3-Ethyl-4-methyl-s-triazolo[2,3-b]benzimidazole (7b)——A mixture of 6 (362 mg) and propionic anhydride (1 ml) was heated at 200° (bath temperature) for 30 min. Work-up as described for the preparation of 4a gave 7b (100 mg, 50%) as hygroscopic crystals, mp 69—71° (from petroleum ether–methylene chloride). IR ν_{max}^{KCl} cm^{-1}: 1625, 1600, 1590, 1505. NMR (in CDCl$_3$) δ: 7.1—7.9 (4H, m), 3.82 (3H, s), 2.90 (2H, q, $J=$ 7 Hz), 1.44 (3H, t, $J=7$ Hz). MS m/e: 200 (M$^+$). This compound formed a picrate, mp 188—189° (from ethanol). Anal. Calcd. for C$_{17}$H$_{15}$N$_7$O$_7$: C, 47.55; H, 3.52; N, 22.84. Found: C, 47.67; H, 3.66; N, 22.70.

4-Methyl-2-phenyl-s-triazolo[3,2-b]benzimidazole (7c)——Using the procedure described for the preparation of 4b, 7c (124 mg, 50%) was obtained from 6 (362 mg), mp 138—139° (petroleum ether–CHCl$_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1605, 1590, 1510, 1490, 1470, 1455. NMR (in CDCl$_3$) δ: 7.2—8.5 (9H, m), 3.75 (3H, s). MS m/e: 248 (M$^+$). Anal. Calcd. for C$_{15}$H$_{12}$N$_4$: C, 72.64; H, 4.89; N, 22.57. Found: C, 72.87; H, 4.99; N, 22.29.

Effect of Antacids on the Dissolution Behavior of Tetracycline and Methacycline

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The effect of antacids on the dissolution behavior of tetracycline hydrochloride and methacycline hydrochloride from commercial capsules was studied. The dissolution of the tetracyclines was found to be markedly retarded by antacids such as aluminium silicate and magnesium trisilicate. An attempt was made to elucidate the mechanism of this effect. The results suggest that the effects of antacids on the dissolution may be due to the adsorption of the drugs on antacid particles as well as to the increased pH of the medium.

A study was also carried out to determine the influence of stomachics using Cinnamomi Cortex as a test material. In dissolution experiments on commercial capsules, a significant dissolution inhibition by the stomachic was found.

Keywords——tetracycline; methacycline; antacids; stomachic; dissolution behavior; adsorption

It is well known that antacids containing divalent or trivalent cations such as Ca^{2+}, Mg^{2+}, or Al^{3+} depress the absorption of orally administered tetracyclines.[2-5] Chelation is usually considered to be the mechanism responsible for the decreased absorption of tetracyclines in the presence of antacids.[6]

On the other hand, antacids may also affect the dissolution of tetracyclines. However, there are very few reports on this possibility.[7]

We describe here the effects of some antacids on the dissolution characteristics of tetracycline hydrochloride and methacycline hydrochloride. The mechanism of interaction between the antibiotics and antacids was also studied. Furthermore, a similar investigation was carried out using a stomachic, Cinnamomi Cortex, which has been used in combination with tetracycline antibiotics.

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Experimental

Materials——Tetracycline hydrochloride powder was a gift from Lederle (Japan) Ltd. Methacycline hydrochloride powder was supplied by Taito Pfizer Co. The following materials were purchased from the cited sources: magnesium trisilicate, JP[8]; synthetic aluminium silicate, JP[9]; aluminium magnesium silicate bismuth,[10] and Cinnamomi Cortex, JP.[11] Aluminium silicate was used after passage through a 170 mesh screen.

Procedure for Dissolution Studies——Dissolution profiles were obtained for 250 mg capsules of tetracycline hydrochloride and 150 mg capsules of methacycline hydrochloride, purchased from Taito Pfizer Co.

Dissolution studies with antacids were carried out using a USP dissolution apparatus with slight modifications. The dissolution rate of a capsule in 100 ml of water maintained at 37° in a waterj-acketed beaker was measured at a stirring speed of 100 rpm. In testing the effect of antacids on dissolution, 2 g of the antacid was added to the dissolution medium. Aliquots were withdrawn periodically and the concentration of antibiotics in solution was measured by the UV absorption method.

The effect of a stomachic on the dissolution was examined in the same manner as for antacids, except that the volume of the dissolution medium was increased to 200 ml and the stirring speed was reduced to 50 rpm. In the presence of UV-absorbing interfering material (Cinnamomi Cortex), the concentration of tetracyclines was determined fluorometrically by Kohn's method.[12]

Data shown in figures are the averages of at least two experiment runs; the results were satisfactorily reproducible.

Adsorption Studies——The desired quantities of antacid and stomachic powders were weighed accurately in 10 ml Erlenmeyer flasks. Aqueous solutions of the tetracycline (2 ml) at appropriate concentrations were added to each flask. The flasks were shaken in a constant temperature bath at 37° for one hour. It had been established previously that equilibrium was attained within this period. At the end of this time, aliquots filtered through a Millipore filter (0.20 μ) were analyzed for residual antibiotic concentration.

The quantities of tetracyclines adsorbed by the antacid and stomachic were determined by subtracting the equilibrium concentration from the initial concentration. No differences in concentration were found in samples to which antacids or the stomachic had not been added.

Elution Procedure——The elution behavior of the adsorbed antibiotics was determined by digesting the residue, obtained by centrifugation of the suspension after the adsorption run, in 10 ml of water (pH 5.5), 0.001 N HCl (pH 3.0), 0.1 N HCl (pH 1.2), or 0.2 N HCl (pH 0.7). The digested material was shaken at 37°, then filtered, and the amount of the antibiotic eluted was determined as a function of time.

Results and Discussion

Effect of Antacids

Figure 1 shows the effect of antacids on the dissolution behavior of tetracycline and methacycline from commercial capsules. As can be seen from these curves, the dissolution rates of both drugs from the capsules decreased in the presence of any antacid (2% w/v) studied. Magnesium trisilicate had the greatest retardation effect on the dissolution of tetracycline. After 30 min, less than 12% of tetracycline was found in solution (Fig. 1A). Aluminium silicate and aluminium magnesium silicate bismuth (Bistmag) also affected the dissolution. The presence of lower levels of antacids, for example 1% w/v magnesium trisilicate, also reduced tetracycline dissolution; the amount dissolved after 30 min was 23.5%. These antacids also markedly reduced the dissolution rate of methacycline from capsules (Fig. 1B).

It is thus clear that the dissolution of tetracycline and methacycline can be retarded by antacids containing polyvalent cations.

It has been suggested that antacids decrease the dissolution of tetracyclines by raising the pH of the medium, since the dissolution rate is markedly reduced at high pH values[7]; Table I shows the pH of the antacid suspensions used. On the other hand, tetracyclines

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9) Normosan, Takeda Chemical Industries.
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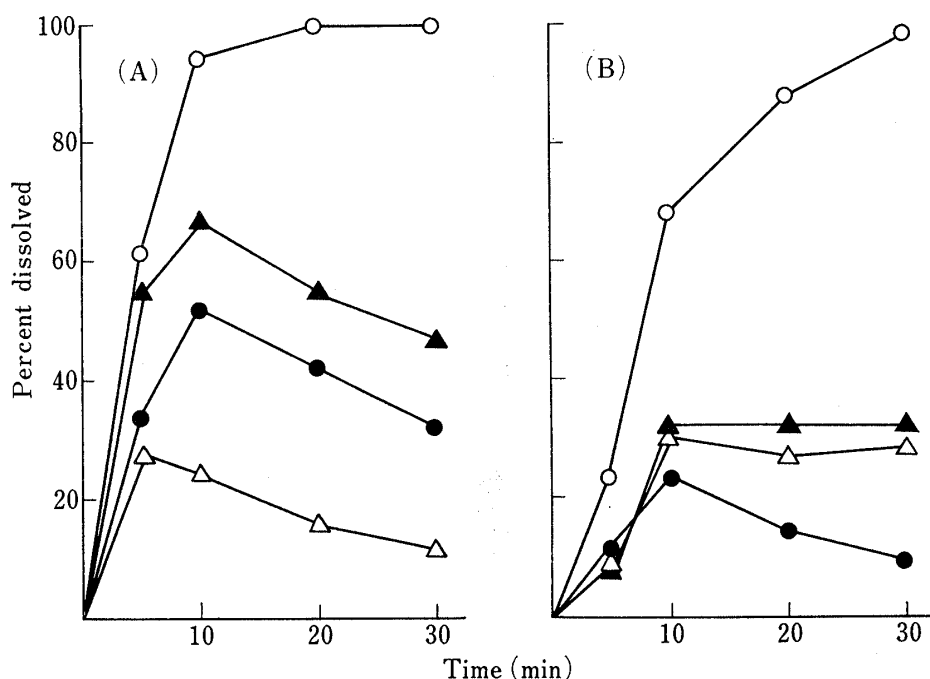12) K.W. Kohn, *Anal. Chem.*, **23**, 862 (1961).

Fig. 1. Effect of Antacids (2% w/v) on the Dissolution Behavior of Tetracycline
(A) and Methacycline (B) from Capsules in Water at 37°

—○—: no antacids.   —●—: aluminium silicate.
—△—: magnesium trisilicate.   —▲—: Bistmag.

have been found to be strongly adsorbed on various antacids.[13-16] Therefore, the adsorption of tetracyclines on antacids was investigated. Figure 2 shows the data plotted according to the Langmuir equation,[17] which may be written as:

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{c}{b}$$

where c is the equilibrium concentration of the solute, x/m is the amount of solute adsorbed per unit weight of the adsorbents, and a and b are constants. The adsorption capacities (b) of the antacids are listed in Table I. Both tetracycline and methacycline were adsorbed significantly. Magnesium trisilicate exhibits relatively higher adsorption capacities for the

TABLE I. Adsorption Capacities[a] of Antacids[b] and a Stomachic[c]

Tetracycline	Aluminium silicate (7.0)[d]	Magnesium trisilicate (10.2)[d]	Bistmag (7.9)[d]	Cinnamomi Cortex (4.6)[d]
Tetracycline	176(0.37)	508(1.06)	225(0.47)	58(0.09)
Methacycline	211(0.44)	280(0.58)	188(0.44)	97(0.20)

a) mg (mmol) per gram.
b) Concentration: 1% w/v.
c) Concentration: 3% w/v.
d) Numbers in parentheses indicate pH values of the suspensions in water measured after equilibration for 1 hr.

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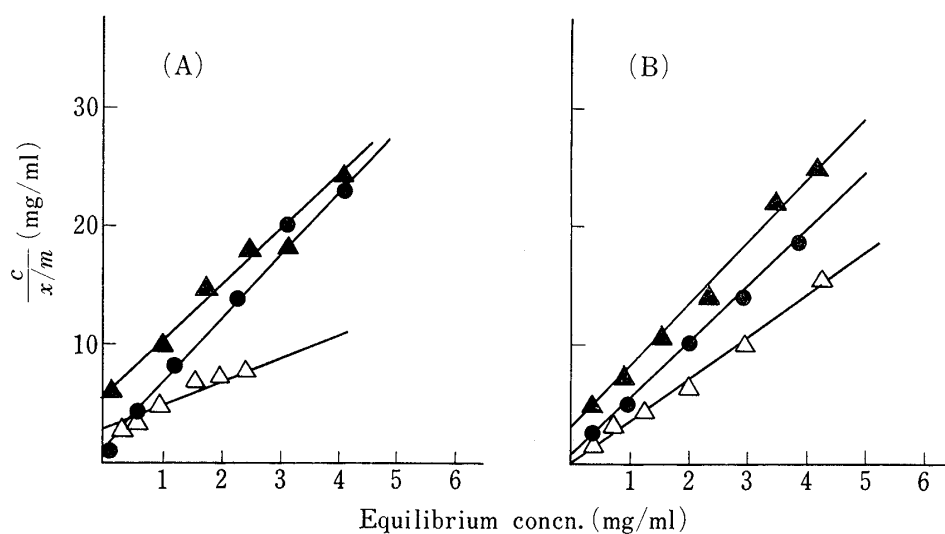17) I. Langmuir, J. Am. Chem. Soc., 39, 1848 (1917).

Fig. 2. Langmuir Plots for the Adsorption of Tetracycline (A) and Methacycline (B) on Antacids (1% w/v) at 37°

—●—: aluminium silicate. —△—: magnesimn trisilicate. —▲—: Bistmag.
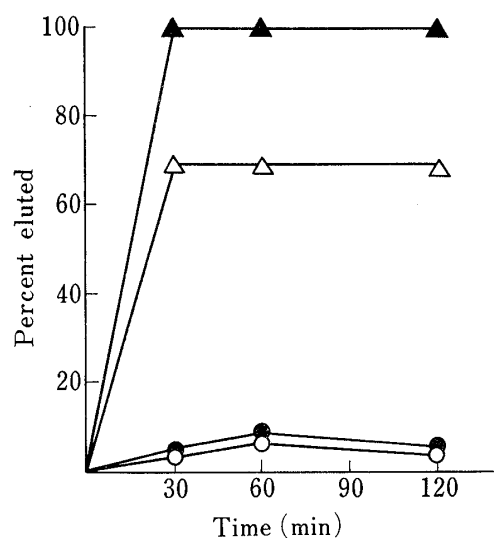

Fig. 3. Elution Behavior of Tetracycline adsorbed on Aluminium Silicate at 37°

—○—: water. —●—: 0.001N HCl.
—△—: 0.1N HCl. —▲—: 0.2N HCl.

two drugs. The differences in the adsorption capacities could be related to the pH of the antacid suspensions.[18] Adsorption by antacids was fast; equilibrium was attained within approximately 10 min in most cases. These results indicate that tetracycline and methacycline are strongly adsorbed on the antacids.

The results of elution experiments using the tetracycline-aluminium silicate system are shown in Fig. 3. The effectiveness of elution depended on the medium used. In water and 0.001 N HCl, the adsorption is essentially irreversible, since only a small amount of tetracycline is eluted; however, in 0.2 N HCl the elution of the adsorbed tetracycline is significant due to the dissolution of the antacid in the medium. This suggests that the adsorption is not physical in nature[19] and is strong.

These results suggest that the adsorption of tetracyclines on antacid particles during dissolution may be responsible for the marked retardation of dissolution. A similar mechanism was reported for the inhibited dissolution of glycosides[20] and contraceptive steroids.[21]

Effect of a Stomachic

Stomachics have also been recommended as a means of reducing the gastrointestinal distress observed with tetracyclines. However, no information is so far available on the dissolution and bioavailability of tetracyclines in the presence of stomachics.

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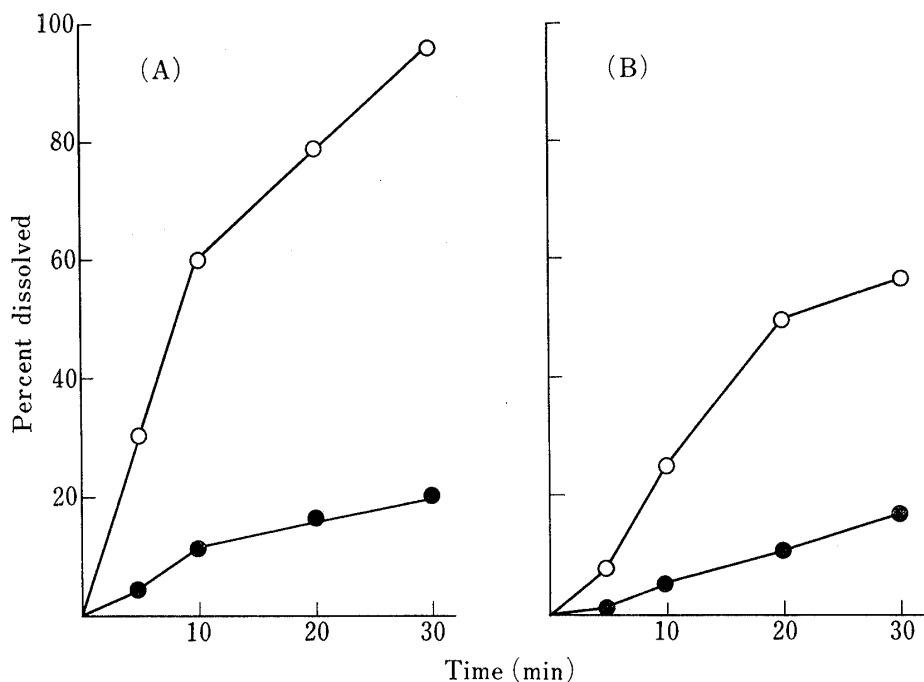21) S.A.H. Khalil and M. Iwuagwu, J. Pharm. Sci., 67, 287 (1978).

Fig. 4. Effect of Cinnamomi Cortex (2% w/v) on the Dissolution Behavior of
Tetracycline (A) and Methacycline (B) from Capsules in Water at 37°

—○—: no stomachic.   —●—: Cinnamomi Cortex.

Dissolution and adsorption experiments to determine the effect of stomachics were carried out using Cinnamomi Cortex as a test material. As shown in Fig. 4, the presence of the stomachic in the medium markedly decreased the concentration of tetracyclines. After 30 min, for example, the amount of tetracycline in solution was less than 20% compared with 97% in water (Fig. 4A). As shown in Fig. 5 and Table I, the reduction in concentration of the tetracyclines was a result of adsorption onto the stomachic particles.

The results of this study suggest that stomachics as well as antacids, which are commonly coadministered with tetracycline antibiotics, markedly affect the dissolution step of the drug absorption process.
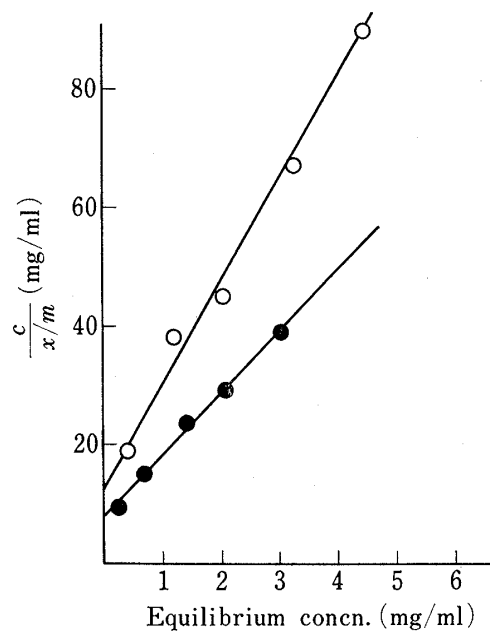
Fig. 5. Langmuir Plots for the Adsorption of Tetracycline (○) and Methacycline (●) on Cinnamomi Cortex (3% w/v) at 37°