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

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Abstract □ Results of dissolution-rate studies on diethylstilbestrol microcrystals in the presence of low concentrations of various certified water-soluble dyes are presented. Under the conditions described, marked and different degrees of inhibition were observed. Information on the dissolution inhibition process was obtained by the study of the dissolution-rate dependence on chemical group, class, and concentration of the dye. The data obtained show that cationic dyes were more reactive in lower concentration than anionic dyes and suggest higher adsorption intensity of the cationic dye molecules at the primary dissolution sources on the crystal surface.

Keyphrases □ Dissolution rates—diethylstilbestrol microcrystals' inhibition by water-soluble dyes □ Dyes, water soluble—drug crystal dissolution, inhibition □ Diethylstilbestrol microcrystals—dissolution rates, dye inhibition □ Crystals, diethylstilbestrol—dissolution rates, dye inhibition

In previous articles (1–3), the inhibitory effect of low concentrations of FD&C Blue No. 1 on the dissolution rate of crystalline drugs was established. The effect of the degree of undersaturation and the dependence of dissolution rate on the inhibitor concentrations of powder systems were also investigated. The data were explained in the light of preferential adsorption of the dye molecules on the primary dissolution sources on the crystal surface.

The purposes of this publication are to: (*a*) determine the effect of other certified water-soluble dyes on the dissolution rate, (*b*) study the influence of the dye concentration on the dissolution rate, and (*c*) correlate the results obtained with the previously suggested mechanism and with the chemical nature of the dyes.

EXPERIMENTAL

Materials—The dyes used in this study were FD&C Blue No. 1[1], FD&C Red No. 2[1], FD&C Red No. 3[1], FD&C Violet No. 1[1], D&C Green No. 5[1], Ext. D&C Blue No. 1[2] (Methylene Blue), and Malachite Green[3]. Diethylstilbestrol[4] was selected as a model substance for poorly water-soluble drugs. The dissolution media was 0.90% NaCl solution[5].

Dissolution-Rate Studies—All dissolution experiments were conducted using the Coulter counter technique (3–6). A suspension of diethylstilbestrol was prepared by adding 1 ml. of ethyl alcohol, containing 10 mg. of drug, to 150 ml. of 0.90% NaCl solution. Magnetic stirring was maintained for 2 hr. The suspended crystals were then sonified for 2 hr. (3).

The dissolution rate of the diethylstilbestrol microcrystals was determined using the Coulter counter equipped with a 30-μ aperture tube. The data were plotted as previously described (3), and the rate of change of radius (dr/dt) was determined for the powder system in the absence and in the presence of the dyes.

[1] Rose & Laflamme Limited, Montreal, Canada.
[2] J. T. Baker Chemical Co., Phillipsburg, N. J.
[3] The British Drug Houses (Canada) Ltd., Toronto, Canada.
[4] Matheson, Coleman & Bell Inc., East Rutherford, N. J.
[5] Normal saline for injection, Abbott Laboratories, Montreal, Canada.

Table I—Effect of 10 mcg./ml. of Various Water-Soluble Dyes on the Dissolution Rate of Diethylstilbestrol[a]

Dye	Dissolution in 0.90% NaCl Containing Dye—Dissolution Rate, cm./sec.
D&C Green No. 5	4.40×10^{-8}
FD&C Red No. 2	2.72×10^{-8}
FD&C Red No. 3	2.64×10^{-8}
FD&C Blue No. 1	2.40×10^{-8}
Malachite Green	1.80×10^{-8}
Ext. D&C Blue No. 1	1.60×10^{-8}
FD&C Violet No. 1	0.64×10^{-8}

[a] Dissolution in 0.90% NaCl = 5.67×10^{-8} cm./sec.

RESULTS AND DISCUSSION

Table I shows the effect of the various water-soluble dyes on the dissolution rate of diethylstilbestrol crystalline powder in normal saline. It permits a comparison between the dissolution rates obtained with these dyes at a concentration as low as 10 mcg./ml. and the dissolution rate in normal saline. Quantitatively, the magnitude of the inhibitory effect of these dyes at the same concentration varied considerably.

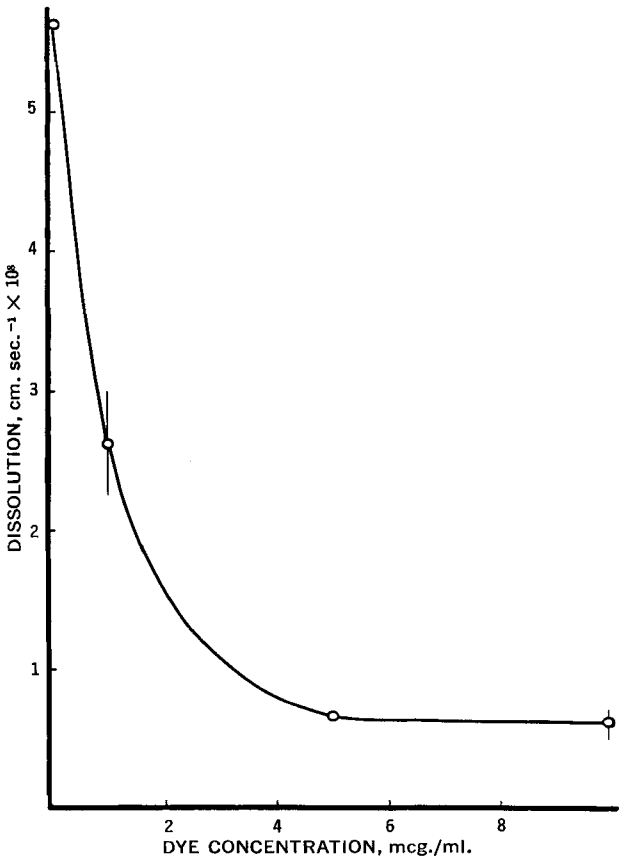

Figure 1—*Effect of FD&C Violet No. 1 concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

Table II—Effect of Various Concentrations of Water-Soluble Dyes on the Dissolution Rate of Diethylstilbestrol

Dye Concentration, mcg./ml.	Dissolution Rate, cm./sec. × 10^5				
	FD&C Violet No. 1	FD&C Red No. 3	D&C Green No. 5	Ext. D&C Blue No. 1	Malachite Green
0	5.67	5.67	5.67	5.67	5.67
0.1	—	—	—	2.40	3.50
0.5	—	—	—	—	2.33
1.0	2.63	—	—	1.79	1.80
5.0	0.67	2.80	4.80	—	—
10.0	0.64	2.64	4.40	1.60	1.80
20.0	—	1.90	3.39	—	—
50.0	—	1.60	3.10	—	—
100.0	—	—	2.11	—	—

The dissolution-rate dependence on inhibitor concentration was systematically determined. The dissolution rates of diethylstilbestrol microcrystals in 0.90% NaCl solution containing various concentrations of five water-soluble dyes are shown in Table II. These data were plotted as dissolution rate *versus* inhibitor concentration (Figs. 1–5). An important property common to all of these dyes is that the curves obtained tend to stabilize after a certain concentration of dye is reached. This fact is consistent with previous findings using a different model substance (sulfaguanidine) and a different method for measuring the dissolution rate (single crystal technique).

Another observation associated with inhibited dissolution by dyes is the concentration level at which the dye activity starts. Unlike other dyes, Ext. D&C Blue No. 1 and Malachite Green showed an outstanding activity on the dissolution rate of diethylstilbestrol at extremely low concentrations. Figures 4 and 5 demonstrate the marked decrease in dissolution rate in the presence of a dye concentration as small as 0.1 mcg./ml. Furthermore, stabilization in the dissolution rate occurs after a concentration of only 1 mcg./ml. of these two dyes is reached.

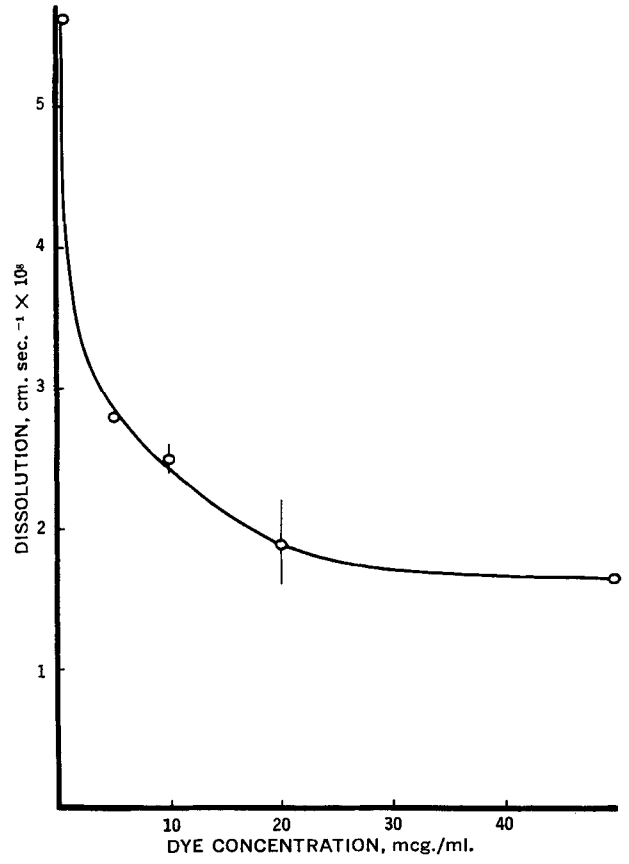

Figure 2—*Effect of FD&C Red No. 3 concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

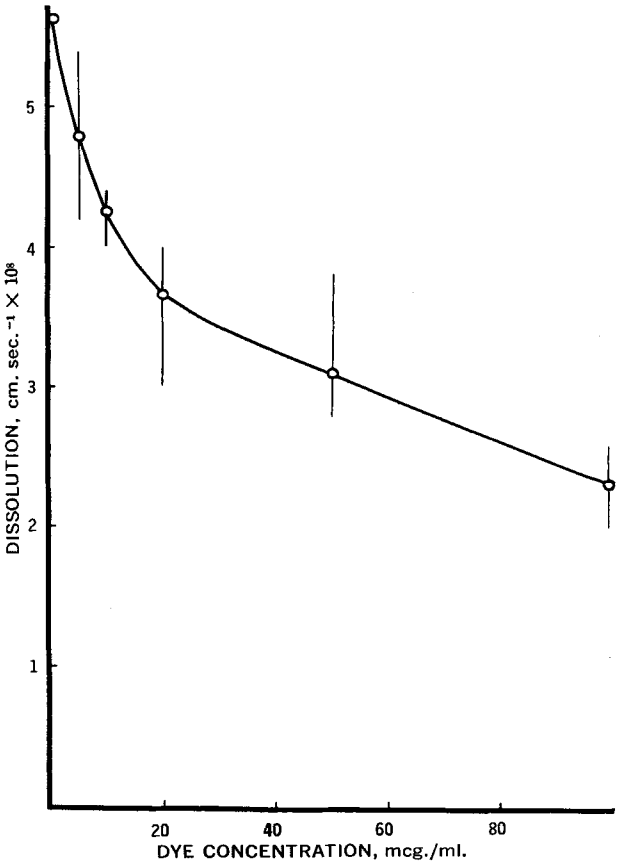

Figure 3—*Effect of D&C Green No. 5 concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

In a previous report (3) on the dissolution inhibition of diethylstilbestrol by FD&C Blue No. 1, results were discussed on the basis of preferred adsorption of the dye molecules on the primary dissolution sources of the crystal surface. A correlation for this situation was then suggested by applying the relationship between dissolution rate and dye concentration (3). The influence of FD&C Blue No. 1 on the dissolution rate could be correlated satisfactorily in terms of a Langmuir adsorption isotherm. If the dissolution rate is considered as a simple function of the dye concentration in solution, the Langmuir adsorption isotherm can be written:

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

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.

The same correlation was applied to the present results, using the data in Figs. 1–5. The K and b values obtained for the different dyes investigated by a method previously described (3), along with their chemical group and class, are given in Table III.

Table III—Adsorption and Dissolution Inhibition Constants for Various Water-Soluble Dyes on Diethylstilbestrol

Dye	Chemical Group	Class	K	b
FD&C Blue No. 1[a]	Triphenylmethane	Anionic	0.77	4.79
FD&C Violet No. 1	Triphenylmethane	Anionic	0.97	1.42
FD&C Red No. 3	Fluorescein	Anionic	0.77	0.29
D&C Green No. 5	Quinone	Anionic	0.74	0.05
Ext. D&C Blue No. 1	Thiazine	Cationic	0.73	13.76
Malachite Green	Triphenylmethane	Cationic	0.69	20.70

[a] For FD&C Blue No. 1, see *Reference 3*.

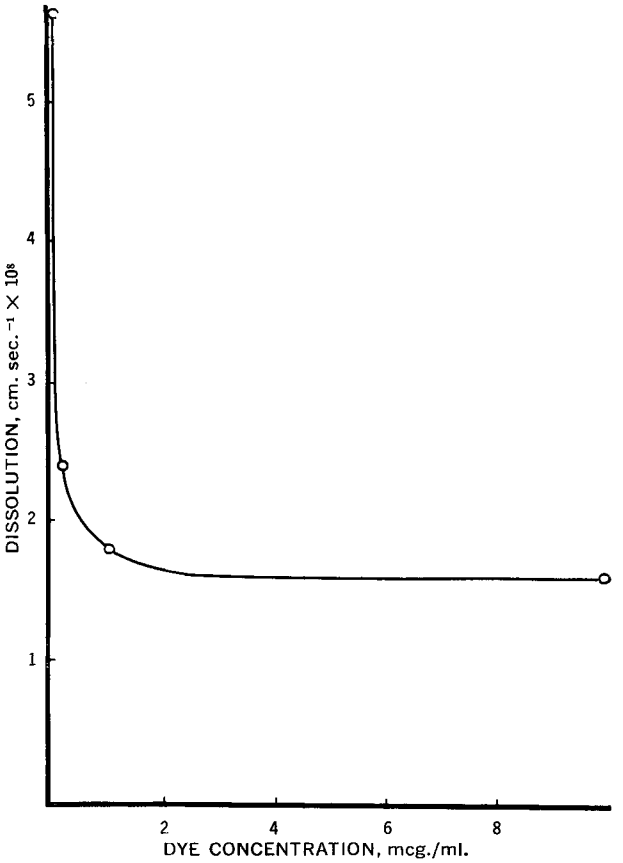

Figure 4—*Effect of Methylene Blue concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

The *b* values are indicative of adsorption intensity, and *K* is a measure of the saturation capacity of the surface for the inhibitor. From these results, it is apparent that the *K* values are smaller than 1.0 for all of the investigated dyes. This fact supports a selective adsorption mechanism rather than complete coverage of the crystal surfaces and is consistent with previous findings (1, 3).

Table III also shows that the *b* values are much greater for cationic dyes than for anionic dyes. This agrees with the results reported by Michaels and Colville (7) in their work on growth inhibition of adipic acid crystals by surfactants. The authors determined the *b* values for anionic and cationic surfactants and found that these values were greater for cationic surface-active agents.

The outstanding activity of these cationic dyes is illustrated in Figs. 4 and 5. The high *b* values obtained indicate that the effect of these dyes can be attributed to a higher adsorption intensity. Quantitative characterization of this behavior in the near future will provide information on growth and dissolution inhibition of drug crystals.

In summary, the results of this investigation established that: (*a*) a relatively large number of the existing certified water-soluble dyes

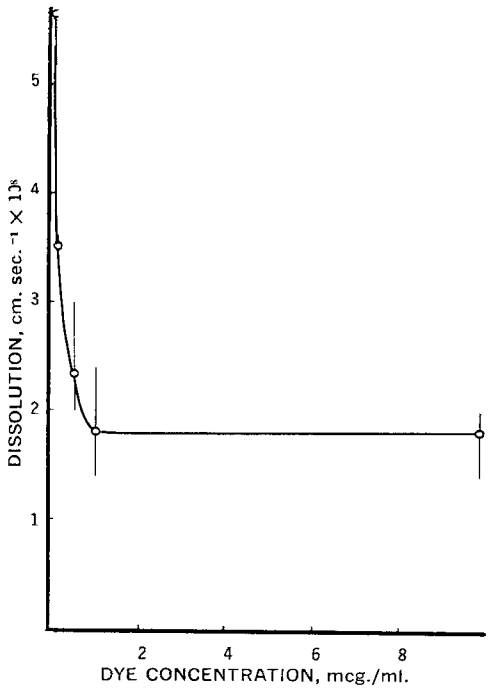

Figure 5—*Effect of Malachite Green concentration on the dissolution rate of diethylstilbestrol crystalline powder.*

exert a significant inhibition on the dissolution rate of diethylstilbestrol, and (*b*) cationic dyes are more reactive in lower concentrations than are anionic dyes.

REFERENCES

(1) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **59,** 56(1970).
(2) R. Tawashi and J. Piccolo, *Pharm. Acta Helv.*, **45,** 653(1970).
(3) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **60,** 59(1971).
(4) W. I. Higuchi and H. Y. Saad, *ibid.*, **54,** 74(1965).
(5) H. Y. Saad and W. I. Higuchi, *ibid.*, **54,** 1303(1965).
(6) I. C. Edmundson and K. A. Lees, *J. Pharm. Pharmacol.*, **17,** 193(1964).
(7) A. S. Michaels and A. R. Colville, Jr., *J. Phys. Chem.*, **64,** 13(1960).

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