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Summary

N-[(4(or 7)-Methoxy-2-benzimidazolyl)methyl]maleimide (Ⅲa) was synthesized as "fluorescence-labeled" protein-sulfhydryl reagent. Polyphosphoric acid was proposed to be a general reagent for imide cyclization reaction. Fluorescent characteristics of some benzimidazole derivatives were described.

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19. Keiji Sekiguchi, Noboru Obi, and Yoshio Ueda: Studies on Absorption of Eutectic Mixture. II.*1,*2 Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits.

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Adjustment of the absorption rate of some kinds of medicinals is an important problem in order to improve their therapeutic effectiveness. For this purpose, chemical, physical and physiological devices were hitherto employed. Immediate or prolonged action is often achieved by modifying the chemical constitution of the original drug compound. For example, prolonged stay of sulfonamides in the body is accomplished by adding some functional groups to their main structure. Physical techniques applied to preparations, such as coated or multi-layered tablets are also effective for the purpose of obtaining desired therapeutic results. Administration of a physiologically active adjuvant, such as probenecid in penicilline therapy, often changes the duration interval.

In the preceding paper, the authors reported that the eutectic mixture of sulfathiazole and urea showed sooner absorption and higher blood levels of sulfathiazole than the ordinary one or their simple mechanical mixture, when administered by oral route. The method for adjusting the rate of absorption by preparing a fused conglomerate is the one entirely different from those that have been attempted in literature, and is thought to have wide applicability.

In the present paper, the authors investigate some physico-chemical properties of the fused conglomerates of chloramphenicol and urea, and examine the effects of them on the absorption of the antibiotics in rabbits.

Experimental and Results

Materials——Size enlargement of chloramphenicol was done by recrystallizing the commercial product from H_2O.*4 Na-CMC was J.P. grade. Urea and other chemicals used were analytical grade.

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*1 Presented at the 81st Annual Meeting of the Pharmaceutical Society of Japan, July, 1961.
*2 Part I. K. Sekiguchi, N. Obi: This Bulletin, **9**, 866 (1961).
*3 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (関口慶二, 小尾 陞, 上田芳雄).
*4 The authors are indebted to Sankyo Co., Ltd. for the supply of the commercial product.

Thermal Analyses——For the system of chloramphenicol and urea, a phase diagram of eutectic type was obtained by the modified thaw-melt method.[1] The eutectic mixture has a composition of 76% of chloramphenicol and 24% of urea by weight, and melts completely at 104° (Fig. 1 and Table I). In order to ascertain the results by the visual method and to examine whether the two components are partially miscible or not, differential thermal analyses were conducted with a semi-micro DTA apparatus using a couple of thermisters for detecting temperature difference. Results shown in Fig. 2 indicate that the eutectic temperature is very nearly the same as the one by the former method and the type of the diagram belongs practically to that of the simple eutectic. No polymorphic forms of the antibiotics were found both with the ordinary and the fused ones between room temperature and its melting point at the atmospheric pressure. The fact that higher values of melting points were obtained in DTA is attributed to the lack of agitation of the samples.

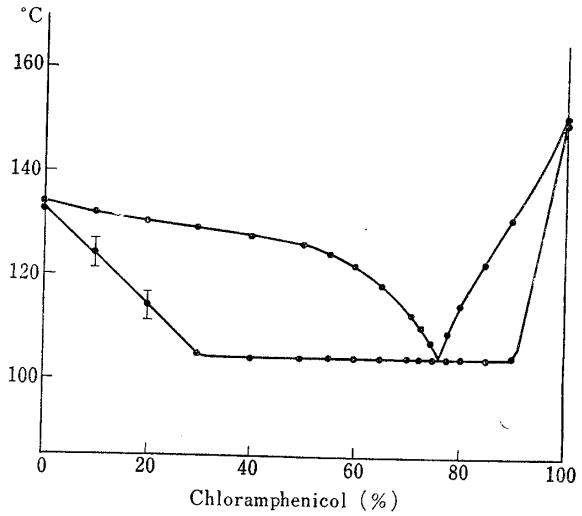


Fig. 1. Phase Diagram of Urea and Chloramphenicol System

Sample Preparation——Samples for absorption, dissolution and solubility studies were listed in Table II, and were prepared as follows.

Table I. Thermal Analysis of Urea and Chloramphenicol System by the Modified Thaw-melt Method

Weight % of CM	Physical mixt.		Evaporated mixt.[a]	
	t.p. (°C)	m.p. (°C)	t.p. (°C)	m.p. (°C)
0.0	132.7	133.5	132.8	133.8
5.6	110~116	132.8		
10.0	106~109	132.0	121~127	132.5
14.8	105.5	131.5		
20.0	105.3	131.0	111~117	130.5
25.0	105.5	130.0		
29.6	105.2	129.5	105.0	129.2
40.0	105.0	127.7	104.2	127.8
49.7	105.0	125.0	104.2	126.2
55.0			104.0	123.8
60.0	105.0	122.5	104.2	122.0
65.0			104.0	118.2
70.0	105.0	116.0	104.2	112.2
72.1			104.0	110.5
75.0	105.0	108.5	104.2	107.2
77.7			104.0	109.5
80.0	105.0	116.0	104.2	114.5
85.0	105.0	123.5	104.2	122.5
90.0	105.0	130.5	104.5	131.0
95.0	105.5	140.0		
100.0	147.5	149.0	149.5	151.0

a) The evaporated mixtures were prepared using ethanol as solvent.

i) Fused mixtures: Mixtures of both components, weighed in specified proportions were carefully heated with stirring until they melted completely, using a paraffin bath or an electric furnace. After fusion, they were poured onto a stainless steel plate and were solidified. The solid masses were then crushed down and the particles were adjusted between 150 and 300 μ (50~100 mesh) using sieves of JIS series.

1) K. Sekiguchi, *et al.*: This Bulletin, **11**, 1108 (1963).

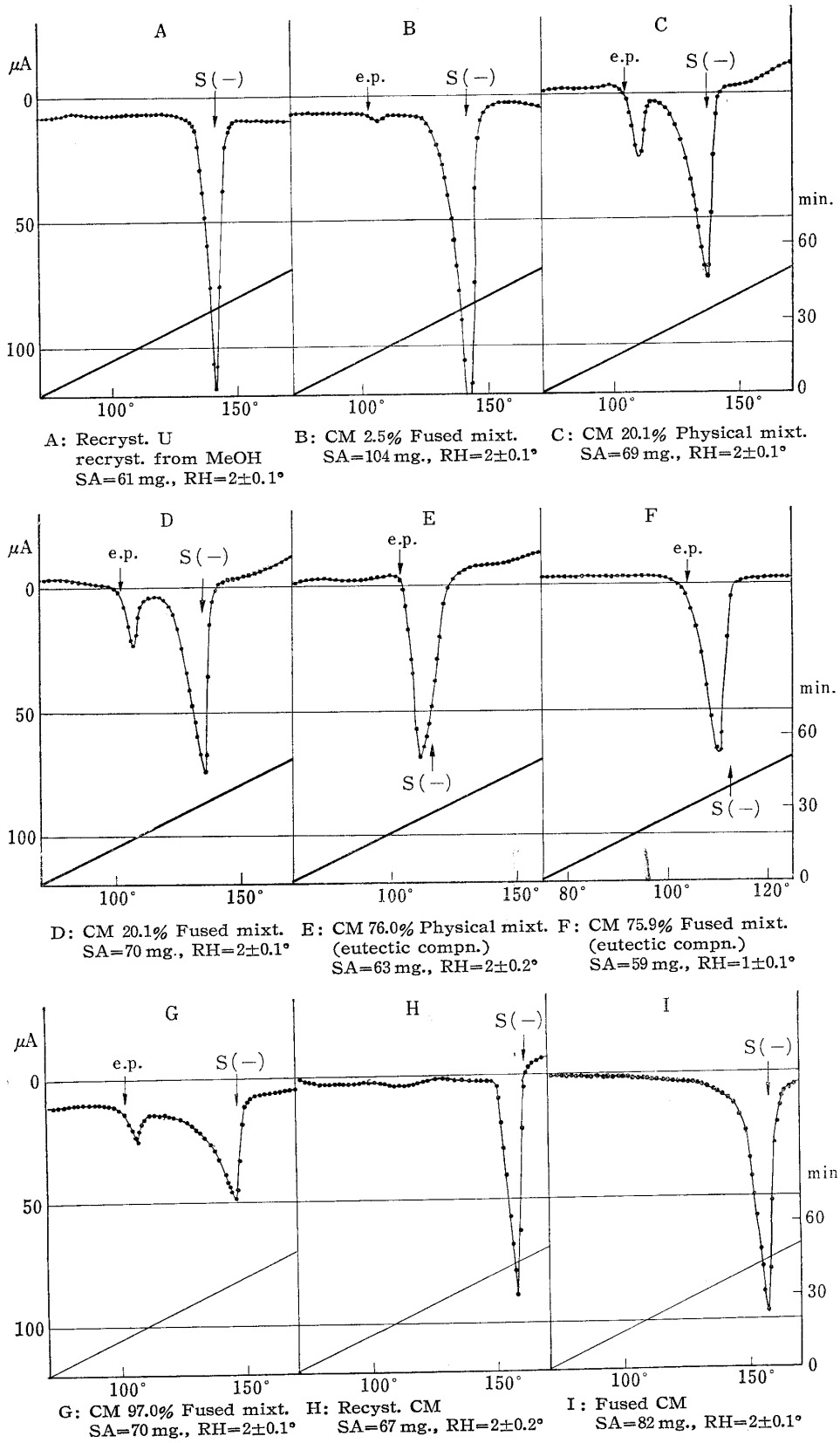


Fig. 2. Differential Thermal Analysis Curves of Urea and Chloramphenicol System

apparatus: semi-micro DTA apparatus permitting visual observation of the sample in a hard glass cell.
standard substance: 71 mg. of freeze-dried KCl.
U, urea; CM, chloramphenicol; SA, sample amount; RH, heating rate; e.p., eutectic point; S(−), temperature at which the last trace of solid phase was observed to disappear.

ii) Chloramphenicol and mechanical mixtures : Particle size of each substance was arranged from 150 to 300 μ by sieving. The mechanical mixtures were prepared by thorough mixing of both sieved components in a stoppered bottle.

Table II. Samples used for Investigation

Sample	Composition by weight chloramphenicol (%)	urea (%)	Procedure[a]
I	100	0	ordinary chloramphenicol
II	76	24	solidification after fusion (eutectic mixture)
III	76	24	mechanical mixing
IV	20	80	solidification after fusion
V	20	80	mechanical mixing

a) Particles of each sample were arranged between 150 and 300 μ by sieving.

Determination of Chloramphenicol——For solubility study, chloramphenicol was determined by spectrophotometry at the wave length of 278 mμ at which urea shows no absorption. For blood specimens, the total aryl nitro method[2] was applied after deproteinization with metaphosphate. Reduction of chloramphenicol was done by hydrosulfite, and Tsuda's reagent (0.5% N-(1-Naphthyl)-N'-diethylethylendiamine) was used for coupling. The wave length for colorimetry was 560 mμ.

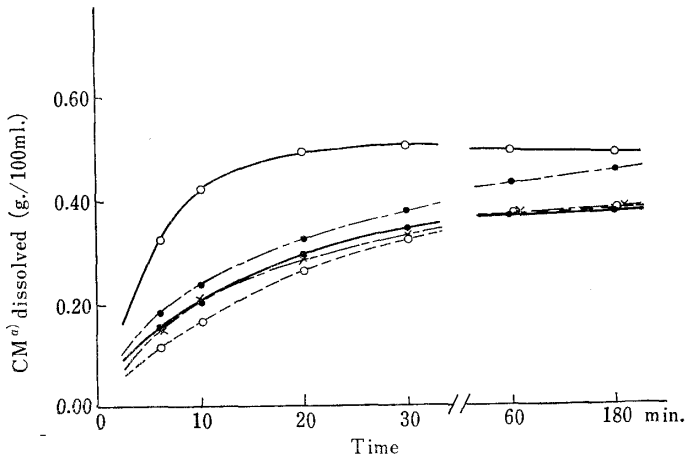
Dissolution Rate of Chloramphenicol——Each sample mixture containing exactly 1 g. of chloramphenicol was added into a 200 ml. Erlenmyer flask in which 100 ml. of redistilled H_2O was previously kept at 25°, in a thermostat equipped with a shaking device. Immediately after the addition, the flask was shaked twice per second with an amplitude of 18 mm. After certain periods of shaking, each 2 ml. of the solution was taken with a pipette at the top of which a filter chip was attached, and the antibiotics was analyzed by spectrophotometry. Similar procedure was adopted for the determination of dissolution rate both in an acidic and in a neutrally buffered solution. The former was prepared by diluting 24 ml. of dil. HCl J.P. with distilled H_2O to make 1 L. The buffered solution was

Table III. Dissolution Rate of Chloramphenicol from Various Samples (at 25±0.05°)

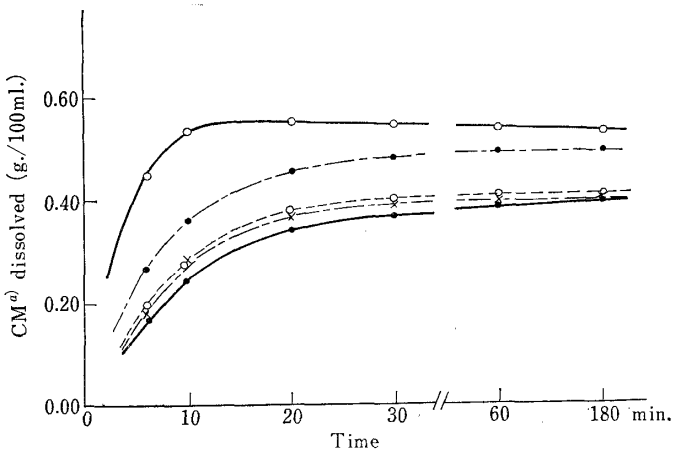
Time (min.) \ CM[a] dissolved (g./100 ml.)	Sample I	II	III	IV	V
A : In distilled water					
6	0.158	0.149	0.166	0.343	0.241
10	0.240	0.242	0.220	0.462	0.323
20	—	—	0.325	0.528	0.420
30	0.373	0.386	0.370	0.532	0.456
60	0.386	0.405	0.388	0.535	0.472
180	0.378	0.389	0.396	0.520	0.477
B : In hydrochloric acid solution (pH 1.3)					
6	0.167	0.194	0.185	0.444	0.263
10	0.245	0.277	0.277	0.536	0.357
20	0.344	0.383	0.374	0.547	0.458
30	0.367	0.401	0.393	0.545	0.481
60	0.391	0.412	0.397	0.536	0.489
180	0.398	0.409	0.399	0.530	0.484
C : In phosphate buffer solution (pH 7.5)[b]					
6	0.155	0.115	0.152	0.318	0.182
10	0.200	0.166	0.209	0.422	0.236
20	0.293	0.258	0.284	0.497	0.322
30	0.342	0.322	0.330	0.501	0.368
60	0.366	0.371	0.371	0.494	0.434
180	0.371	0.375	0.377	0.491	0.456

a) CM=chloramphenicol
b) a mixture of 15.9 ml. of *M*/15 KH_2PO_4 and 84.1 ml. of *M*/15 Na_2HPO_4

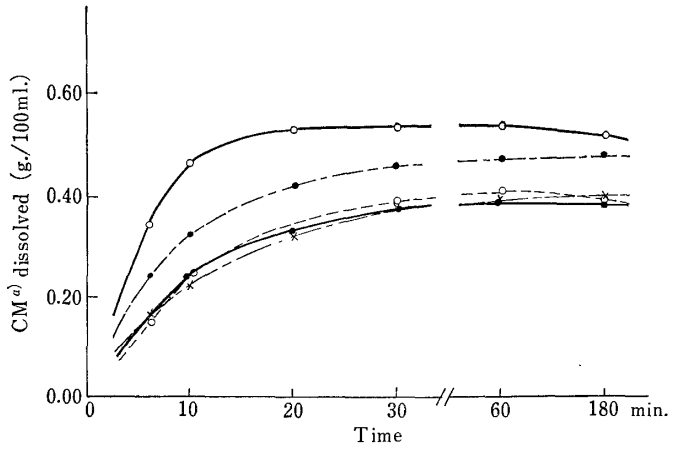
2) A. J. Glazko, L. M. Wolf, W. A. Dill : Arch. Biochem., 23, 411 (1949).



A: In distilled water



B: In hydrochloric acid solution (pH 1.3)



C: In phosphate buffer solution (pH 7.5)

Fig. 3.
Dissolution Rate of Chloramphenicol from Various Samples (at 25±0.05°)

Each sample containing 1.000 g. of chloramphenicol was added to 100 ml. of distilled H_2O, acid, or buffer solution.

a) CM=chloramphenicol

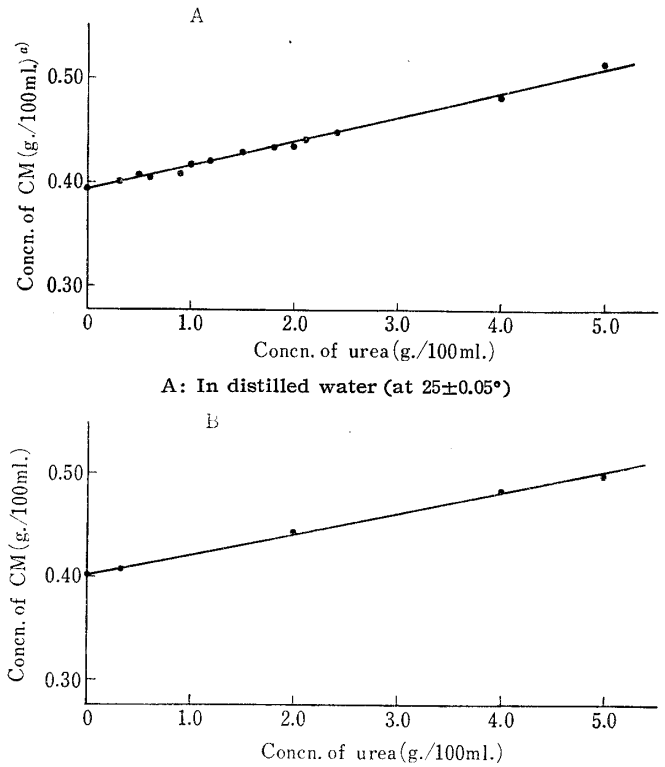
Sample: —●— I ---○--- II ---×--- III —○— IV —●— V

a mixture of 15.9 ml. of *M*/15 KH_2PO_4 and 84.1 ml. of *M*/15 Na_2HPO_4 solution and had a pH of 7.5. The pH increase was found below 0.2 unit in the acidic solution and 0.1 unit in the buffered one after dissolution of samples. Results are shown in Fig. 3 and Table III.

Solubilizing Action of Urea——Excess amount of chloramphenicol and a solution of a fixed concentration of urea were placed in a flask and stirred at a constant temperature of 25±0.05° for over 5 hr. until complete saturation of the antibiotics was attained. A definite amount of the clear solution taken by filtering off the solid residue was analyzed and the solubility curves of the antibiotics in the presence of various amount of urea were obtained as shown in Fig. 4 and Table Ⅳ. Urea in the final solutions was also determined by the colorimetric method using diacetylmonoxime,[3] and was found to be equal to the initial concentrations within the limit of experimental error.

Chloramphenicol Absorption in Rabbits——Rabbits of the same littermate weighing from 1.8 to 2.0 kg. were used as test animals. After they were fasted overnight, suspensions or capsules of the sample mixtures were administered by the oral route and blood specimens were taken by venipuncture from ears at different time intervals. 200 mg. of chloramphenicol or the equivalent dose of the other sample was given in each experiment.

i) Absorption of suspensions: Four kinds of suspensions were prepared by mixing each of the samples with 20 ml. of 1% Na-CMC solution. Upon mixing the sample (Ⅳ) with the diluent, rapid disintegration of the conglomerate particles was observed along with the dissolution of urea, and a stable suspension containing very finely divided crystals of



A: In distilled water (at 25±0.05°)

B: In hydrochloric acid solution (pH 1.3, at 25±0.05°)

Fig. 4. Solubility of Chloramphenicol in the Presence of Urea

a) CM=chloramphenicol

Table Ⅳ. Solubility Increase of Chloramphenicol in the Presence of Various Amount of Urea (at 25±0.05°)

Original concn. of urea (g./100 ml.)	Solubility of chloramphenicol (g./100 ml.)	Original concn. of urea (g./100 ml.)	Solubility of chloramphenicol (g./100 ml.)
A : In distilled water			
0.000	0.395	1.200	0.420
0.060	0.395	1.500 (1.488)	0.430
0.300	0.399	1.800	0.431
0.316	0.402	2.000 (1.975)	0.434
0.502 (0.492)[a)]	0.407	2.100	0.440
0.600	0.405	2.400	0.448
0.900	0.408	4.000	0.482
1.000 (1.021)	0.416	5.000	0.513
B : In hydrochloric acid solution (pH 1.3)			
0.000	0.400	4.000	0.484
0.316	0.407	5.003	0.496
2.021	0.442		

a) Figures in brackets are final concentrations of urea measured by colorimetric method.

3) J. Kurata, T. Iwata: Kagaku-no-Ryoiki, extra number, **34**, 53 (1958).

chloramphenicol was formed.*5 Administration of these suspensions was done using the Nelaton's catheter following the addition of 50 ml. of distilled H_2O to rinse out adhering particles on the inner wall of the tube. Blood serum levels in rabbits recieving equivalent doses of various suspensions of the antibiotics were analyzed and the results are shown in Fig. 5 and Table V. From these data, it is evident that the suspension of the sample (Ⅳ) was absorbed much more rapidly and to a greater extent than the other three. In fact, the maximum blood level was reached only within 30 min. and was about 70% higher than those with other suspensions. Statistical treatment of the data by two methods of comparison*6 indicates that the differences between the sample (Ⅳ) and the other three are significant within the level of 5%, however, between the latter ones no significant differences were observed (Table Ⅶ).

ii) Absorption of capsules: Samples (I, Ⅱ or Ⅳ) containing each 200 mg. of chloramphenicol was filled into three gelatin capsules of J.P. Ⅵ (size No. 1). Rabbits were administered these capsules in a single oral dose, and then given 70 ml. of distilled H_2O in order to keep their digestive organs in similar experimental conditions. Absorption of chloramphenicol after ingestion of each sample was tested six times respectively using six different rabbits, and the results were shown in Fig. 6 and Table Ⅵ. Similar patterns of time-blood level curves were obtained as in the medication of suspensions. More rapid and higher rise in blood concentration of the antibiotics was observed with rabbits

Table V. Blood Levels of Chloramphenicol Following Oral Administration of Various Kinds of Suspensions

No. of expt.	Concn. of chloramphenicol (μg./ml.) after dose				
	0.5	1	2	4	6 hr.
A : Suspension of sample (I)					
1	13.3	16.7	16.0	10.7	4.8
2	16.7	19.5	17.3	10.0	5.2
3	21.8	23.3	22.7	16.0	4.0
4	21.3	22.1	22.0	9.3	2.7
5	29.3	30.0	20.0	6.1	1.3
6	18.0	21.2	24.3	11.9	4.2
7	8.0	11.3	12.0	10.2	3.7
mean	18.3	20.6	19.2	10.6	3.7
B : Suspension of sample (Ⅱ)					
1	8.1	14.0	14.1	9.3	4.0
2	16.7	18.5	21.3	8.0	1.9
3	13.3	16.7	19.3	10.7	2.8
mean	12.7	16.4	18.2	9.3	2.9
C : Suspension of sample (Ⅳ)					
1	47.3	36.1	21.3	5.3	2.5
2	24.7	25.3	14.7	10.0	3.8
3	22.2	24.0	20.7	4.0	2.0
4	33.3	22.5	18.0	6.7	2.7
5	32.0	30.0	16.7	6.7	3.3
6	38.7	24.7	16.0	6.7	4.5
7	24.0	21.3	14.7	7.3	3.5
mean	31.7	26.3	17.4	6.7	3.2
D : Suspension of sample (V)					
1	16.1	24.7	25.3	8.0	3.6
2	18.0	18.5	20.0	16.1	6.8
3	20.7	21.8	22.5	6.7	3.0
4	12.0	13.8	14.7	8.0	2.5
mean	16.7	19.7	20.6	9.7	4.0

These suspensions were prepared by mixing each of the samples containing 200 mg. chloramphenicol with 20 ml. of 1% Na-CMC solution.

*5 About 1～2 μ by microscopic observation.

*6 The one is the method of comparison of two curves on which the authors have mentioned in the preceding paper. The other is the usual one of comparison of two sample means at a definite time interval.

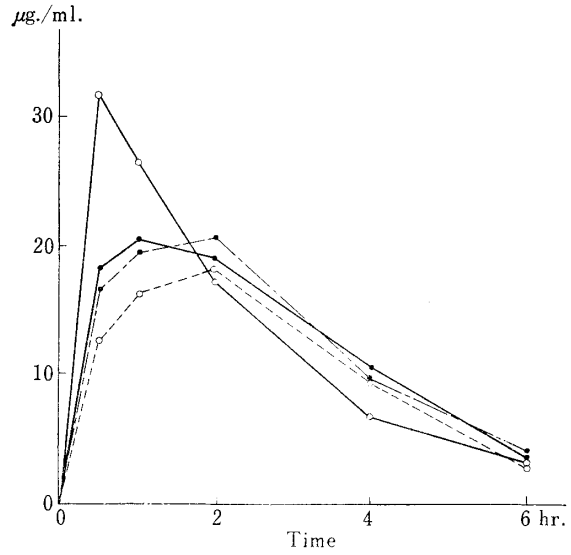


Fig. 5. Mean Blood Levels of Chloramphenicol in Rabbits Following Oral Administration of Various Kinds of Suspensions

Each rabbit was administered a single oral dose equivalent to 200 mg. chloramphenicol.
Sample : —●— Ⅰ ---○--- Ⅱ —○— Ⅳ —●— Ⅴ

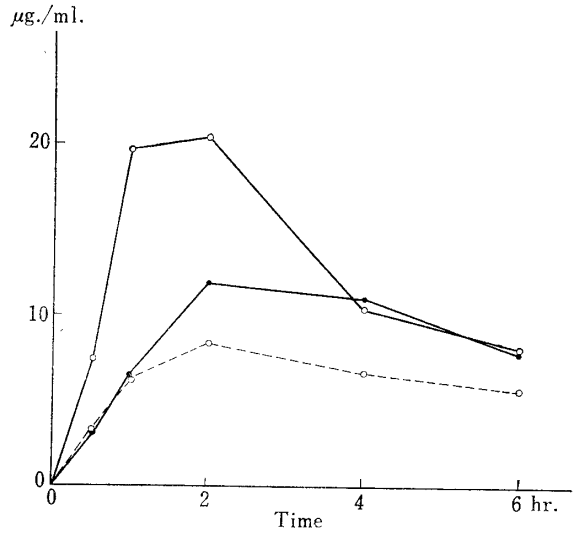


Fig. 6. Mean Blood Levels of Chloramphenicol in Rabbits Following Oral Administration of Various Kinds of Capsules

Each rabbit was administered a single oral dose equivalent to 200 mg. chloramphenicol.
Sample : —●— Ⅰ ---○--- Ⅱ —○— Ⅳ

TABLE Ⅵ. Blood Levels of Chloramphenicol Following Oral Administration of Various Kinds of Capsules

No. of expt.	Concn. of chloramphenicol (μg./ml.) after dose				
	0.5	1	2	4	6 hr.
A : Capsules of sample (Ⅰ)					
1	9.3	11.4	12.7	14.0	11.3
2	0.2	1.1	2.7	9.1	4.0
3	4.0	6.7	8.0	10.0	8.7
4	2.1	10.0	14.7	16.7	14.7
5	1.3	2.5	10.7	4.7	4.0
6	1.3	7.3	22.7	11.3	3.3
mean	3.0	6.5	11.9	11.0	7.7
B : Capsules of sample (Ⅱ)					
1	4.0	5.3	7.3	3.6	2.7
2	0.3	2.7	5.3	5.5	8.0
3	3.3	4.5	6.7	5.3	4.8
4	5.2	9.3	10.7	6.0	4.7
5	6.0	10.7	11.2	12.0	6.7
6	0.5	4.7	8.7	7.2	6.7
mean	3.2	6.2	8.3	6.6	5.6
C : Capsules of sample (Ⅳ)					
1	2.2	12.0	20.7	11.3	10.0
2	3.4	17.3	14.7	10.7	8.7
3	9.5	28.0	21.3	9.3	7.2
4	0.4	13.3	9.3	7.3	7.0
5	2.7	16.0	24.0	12.0	6.0
6	26.0	30.7	32.0	10.7	9.3
mean	7.4	19.6	20.3	10.2	8.0

Each sample containing 200 mg. chloramphenicol was filled into three gelatin capsules of J.P. Ⅵ.

recieving capsules of the sample (Ⅳ). The difference between this and the rest of the samples is significant for the first 4 hr. (Table Ⅶ). The absorption behaviors of the simple mechanical mixtures were not examined, since the results obtained with suspensions of the sample (Ⅴ) indicate that urea in them has no significant influence upon the absorption of chloramphenicol.

Table Ⅶ. Statistical Treatment of Blood Levels of Chloramphenicol

1. Comparison of absorption curves[a)]

Sample	Level of significance of difference	
	Suspension (%) (up to 2 hr.)	Capsule (%) (up to 4 hr.)
Ⅰ : Ⅳ	2.5	2.5
Ⅱ : Ⅳ	5	0.5
Ⅳ : Ⅴ	2.5	

2. Comparison of blood levels at each time after administration

Time (hr.)	Level of significance of difference					
	Suspension			Capsule		
	Ⅰ : Ⅳ	Ⅱ : Ⅳ	Ⅳ : Ⅴ	Ⅰ : Ⅱ	Ⅰ : Ⅳ	Ⅱ : Ⅳ
0.5	1	1	2.5	—	—	—
1	10	2.5	10	—	0.5	0.5
2	—[b)]	—	—	—	10	1
4	—	—	—	10	—	10
6	—	—	—	—	—	—

a) The method for comparison of two curves is similar to the one shown in the preceding paper.
b) No significance at the level of 10%

Discussion

The effect of urea on the solubility of ordinary chloramphenicol is found to be relatively weak within the concentration range examined, as shown in the solubility measurement. On the other hand, marked differences in dissolution rate between the kinds of samples are noted in all three media. The most peculiar dissolution was observed with the sample (Ⅳ) which is consisted of both the eutectic mixture and the primary crystals of urea as is seen in the phase diagram. The sample dissolves most rapidly forming a suspension. Within 20 or 30 minutes, the concentration reaches to the maximum which is a little greater than the equilibrium value of chloramphenicol in the presence of the same amount of urea (40 mg./ml.). By subsequent shaking, it gradually falls to the solubility of the sample (Ⅴ) with separation of excess chloramphenicol. When the sample (Ⅴ), a simple mechanical mixture having the same composition as that of Ⅳ is used, somewhat quicker rise of concentration due to solubilizing action of urea was observed in the initial stage of dissolution; however, the curve resembles those of the rest ones and shows no fall in contrast to that of the sample (Ⅳ). Little differences are noticed between dissolution curves of the samples (Ⅰ, Ⅱ, and Ⅲ). It is not strange that the final concentrations of them are similar, since the amount of urea in the latter two is so small that the solubilizing action is practically negligible. However, the fact that the eutectic mixture itself does not dissolve rapidly may be attributed to some variable factors hidden in the heat treatment during sample preparation such as the hardening effect of the eutectic mixture, or in some cases, the occurrence of supersaturation of urea during cooling process by which effective size reduction will not be attained. On the other hand, the primary crystals of urea in the sample (Ⅳ) take the dendrite structure having a large surface area, between which minute crystals

of both components separate out side by side as the eutectic mixture. Since in this case, the heat of crystallization of primary urea prevents rapid cooling of the melt, hardening by quenching will be suppressed. Thus, the process of dissolution of the sample (Ⅳ) is supposed to take two steps. At first, the primary crystals of urea dissolve quickly, leaving a large number of secondary particles of the eutectic mixture. The following step is the disintegration of these particles by which a very finely divided suspensions is formed. It is thought that particles of the eutectic mixture in the sample(Ⅳ) is smaller and less rigid than those of the eutectic mixture itself; therefore, a more rapid rise of the concentration of chloramphenicol will become possible. The abnormal increase of the concentration in the midst of dissolution is supposed to be due to either or both of the fact that the size of suspended chloramphenicol particles approaches nearly to the larger limit of colloidal dimension, or/and the fact that in the earlier stages of dissolution, urea concentration near the solid particles is much higher than those of the other parts of the solution. However, in the latter case, the curve of solubilization in Fig. 4 must be concave upwardly, although in this experiment, solubilities of the antibiotics in much higher concentrations of urea were not investigated. The gradual decrease in the dissolution curves of the sample (Ⅳ) can be explained by crystallization of excess chloramphenicol or by size enlargement of the minute particles formed in the initial stage. It is evident that the differences in the dissolution experiments are caused not by chemical change of one or both of the components,*[7] but merely by change of physical state.

In the absorption studies using suspensions of various samples, rabbits received the sample (Ⅳ) showed outstandingly quicker rise of blood concentration; moreover, the highest level was found to be about 70% greater than those of rabbits received the other suspensions. Comparison of the results obtained with the samples (Ⅳ and Ⅴ), both of which have the same urea content indicates that urea itself dose not exert physiological influence upon the absorption of chloramphenicol.

When samples of Ⅰ, Ⅱ, and Ⅳ filled into capsules were administered, similar differences in absorption as with suspension forms were observed. However, since it takes some time for the gelatin wall of a capsule to disintegrate in the gastric juice, a delay in absorption was noted with each sample. Also, the less consistent results obtained with repeated runs using the same kind of sample may probably be attributed to the variation of the time required for the vehicle to release its content. On administration of capsules of the sample (Ⅳ), the total amount of chloramphenicol absorbed for the first two hours was about three times greater than the absorbed amount after ingestion of the antibiotics alone. Even up to four hours period during which the blood level with the sample (Ⅳ) began to fall, an almost doubled amount of the drug was absorbed from capsules of this sample as compared with that of ordinary chloramphenicol.

The observations presented here show that the dissolution rate of the antibiotics exerts a great influence upon the intestinal absorption. Furthermore, the increase of the rate of dissolution is closely related to the ease of disintegration of the conglomerate particles containing the eutectic mixture from which minute crystals of chloramphenicol are produced, resulting in a greater surface area available for the direct contact with the surrounding solution. Also, these experimental evidences support the view that the drug absorption, in general, can not be treated as a process in a state of equilibrium, but as a rate process. Accordingly, even the metastable increase of solubility of a drug will enhance its body absorption.

Rather poor uptake of the antibiotics from eutectic mixture itself can be attributed to the difficulty of disintegration. However, it seems necessary for the authors to carry

*[7] The IR and UV spectra of samples prepared by simple mixing and by fusion were the same.

out further investigations concerning the processes of preparing eutectic mixtures and the properties of component substances, since the one of sulfathiazole and urea was readily absorbed with rapid disintegration.

Because urea is an entirely nontoxic substance and the preparation of the fused mixture is a simple process, even on a manufacturing scale, these data on absorption of chloramphenicol by rabbits will suggest that such an original form of medication as the sample (Ⅳ) can be effectively applied for therapeutical purposes when blood levels should be achieved as rapidly as possible and yet patients can not accept the drug by injection.

Size reduction of solid materials is often an important problem for pharmaceutical and cosmetic industries; nevertheless, methods hitherto adopted are essentially few. They are mechanical processes such as crushing, grinding and cutting or precipitation by mixing a solution of the drug with insoluble solvents, among which only the last one is suitable for preparing very fine powders. Although particle size of a drug substance is largely reduced by preparing an eutectic mixture, it is always accompanied with the other substance; however, if it is possible to choose any volatile solvent as the second component, very fine powders of the drug itself will be obtained by freezing a solution containing the drug less than the eutectic composition, and then sublimating the solvent component in the frozen state.*[8] The authors believe that this new method of preparing fine powders will be available on an industrial scale at least for expensive drug substances.

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Summary

Thermal analyses of the system of chloramphenicol and urea were carried out both by the thaw-melt and the DTA method. The system gave a phase diagram of simple eutectic type. The eutectic mixture melts at 104° and has a composition of 76% of the antibiotics and 24% of urea by weight.

Dissolution rates of ordinary chloramphenicol, and four kinds of samples prepared by mechanical mixing or by fusion of both substances were investigated. Although the eutectic mixture itself did not dissolve rapidly, the fused conglomerate having a weight ratio of 1:4 dissolved much more rapidly, and a maximum was observed in its dissolution curve. Such a peculiar dissolution can be attributed to the size reduction of chloramphenicol by the formation of eutectic mixture and the presence of easily soluble primary crystals of urea which have much greater surface available for contact with the surrounding solution. When the fused conglomerate of this composition was administered to rabbits in suspension or capsule form, the antibiotics was absorbed much more rapidly and to a greater extent. High correspondence between dissolution and absorption rate indicates that the absorption of chloramphenicol is largely dependent on the rate of dissolution which is intimately related to the physical state.

It is thought that this new form of medication will be effectively applied for therapeutical purpose, when blood concentration should be achieved as rapidly as possible and yet patients can not receive the antibiotics by injection.

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*[8] On this method of size reduction, one of the authors has briefly mentioned in his report concerning the method of thermal analysis. This Bulletin, **11**, 1123 (1963).