due to a difference in the length of the alkyl chain. Considering the preferred conformation of polyethylene glycol, the long alkyl chains of butyl parabens, whose OH are hydrogen bonded to alternate oxygens of the polyethylene glycol, can overlap and become stabilized by van der Waals' force. The semirigid structure illustrated in Structure I and/or analogously crosslinked structures, formed as a result of overlap between alkyl chains of butyl paraben, hydrogen bonded to two different polyethylene glycol molecules, can contribute to the lowering of the polarity of the medium upon increasing the concentration more than with methyl paraben, in which such linking is not possible.

The solubility of benzyl paraben in various solutions of each alkyl paraben (methyl, ethyl, *n*-propyl, and *n*-butyl) with known dielectric constants were determined. The plots are depicted in Fig. 8. The results indicate that the solubility of benzyl paraben in a solution of alkyl paraben is not solely dependent on the dielectric constant-lowering potential of the alkyl paraben. Reference to Fig. 8 and solubility values of benzyl parabens in various concentrations of alkyl parabens, reported in the previous communication (1), clarifies this contrast. The 0.4 *M* concentrations of butyl paraben and propyl paraben have dielectric constants $k = 40.59$ and $k = 40.67$, respectively. The solubility of benzyl paraben in these solutions is 0.52 and 0.59 *M*, respectively, obviously opposite of what would have been expected from their dielectric constant values. The most conspicuous results were obtained from 0.1 *M* ethyl paraben and 0.1 *M* methyl *p*-methoxybenzoate, both with $k = 43.2$, in whose solutions the solubility of benzyl paraben was found to be 0.37 and 0.44 *M*, respectively.

In summary, there exists a relationship between the dielectric constant and solubility of parabens. The solubility data of combinations of two parabens, however, indicate the involvement of factors other than dielectric constants. A theoretical consideration of these will be given in a future communication.

REFERENCES

(1) F. Shihab, W. Sheffield, J. Sprowls, and J. Nematollahi, *J. Pharm. Sci.*, **59**, 1574(1970).

(2) P. Sherrick, G. Dawe, R. Kerr, and E. Ewen, "Manual of Chemical Oscillometry," E. H. Sargent, Chicago, Ill., 1954.

(3) A. N. Paruta, *J. Pharm. Sci.*, **58**, 204(1969).

(4) *Ibid.*, **58**, 364(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received May 25, 1970, from the *College of Pharmacy, University of Texas at Austin, Austin, TX 78712*

Accepted for publication July 20, 1970.

This investigation was supported in part by a grant from the Graduate School, University of Texas.

Inhibited Dissolution of Drug Crystals by Certified Water-Soluble Dyes II

J. PICCOLO* and R. TAWASHI

Abstract □ Experiments on dissolution inhibition of poorly water-soluble drug crystals (sulfathiazole and diethylstilbestrol) in the presence of low concentrations of certified water-soluble dyes are presented. The effect of the degree of undersaturation and the dependence of dissolution rate on the inhibitor concentration of powder systems were investigated. Data obtained are consistent with previous findings and suggest preferential adsorption at the primary dissolution sources on the crystal surface. Further dissolution studies in the presence of 0.04 *M* sodium cholate showed that the dye caused substantial reduction in surface dissolution of the sulfathiazole single crystal. Biological implications in these systems are considered.

Keyphrases □ Dyes, water-soluble—drug crystal dissolution, inhibition □ Dissolution rates, crystals—water-soluble dye effect □ Crystals, sulfathiazole, diethylstilbestrol—dissolution rates, dye effect □ Sodium cholate effect, dissolution—crystals–dyes

In previous communications, the effect of low concentrations of FD&C Blue No. 1 on the dissolution rate of certain crystalline drugs was reported (1, 2). Concentrations of 5–10 mcg./ml. were sufficient to exert a remarkable inhibition on the surface dissolution of sulfathiazole, sulfaguanidine, and phenobarbital monohydrate single crystals. Additional dissolution experiments on compressed disks of the pure drug gave similar results. Studies made on a powder system showed a marked inhibition of the dissolution rate; however, the results of only one powder system were insufficient to draw definite conclusions.

The present work was undertaken to: (*a*) determine the influence of the dye incorporated in a compressed disk rather than dissolved in the test media; (*b*) define the manner in which undersaturation of the solution and concentration of the dye affect dissolution in powder systems; and (*c*) investigate the influence of the dye on micellar solubilization.

EXPERIMENTAL

Materials—Sulfathiazole Form I crystals were obtained using the method previously described (1). Diethylstilbestrol,[1] sodium chlorate,[1] and 0.90% NaCl solution[2] were USP grade; all other solvents were purified before use.

Dissolution-Rate Studies—Dissolution experiments to determine the influence of FD&C Blue No. 1 incorporated in a compressed disk were carried out using sulfathiazole Form I as a test material. Tablets of drug crystals alone and of drug crystals containing 5 mg. of the dye were compressed under the same pressure (Fig. 1). The dissolution rate was determined using a method described in a previous communication (1).

To substantiate earlier results obtained in the surface dissolution studies, a series of experiments was carried out on a powder system using diethylstilbestrol as a model substance. The Coulter counter method, described by Higuchi and Saad (3, 4) and by Edmundson and Lees (5), was used in these experiments. A suspension of diethylstilbestrol was prepared using the following method: 1 ml. of ethyl alcohol containing 10 mg. of diethylstilbestrol was added to 150 ml. of 0.90% NaCl solution. Magnetic stirring was maintained for 2 hr. The suspended crystals were then sonified for 2 hr. (using a Sonifier Cell Disruptor model W, 140 D)[3] to get a particle size

[1] Obtained from Matheson Coleman & Bell Inc., East Rutherford, N. J.

[2] Normal saline for injection. Abbott Laboratories, Montreal, Canada.

[3] Ultrasonic Inc., Plainview, N. J.

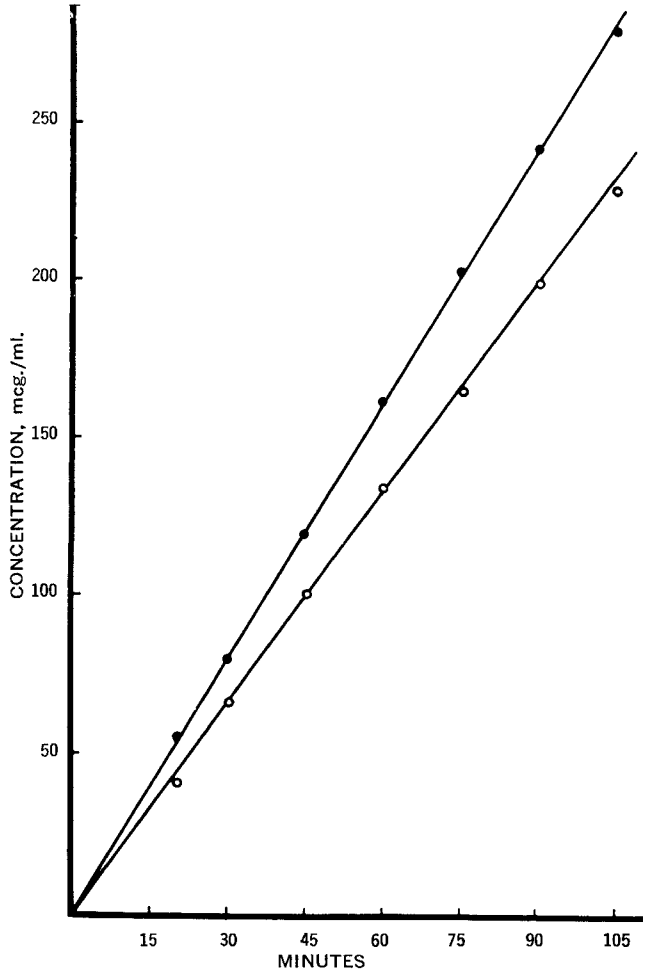

Figure 1—*Dissolution behavior of sulfathiazole compressed disks. Key: ●, compressed disks of drug crystals alone; and ○, compressed disks of drug crystals containing 5 mg. FD&C Blue No. 1.*

suitable for the Coulter counter technique. The resulting crystals were in the range of 1–2 μ in diameter.

The Coulter counter was calibrated with polystyrene latex, having a diameter of 1.305 μ, using a 30-μ aperture tube. For each experiment, 15 ml. of the diethylstilbestrol suspension was added to 135 ml. of 0.90% NaCl solution. Stirring was provided during and after addition of the aliquot. The data were plotted as number of particles *versus* time at various threshold settings, each threshold setting corresponding to a certain diameter (Fig. 2). From these graphs, other sets of curves were constructed, showing the number of particles above given size *versus* the diameter for different times (Fig. 3). The rate of change in radius (dr/dt) was then determined for the powder system in the absence and in the presence of the dye.

The influence of Blue No. 1 on the solubilizing effect of sodium cholate was studied on sulfathiazole single crystals. The dissolution rate of the single crystals was determined in distilled water, in a 0.04 *M* solution of sodium cholate, and in a 0.04 *M* solution of sodium cholate containing 5 mcg./ml. of FD&C Blue No. 1. The procedure used to determine the dissolution rate of the single crystals was identical to that described in a previous communication (1).

RESULTS AND DISCUSSION

Figure 1 shows the dissolution behavior of compressed disks of sulfathiazole crystals alone and of sulfathiazole crystals containing 5 mg. of FD&C Blue No. 1. A significant dissolution inhibition by the action of the incorporated dye is present, as in the previous study where the dye was present in the dissolution media.

Since most pharmaceutical systems contain a large number of solutes that should act in a similar manner, in varying degrees, toward dyes, the study of the effect of the dye on a powder system with high surface area would be of major interest. Figures 2 and 3 summarize the data obtained with diethylstilbestrol microcrystals suspended in normal saline. A concentration of 10 mcg./ml. of Blue No. 1 (triphenylmethane dye) was sufficient to reduce the dissolution rate of diethylstilbestrol from 6.00×10^{-8} cm./sec. to 2.4×10^{-8} cm./sec.

Additional experiments using Red No. 3 (a fluorescein dye) gave a marked inhibition of the dissolution rate in the same system. Figure 4 permits a comparison between the relative dissolution rates obtained with FD&C Blue No. 1 and Red No. 3. The marked decrease in dissolution rate at such a low concentration strengthens

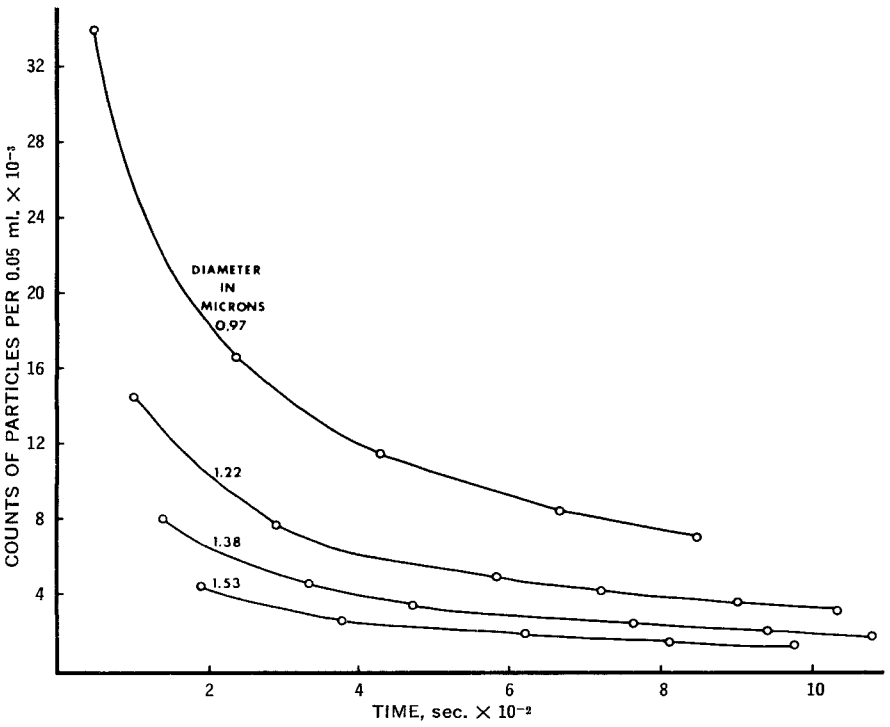

Figure 2—*Coulter counter data showing the decrease in cumulative counts with time at various threshold settings as diethylstilbestrol particles dissolve in 0.9% NaCl solution.*

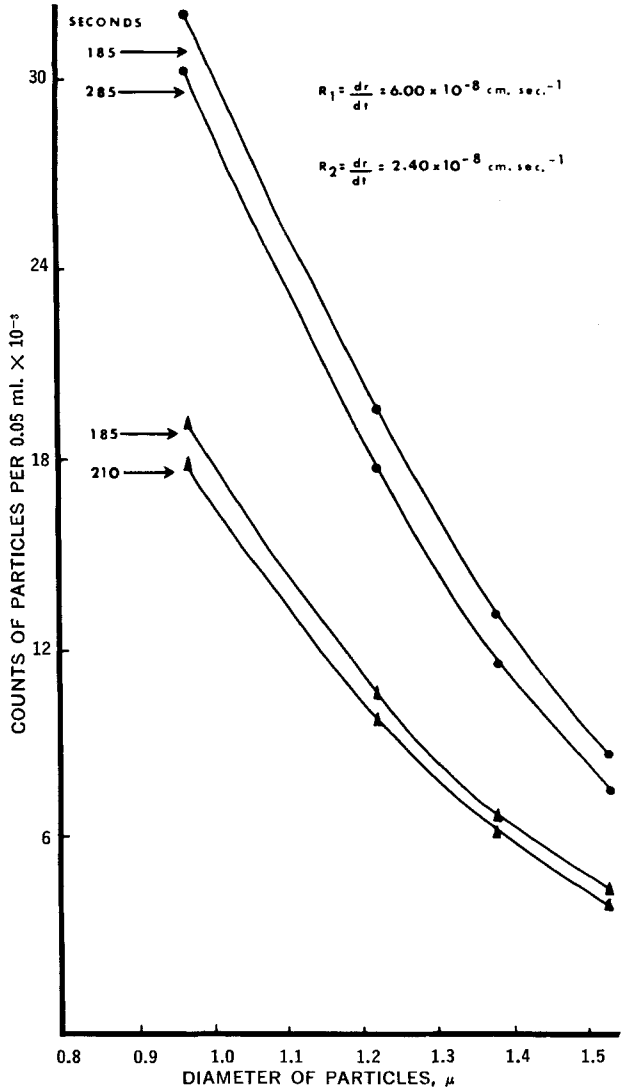

Figure 3—*Cumulative particle-size distribution curves constructed from Coulter counter data. Key: ▲, in 0.90% NaCl solution; and ●, in 0.90% NaCl solution containing 10 mcg./ml. FD&C Blue No. 1.*

the possibilities that these dyes play an important part in the dissolution step of the drug-absorption process.

Studies confined to surface dissolution of the single crystal in the presence of dyes gave results that might appear dramatic to the user of polycrystalline material. The application of the Coulter counter method to study crystal poisoning of diethylstilbestrol microcrystals at different saturation ratios and with different inhibitor concentrations gave good agreement with surface dissolution measurements. For instance, Fig. 5 shows the influence of undersaturation on the dissolution inhibition of diethylstilbestrol. A concentration of 10 mcg./ml. of the dye reduced the dissolution rate to an unmeasurable value at a fraction of the saturation condition. This result agrees well with those of Ives and Plewes (6) in their study on lithium fluoride surface dissolution using ferric ion as an inhibitor.

The study of dissolution-rate dependence on inhibitor concentration gave similar kinetics to single-crystal work. Data in Fig. 6 show the effect of dye concentration on the dissolution rate of diethylstilbestrol microcrystals in normal saline. The curve tends to stabilize after a concentration of 50 mcg./ml. of Blue No. 1, and it agrees well with previous findings on sulfaguanidine single crystal (1). Those results were discussed on the basis of the kink mechanism, proposed by Gilman *et al.* (7) and Ives (8), which involves preferred adsorption of the dye molecules on the primary dissolution sources of the crystal surface. Such selective adsorption could also explain the dissolution inhibition of diethylstilbestrol microcrystals in the

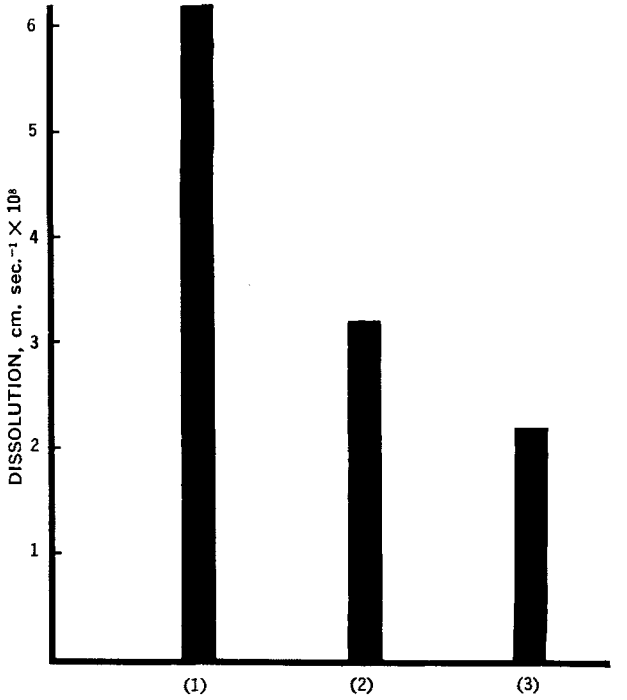

Figure 4—*Influence of water-soluble dyes on the dissolution rate of diethylstilbestrol. Key: (1) dissolution in 0.90% NaCl solution; (2) dissolution in 0.90% NaCl solution containing 10 mcg./ml. FD&C Red No. 3; and (3) dissolution in 0.90% NaCl solution containing 10 mcg./ml. FD&C Blue No. 1.*

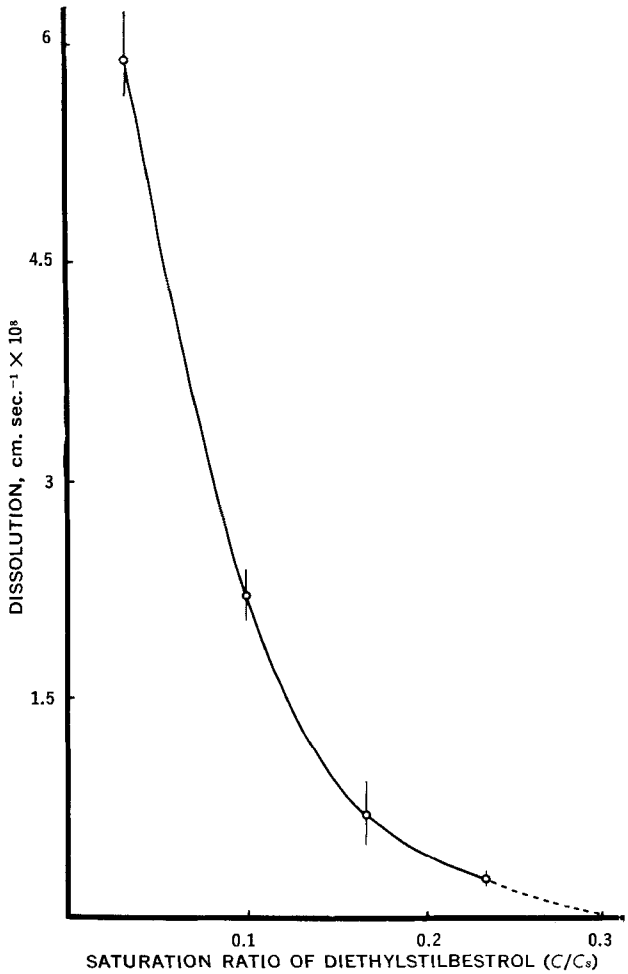

Figure 5—*Effect of undersaturation on the dissolution rate of diethylstilbestrol in the presence of 10 mcg./ml. FD&C Blue No. 1.*

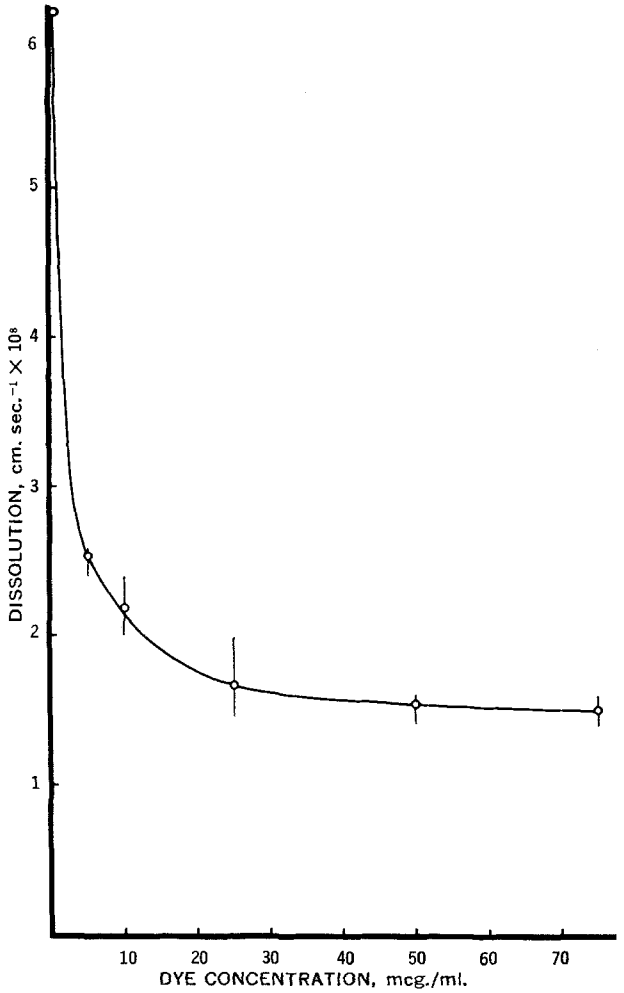

Figure 6—*Effect of FD&C Blue No. 1 concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

presence of low concentrations of the dye. By applying the relationship between the relative differences in dissolution rates and the inhibitor concentration, a correlation can be suggested for this situation. If it is assumed that: (*a*) the fractional rate reduction caused by the dye is proportional to the fraction of the surface covered by the adsorbed dye, and (*b*) the dye adsorption can be represented by a simple Langmuir isotherm (9), the dissolution rate can be expressed as a simple function of the dye concentration in solution:

$$R = R_0\left(1 - \frac{KbC}{1 + bC}\right) \qquad \text{(Eq. 1)}$$

where R = dissolution rate with dye, R_0 = dissolution rate without dye, K = fraction of surface covered when the surface is "saturated" with dye, C = dye concentration in bulk solution, and b = Langmuir isotherm constant.

This relationship was applied to diethylstilbestrol, using the data in Fig. 5, and to sulfaguanidine single crystals reported in a previous communication (1). These results can be represented by such a correlation within the limits of experimental accuracy (Fig. 7). The values of the constants K and b are given in Table I.

The b values are indicative of adsorption intensity, and K is a measure of the saturation capacity of the surface for FD&C

Table I—Adsorption and Dissolution Inhibition Constants for FD&C Blue No. 1 on Diethylstilbestrol and Sulfaguanidine

Material	K	b
Diethylstilbestrol (microcrystalline powder)	0.77	4.79
Sulfaguanidine (single crystal)	0.61	0.76

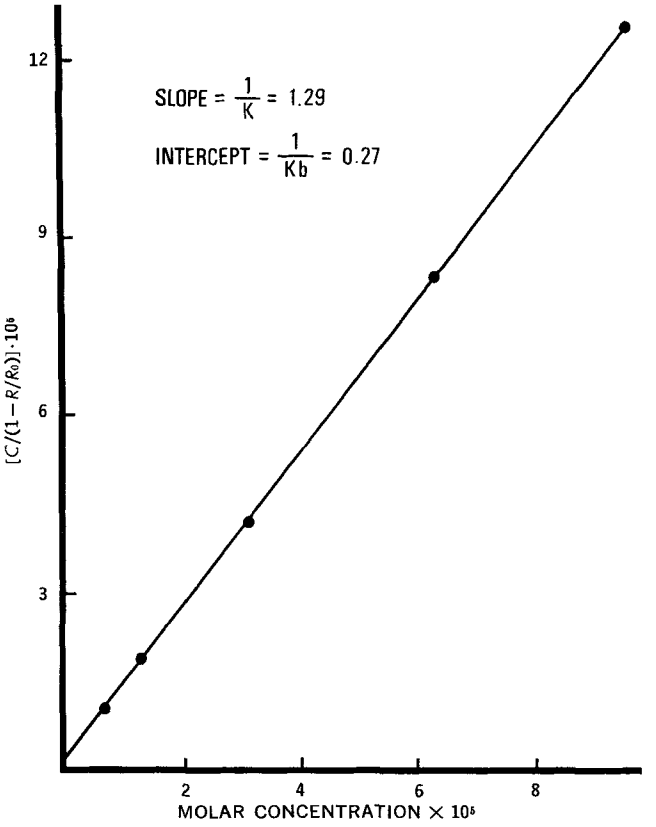

Figure 7—*Determination of adsorption and dissolution-inhibition constants for diethylstilbestrol in the presence of FD&C Blue No. 1.*

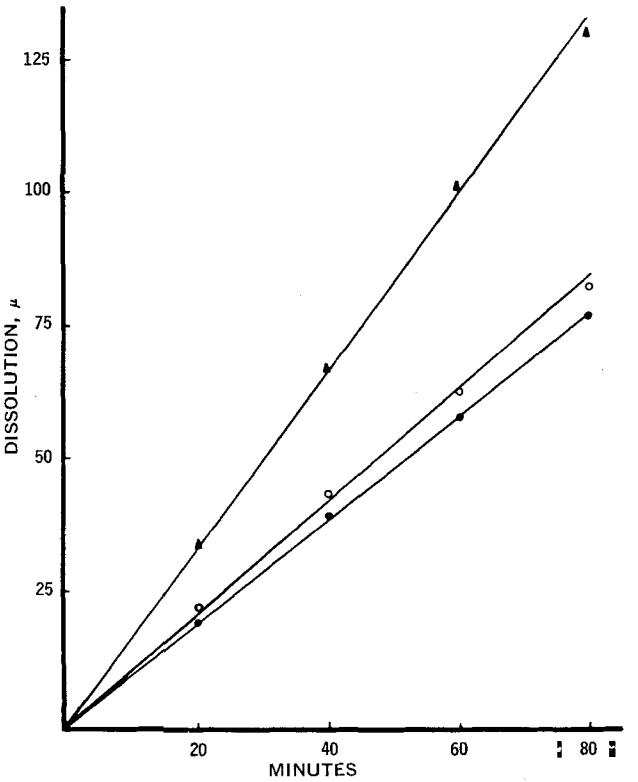

Figure 8—*Single-crystal dissolution of sulfathiazole as a function of time. Key: ●, in distilled water; ▲, in 0.04 M solution of sodium cholate; and ○, in 0.04 M solution of sodium cholate containing 5 mcg./ml. FD&C Blue No. 1.*

Blue No. 1. The fact the K values are smaller than 1.0 for both drugs supports a selective adsorption mechanism rather than complete coverage of the crystal surfaces by the dye.

It has been reported (10–12) that bile salts increase the solubility of poorly soluble drugs by micellar solubilization. Consequently, the dissolution rate is expected to increase in the presence of sodium cholate. The influence of Blue No. 1 on the solubilizing effect by 0.04 M sodium cholate was studied using sulfathiazole Form I (single crystal) as the model substance. Data obtained in Fig. 8 show that Blue No. 1 modified markedly the dissolution kinetics of sulfathiazole in sodium cholate solution. A concentration of 5 mcg./ml. brought the dissolution rate to a value very close to that in distilled water. The solubility of sulfathiazole at 25° was found to be 0.85 mg./ml. in both 0.04 M sodium cholate and in 0.04 M sodium cholate containing 5 mcg./ml. Blue No. 1. In distilled water, the solubility was 0.47 mg./ml. Therefore, the dissolution of sulfathiazole in the cholate–dye system does not follow the laws predicted by simple diffusion kinetics and suggests an interfacial mechanism.

This observation is extremely interesting in relation to the intestinal absorption process in the presence of water-soluble dyes. More studies are necessary for complete characterization of this problem from the physical-chemical standpoint. Such studies will be generally important to the eventual understanding of the role of water-soluble dyes in dissolution and drug transport.

REFERENCES

(1) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **59**, 56(1970).

(2) R. Tawashi and J. Piccolo, to be published.

(3) W. I. Higuchi and H. Y. Saad, *J. Pharm. Sci.*, **54**, 74(1965).

(4) H. Y. Saad and W. I. Higuchi, *ibid.*, **54**, 1303(1965).

(5) I. C. Edmundson and K. A. Lees, *J. Pharm. Pharmacol.*, **17**, 193(1964).

(6) M. B. Ives and J. T. Plewes, *J. Chem. Phys.*, **42**, 293(1965).

(7) J. J. Gilman, W. G. Johnston, and G. W. Sears, *J. Appl. Phys.*, **29**, 747(1968).

(8) M. B. Ives, *J. Phys. Chem. Solids*, **24**, 275(1963).

(9) A. S. Michaels and A. R. Colville, Jr., *J. Phys. Chem.*, **64**, 13(1960).

(10) T. R. Bates, M. Gibaldi, and J. F. Kanig, *J. Pharm. Sci.*, **55**, 191(1966).

(11) *Ibid.*, **55**, 901(1966).

(12) T. R. Bates, M. Gibaldi, and J. F. Kanig, *Nature*, **210**, 1331 (1966).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 1, 1970, from the *Faculty of Pharmacy, University of Montreal, Quebec, Canada.*

Accepted for publication July 28, 1970.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

This investigation was supported by the Medical Research Council of Canada.

* MRC graduate research studentship.

Survey of a Laboratory Building for Airborne Antibiotics

MARY ANN GARTH, HENRY BRYANT, JULIAN KRAMER, and AMIEL KIRSHBAUM

Abstract □ Antibiotics are routinely examined by laboratory analysis in a six-story building which houses the laboratories of the National Center for Antibiotics and Insulin Analysis (NCAIA) on the second floor. A survey was performed to determine if antibiotic dust was being disseminated throughout the building. Air throughout the building was analyzed both quantitatively and qualitatively for residues of penicillin and tetracyclines. The microbiological assay plates used were sensitive enough to detect 0.001 unit of penicllin and 0.0004 mcg. of chlortetracycline in the air. Results of this study showed that, outside of the actual laboratories of NCAIA, the incidence of antibiotic contamination of the air was negligible. In the immediate areas where antibiotics were physically handled, 0.012 unit of penicillin and 0.0185 mcg. of chlortetracycline per cubic foot of air were detected.

Keyphrases □ Antibiotic, airborne dissemination—laboratory building □ Cultures, plate—antibiotic detection □ Air sampling—vacuum collection through membrane □ Laboratory contamination—antibiotics, airborne

As the use of chemicals becomes more diversified in modern life, the extent to which these substances contaminate the environment becomes a matter of increasing concern. Similarly, for some years, effort has been directed toward the study of the incidence of microbial contamination of the environment, especially in hospitals (1, 2), and the control of this contamination. Recently, attention has been directed toward microbe-free environments for the assembly of aerospace equipment (3, 4).

Work in the laboratories of the National Center for Antibiotics and Insulin Analysis (NCAIA) involves the possibility of a special kind of contamination. Approximately 100 chemists and microbiologists perform laboratory analyses of antibiotic drugs. There is little information concerning the extent to which these antibiotics may permeate the atmosphere as the result of manipulations in the course of analysis. Welch *et al.* (5) demonstrated that a group of antibiotics analysts carried nasal staphylococci possessing a significantly higher incidence of antibiotic resistance than did control groups. The antibiotic resistance was attributed to antibiotic dusts and aerosols, but the amount of antibiotics in the air of the laboratory was not determined. The authors, therefore, surveyed the atmosphere of laboratories and of the entire building in which they are housed for the presence of two of the most frequently tested groups of antibiotics: penicillins and tetracyclines.

NCAIA is located mainly on the second floor of the U. S. Food and Drug Administration (FDA) Building in Washington, D. C.; at the time of this study, it also had ancillary laboratory space on the first and third floors, used for penicillin contamination and for turbidimetric assays, respectively. This modern well-equipped laboratory building consists of six floors, a basement, and a subbasement. All air enters by way of five separate air-conditioning systems using 15 induction fans