Inhibited Dissolution of Drug Crystals by a Certified Water-Soluble Dye

J. PICCOLO and R. TAWASHI

Abstract ☐ Quantitative experiments to investigate the effect of FD&C Blue No. 1 on the dissolution of single crystals of sulfathiazole, phenobarbital, thymol, and sulfaguanidine under controlled conditions, are described. At a very low concentration FD&C Blue No. 1 exerted a remarkable inhibition on dissolution. Dissolution experiments on compressed disks and crystalline powder, gave a significantly lower dissolution rate than the pure drug alone. The dependence of the dissolution rate on the inhibitor concentration was studied in sulfaguanidine crystals, and a concentration of 100 mcg./ml. reduced the dissolution rate by 55%. The data presented is in agreement with the current theories concerning dissolution inhibition by small concentrations of impurities and suggests the dye molecules are preferentially adsorbed at the primary dissolution sources in the crystals investigated.

Keyphrases ☐ Drug crystal dissolution—inhibition ☐ Crystal dissolution inhibition—water-soluble dye ☐ Dissolution rates, behavior—single crystals, compressed disks ☐ FD&C Blue No. 1—crystal dissolution inhibition

Figure 1—*Single-crystal dissolution of phenobarbital monohydrate as a function of time. Key:* ▲, *in 0.1 N HCl;* ■, *in 0.1 N HCl containing 10 mcg./ml. FD & C Blue No. 1.*

The effect of small quantities of dissolved impurities on the dissolution, growth, and habit modification of crystalline materials has been a subject of different papers (1–3). The development of the dislocation theory, supported by the fact that many organic and inorganic crystals grow by dislocation (4), offered a new basis for examining the influence of impurities on dissolution and growth of crystals.

Albon and Dunning (5) found that a low concentration of raffinose (1 part in 10,000 parts) lowered the rate of step movement of sucrose crystals. The inhibitory action of raffinose and the retardation of step advancement was explained as being governed by the adsorption of raffinose on the steps of sucrose crystals. Ives *et al.* (6, 7) studied the dissolution kinetics in single crystals of lithium fluoride. The dissolution rate of lithium fluoride was inhibited by small concentrations of ferric ion (1 p.p.m.). The concept of impurity adsorption on the kinks—the primary dissolution sources—was discussed.

Crystal poisoning and habit modification by dyes were reported by Buckley (2), Whetstone (8), and Engelhardt (9). At the present, certified water-soluble dyes are used extensively as colorants in drug formulations, e.g., in tablets, tablet-coating, suspensions, *etc.* The possible effect of these colorants on drug dissolution and eventually drug availability needs a careful study. The purpose of this report is to investigate quantitatively the effect of FD & C Blue No. 1 (as an example of certified dyes) on the dissolution behavior of some drug crystals.

EXPERIMENTAL

Materials—Conditions have been selected to grow nearly perfect drug crystals, suitable for single-crystal work. Crystals of sulfaguanidine, thymol, and phenobarbital monohydrate were grown by slow evapora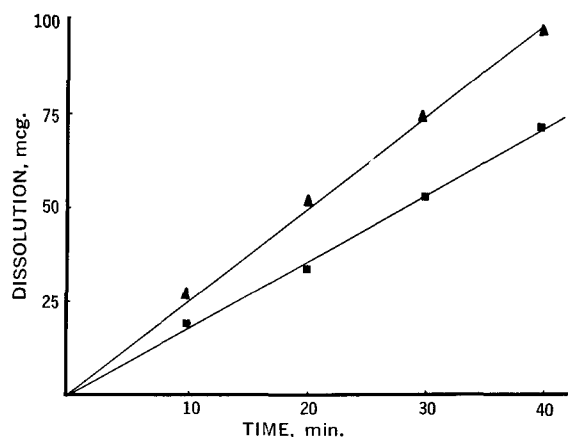tion at room temperature from a saturated solution of the appropriate solvent. The solvents used were acetone for sulfaguanidine, carbon tetrachloride for thymol (10), and a mixture of 50% acetone in water for phenobarbital monohydrate (11). Sulfathiazole Form I crystals were prepared from a saturated solution of sulfathiazole in 95% ethanol using the method described by Grove and Keenan (12). The materials used in this study are USP grade and solvents were purified before use.

Dissolution Rate Studies—The linear dissolution rate was measured by a direct optical method which has been previously described (13, 14). A single crystal was fixed in a rubber slit and placed in a jacketed dissolution cell. The cell was then filled with 200 ml. of 0.1 N HCl at 30°, stirring was maintained at 150 r.p.m. by synchronized motor (Hurst Corp., Princeton, Ind.). The distance between the two parallel faces and boundary movement were measured as function of time. Measurements were done with a microscope fitted with a special filar micrometer (Zeiss). Each point represents the average of ten determinations. The rate of dissolution was determined in absence and in presence of low concentrations of FD&C Blue No. 1 (5–100 mcg./ml.).

To study the dissolution behavior from compressed disks, the same apparatus was used after a slight modification. Tablets from the drug crystals were prepared, having the same diameter (1.88 cm.) and compressed under the same pressure. The tablets were
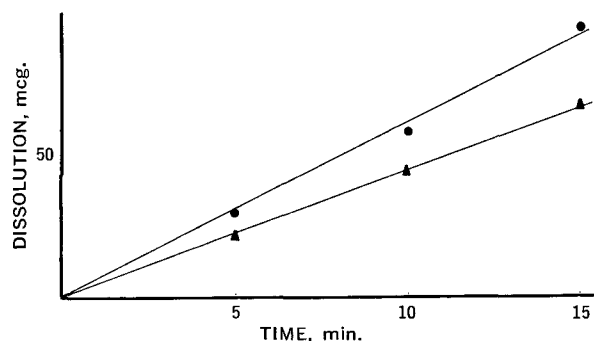

Figure 2—*Single-crystal dissolution of sulfathiazole as a function of time. Key:* ●, *in 0.1 N HCl;* ▲, *in 0.1 N HCl containing 5 mcg./ml. FD&C Blue No. 1.*

Table I—Single-Crystal Dissolution Rate in cm./sec.

Material	Dissolution Rate in 0.1 N HCl	Dissolution Rate in 0.1 N HCl Containing 10 mcg./ml. Dye
Phenobarbital monohydrate	4.2×10^{-6}	2.9×10^{-6}
Sulfathiazole	8.8×10^{-6}	5.1×10^{-6}
Sulfaguanidine	6.8×10^{-5}	4.6×10^{-5}

prepared without the use of any fillers, antiadhesives, or lubricants. The tablet was placed in one end of a short glass tube having the same diameter as the tablet, the other end of the tube was filled with molten white bees wax and left to set. At time zero, the tube was introduced into the dissolution cell containing 200 ml. of 0.1 N HCl at 30°, stirring at 150 r.p.m. Samples were pipeted out at specified time and assayed spectrophotometrically for drug content at the appropriate wavelength in the UV region of the spectrum. The dissolution behavior was studied in absence and in presence of FD&C Blue No. 1. A blank having the same concentration of FD& C Blue No. 1 as the dissolution media was used as a reference in determining the drug release in presence of the dye.

Dissolution behavior of the crystalline powder was determined in absence and in presence of FD&C Blue No. 1 using the same dissolution cell. The crystalline powder was introduced into the dissolution cell at time zero; samples were pipeted out at specified time and assayed for drug content. To exclude the effect of particle size on the dissolution rate, the crystals used in the dissolution study came from the same batch.

RESULTS AND DISCUSSION

The results in Figs. 1–3 show that small concentrations of FD&C Blue No. 1 exerted a remarkable effect on the dissolution behavior of phenobarbital monohydrate, sulfathiazole, and sulfaguanidine. The linear dissolution rates in 0.1 N HCl and in 0.1 N HCl containing 10 mcg./ml. Blue No. 1 are given in Table I.

The dissolution behavior of sulfaguanidine single crystals was studied in presence of variable concentrations of FD&C Blue No. 1 ranging from 0–100 mcg./ml. The data presented in Fig. 3 shows inhibiting effect of the dye on dissolution and Fig. 4 demonstrates
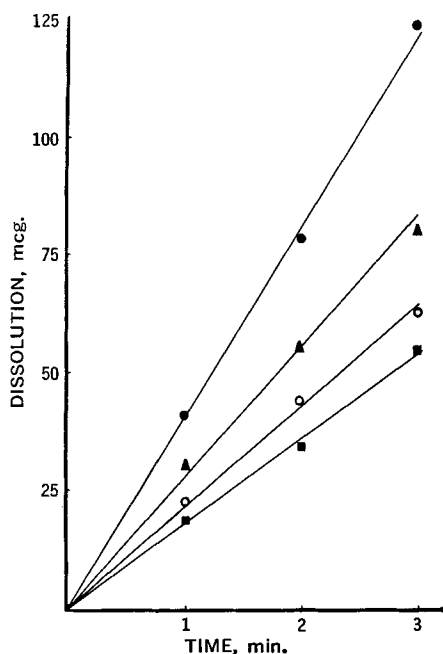

Figure 4—*Effect of dye concentration on the dissolution rate of sulfaguanidine single crystals.*

the dissolution rate dependence on the inhibitor concentration. It is obvious that this curve tends to stabilize after 50 mcg./ml.

Dissolution from the planar surface of a compressed disk was carried out to substantiate the results obtained from single crystals. Figure 5 shows the dissolution behavior of sulfathiazole compressed disks in 0.1 N HCl and in 0.1 N HCl containing 5 mcg./ml. Blue No. 1. The inhibition obtained is in close agreement with that obtained from a sulfathiazole single crystal.

Figure 6 represents the same phenomenon in compressed disks of thymol. The thymol crystals used in preparing the tablet were grown from CCl_4. These crystals exhibited spiral steps as shown in Fig. 7. Because of the fragile nature and shape irregularities of these crystals, it was difficult, in practice, to measure the dissolution rate of single crystals.

The effect of 50 mcg/ml. of dye on 1.5 g. of sulfathiazole crystalline powder is shown in Fig. 8. Although the dye concentration is high, the dissolution rate was reduced by a value smaller than those obtained from studies on single crystals and tablets. This can be explained by the relatively large surface area provided by 1.5 g. of the crystalline powder.

Figure 3—*Single-crystal dissolution of sulfaguanidine as a function of time. Key: ●, in 0.1 N HCl; ▲, in 0.1 N HCl containing 10 mcg./ml. FD&C Blue No. 1; ○, in 0.1 N HCl containing 50 mcg./ml. FD&C Blue No. 1; ■, in 0.1 N HCl containing 100 mcg./ml. FD&C Blue No. 1.*
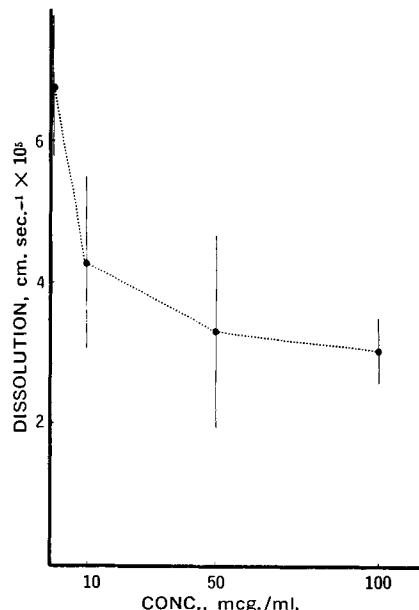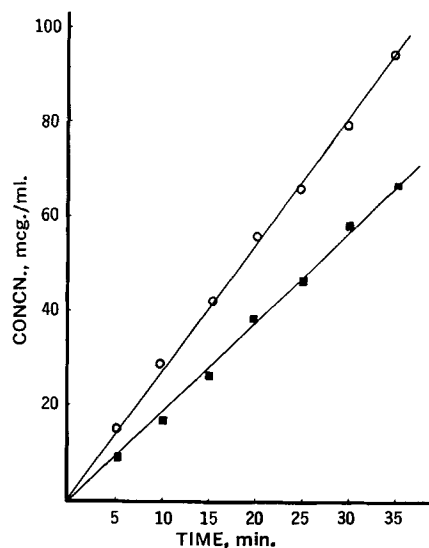

Figure 5—*Dissolution behavior of sulfathiazole compressed disks. Key: ○, in 0.1 N HCl; ■, in 0.1 N HCl containing 5 mcg/ml. FD&C Blue No. 1.*
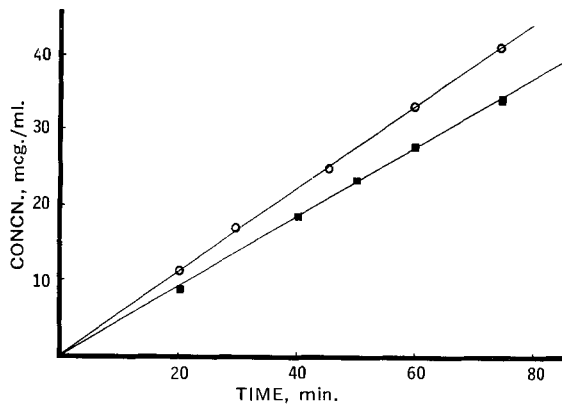
Figure 6—*Dissolution behavior of thymol compressed disks. Key: O, in 0.1 N HCl; ■, in 0.1 N HCl containing 5 mcg./ml. FD&C Blue No. 1.*

The inhibitory effect of Blue No. 1 on the dissolution of the investigated drug crystals, is in agreement with the work of Saad and Higuchi (1), representing a situation where a relatively large amount of sodium cholate retarded the growth and dissolution rates of cholestrol crystals. The inhibition of the surface dissolution rate by the dye is in agreement with the studies of Ives *et al.* dealing with the effect of traces of ferric ion on the dissolution kinetics of a single crystal of lithium fluoride.

The data obtained are consistent with the kink mechanism proposed by Gilman *et al.* (15) and Ives (16). The mechanism involves preferred adsorption of the dye molecules at the primary dissolution sources of the crystal surface. The kinks in crystal ledges are the primary dissolution sources, where individual drug molecules can deposit or escape readily.

In absence of dye, the drug molecules will be lost preferentially from the kinks where binding is weakest and effect a motion of the kinks along the ledges. The mean time for stripping will always be a simple factor of the ledge length. Continuous dissolution will require successive nucleation of the kinks. In presence of dye inhibition, the dye molecules tend to deposit on the kinks and reduce the kink nucleation rate.

The fact that the curve in Fig. 4 tends to stabilize after a certain concentration of dye is in agreement with previous observations reported by Ives and Plewes (7). It is in accord with the postulate that the observed optimum concentration in the plot of rate of dissolution *versus* inhibitor concentration represents a situation where mono-kink adsorption is attained.

A further evidence was found in investigating the morphological changes produced by the dye on the dissolving faces of sulfaguanidine and sulfathiazole crystals. Figures 9 and 10 show the dissolution features produced by 0.1 *N* HCl and 0.1 *N* HCl containing 50
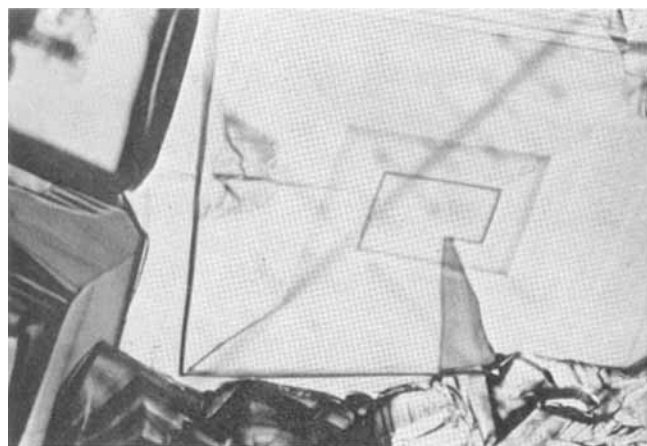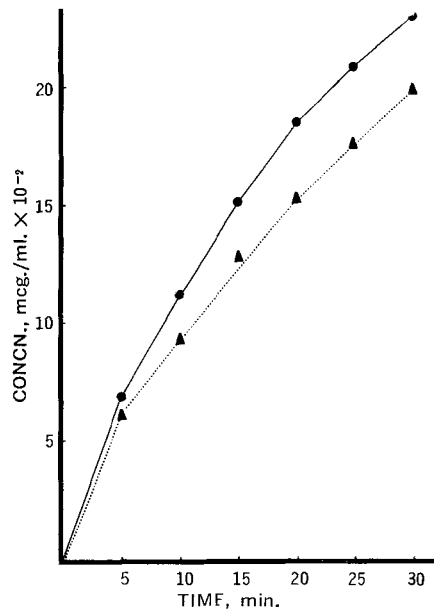

Figure 8—*Dissolution behavior of sulfathiazole crystalline powder. Key: ●, in 0.1 N HCl; ▲, in 0.1 N HCl containing 50 mcg./ml. FD&C Blue No. 1.*

μ/ml. of the dye for a limited period of time. FD&C Blue No. 1 seems to act as an etchant producing etch pits on these dissolving faces. The observations are similar to those obtained by Gilman *et al.* (15) in their study of dislocation etch pit formation in lithium fluoride in presence of ferric ion as dissolution inhibitor.

The major emphasis in this study is on surface dissolution of single crystals and of compressed disks of the drug crystals. For the present, the inhibited dissolution in presence of Blue No. 1, is
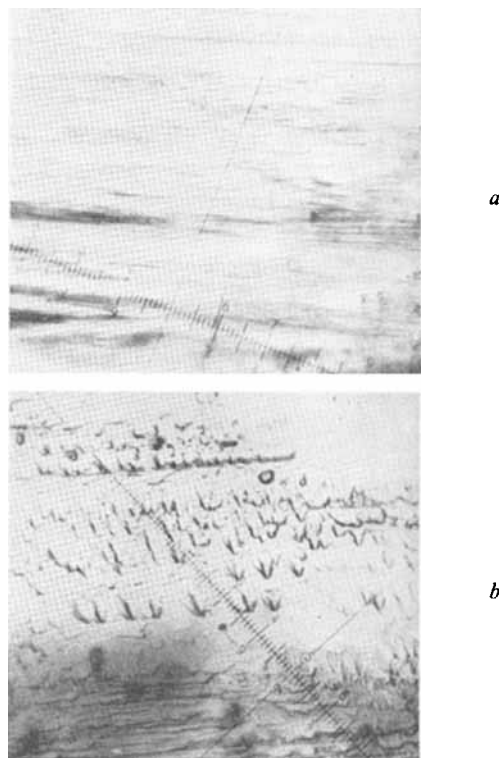

a

b

Figure 9—*Effect of FD&C Blue No. 1 on the dissolving face of sulfaguanidine single crystal after 15 min. Key: a, in 0.1 N HCl, b in 0.1 N HCl containing 50 mcg./ml. FD&C Blue No. 1. Magnification: 125×.*

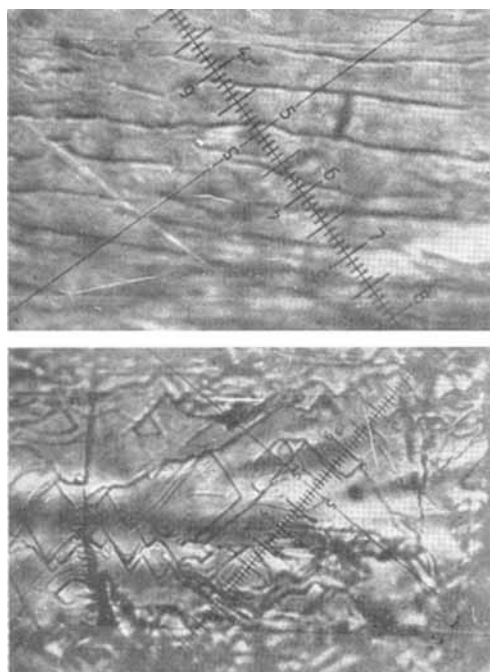**Figure 7**—*Thymol crystal exhibiting spiral steps. Magnification: 125×.*

Figure 10—*Effect of FD&C Blue No. 1 on the dissolving face of sulfathiazole single crystal after 15 min. Key: a, in 0.1 N HCl, b, in 0.1 N HCl containing 50 mcg./ml. FD&C Blue No. 1. Magnification: 500×.*

limited to the systems that have been studied, and to the experimental conditions described. The significance of dissolution inhibition in powder systems in presence of a low concentration of the dye is not clear yet. The extension of this study to other powder systems and other water-soluble dyes will contribute to better understanding of the role of water-soluble colorants in drug formulations.

REFERENCES

(1) H. Y. Saad and W. I. Higuchi, *J. Pharm. Sci.*, **54**, 1303 (1965).
(2) H. E. Buckley, "Crystal Growth," Chapman and Hall, London, England, 1951.
(3) M. B. Ives, *Ind. Eng. Chem.*, **57**, No. 6, 34(1965).
(4) D. Fox, B. H. Labes, and A. Weisberger, "Physics and Chemistry of Organic Solids State," vol. I, Interscience, New York, N. Y., 1963.
(5) N. Albon and W. J. Dunning, *Acta Cryst.*, **15**, 479(1962).
(6) M. B. Ives and J. P. Hirth, *J. Chem. Phys.*, **33**, 517(1960).
(7) M. B. Ives and J. T. Plewes, *ibid.*, **42**, 292(1965).
(8) J. Whetstone, *J. Chem. Soc.*, **1957**, 4289.
(9) W. V. Engelhardt, "International Congress of Surface Activity," vol. 2, 1961, pp. 202–217.
(10) E. Votava, S. Amelinckx, and W. Dekeyser, *Naturwissenschaften*, **40**, 143(1953).
(11) S. Chopra and R. Tawashi, *Pharm. Ind.*, **31**, 489(1969).
(12) D. C. Grove and G. L. Keenan, *J. Am. Chem. Soc.*, **63**, 97(1941).
(13) P. D. Bernardo, Ph.D. thesis, University of Michigan, 1966.
(14) R. Tawashi, *Science*, **160**, 76(1968).
(15) J. J. Gilman, W. G. Johnston, and G. W. Sears, *J. Appl. Phys.*, **29**, 747(1968).
(16) M. B. Ives, *J. Phys. Chem. Solids*, **24**, 275(1963).

Phenylisoquinolines and Hydroisoquinolines

J. SAM, R. M. SHAFIK*, and K. APARAJITHAN

Abstract ☐ The synthesis of some derivatives of 5-, 6-, and 7-phenylisoquinoline, 3,4-dihydroisoquinoline, and 1,2,3,4-tetrahydroisoquinoline are described. Results of preliminary pharmacological tests are reported.

Keyphrases ☐ Phenylisoquinolines—synthesis ☐ Hydroisoquinolines—synthesis ☐ Pharmacological screening—phenylisoquinolines, hydroisoquinolines ☐ IR spectrophotometry—identity

Several alkaloids which incorporate the 1-benzylisoquinoline (I) or tetrahydroisoquinoline (II) moiety in their structures possess interesting biological properties (1, 2). The latter structural feature has been proposed (3) as a precursor in the biosynthesis of the aporphine alkaloids (III). Whereas, extensive investigations (4, 5) have been directed toward the synthesis of 1-benzylisoquinolines, little effort has been expended in studies of arylisoquinolines (VII) and the corresponding hydrogenated derivatives (VIII, X, and XI) (6). Consequently,

I   II   III
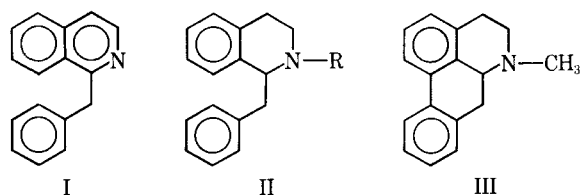
it was of interest to determine whether compounds such as VII and hydrogenated VII possess CNS properties similar to known aporphines (7) (bulbocapnine) and/or cardiovascular properties.

The synthetic approach followed is shown in Scheme I. The nitration of isoquinoline yielded 5-nitroisoquinoline (V) (8). The reduction of the latter compound to 5-aminoisoquinoline (VI) (9, 10) followed by diazotization and coupling with benzene, according to a procedure similar to that described by Cadogan (11) for the preparation of biphenyls, provided 5-phenylisoquinoline. Hydrogenation of VIIa hydrochloride using plati-