September 2003

Chem. Pharm. Bull. **51**(9) 1021—1024 (2003)

1021

Abnormal Dissolutions of Chlorpromazine Hydrochloride Tablets in Water by Paddle Method under a High Agitation Condition

Nobuo Aoyagi,*,[a] Annie Policarpio Rimando,[b] Kenichi Izutsu,[a] Noriko Katori,[a] and Shigeo Kojima[a]

[a] National Institute of Health Sciences; 1–18–1 Kamiyoga, Setagaya-ku, Tokyo 158–8501, Japan: and [b] Bureau of Food and Drugs; Alabang Muntinlupa City, Phillipines, 1770.   Received January 28, 2003; accepted July 2, 2003

All sugar-coated tablets of chlorpromazine hydrochloride except for those produced by one manufacture showed concave dissolution profiles in water by paddle method at 100 rpm but not at 50 rpm. The study was undertaken to clarify the agitation-dependent abnormal dissolutions. The strange dissolutions were also observed in water at different ionic strengths but not in buffer solutions of pH 1.2, 4.0 and 6.8. When monitored, the pH's of water in dissolution vessels for the abnormal tablets increased with time at 100 rpm and some of them exceeded pH 8 but did not at 50 rpm. The solubility of chlorpromazine hydrochloride decreased with the increase of pH which was too low to dissolve the whole amount of drug contained in a tablet at pH 8. The elevation of pH seemed to be mainly brought about by dissolution of calcium carbonate popularly used for sugar-coated tablets, because larger amount of calcium ion was dissolved out from the abnormal tablets at 100 rpm than from a normal tablet and from them at 50 rpm. These findings indicate that the concave dissolution profiles should be caused by the decrease of drug solubility with increase in pH of water, probably because of dissolution of calcium carbonate. We should pay attention to the change in pH of water which may differ depending on the agitation speed of dissolution tests.

Key words   dissolution test; chlorpromazine hydrochloride tablet; change in pH; precipitation; paddle method

In vitro dissolution tests for oral drugs are generally carried out at a low agitation speed in order to discriminate bioinequivalent products well.[1] However, tablets or capsules containing a large amount of low solubility drugs or insoluble excipients sometimes produce a mound at the bottom of the vessel after their disintegration by the paddle method,[2] resulting in the incomplete dissolution. For those products, the application of high agitation speeds seems to be preferable, which, however, may decrease the discriminating power of dissolution tests. In order to investigate the discrimination power, we carried out dissolution tests by JP paddle method at 50 and 100 rpm, using sugar-coated tablets of chlorpromazine hydrochloride as model products. During the study, we found agitation-dependent abnormal dissolution behaviors (concave dissolution profiles at 100 rpm but normal at 50 rpm) for most tablets. We have never seen such strange dissolution behaviors and could not understand why they showed the concave profiles only at the high speed. The present study was undertaken to clarify the abnormal dissolution.

Experimental
Formulation   Sugar-coated tablets of four different manufactures (A, B, C and D) containing 12.5—100 mg of chlorpromazine hydrochloride were used. The 25 mg tablet of manufacture A is shown as A-25.

Dissolution Test   Dissolution tests were carried out at 37 °C by JP paddle method, using 900 ml of water, the 1st fluid of JP (pH 1.2), 0.05 M sodium acetate buffer (pH 4.0), pH 6.8 solution (JP pH 6.8 sodium phosphate buffer : water=1 : 1) and JP pH 7.0—8.0 phosphate buffer solutions. The amount of drug dissolved was spectrophotometrically measured.

Solubility   Fifty milligrams of chlorpromazine hydrochloride powder was added to 20 ml of pH 7.0, 7.6, 8.0 and 8.2 phosphate buffer solutions prepared referring to JP phosphate buffer solutions. The amount of drug dissolved was spectrophotometrically measured after shaking the test tubes containing each buffer solution at 37 °C for 24 h.

Effect of Excipient on Medium pH and Dissolved Amount of Drug   Dissolution tests for chlorpromazine hydrochloride tablets were performed in 900 ml of water for 3 h at 50 or 100 rpm. Then, the supernatant fluid was discarded and 900 ml of aqueous solution containing 50 mg of chlorpromazine hydrochloride was added to the residue which was agitated at 100 rpm. The changes in the medium pH and amount of drug dissolved in the fluid were monitored. In the experiment investigating effects of calcium carbonate, 20 mg calcium carbonate (JP) was added to aqueous solution of chlorpromazine hydrochloride (50 mg in 900 ml) agitated at 100 rpm.

Determination of Calcium Ion Dissolved from Tablet   Dissolution tests for chlorpromazine hydrochloride tablets were performed in 900 ml of water at 50 and 100 rpm and the concentration of calcium ion was measured by ion chromatography with a conductivity detector (Shimadzu CDD-10Avp) under the following condition: cation column, Shim-pack IC-C3 (100×4.6 mm I.D., Shimadzu Co., Kyoto); column temperature, 40 °C; mobile phase, 2.5 mM oxalic acid; flow rate, 1.2 ml/min.

Results and Discussion
Dissolution of Chlorpromazine Hydrochloride Tablet   Dissolution tests were first carried out, using A-50 in water by JP paddle method at 50 and 100 rpm. It exhibited normal dissolution at 50 rpm but concave dissolution profiles at 100 rpm (Fig. 1). Dissolutions of other tablets were also measured which revealed that all products except for those of manufacture D similarly gave uncommon dissolutions at
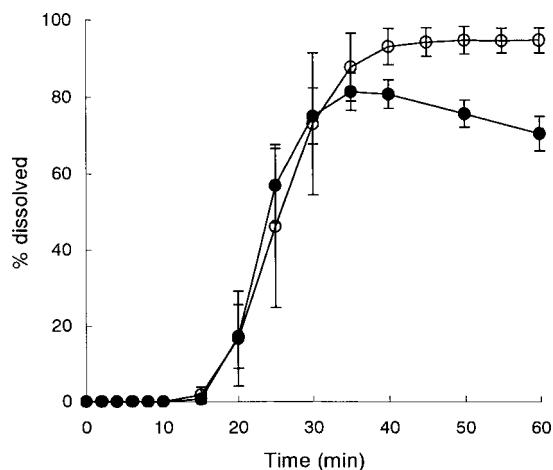

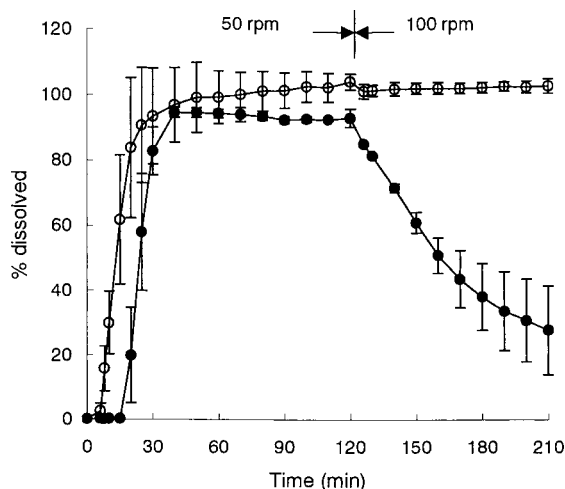Fig. 1.   Dissolution Profiles (Mean±S.D., *n*=6) of A-50 by JP Paddle Method at 50 (○) and 100 rpm (●)

Fig. 2.   Dissolution Profiles (Mean±S.D., $n=3$) of A-50 (●) and D-50 (○) by JP Paddle Method at 50 rpm by 120 min and Thereafter at 100 rpm
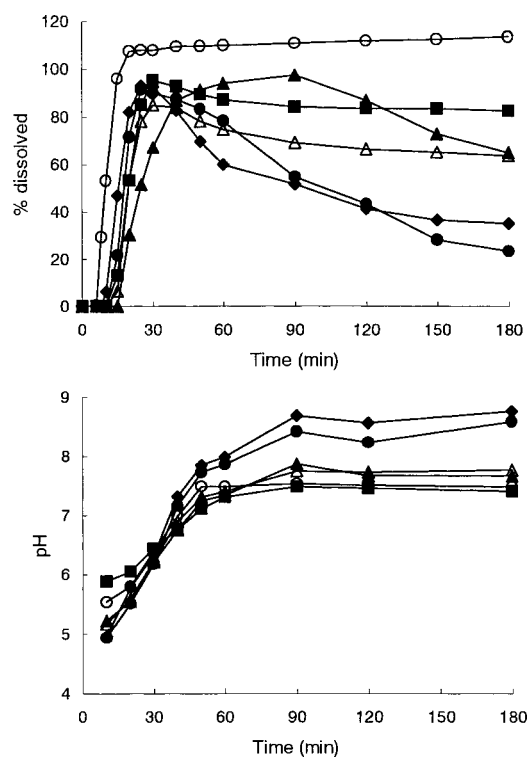

Fig. 3.   Dissolution Profiles and Changes in pH of Water for A-12.5 (◆), A-25 (●), A-100 (△), B-100 (■), C-25 (▲) and D-25 (○) by JP Paddle Method at 100 rpm

100 rpm (data not shown), although all tablets showed ordinal dissolutions at 50 rpm. When dissolution tests for A-50 and D-50 giving abnormal and normal dissolutions, respectively, were carried out at 50 rpm for the first 120 min and then at 100 rpm, A-50 showed a significant decrease in the dissolved amount just after the increase in the rotation speed but D-50 did not (Fig. 2). There has been no report on such a strange dissolution by now, which specifically occurred only at a high agitation speed. However, A-50 showed a normal dissolution in pH 1.2, pH 4.0 and 6.8 buffer solutions even at 100 rpm (data not shown). These findings indicated that the abnormal dissolution behaviors at the high speed should be related with the low ionic strength or variable pH of water. To clarify it, the dissolution of drug from A-50 was measured in water containing 0.01 and 0.1 mol/l sodium chloride at 100 rpm but it still showed the concave dissolution profiles regardless of the ionic strength.

Change in pH of Water during Dissolution Test   The remaining possible factor affecting the dissolution is variable pH of water. Thus, we measured the pH of water in each vessel during dissolution tests which revealed that pH's of water were below pH 7 at 50 rpm for all tablets but those at 100 rpm for abnormal tablets increased with time as shown in Fig. 3, in which the pH's for A-12.5 and A-25 showing profound concave dissolution profiles provided very high pHs (>pH 8.5). When the solubility of chlorpromazine hydrochloride ($pK_a=9.2$)[3] was measured, the solubility significantly decreased with the increase of pH (solubility: >2.5, 0.104, 0.075, 0.008 mg/ml at pH 7.0, 7.6, 8.0, 8.2, respectively). It suggested that the concave dissolution profile at 100 rpm should be brought about by the precipitation of the drug due to the decrease of drug solubility with the increase of medium pH. The precipitation at a high pH was observed when 100 ml of aqueous solution containing 25 mg chlorpromazine hydrochloride was added to 800 ml of 8.0 buffer at 37 °C and stirred at 100 rpm where white fine particles were attached to the metal blade.

Effect of Excipient on Medium pH and Dissolved Amount of Drug   The increase in pH of water should be caused by the dissolution of alkaline excipients contained in abnormal tablets. However, it was not understandable why

they dissolved only at 100 rpm. When carefully observed, all tablets disintegrated into fine particles at 100 rpm which were dispersed well in the test fluid, although all tablets formed mounds at the bottom of vessel after the disintegration at 50 rpm. The observation indicated that some alkaline excipients which remained in the mound at 50 rpm should be dissolved under the high agitation condition and increase the pH of water. To clarify it, we carried out dissolution tests using A-50 and D-50 showing abnormal and normal dissolutions at 50 rpm or 100 rpm for 3 h and the supernatants were discarded. To the residues, 900 ml of aqueous solution containing 50 mg chlorpromazine hydrochloride was added and stirred at 100 rpm. The medium pH and the dissolved amount of drug were monitored. As shown in Fig. 4, the medium pH more increased with the decrease in dissolved amount of drug in the presence of residual excipients obtained from A-50 at 50 rpm than in the presence of those of D-50, indicating that A-50 should contain larger amount of alkaline excipients. On the other hand, there were no significant changes in medium pH and dissolved amount in the presence of residual excipients of A-50 as well as D-50 which were obtained from dissolution tests at 100 rpm. The findings suggest that the alkaline excipients should be almost dissolved under the vigorous agitation condition at 100 rpm and should not remain in the residue.

Calcium Ion Dissolved from Tablet   As the alkaline excipient, calcium carbonate was deduced, since it is popularly used for sugar-coated tablets[4] and, because of the low solubility and heavy specific gravity, the excipient will not disperse and hence dissolve well in the test fluid at 50 rpm, a low speed. Accordingly, we measured calcium ion dissolved from tablets in water during dissolution tests. The experiment
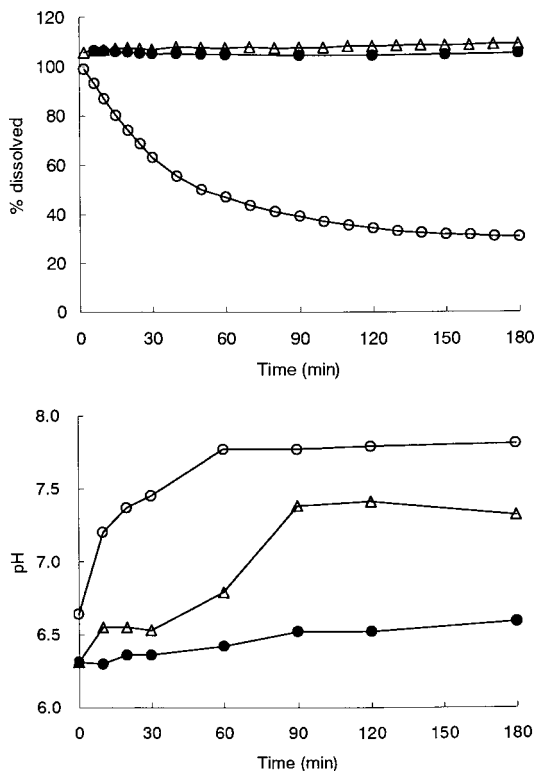
Fig. 4. Changes in Dissolved Amount of Drug (Upper Figure) and pH of Water (Lower Figure) at 100 rpm in the Presence of Residual Excipients of Tablets Obtained from A-50 (○) and D-50 (△) by Dissolution Tests in Water at 50 rpm for 3 h and from A-50 (●) at 100 rpm
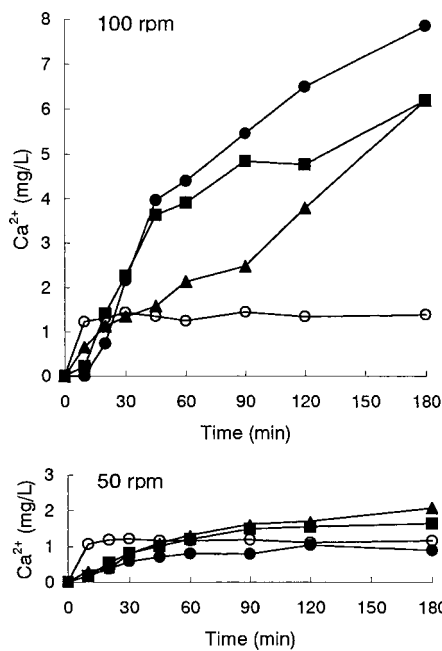

Fig. 5. Dissolution of Calcium Ion from A-50 (●), B-100 (■), C-25 (▲) and D-50 (○) in Water by Paddle Method at 100 rpm and at 50 rpm

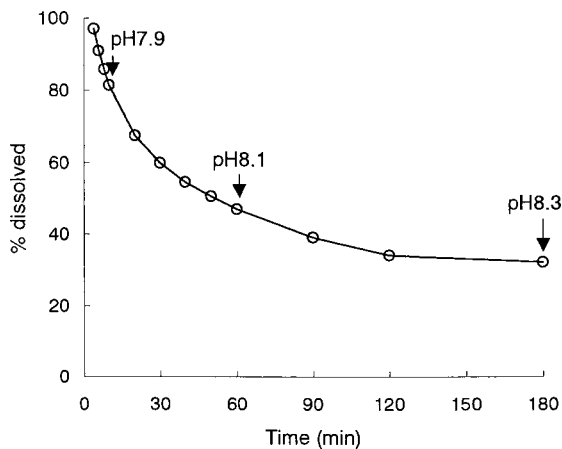Fig. 6. Changes in Dissolved Amount of Drug (50 mg/900 ml) and pH of Water at 100 rpm in the Presence of 20 mg Calcium Carbonate

revealed that calcium ion dissolved more from A-50, B-100 and C-25 at 100 rpm than from D-50 showing normal dissolution (Fig. 5). Calcium ion did not dissolve much from any tablets at 50 rpm. The calcium concentration (approximately 8 mg/l) at 3 h for A-50 almost corresponds to 20 mg calcium carbonate dissolved. When 20 mg calcium carbonate was added to aqueous solution of chlorpromazine hydrochloride (50 mg/900 ml) stirred at 100 rpm, the dissolved amount of drug significantly decreased with time as shown in Fig. 6, where the fluid pH was near to pH 8. The profile of dissolved amount and fluid pH were similar to those observed for the residual excipients of A-50 in Fig. 4. The findings indicate that the increase in pH of water for abnormal tablets at 100 rpm should be mainly caused by the dissolution of calcium carbonate employed for sugar-coated tablets, although other excipients might affect the pH of water as well. The content of calcium carbonate in tablets of manufacture D might be smaller than others or the dissolution of calcium carbonate might be limited due to the incomplete disintegration into fine particles.

Our previous study on indomethacin preparations showed that water is advantageous for discriminating poorly available products compared with other pH solutions.[5] However, there have been very limited studies on the relation between dissolution tests in water and bioavailability until now. Therefore, it is difficult to predict whether the tablets showing abnormal dissolution in water will also show strange *in vivo* absorptions or not. Water is empirically known as a discriminative medium[6] and used as a test fluid together with other physiological pH buffers for *in vitro* equivalence tests for minor changes in formulation of oral dosage forms in Japan[7] as

well as in U.S.A.,[8] where water is employed for low solubility drugs. However, the use of water has been criticized because of the non-physiological medium, variable pH and surface tension.[9,10] Here, we have to consider the main purpose of the *in vitro* equivalence test employed as a surrogate for human study, which will be to assess the potential risk of bioinequivalence. For the purpose, it is desirable to carry out dissolution tests not only in physiological pH fluids but also in water, a discriminative medium, to assure bioequivalence by *in vitro* tests without human studies. This approach is recommendable to avoid the risk of bioinequivalence if it is not much difficult to prepare test products showing similar dissolution even in water with the reference product. However, water should be removed from the test fluids when it is clarified that water is not suitable for the *in vitro* equivalence due to poor *in vitro–in vivo* relations.

The present study gave a conclusion that the agitation-dependent abnormal dissolutions in water should be caused by

the precipitation of the drug because of the decease of drug solubility with the increase in pH of water. The change in pH was probably ascribed to the dissolution of calcium carbonate, an alkaline excipient, widely used for sugar-coated tablets. The findings tell us that we have to pay attention to the change in pH of water which may differ depending on the agitation speed of dissolution testing.

References and Notes
1) Shah V. P, Gurbarg M., Noory A., Dighe S., Skelly J. P., *J. Pharm. Sci.*, **81**, 500—503 (1992).
2) Qureshi S. A., Shabnam J., *Eur. J. Pharmaceut. Sci.*, **12**, 271—276 (2001).
3) Chatten J. G., Harris L. E., *Anal. Chem.*, **34**, 1459—1501 (1962).
4) Takagishi Y., Nagata S., "Iyakuhin no Kaihatsu: Seizai Sozai 1," ed. by Ichibagase H., Uekama K., Otagiri M., Hirokawa Publishing, Tokyo, 1990, pp. 198—214.
5) Aoyagi N., Morihara M., Ishi F., Ogata H., Abstract 3 of the 120th Meeting of the Pharmaceutical Society of Japan, 2000, p. 124.
6) Leeson L. J., *Dissolution Technologies*, **7**, 16—19 (2000).
7) Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms ⟨http://www.nihs.go.jp/drug/DrugDiv-E.html⟩
8) SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation: ⟨http://www.fda.gov/cder/guidance/⟩.
9) Noory C., Tran N., Ouderkirk L., Brown S., Perry J., Lopez J., Colon M., Faberlle M., Henry K., Rorberg J., Ali S. N., Shah V., *Dissolution Technologies*, **6**, 6—7 (1999).
10) FIP guideline for dissolution testing of solid oral products (final draft, 1995), *Drug Information J.*, **30**, 1071—1084 (1996).