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Effect of Formulation Additives on the Dissolution Behavior of Tetracycline Antibiotics[1]

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The effect of various formulation additives on the dissolution behavior of three tetracycline antibiotics from compressed tablets (prepared by direct compression) was studied. In general, the dissolution of the antibiotics was found to be retarded by the addition of binding agents such as gelatin and acacia, when they were incorporated in compressed tablets. A study was also undertaken to determine the influence of gelatin and acacia dissolved in the test media. In dissolution experiments on compressed tablets and crystalline powders, a significant dissolution inhibition by the action of the dissolved additives was present, as in the study where additives were incorporated in compressed tablets. It was thought that the possible mechanisms for the retardation effect included the formation of a poor soluble complex between the drug and the additives and the increased viscosity of the medium.

A blood level study was also conducted in rats using CTC-HCl and TC-HCl as test materials to determine whether gelatin and acacia affect the membrane permeability of drugs from solutions. Blood concentrations after intraduodenal administration of these two drug solutions with gelatin and acacia were compared to each control level produced by the drug given alone. These two additives resulted in lower blood levels compared to control values.

Keywords——tetracyclines-dissolution from compressed tablets and powders; formulation effects-tetracyclines dissolution rates, behavior; formulation additives-effect of tetracyclines dissolution; dissolution, tetracyclines-formulation additive effect on; tetracyclines absorption from solution-effect of formulation additive

In the preparation of solid dosage forms, a number of so-called inert excepients are used as diluents, binders, disintegrants, and lubricants. Since they constitute a considerable portion of dosage forms, there is a good reason to believe that they might influence the dissolution and absorption characteristics of the active ingredient. Numerous publications have discussed the effect of binder concentration,[3] types of binders,[4] starch concentration,[5] types of starches,[6] lubricants,[7] and disintegrant[8] on the drug release from a solid dosage form.

Marked differences in the bioavailability of tetracycline antibiotics from commercial solid dosage forms have been reported.[9–13] Since tetracyclines are susceptible to varied

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bioavailability due to the effect of formulation components, one or more formulation components can contribute to the wide variation in the bioavailability. The bioavailability of tetracycline antibiotics from their dosage forms has been shown to be influenced by drug-excipient interaction such as complexation with bivalent and trivalent cations.[14–16] The possibilities for drug complexation with formulation additives are often exaggerated in multi-component drug product. However, the formulation additives which may control the release of drugs from solid dosage forms have not yet been fully elucidated.[17]

The purpose of this investigation is to study the effect of commonly used formulation additives on the dissolution behavior of some tetracycline antibiotics. Furthermore, a study was undertaken to determine the effect of additives on the gastrointestinal absorption of the drugs from solutions.

Experimental

Materials——Chlortetracycline hydrochloride and tetracycline hydrochloride were the generous gifts from Lederle (JAPAN), LTD. Oxytetracycline hydrochloride was generously supplied by Taito Pfizer Co. The following materials were obtained from commercial sources: microcrystalline cellulose, Avicel PH101[18]; sodium carboxymethylcellulose[19]; acacia, JP[20]; polyethylene glycol 6000[19]; potato starch[21]; bentonite[21]; talc[21]; sodium lauryl sulfate[22]; magnesium stearate[21]; and gelatin.[23] Gelatin was used after passing through a 170-mesh screen.

Preparation of Tablets——Compressed tablets were prepared by direct compression using a die and hydraulic press for KBr tablet. A 300 mg amount of powders containing 210 mg tetracycline antibiotics and Avicel and an appropriate amount of additives was accurately weighed and compressed at 200 kg/cm^2. The finished flat faced tablets were 13 mm in diameter and about 1.6 mm in thickness.

Measurement of Tablet Disintegration Time——Disintegration tests on tablets were performed in 0.1N HCl using a JP VIII disintegration apparatus without disks.

Measurement of Tablet Hardness——The hardness of tablets were determined with a Monsanto tablet hardness tester, which can be applied to measure a hardness below 30 kg.

Dissolution Rates Determination——Dissolution rates of compressed tablets were measured with the USP dissolution apparatus, using 900 ml of distilled water or 0.1N HCl as the dissolution medium and a stirring speed of 50 rpm. Sample solutions were pipetted out periodically by a cotton-filter attached pipette. In one instance, the volume of dissolution medium was reduced to 300 ml.

Dissolution rate studies on crystalline powders were carried out as previously described,[24] except that the volume of dissolution medium was increased to 2 ml and the speed of shaking was reduced to 50 strokes/min. The method of Shefter and Higuchi[25] was employed with slight modification in one experiment. A weighed sample of drug was rapidly added to exactly 100 ml of dissolution medium maintained at 37° in a water-jacketed beaker. The solution was agitated by means of an overhead stirrer (5-cm blade) with a stirring speed of 50 rpm. Sample solutions were filtered through a Millipore filter (0.20 μm).

The concentrations of antibiotics in solution were measured by ultraviolet absorption method following appropriate dilution with 0.1N sulfuric acid. All dissolution studies were carried out at 37±0.2°. Except where otherwise indicated, all data shown in the figures represent the average of two dissolution runs.

Solubility Determination——Solubility values of tetracycline antibiotics were determined in water containing different concentrations of additives at 37°. Excess amounts of samples were suspended in 2 ml of the additive solutions. These suspensions were shaken overnight and the aliquots filtered with a Millipore filter (0.20 μm) were assayed using a Hitachi Type 139 spectrophotometer.

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18) Asahi Kasei Kogyo Co., Lot 1394.
19) Koso Chemical Co.
20) Iwaki Seiyaku Co., Lot 54C717K.
21) Wako Pure Chemical Industries.
22) Kanto Chemical Co.
23) Difco Laboratories, Lot 0143-01.
24) S. Miyazaki, T. Arita, R. Hori, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **22**, 638 (1974).
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Procedure for Absorption Studies——Male Wistar rats, weighing 240—280 g, were fasted overnight before the experiment. The 10 mg of the drug dissolved in 2 ml of water or additive solutions was injected by means of a syringe near an opening of biliary duct in the duodenum. Blood collections were made at various times during the experiment through polyethylene catheter inserted to the carotid artery. The specimens were analysed following Kohn's method[26] using a Hitachi Type 203 fluorospectrophotometer.

Results and Discussion

Effect of Formulation Additives Incorporated in a Compressed Tablet on the Dissolution Behavior

Dissolution experiments to determine the effect of formulation additives were carried out using chlortetracycline hydrochloride (CTC-HCl) as a test material, when they were incorporated in a compressed tablet. The results were shown in Fig. 1—4. The disintegration time and dissolution rate (percentage dissolved in 10 min) are shown in Table I. As shown in Fig. 1, the dissolution rate of CTC-HCl from a compressed tablet is decreased by the addition of any of binder (10% w/w) studied in both test media. Gelatin and acacia manifest the greatest retardation effect on the dissolution. Sodium carboxymethylcellulose (CMC-Na) and polyethylene glycol 6000 (PEG 6000) also appear to have a measureable effect on the dissolution. The presence of lower level of binder, for example 5% w/w gelatin, was also sufficient to reduce the drug dissolution; percentage dissolved after 10 min was 14.4 in 0.1 N HCl. The dissolution rate retarding effect of gelatin, acacia, and PEG 6000 could be the result of delayed tablet disintegration and reduced contact between the drug and solvents. Tablet binders ordinarily tend to retard dissolution, because they delay disintegration and form a layer of viscous solution around drug particle.[27] The one reason why CTC-HCl dissolved slowly from a tablet prepared with CMC-Na is probably the increased viscosity in the diffusion layer of the dissolving particle.[28] Krowczynski, *et al.*[29] reported that tablets prepared with

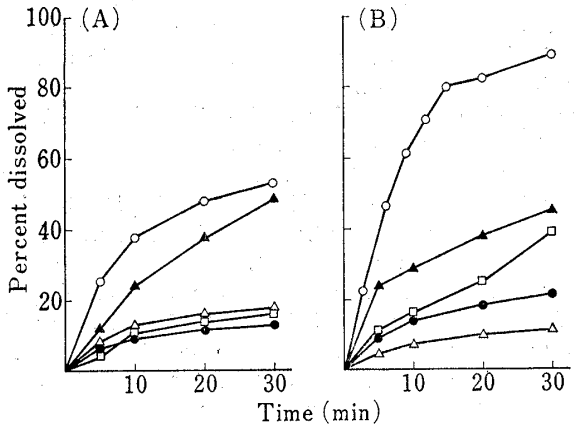

Fig. 1. Effect of Binders (10% w/w) on the Dissolution Behavior of Chlortetracycline Hydrochloride from Compressed Tablets in Water(A) and 0.1N HCl(B) at 37°

—○—: no binder
—●—: gelatin
—△—: acacia
—▲—: sodium carboxymethylcellulose
—□—: polyethylene glycol 6000

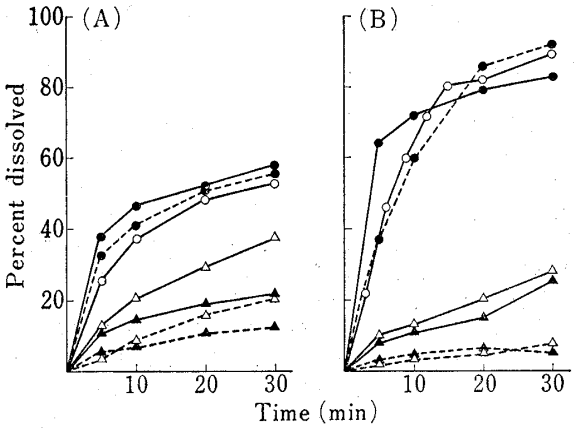

Fig. 2. Effect of Lubricants on the Dissolution Behavior of Chlortetracycline Hydrochloride from Compressed Tablets in Water (A) and 0.1N HCl (B) at 37°

—○—: no lubricant
—●—: 1% w/w talc
---●---: 5% w/w talc
—△—: 1% w/w sodium lauryl sulfate
---△---: 5% w/w sodium lauryl sulfate
—▲—: 1% w/w magnesium stearate
---▲---: 5% w/w magnesium stearate

26) K.W. Kohn, *Anal. Chem.*, 23, 862 (1961).
27) J.B. Sprowls, Jr., (ed.), "Prescription Pharmacy," 2nd ed., J.B. Lippincott Company, Philadelphia, 1970, p. 81.
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Table I. Dissolution Rates and Disintegration Time of Chlortetracycline Hydrochloride Compressed Tablets Prepared with Different Formulation Additives at 37°

Additive	Concn. (w/w%)	Percent dissolved in 10 min[a]		Disintegration time[b] (min)	Hardness[c] (kg)
		in water	in 0.1N HCl	in 0.1N HCl	
No additive	—	37.4(7)	60.7(7)[d]	0.9	14.9
Sodium carboxymethylcellulose	10	24.7(2)	28.8(4)	0.5	9.4
Polyethyleneglycol 6000	10	9.9(2)	15.6(6)	14.0	10.1
Gelatin	10	9.2(2)	13.9(4)	*e*)	11.8
Acacia	10	13.2(2)	6.9(4)	*e*)	11.2
Talc	1	53.3(2)	72.1(2)	0.8	10.7
Talc	5	41.0(2)	61.0(3)	0.6	15.0
Sodium lauryl sulfate	1	20.8(2)	13.5(2)	0.6	7.0
Sodium lauryl sulfate	5	9.0(2)	3.4(2)	5.3	7.0
Magnesium sterate	1	14.9(2)	13.7(2)	0.7	10.2
Magnesium sterate	5	8.3(2)	3.1(4)	13.8	7.6
Bentonite	5	93.9(2)	79.8(2)	0.4	15.5
Starch	5	69.4(2)	70.5(2)	0.8	10.7
Starch	20	64.5(2)[d]	49.1(5)[d]	*f*)	*f*)

a) Number in parentheses indicates the numbers of the experiments.
b) Determined by JP VIII procedure in 0.1N HCl. Each value represents the mean of 2 determinations.
c) Each value represents the mean of 2 determinations.
d) percent dissolved in 9 min
e) Disintegration was not completed within 60 min.
f) not determined

low viscosity binders may tend to release a soluble active ingredient more rapidly than those prepared with higher viscosity binders.

Lubricants are usually required in tablet and capsule formulations. The effect of lubricants such as talc, sodium lauryl sulfate, and magnesium stearate on the dissolution of the drug are shown in Fig. 2.

Talc in concentration at 1% w/w produced only a minor change on the dissolution when tested in water and 0.1 N HCl, the higher level (5% w/w) also producing a minor change. Talc produced insignificant effect on the disintegration time and the subsequent dissolution.

On the other hand, sodium lauryl sulfate and magnesium stearate exhibited a rate-retarding effect with the 1% and 5% concentrations. In the presence of both lubricants at the 1% concentration, the disintegration time was not extended but the dissolution was suppressed. No correlation was found between the disintegration time and the dissolution rate. During the dissolution experiments on tablets prepared from both lubricants, it was noticed that a part of tablet core was still intact on completion of the experiment. This might explain the slow release of CTC-HCl.

When bentonite and potato starch were incorporated as disintegrants, the dissolution rate of CTC-HCl from the tablet is increased in water (Fig. 3A), probably becaused of more efficient disintegration of the granules to primary particle and increased surface area. The presence of potato starch at a 5% concentration increased the dissolution rate, but there was no further increase when the content increased to 20%. When 0.1 N HCl was used as the test media, both disintegrants exhibited no effect.

The effect of gelatin and acacia on the dissolution behavior of tetracycline hydrochloride (TC-HCl) and oxytetracycline hydrochloride (OTC-HCl) from compressed tablets in 0.1 N HCl is shown in Fig. 4. The gelatin and acacia were chosen as formulation additives for this study because they have the greatest influence on the dissolution and disintegration behaviors of CTC-HCl compressed tablets. Furthermore, gelatin and acacia are widely used as formula-

tion adjuvants (binders, suspending agents, emulsifying agents, *etc.*) in the manufacturing of dosage forms.

The results show that both gelatin and acacia exerted a remarkable retardation effect on the dissolution behavior of TC-HCl tablets in 0.1 N HCl. However, little effect was observed in case of OTC-HCl.

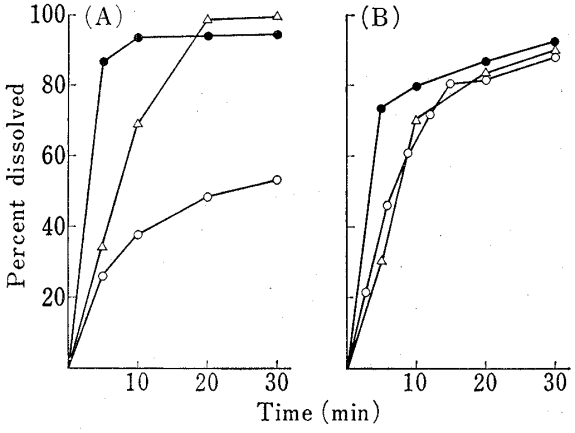

Fig. 3. Effect of Disintegrants on the Dissolution Behavior of Chlortetracycline Hydrochroride from Compressed Tablets in Water (A) and 0.1N HCl (B) at 37°

—○—: no disintegrant
—●—: 5% w/w bentonite
—△—: 5% and 20% w/w starch

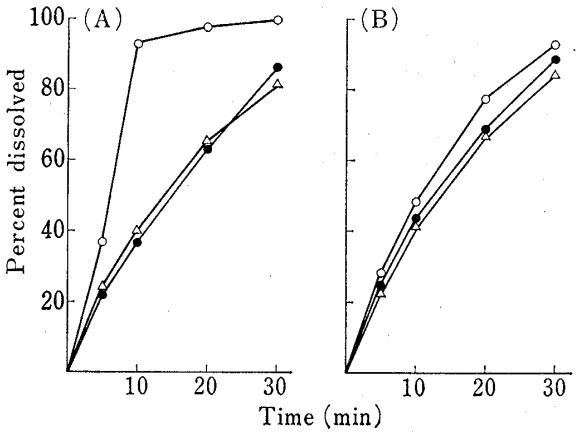

Fig. 4. Effect of Gelatin and Acacia (10% w/w) on the Dissolution Behavior of Tetracycline Hydrochloride (A) and Oxytetracycline Hydrochloride (B) from Compressed Tablets in 0.1N HCl at 37°

—○—: no additive —●—: gelatin —△—: acacia

Effect of Formulation Additives Dissolved in Test Media on the Dissolution Behavior

A study was undertaken to determine the influence of additives dissolved in the test media rather than incorporated in a compressed tablet. Because gelatin and acacia had the greatest influence on the dissolution behavior of some tertacycline antibiotics when they were incorporated in a compressed tablet, they were selected for this study.

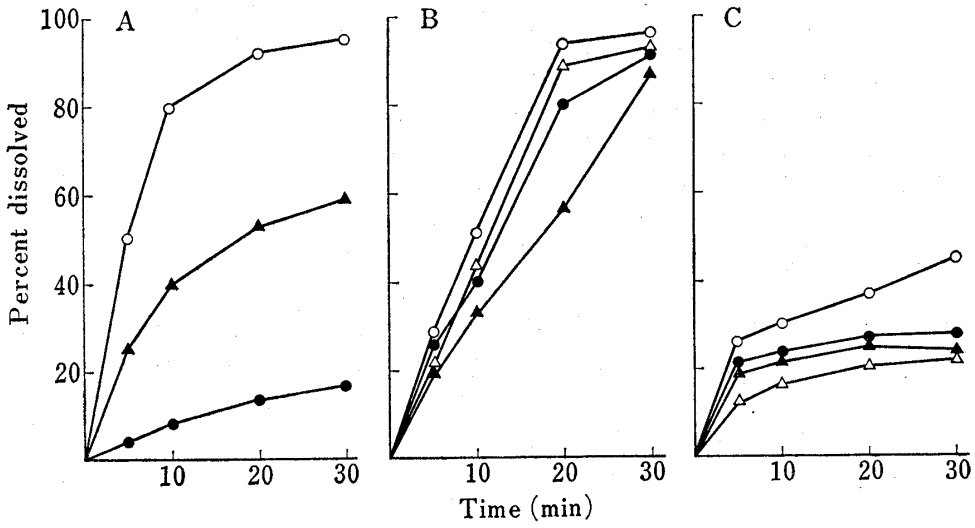

Fig. 5. Dissolution Behavior of Chlortetracycline Hydrochloride(A), Tetracycline Hydrochloride (B), and Oxytetracycline Hydrochloride (C) in Water, both in the Presence and Absence of Gelatin and Acacia from Compressed Tablets at 37°

—○—: in distillld water —△—: in 5% w/v gelatin solution
—●—: in 3% w/v gelatin solution —▲—: in 3% w/v acacia solution
The volume of dissolution medium was 300 ml.

Figure 5(A) shows the dissolution behavior of CTC-HCl compressed tablets in water, both in the presence and absence of the additives at 37°. A significant dissolution inhibition by the dissolved additives is present, as in the study where the additives were incorporated in a compressed tablet.

As shown in Fig. 5(B) and (C), in cases of TC-HCl and OTC-HCl the effect of gelatin and acacia were less pronounced than with CTC-HCl. The addition of gelatin (3% w/v) in test medium did not produced a significant effect on the dissolution of TC-HCl, with the exception of higher level of gelatin (5% w/v). The dissolution of OTC-HCl tablets was slightly reduced in gelatin and acacia solutions.

To substantiate the results obtained from a compressed tablet, a series of experiments was carried out on a powder system. Figure 6 shows the dissolution behavior of CTC-HCl crystalline powder in water, 3% gelatin and 3% acacia at 37°. The concentration curves of CTC-HCl, at any time, substantially smaller than that in water. The dissolution inhibition obtained is in close agreement with that obtained from a CTC-HCl compressed tablet. The dissolution rate was reduced by a value smaller than that obtained from studies on compressed tablets. This can be explained by the relatively larger surface area provided by the crystalline powder. During the dissolution study of the drug in 3% gelatin solution, on the other hand, a maximum occurred at 20 min and thereafter the concentration of drug in solution decreased.

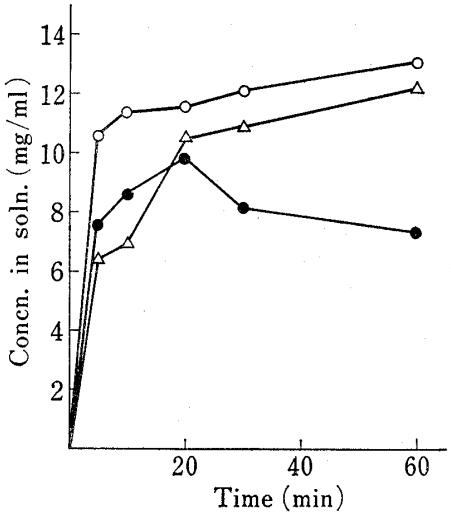

Fig. 6. Dissolution Behavior of Chlortetracycline Hydrochloride in Water, both in the Presence and Absence of Gelatin and Acacia from Crystalline Powders at 37°

—○—: in distilled water
—●—: in 3% w/v gelatin solution
—△—: in 3% w/v acacia solution
sample: 60 mg per 2 ml of solvent

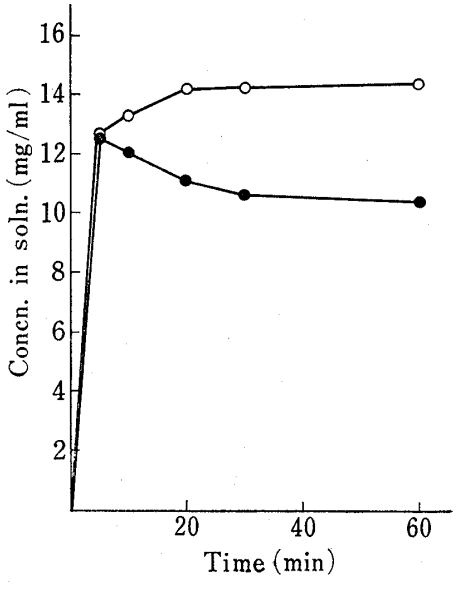

Fig. 7. Dissolution Behavior of Chlortetracycline Hydrochloride in Water, both in the Presence and Absence of Gelatin from Crystalline Powders at 37°, Determined by the Method of Shefter and Higuchi

—○—: in distilled water
—●—: in 3% w/v gelatin solution
sample: 3 g per 100 ml of solvent

In this instance, the dissolution rate determination was also made with the method of Shefter and Higuchi[25] (Fig. 7), and the similar dissolution pattern was obtained. The decrease in concentration in solution with time after a peak solubility was observed for 3% gelatin within a short time, as was observed in the insoluble complex formation.[30] After one hour, stirring was stopped and two distinct solid phases were observed.

30) M. Gibaldi and H. Weintraub, *J. Pharm. Sci.*, **57**, 832 (1968).

Solubility determinations were designed to test the presence of (or absence of) any appreciable intereaction between CTC-HCl and gelatin. As shown in Table II, equilibrium solubility determination indicated a continuous decrease in apparent solubility of the drug as a function of gelatin concentration. Solubility determinations of CTC-HCl crystalline powders at high gelatin concentrations showed the formation of amorphous-like precipitate.

Table II. Solubility of Chlortetracycline Hydrochloride in the Presence of Gelatin and Acacia, and Relative Viscosity of Their Solutions at 37°

Additive	Concentration (w/v %)	Solubility of CTC-HCl (mg/ml)	Relative viscosity[a)]
No additive (water)	—	14.23	1.0
Gelatin	1.0	13.62	1.3
	2.0	12.70	1.6
	3.0	12.70	2.0
	4.0	12.24	2.8
	5.0	8.93	3.5
	6.0	8.35	*b*)
Acacia	1.0	13.38	1.4
	2.0	11.70[c)]	1.6
	3.0	11.86	2.0
	4.0	11.67	2.3
	5.0	10.96	2.6

a) Relative viscosity measurements were made with an Ostwald viscometer at 37°.
b) not determined
c) solubility at 2.5% w/v concentration

From these results, it may be assumed that this precipitate was indicative of the formation of a poorly soluble complex between CTC-HCl and gelatin. Gelatin has been reported to interact with drugs, resulting in the formation of an insoluble complex.[31,32)] Furthermore, chlortetracycline is known to be most highly bound to plasma protein.[33)]

In addition, the interaction between CTC-HCl and gelatin during the dissolution may be responsible for the delayed dissolution. This may also be the case for acacia (Table II). Other possible mechanisms for interference with the drug dissolution by gelatin and acacia would be the increased viscosity in the dissolution medium. The relative viscosity measurements showed a slight increase in the viscosity in the presence of gelatin and acacia.

The dissolution curves for TC-HCl and OTC-HCl in each dissolution medium are shown in Fig. 8. It can be seen from these curves that the presence of gelatin and acacia in the dissolution medium reduces the rate of dissolution of both drugs compared to the rate found in water.

The decrease in the dissolution rates of these tetracycline antibiotics in the presence of gelatin and acacia serves to strengthen the possibility that both formulation additives play an important part in the dissolution step of the drug absorption process.

Effect of Formulation Additives on Gastrointestinal Absorption of CTC-HCl and TC-HCl from Solution

It is known that the drug absorption is affected by formulation additives. Magnesium stearate was proved to chelate with tetracycline and therefore to decrease its absorption from the gastrointestinal tract.[34)] An example of drug-excipient interaction was also observed

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32) N. Tanaka, S. Takino, and I. Utsumi, *J. Pharm. Sci.*, **52**, 664 (1963).
33) C.M. Kunin and M. Finland, *Clin. Pharmacol. Therap.*, **2**, 51 (1961).
34) H.A. Hirsh and M. Finland, *New Eng. J. Med*, **260**, 109 (1959).

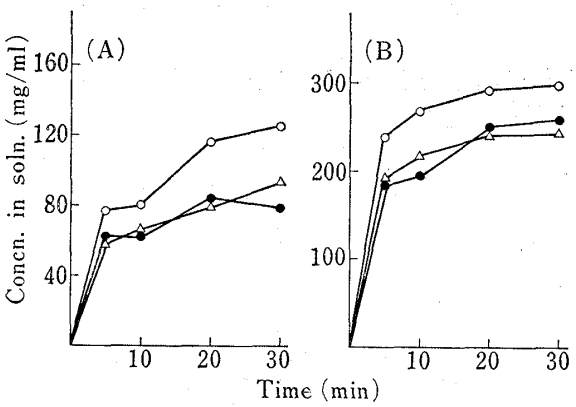

Fig. 8. Dissolution Behavior of Tetracycline Hydrochloride (A) and Oxytetracycline Hydrochloride (B) in Water, both in the Presence and Absence of Gelatin and Acacia from Crystalline Powders at 37°

—○—: in distilled water
—●—: in 3% w/v gelatin solution
—△—: in 3% w/v acacia solution
sample: 600 mg (A) and 800 mg (B) per 2 ml of solvent

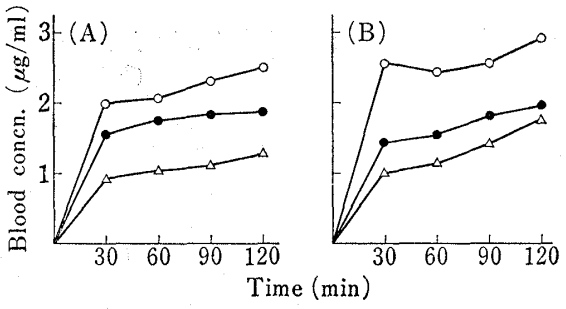

Fig. 9. Effect of Additives on Blood Levels after Intraduodenal Administration of Chlortetracycline Hydrochloride (A) and Tetracycline Hydrochloride (B) Solutions to Rats

—○—: drug alone
—●—: in the presence of 2% w/v gelatin
—△—: in the presence of 2% w/v acacia
The 10 mg of samples dissolved in 2 ml of water or additive solutions was administered. Each point represents the mean of 3 experiments.

when dicalcium phosphate was used as a vehicle with tetracycline.[15] A poorly soluble and poorly absorbable calcium-tetracycline complex was formed at the interface as dissolution occurred and bioavailability of the antibiotic was significantly reduced.

Some agents such as gelatin and acacia were found to retard the dissolution rate of tetracycline antibiotics from the results mentioned above. On the other hand, formulation additives may also play a role in the membrane permeation step of drug absorption process. A blood level study was conducted in rats to determine whether they affect permeability of drug from solutions using CTC-HCl and TC-HCl as test materials. Blood concentrations after intraduodenal administration of drugs with additives were compared to respective control levels produced by the drug given alone.

Figure 9 shows the blood concentrations of CTC-HCl and TC-HCl obtained following intraduodenal administration of drugs to rats in the presence and absence of additives. As shown in Fig. 9A, CTC-HCl concentrations in the presence of gelatin and acacia were lower than those in its absence. Similarly, the additives lowered blood levels of TC-HCl (Fig. 9B).

The results of this study indicate that gelatin and acacia, which are commonly coadministered with drugs, indeed affect the membrane permeation step of drug absorption process. From a standpoint of drug bioavailability, these findings indicate that special precautions should be taken when gelatin or acacia are used as formulation adjuvants.