Dissolution Rates of Doxycycline Free Base and Hydrochloride Salts

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Abstract □ The dissolution rates of doxycycline monohydrate, hyclate, and hydrochloride dihydrate crystal forms were investigated using the static pellet method. Solubility product equilibria with chloride ion strongly suppressed the dissolution rate of the hydrochloride dihydrate salt. This form dissolved about fourfold slower in 0.1 *N* HCl than in water, which was consistent with its solubility in these media. Specificity for chloride was demonstrated by the rapid dissolution rate for the hydrochloride dihydrate in 0.1 *N* methanesulfonic acid. The dissolution rates of the hyclate, a solvated hydrochloride salt, and the free base were not sensitive to chloride ion. The results show that common ion equilibria with chloride can strongly reduce the dissolution rate of a thermodynamically stable hydrochloride salt form, while the free base or a metastable hydrochloride salt are not similarly affected.

Keyphrases □ Doxycycline—dissolution rates, free base and hydrochloride salts □ Dissolution rates—doxycycline free base and hydrochloride salts □ Antibacterials—doxycycline, dissolution rates of free base and hydrochloride salts

Aqueous solubilities of doxycycline monohydrate (Ia), hyclate (Ib), and hydrochloride dihydrate (Ic) crystal forms have been studied (1). Solubility product equilibria involving chloride ion and self-association were major factors affecting the aqueous solubility of the hydrochloride dihydrate salt (Ic). Common ion effects also influenced the solubilities and dissolution rates of the hydrochloride salts of chlortetracycline, demeclocycline, and methacycline (2). Evidence was presented for greater bioavailability from the chlortetracycline and methacycline free bases compared to the hydrochloride salts (3).

In contrast with other tetracyclines, several studies have found doxycycline to be well absorbed orally (4–8). In a crossover study, a suspension of Ia had a significantly more rapid absorption rate but equivalent area under the curve values compared to capsules and an oral solution containing Ib (4). Serum doxycycline levels were less affected by food than those of tetracycline or demeclocycline (5, 6).

The purposes of the present investigation were to examine factors affecting the intrinsic dissolution rate of doxycycline forms (Ia–Ic) in various media and to correlate these findings with previously reported solubility behavior (1).

EXPERIMENTAL

Materials—Compounds Ia and Ib were USP grade and were used as received[1]. Compound Ic was prepared as described previously (1) and ground in a mortar and pestle before compression. Buffer materials were reagent grade. Water was deionized and double distilled.

Dissolution Rate Determination—The static pellet method was used (9). Pellets were prepared by directly compressing 500 mg of powder in a 1.27-cm diameter die. A laboratory press[2] was used at 211 kg/cm² (3000 psi) for 20 sec. After the lower side was masked, the die with the pellet was positioned facing up in the bottom of a water-jacketed beaker containing 800 ml of dissolution medium at 25.0 ± 0.2°. The solution was stirred[3] by a paddle rotating at 50 rpm.

Samples were withdrawn at appropriate intervals and assayed spectrophotometrically[4] at 345 nm. Filtration was not necessary since significant pellet disintegration did not occur. The I concentration (free base equivalent) was determined from Beer's law plots prepared using Ib in the solvent of the dissolution experiment. The results are reported as the average of two or more runs.

RESULTS AND DISCUSSION

Dissolution curves for Ia–Ic under several conditions are shown in Figs. 1 and 2. Dissolution rate constants given in Table I were calculated as linear regression slopes. In several cases, the dissolution medium solubility is not meaningful since conversion to a more stable crystalline form occurred during the equilibration period. For example, solutions of the hyclate salt (Ib) in 0.1 *N* HCl will ultimately crystallize as the more stable hydrochloride salt form (Ic). Similarly, addition of sufficient Ic to pH 4.0 or 7.0 buffers results in its conversion to the less soluble free base (Ia), assuming sufficient buffer capacity. Thus, the original crystalline form, for which a solubility value was desired, does not exist at equilibrium.

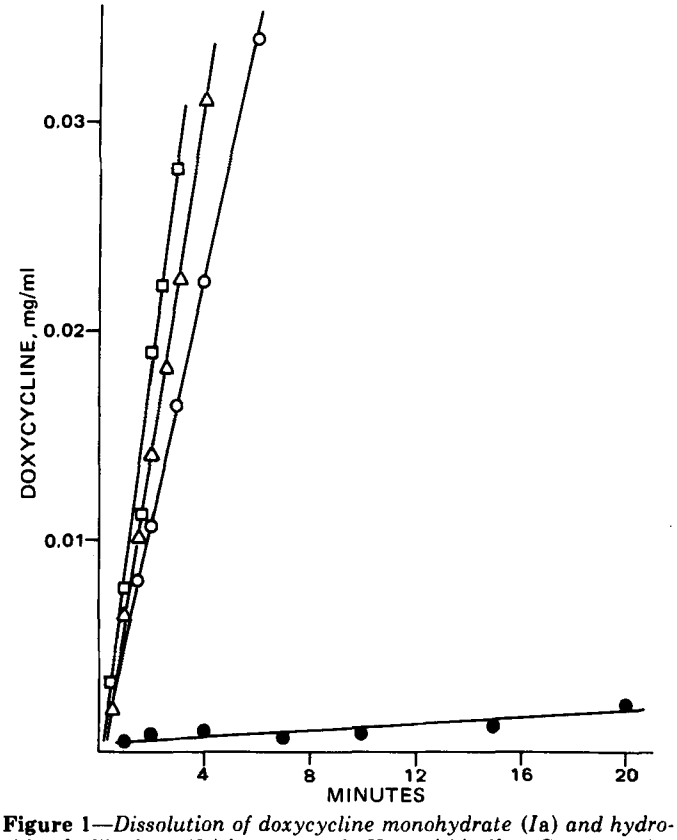

Figure 1—*Dissolution of doxycycline monohydrate (Ia) and hydrochloride dihydrate (Ic) in water and pH 4 and 7 buffers. Concentration is expressed as free base equivalent. Key: □, Ic in 0.1 M acetate buffer, pH 4.0; △, Ic in 0.1 M sodium phosphate buffer, pH 7.0; ○, Ic in water (pH 6.8–7.0 during run); and ●, Ia in 0.1 M acetate buffer, pH 4.0. Buffers did not contain chloride ion.*

[1] Pfizer Inc.
[2] Carver.
[3] Servodyne, Cole-Palmer.
[4] Model 240, Gilford.

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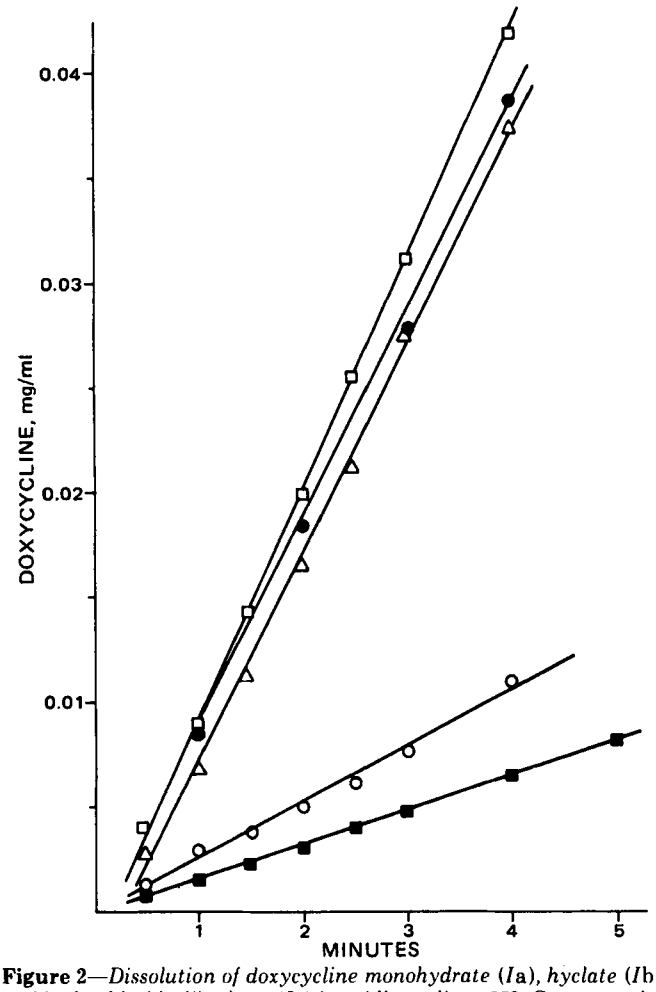

Figure 2—*Dissolution of doxycycline monohydrate (Ia), hyclate (Ib), and hydrochloride dihydrate (Ic) in acidic media at 25°. Concentration is expressed as free base equivalent. Key: □, Ib in 0.1 N HCl; ●, Ia in 0.1 N HCl; △, Ic in 0.1 N CH_3SO_3H; ○, Ic in 0.05 N HCl; and ■, Ic in 0.1 N HCl.*

Compound Ic dissolved rapidly in water and pH 4.0 and 7.0 buffers (Fig. 1), whereas Ia dissolved approximately 100-fold slower at pH 4. Precipitation of Ia could occur on the pellet surface during Ic dissolution in pH 4.0 or 7.0 buffers. A phenomenon of this type resulted in nonlinear dissolution rates for tolazamide sodium in phosphate buffers due to apparent surface conversion to the acid form (10). The good linearity and rapid dissolution rates in Fig. 1 indicate that significant conversion to Ia did not occur during dissolution of Ic.

The dissolution rate order of Ic > Ia applicable to neutral pH values was reversed in dilute hydrochloric acid (Fig. 2). The common ion effect of chloride inhibited dissolution of the thermodynamically stable form (Ic). In 0.1 *N* HCl, Ic dissolved four- to sixfold slower than in water and pH 4 or 7 buffers. Reduction of hydrochloric acid from 0.1 to 0.05 *N* caused a 70% increase in the dissolution rate. The expected chloride-ion specificity was confirmed by measurement of the dissolution rate of Ic in 0.1 *N* CH_3SO_3H. In this medium of similar acidity but without chloride, the Ic dissolution rate was equivalent to that found for Ia or Ib in 0.1 *N* HCl. The solubility product equilibrium of Ic with chloride ion was reported with a K^0_{sp} value of $1.8 \times 10^{-3}\ M^2$ (1). Compound Ic was about fivefold less soluble in 0.1 *N* HCl than in water, consistent with the dissolution rate data.

The dissolution rates of Ia and Ib in hydrochloric acid were apparently insensitive to chloride ion, indicating that conversion to Ic did not occur on the pellet surface. Doxycycline solubility is complicated by self-association in relatively concentrated solutions to form a dimer and higher order forms (1). Therefore, self-association in the diffusion layer probably prevents Ic crystallization during the dissolution experiments.

When an acid–base reaction occurs between buffer species and the dissolving substance, dissolution rates cannot be compared with solubilities. A study of the benzoic acid dissolution rate in basic and buffered media showed that the dissolution rate was dependent on the strength, diffusivity, and concentration of the basic-buffer species (11). Examples of similar dissolution behavior from the present data are Ia in 0.1 *N* HCl, Ic in pH 4.0 buffer, and Ic in pH 7.0 buffer. The rapid dissolution of Ia in 0.1 *N* HCl compared to pH 4.0 buffer is analogous to the acid–buffer interaction already discussed. The hydrochloric acid strength and diffusivity are largely responsible for the rapid dissolution of poorly water-soluble Ia (11, 12). The more rapid dissolution rate for Ic in pH 4.0 and 7.0 buffers compared to water is due to the rate-increasing effects of the basic buffer components.

Table I—Dissolution Rates and Solubilities of Doxycycline Forms at 25°

Doxycycline Form	Medium	Dissolution Rate, mg/(min cm²)	Equilibrium Solubility, mg/ml
Ia	0.1 *N* HCl	6.3	—[a]
Ib	0.1 *N* HCl	6.9	—[a]
Ic	0.1 *N* HCl	1.0	9.9[b]
Ic	0.05 *N* HCl	1.7	23.5[b]
Ic	0.1 *N* CH_3SO_3H	6.3	—
Ic	pH 4.0 buffer	6.3	—[a]
Ic	pH 7.0 buffer	5.0	—[a]
Ic	Water (pH 6.8–7.0)	3.8	50[b]
Ia	pH 4.0 buffer	0.05	0.75[b]

[a] No value is given since the solubility of the stated crystalline form is not measurable in this medium. Conversion to a thermodynamically more stable form occurs. [b] Reference 1.

The hyclate salt (Ib) is a solvated hydrochloride containing 0.5 mole each of ethanol and water. Without consideration of common ion effects, the intrinsic dissolution rate of this metastable salt form should be greater than that of the stable form (Ic) due to its higher thermodynamic activity (13). In the present system, Ib had the significant advantage of not taking part in a common ion equilibrium with chloride ion. This difference may be important in oral dosage forms due to the high chloride level in human gastric juice, 0.07–0.16 *M* (14). This amount of chloride is sufficient to alter markedly the dissolution properties of Ic but not of Ia or Ib. Under identical conditions of pH and chloride concentration, Ia–Ic all must yield the same equilibrium solubility in dilute hydrochloric acid, *i.e.*, that of the thermodynamically stable form (Ic).

The results of this study indicate that solubility product equilibria can be a major factor affecting dissolution of hydrochloride salts in chloride-containing media. In such cases, selection of an alternative salt form or "less soluble" free base may improve dissolution and bioavailability.

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