	4
1	+154.3946	− 76.4147	+ 19.3593	− 1.0321
2	− 76.4147	+134.8320	−105.3792	+ 41.4799
3	+ 19.3593	−105.3792	+149.7501	− 68.6150
4	− 1.0321	+ 41.4799	− 68.6150	+116.1921

$(\bar{x}_\alpha-\bar{y}_\alpha)(\bar{x}_\beta-\bar{y}_\beta)$

$\beta \backslash \alpha$	1	2	3	4
1	441	903	693	483
2	903	1849	1419	989
3	693	1419	1089	759
4	483	989	759	529

determinant $\phi_{\alpha\beta}=8.5079\times10^{11}$

$\varphi_{\alpha\beta}$ $\times 10^4$

$\beta \backslash \alpha$	1	2	3	4
1	+18.1472	− 8.9816	+ 2.2755	− 0.1213
2	− 8.9816	+15.8479	−12.3861	+ 4.8755
3	+ 2.2755	−12.3861	+17.6013	− 8.0649
4	− 0.1213	+ 4.8755	− 8.0649	+12.9518

$$\sum_{\alpha=1}^{4}\sum_{\beta=1}^{4}\varphi_{\alpha\beta}(\bar{x}_\alpha-\bar{y}_\alpha)(\bar{x}_\beta-\bar{y}_\beta)=1.239$$

$$F_0=\frac{(6+6-4-1)}{4\times(6+6)}\times 1.239=6.51$$

$P_r\{F>F_0\}<0.05$

$n_1=k \quad =4$

$n_2=M+N-k-1=7$

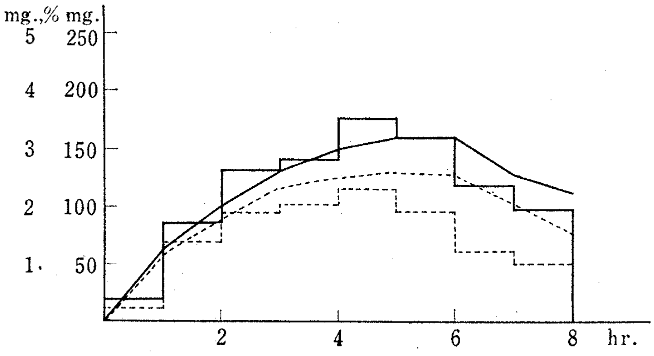


Fig. 9. Concentration in Blood (curve) and Amount excreted in Urine (histogram) after Ingestion of Ordinary Sulfathiazole

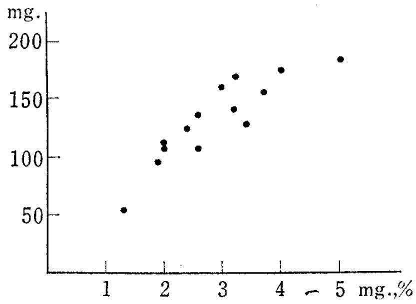


Fig. 10. Scatter Diagram of Total Sulfathiazole Concentration in Blood to Total Sulfathiazole excreted in Urine

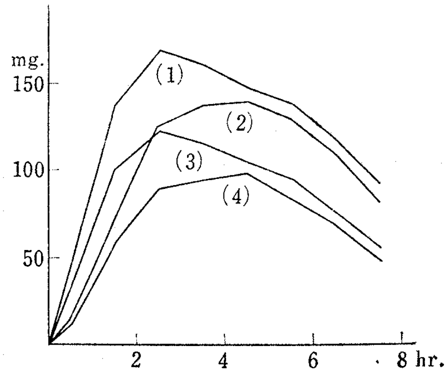


Fig. 11. Average Amount of Sulfathiazole in Urine at Timed Intervals after Ingestion

(1) eutectic mixture total
(2) ordinary sulfathiazole total
(3) eutectic mixture free
(4) ordinary sulfathiazole free

thermostat for 3 hr. at 25°±0.1°. Saturated solutions were taken by a pippet equipped with a small filter. After suitable dilution and adjustment to pH below 1,[6] optical density was measured at 280 mμ against water as a blank. No increased solubility of sulfathiazole in the presence of urea was observed, as shown in Fig. 12.

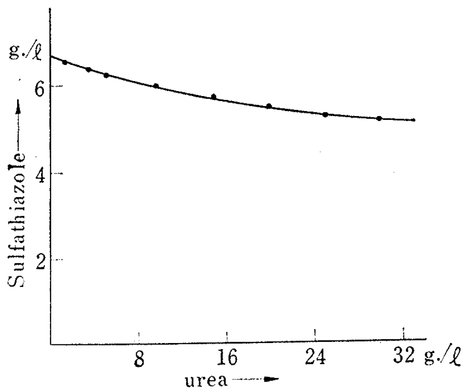


Fig. 12. Solubility Change of Sulfathiazole in the Presence of Urea

6) Absorption spectrum of sulfathiazole solution varies with pH but it becomes constant below pH 1.

Discussion

The observation presented here indicates that in an ordinary mixture of sulfathiazole and urea, urea itself does not enhance the absorption of sulfathiazole, either physiologically or physicochemically. When a eutectic mixture of sulfathiazole and urea is administered by mouth, blood level of sulfathiazole reaches the maximum sooner, and the amount absorbed and excreted increase obviously. There is little doubt that this difference must be attributed to the fact that microcrystalline suspension of sulfathiazole is more easily formed in the intestine and accordingly, the rate of solution becomes larger after administration of sulfathiazole in a eutectic form.

Frem these findings, it is generally supposed that medicines that can form a eutectic mixture with easily soluble compounds will be absorbed more rapidly when administered orally. This may give some means of adjusting the therapeutic effect of a medicine.

The authors are deeply grateful for the great encouragement of Prof. H. Hayashi throughout this work.

Summary

1) Sulfathiazole forms eutectic mixtures with urea, *l*-ascorbic acid, acetamide, nicotinic acid, nicotinamide, or succinimide. It was observed that a eutectic mixture of sulfathiazole and urea produces a microcrystalline suspension of sulfathiazole in water.

2) Sulfathiazole in a eutectic mixture with urea shows higher absorption and excretion after oral administration than ordinary sulfathiazole.

3) Since urea does not possess solubilizing action on sulfathiazole and also it does not enhance absorption of the drug physiologically, the accelerated absorption or excretion must be attributed to the physical state of sulfathiazole in its eutectic mixture with easily soluble compound, such as urea.

4) It is assumed that this new form of preparation will give a means of adjusting therapeutic effect of medical compounds.

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