

Effect of Antacids on the Dissolution Behaviour of Methacycline and Doxycycline

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Abstract

The effect of antacids on the dissolution behaviour of methacycline and doxycycline capsules from commercial dosage forms were studied. The dissolution of both tetracyclines was found to be markedly retarded by antacids such as magnesium trisilicate and magnesium oxide. An attempt was made to elucidate the mechanism of this effect. The results suggest that the effect of antacids on the dissolution may be due to the absorption of the drugs on antacids particles, as well as to the increased pH of the medium (JPMA 34: 59, 1984).

Introduction

The tetracyclines are incompletely and irregularly absorbed from the gastrointestinal tract. Absorption is most active in the stomach and upper small intestine and is greater in the fasting state. It is much less complete from the lower portions of the intestinal tract and is negligible from the colon. The degree of absorption is diminished by the soluble salts of divalent and trivalent cations with which they form stable complexes and to variable degree by milk or food (Martindale, 1977; Dilling, 1974; Goodman and Gilman, 1975).

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 (Waisbrent and Hueckel, 1950; Barr et al., 1972; Scheiner and Altemeier, 1962). Chelation is generally considered to be the mechanism responsible for the decreased absorption of tetracyclines in the presence of antacids (Hansten, 1971). Other antacids without divalent or trivalent cations may also affect the dissolution of tetracyclines. However, there are very few reports on this possibility (Barr et al., 1971).

We describe here the effect of aluminium hydroxide, magnesium oxide, magnesium trisilicate and sodium bicarbonate on the dissolution characteristics of methacycline hydrochloride and doxycycline hydrochloride. The mechanism of interaction between antibiotics and antacids were also studied.

Material and Method

Material.

Standard Methacycline hydrochloride base activity 924 mcg/mg and Doxycycline hydrochloride standard equivalent to 860 mcg/mg doxycycline base activity was a gift from Pfizer Laboratories Pakistan. Methacycline hydrochloride capsules 300 mg and Doxycycline capsules 100 mg (marked as Randomycin and vibramycin, Pfizer Laboratories, Pakistan) were purchased from the market. Aluminium hydroxide, magnesium oxide, magnesium trisilicate and sodium bicarbonate were of pharmaceutical grade and were purchased from the market. All antacids were used after passage through 170 mesh screen. Hydrochloric acid, methanol and other laboratory chemicals used were of analytical grade (Merck).

Equipment:

The dissolution equipment (Wagner et al., 1973) was manufactured to B.P. 1980 standards, which

included the dissolution motor and variable speed controller with a stainless steel basket assembly. The dissolution vessel was flat bottom glass vessel with an internal diameter of 100 mm and with a capacity of 1 litre dissolution fluid. The variable speed motor was modified to reduce unwanted vibrations by the incorporation of 1000 UF capacitor in the speed control circuit, and was maintained within $\pm 1\%$ of the required speed.

The rotation speed of the basket assembly was fixed at 50 ± 0.5 rpm through out the experiment. The dissolution assembly was immersed in a water bath at $37 \pm 0.1^\circ\text{C}$. The UV absorbance was measured on a Beckman 25 Spectrophotometer.

Procedure for Dissolution Studies:

Dissolution profiles were obtained for 300 mg capsules of Methacycline hydrochloride and 100 mg capsules of Doxycycline hydrochloride on the dissolution apparatus as detailed above. The dissolution fluid was 1 litre of 0.1N HCl and samples were withdrawn periodically with the interval of 5 minutes for 60 mins. The volume of the dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which has previously been maintained at the same temperature in the same bath. In testing the effect of antacids on dissolution, 2 gm of the antacid was added to the dissolution medium; the aliquots were withdrawn similarly and the concentration of the antibiotics in solution was determined by measuring the absorbance at 351 nm by UV absorption method (B.P. 1980).

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

Results and Discussion

The results of the effect of antacids on the solubility of drugs are mentioned in Table I and II and are plotted in figures I and 2.

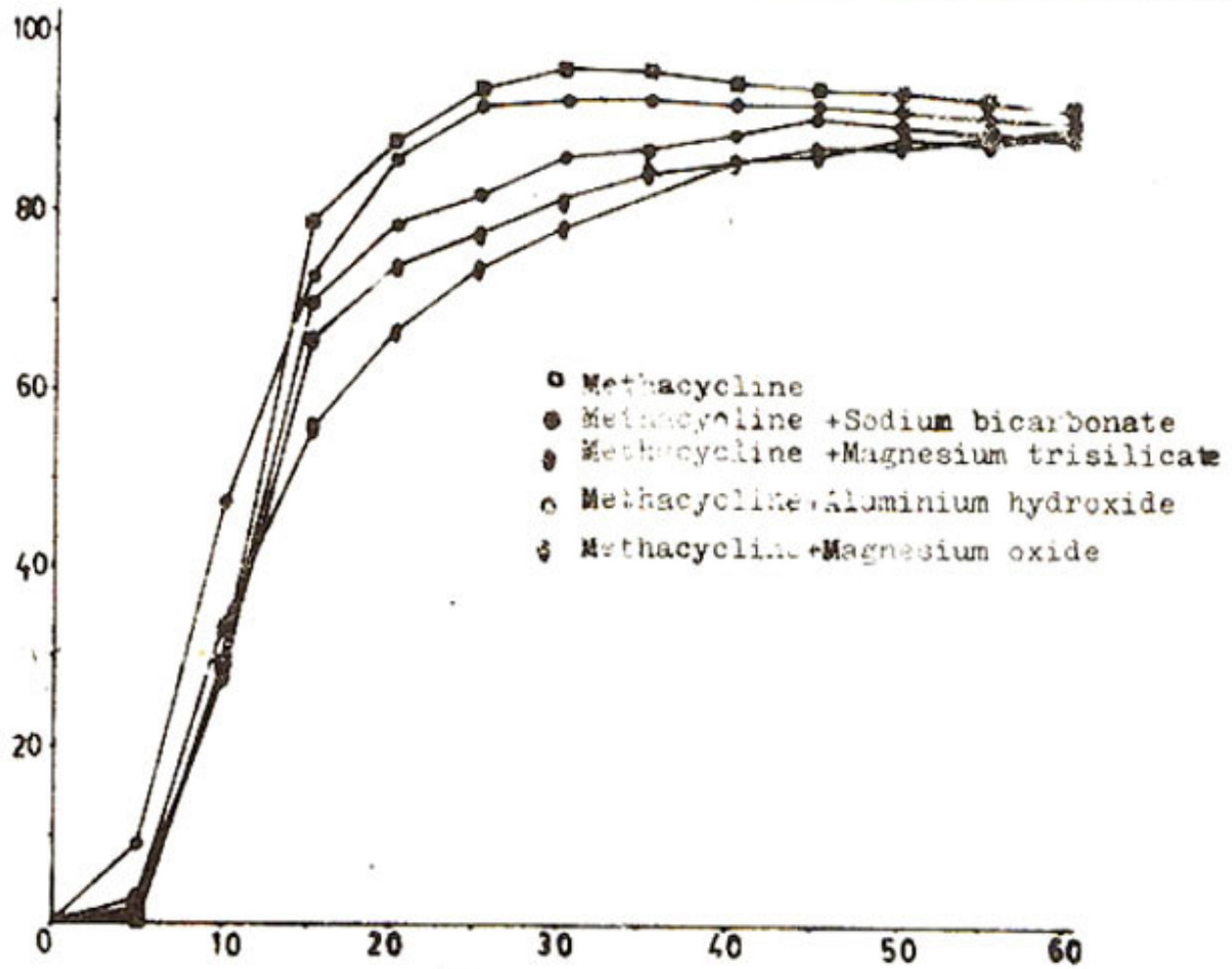
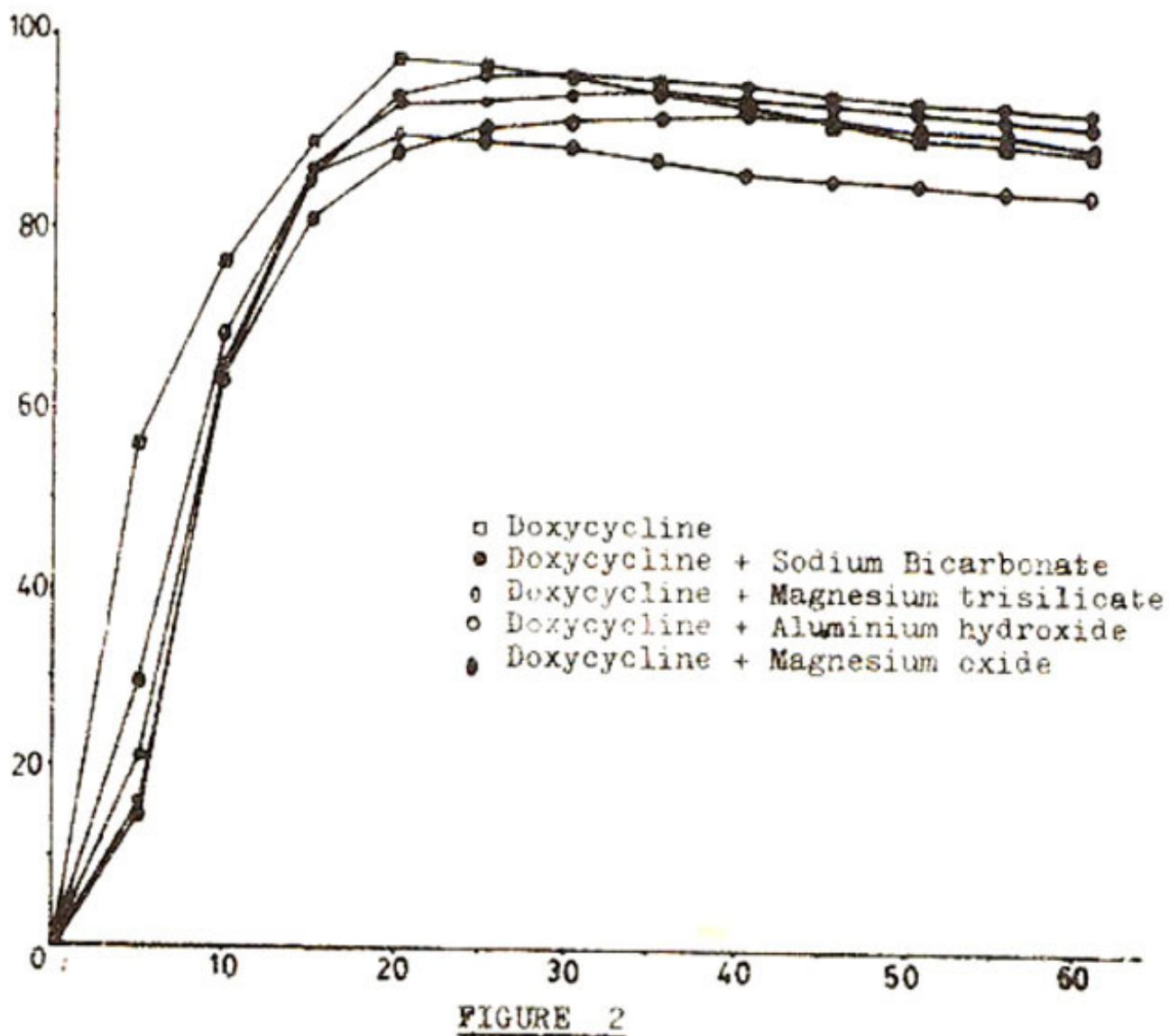


FIGURE I



As can be seen from these curves, the dissolution rates of both drugs from the capsules decreased in the presence of antacids (0.2% w/v) studied. Magnesium trisilicate had the greatest retardation effect on the dissolution of both antibiotics (Fig. I & 2), and magnesium oxide on methacycline. There was not any significant difference in magnesium trisilicate and magnesium oxide on the retardation of dissolution of methacycline. After 30 minutes less than 80% of methacycline was found in solution (Fig. I). The presence of lower levels of aluminium hydroxide and sodium bicarbonate (0.2% w/v) also reduced the dissolution of both antibiotics.

Thus it is clear that the dissolution of both antibiotics can be retarded by small amount of antacids containing polyvalent cations. It has also 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 (Barr et al., 1971).

Table -III
pH Studies of Antacids in Water and in 0.1 N HCl.

S. No.	Antacid	Concentration	pH in Distilled water	pH in 0.1N HCl
1.	Sodium Bicarbonate	0.2%	8.73	1.33
2.	Magnesium Trisilicate	0.2%	9.60	1.37
3.	Aluminium Hydroxide	0.2%	7.60	1.25
4.	Magnesium Oxide	0.2%	10.70	1.85

Table III shows the pH of the antacids in distilled water and 0.1N HCl.

During dissolution studies of methacycline capsules in presence of sodium bicarbonate, it was observed that although gelatin was dissolved but the blend remained in the suspended form. This behaviour was followed in the latter stages and the dissolution of the Be suspended and settled particles followed at a very slow rate as compared to normal dissolution behaviour. Sodium bicarbonate had a very little effect on the dissolution efficacy of doxycycline.

Barr et al. (1971) found that there is a decrease of tetracycline absorption in man by sodium bicarbonate. They used eight subjects taking 250 mg tetracycline capsules with 0.2 g sodium bicarbonate and compared them with those taking the antibiotic alone. They found that the absorption of the drug was reduced by approximately 50% by the presence of sodium bicarbonate. They concluded that the reduction in absorption was due to the increase in pH of the gastric contents which reduces the dissolution of the tetracycline long enough for 20% to 50% of the undissolved drug particles to pass into the duodenum where the pH (5 to 6) was unfavourable for dissolution.

Elliot and Armstrong (1972) concluded that all capsular medications are functionally inactive when given under condition in which the contents of the stomach are neutral or alkaline. He proposed an inhibitory effect of increased pH on the dissolution of capsule itself.

According to Jubi and Blaug (1973) pH is probably not a major factor for the dissolution of capsule

medications. He found that at body temperature, varying pH did not affect the average release time of the capsule, however at room temperature pH did affect the release times.

In our studies when sodium bicarbonate is added to the dissolution medium (0.1N HCl), the concentration of hydrogen ion decreases due to the evolution of CO₂, which leads to increase in pH. A pH study of 0.2% solution of sodium bicarbonate in distilled water and in 0.1N hydrochloric acid were also carried out and were compared with the pH of distilled water and 0.1N hydrochloric acid (Table III), it shows that only pH is responsible for delayed rate of dissolution. As a result of the reaction between sodium bicarbonate and dissolution medium, an increase in pH causes a complex formation between the ingredient of formulation and the medicament during the dissolution test, leading to prolonged and incomplete dissolution of the capsules.

Magnesium oxide which is soluble in 0.1N hydrochloric acid exhibited a pronounced effect on the rate of dissolution of both antibiotics and prolonged and incomplete dissolution were achieved. pH studies of 0.2% solution of magnesium oxide in distilled water and in 0.1N hydrochloric acid showed that pH values moved to a very higher range leading to prolonged dissolution rate of the dosage forms. Besides, chelating effect of tetracyclines with Mg⁺⁺ is also responsible for incomplete rate of dissolution.

Similar studies indicate that although doxycycline complexes calcium to a lesser extent than other tetracyclines, absorption is hindered by calcium as well as by other nonsystemic antacids and by iron preparations (Arthur, 1975; Martindale, 1977).

From the results as listed in tables I-II,

Table - I
Concentration of Methacycline (%) in Presence of Antacids at Different Time Intervals.

S. Samples No.	5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.	40 Min.	45 Min.	50 Min.	55 Min.	60 Min.
1. Methacycline	00.00	29.51	79.23	88.52	94.67	97.13	96.13	95.31	95.76	95.22	94.60	93.88
2. Methacycline + Sodium Bicarbonate	2.59	27.87	70.49	79.23	82.78	87.16	88.38	90.84	92.48	91.53	91.12	90.57
3. Methacycline + Magnesium Oxide	00.41	28.55	66.12	74.59	78.41	82.78	86.06	87.57	87.98	90.16	90.44	90.57
4. Methacycline + Magnesium Trisilicate	1.37	33.88	56.28	67.21	74.45	79.37	86.88	87.43	88.80	88.93	90.84	92.21
5. Methacycline + Aluminium Hydroxide	8.71	47.62	73.47	86.40	92.79	93.60	93.88	93.88	93.60	93.20	92.79	92.38

Table - II

Concentration of Doxycycline (%) in Presence of Antacids at Different Time Intervals.

S. Samples No.	5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.	40 Min.	45 Min.	50 Min.	55 Min.	60 Min.
1. Doxycycline	56.31	76.69	94.02	99.56	98.82	97.71	95.87	94.76	92.92	91.07	90.88	90.13
2. Doxycycline + Sodium Bicarbonate	16.22	63.80	86.28	95.50	97.71	98.08	97.71	97.34	96.24	95.50	95.13	94.76
3. Doxycycline + Magnesium Oxide	14.75	63.80	81.50	89.23	92.18	92.92	93.65	94.02	93.30	92.55	92.18	91.07
4. Doxycycline + Magnesium Trisilicate	29.86	68.58	86.65	91.07	90.34	89.97	88.49	87.02	86.65	86.28	85.54	85.54
5. Doxycycline + Aluminium Hydroxide	21.38	65.26	86.65	94.40	94.76	95.87	96.24	95.50	95.13	94.40	93.65	93.29

it is quite clear that the dissolution rates of both drugs from the capsules decreased in presence of magnesium trisilicate (0.2% w/v). Shozo et al. (1973) found that magnesium trisilicate in a concentration of 0.2% w/v had the greatest retardation effect on the dissolution of tetracycline. After 30 minutes, less than 12% of tetracycline was found in solution. The presence of lower levels of antacids (1% w/v magnesium trisilicate), also reduced tetracycline dissolution; the amount dissolved after 30 minutes was 23.5%. In our studies, 0.2% w/v magnesium trisilicate leads to dissolution of 79.37% of methacycline in 30 minutes. Magnesium trisilicate also markedly reduced the dissolution rate of doxycycline. When aluminium hydroxide and magnesium trisilicate were added to the dissolution medium they remained in suspended undissolved state. There are two possibilities for the slow rate of dissolution of these drugs, either due to increase in pH or adsorbent properties of these two antacids. From the pH studies it is quite obvious that for aluminium hydroxide pH is not a major factor for prolonged dissolution behaviour. Whereas the pH of magnesium trisilicate suspension indicates that despite of other factors, pH also plays a dominant role in retarding the dissolution behaviour of these drugs.

Adsorption properties of these two antacids were studied by passing the drug solution through the column of each of both antacids. Columns were washed with water, final washing showed traces of active ingredients. Then the columns were eluted with 0.1N hydrochloric acid. The eluent gave a positive identification test for doxycycline, and methacycline when treated with ferric chloride. These studies indicate that doxycycline and methacycline are strongly adsorbed on antacids. Magnesium trisilicate exhibits relatively higher adsorption capacities for these drugs. The differences in the adsorption capacities could be related to the pH of the antacid suspensions.

These results suggest that adsorption of methacycline and doxycycline on antacid particles as well as changes in pH of the dissolution medium by the addition of antacids may be responsible for the marked retardation of dissolution and hence the absorption of these antibiotics. A similar mechanism was reported for the inhibited dissolution of glycosides (Khalil, 1974).

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