DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(5), 759-774 (1982)

INFLUENCE OF CERTAIN ADDITIVES ON THE PHOTOSTABILIZING EFFECT OF URIC ACID FOR SOLUTIONS OF FD&C BLUE NO. 2

Ahmed F. Asker* and Denise Y. Colbert

ABSTRACT

The influence of certain pharmaceutical materials on the photostabilizing effect of uric acid for solutions of FD&C Blue No.2 was investigated. Uric acid in a concentration of 2.5 mg % was found to excercise its effect as a photoprotective agent in presence of DL-methionine, DL-leucine, Tween 80, lactose, sodium benzoate and methylparaben. These materials were noted to accelerate the rate of fading of the dye solutions. On the other hand, uric acid appeared to be practically ineffective in presence of sodium edetate and tartaric acid. Uric acid demonstrated the greatest photoprotective action in presence of sodium benzoate or methylparaben.

* School of Pharmacy, Florida A&M University, Tallahassee, Florida, 32307

INTRODUCTION

In a previous report by Asker and Collier (1), uric acid was found to be an effective photoprotective agent for various solutions of FD&C Blue No.2. The photostabilizing effect of uric acid was reported to be influenced by the pH of solution, glycerin concentration and buffer species.

Several reports have been published on the effect of some pharmaceutical materials on the fading of FD&C Blue No.2. Kuramoto and his associates (2), reported that sugars such as dextrose, lactose and sucrose increased the rate of fading of solutions of FD&C Blue No.2, whereas sugar alcohols such as mannitol and sorbitol did not appreciably affect the rate of fading. Antioxidants such as hydroquinone, p-hydroxypropiophenone and hydroquinone monomethyl ether were also found not to appreciably retard the fading due to reducing sugars. In the case of nordihydroguaiaretic acid, however, the rate of fading due to dextrose was substantially reduced. The authors concluded that the rate of fading of FD&C Blue No.2 appeared to be catalyzed in the presence of reducing compounds. Brownley and Lachman (3) reported that FD&C Blue No.2 was very unstable in presence of lactose, spray-dried lactose and their primary hydrolysis products, d-glucose and d-galactose.

Metallic ions have been reported to catalyze the oxidation or reduction of indigo-type colors (4-6).

FD&C Blue No.2 was reported by Scott et al.(7), to be most sensitive to the action of nonionic surfactants. Turi and his associates (8), have reported that the wetting agent poloxalene and polyethylene glycol have only a moderate effect on the fading rate of solutions of FD&C Blue No.2 Polyvinylpyrrolidone, ascorbic acid and citric acid were also found by these investigators to cause a rapid fading of the indigo carmine solution.

It is apparent from the above cited references that the fading of FD&C Blue No.2 is readily affected by a number of pharmaceutical additives which would be incorporated with the dye in various pharmaceutical formulations. Therefore, since uric acid was found in a previous report (1) to have a significant photoprotective action on FD&C Blue No.2, it appeared desirable to investigate the photostabilizing effect of uric acid in presence of these additives. The additives selected belong to various classes of pharmaceutical adjuvants such as antioxidants, chelating agents, surfactants, sugars and preservatives.

EXPERIMENTAL

Materials: FD&C Blue No.2 (indigo carmine), uric acid, glycerin, tartaric acid, sodium edetate, DL-methionine, DL-leucine, lactose, sodium benzoate, methylparaben, Tween 80, sodium hydroxide and monobasic potassium phosphate were obtained from commercial sources in reagent or

pharmaceutical grade and were used without furter purification.

Equipment: The following equipment were used: a light stability cabinet equipped with an 18-inch 15-watt Westinghouse long wavelength ultraviolet "black light" tube emitting most of its radiations at approximately 3660 Å to serve as the light source; a Spectronic 20 spectrophotometer; Orion digital pH meter.

Procedure: The typical experimental procedure was as described previously (1). Absorbance readings were made at various time intervals on the Spectronic 20 at 610 nm.

Because of the poor solubility of uric acid in water, solution was made by dissolving 100 mg of uric acid in 400 g of glycerin previously heated to 100° for 15 minutes. A magnetic stirrer was used to enhance the rate of solution. Solutions were made to contain 2.5 mg % of uric acid, 1 mg % of the dye and the following concentrations of the various adjuvants used: 0.2 % of each of sodium edetate and tartaric acid, 0.1 % of each of DL-methionine and DL-leucine, 0.1 % of sodium benzoate, 0.01 % of methylparaben, 0.2 % lactose and 0.5 % w/v of Tween 80.

In case of solutions containing methylparaben or DL-leucine, these materials were first dissolved with the aid of heat in portions of the phosphate buffer.

Solutions containing no uric acid to serve as control were made to contain the same percentage of gly-

cerin, since the latter was found to affect the rate of fading of the dye solution (1).

DISCUSSION OF RESULTS

Effect of Antioxidants:

Figures 1 and 2 illustrate the effects of DL-methionine and DL-leucine on the photodegradation of FD&C Blue No. 2 in presence and absence of uric acid. It is evident from both figures that these antioxidants accelerate the photodegradation of the dye solution. The results are in agreement with published reports (2,3) that reducing agents accelerated the fading of solution of FD&C Blue No.2. Uric acid appears to demonstrate a photoprotective action for the dye solutions containing these antioxidants.

Effect of Tween 80:

Figure 3 shows that the addition of Tween 80 to FD&C Blue No.2 solution extensively enhances the photodegradation of the dye. Scott et al. (7) reported accelerated color loss of FD&C Blue No.2 in presence of nonionic surfactants. Waibel (9) has reported that ethoxylated nonionic surfactants exist in solution as polyoxonium compounds which actually are not nonionic, but weakly cationic. He states that these positively charged ions are capable of reacting with anionic coloring agents. Kowarski (10) has reported that polysorbate 80 increases the rate of formation of the semi-

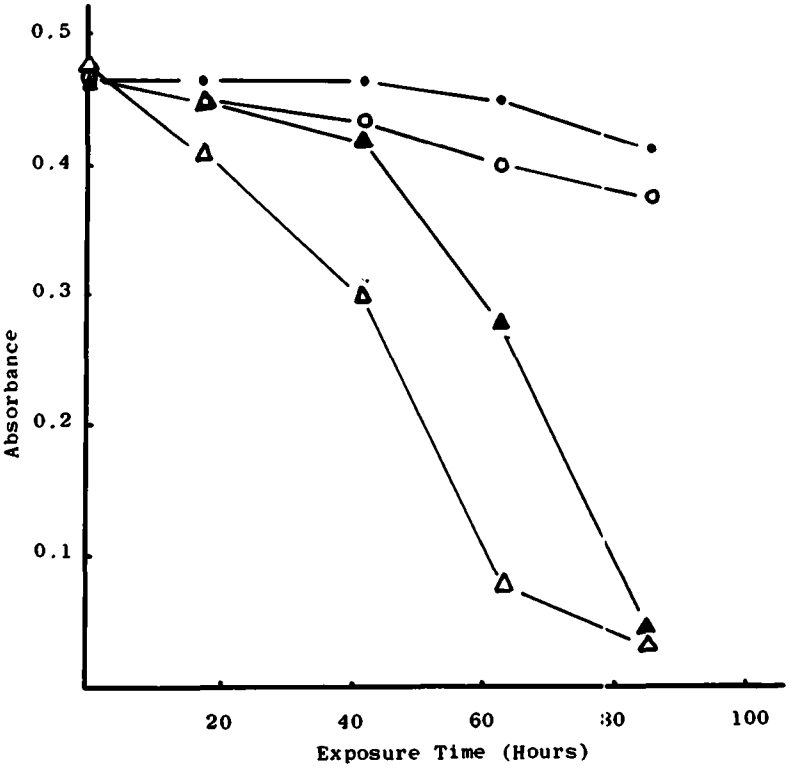

FIGURE 1. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing DL-Methionine

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing DL-Methionine

▲ Dye Solution Containing DL-Methionine and Uric Acid

quinone radical. The incorporation of uric acid in the dye solution containing Tween 80 resulted in a substantial photoprotection of the dye.

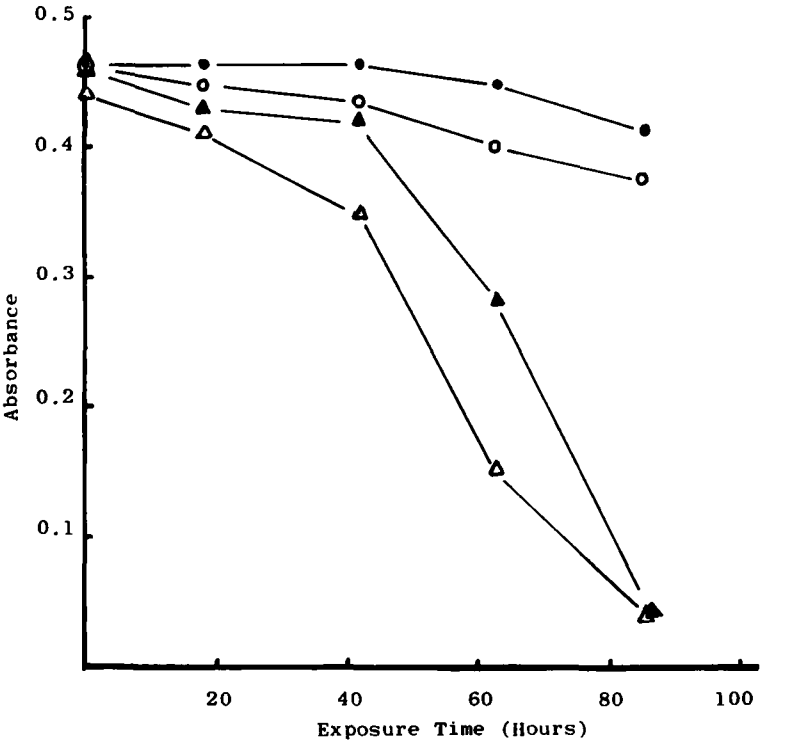

FIGURE 2. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing DL-Leucine

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing DL-Leucine

▲ Dye Solution Containing DL-Leucine and Uric Acid

Effect of Lactose:

The addition of lactose to FD&C Blue No.2 solution appears to accelerate the photodegradation of the dye as shown in Figure 4. The results are in agreement with

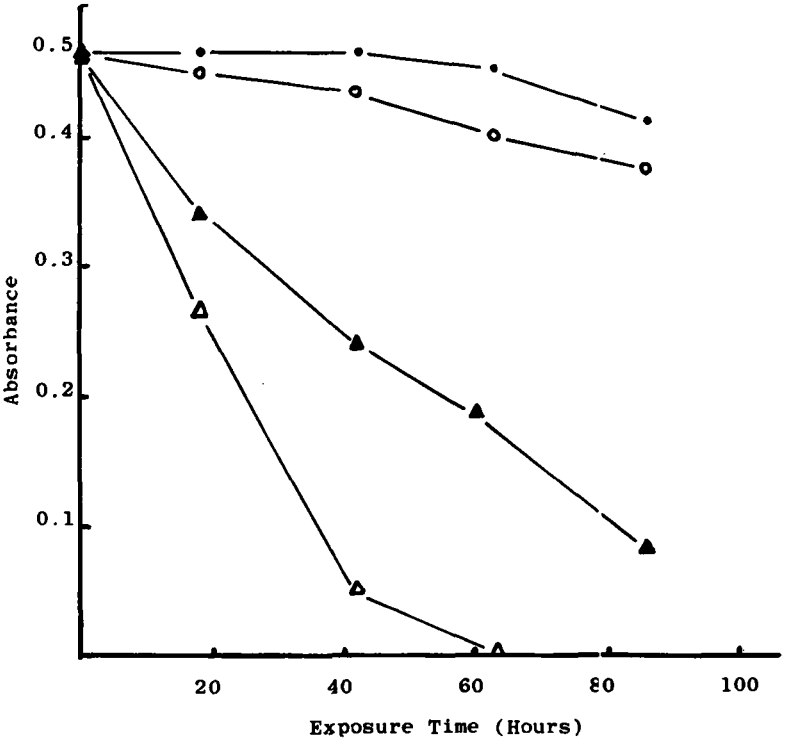

FIGURE 3. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Tween 80

○ Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing Tween 80

▲ Dye Solution Containing Tween 80 and Uric Acid

those previously published (2,3). The incorporation of uric acid appears to retard the photodegradation of the dye solution in presence of lactose.

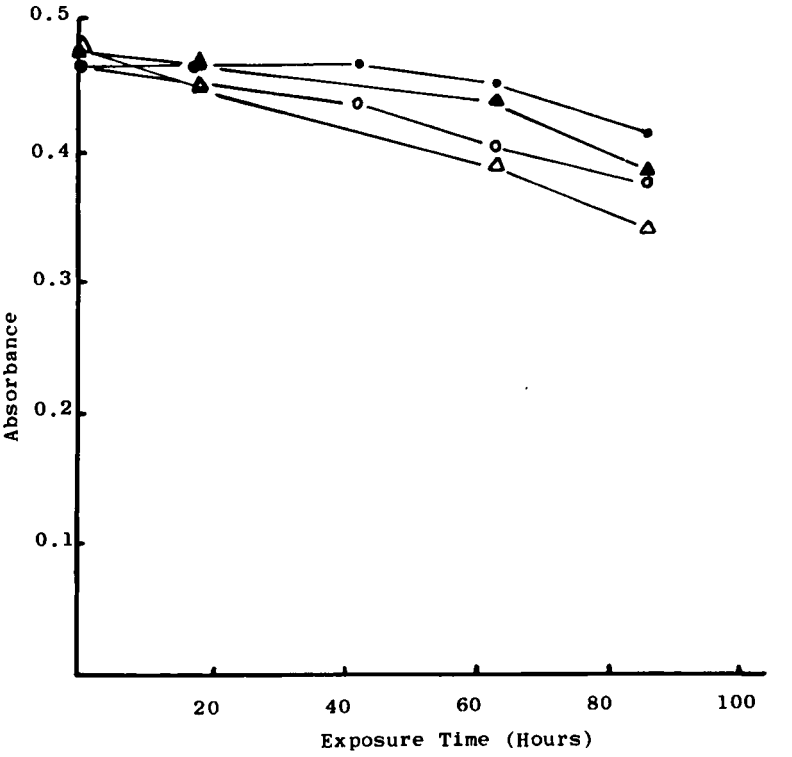

FIGURE 4. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Lactose

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing Lactose

▲ Dye Solution Containing Lactose and Uric Acid

Effect of Preservatives:

It can be seen from Figures 5 and 6 that sodium benzoate and methylparaben accelerate the rate of fading of the dye solution. However, the addition of uric acid

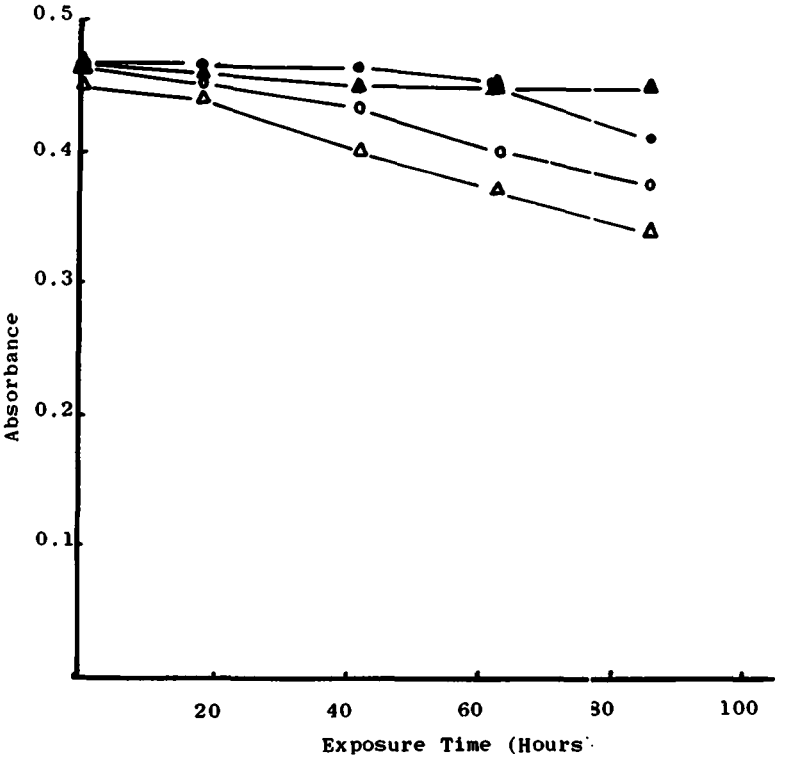

FIGURE 5. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Sodium Benzoate

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing Sodium Benzoate

▲ Dye Solution Containing Sodium Benzoate and Uric Acid

resulted in retardation of the rate of fading. It appears also that sodium benzoate or methylparaben in presence of uric acid demonstrated the greatest photo-

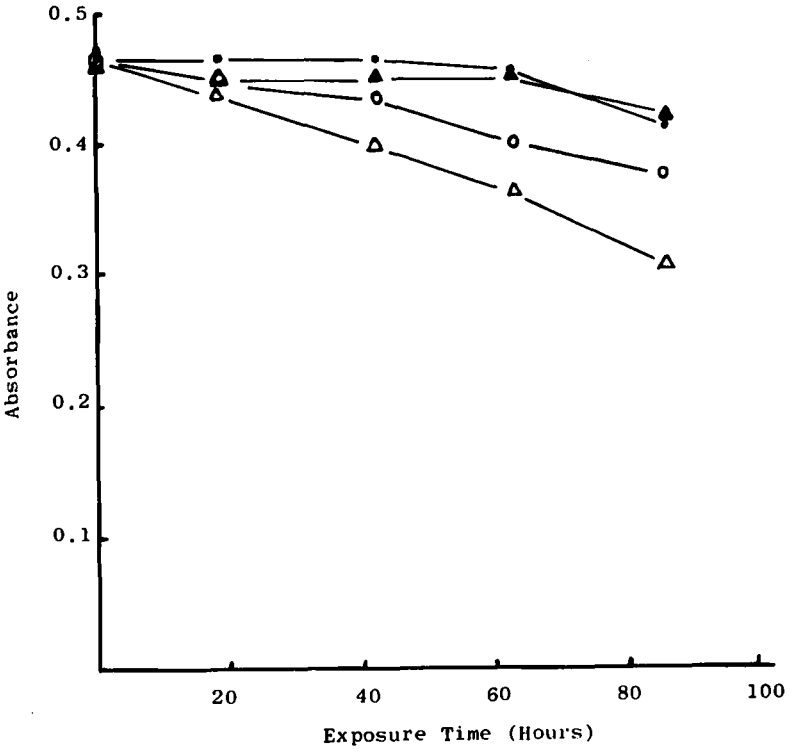

FIGURE 6. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Methylparaben

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing Methylparaben

▲ Dye Solution Containing Methylparaben and Uric Acid

protective action when compared with the results obtained with the other pharmaceutical adjuvants used in this study.

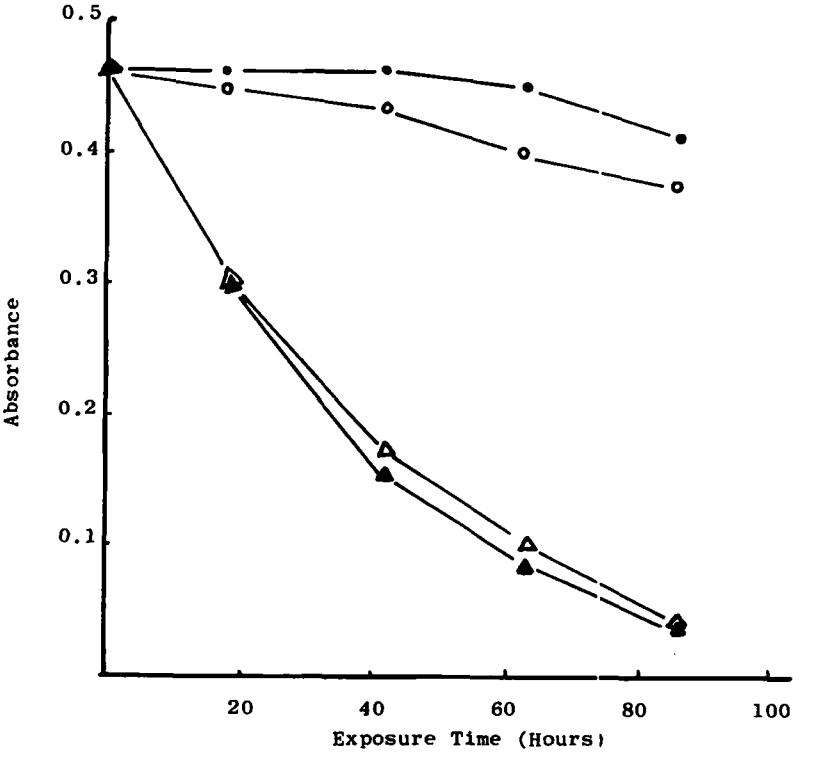

FIGURE 7. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Sodium Edetate

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

△ Dye Solution Containing Sodium Edetate

▲ Dye Solution Containing Sodium Edetate and Uric Acid

Effect of Chelating Agents:

Figure 7 shows that disodium edetate substantially enhanced the photodegradation of the dye solution and that destabilization of the dye was also operative to a very slightly greater extent in presence of uric acid.

Disodium edetate has been reported to prevent discoloration of many pharmaceuticals (11-17). However, Hodges and Walton (18) reported that the addition of disodium edetate was detrimental to neomycin solutions stored at 30°. Ethylenediaminetetraacetic acid or its disodium salt were also found to increase the degradation rate of epinephrine (19), physostigmine (20) and isoproterenol (21). Oster and Wotherspoon (22) have found that methylene blue in presence of EDTA is reduced to the leuco dye on irradiation with red light. EDTA has been reported to be consumed in the reaction, suggesting that it is oxidized, although it doe not normally function as a reducing agent. Straus and Nickerson (23) reported promotion of photodegradation of air-free riboflavine solution in presence of EDTA. The reaction was attributed to EDTA acting as an acceptor for the oxygen moiety derived from the photochemical cleavage of water. The decomposition of FD& C Blue No.2 has been reported by Brownley and Lachman (3) and Kuramoto et al. (2) to proceed by reduction to a semiquinone followed by oxidation. It appears, therefore that EDTA accelerates the rate of fading of FD&C Blue No.2 through acting as an electron donor in the photodegradation mechanism and that such action is only slightly affected by the presence of uric acid.

In Figure 8, tartaric acid is noted to enhance the photodegradation of the dye solution. Turi et al.

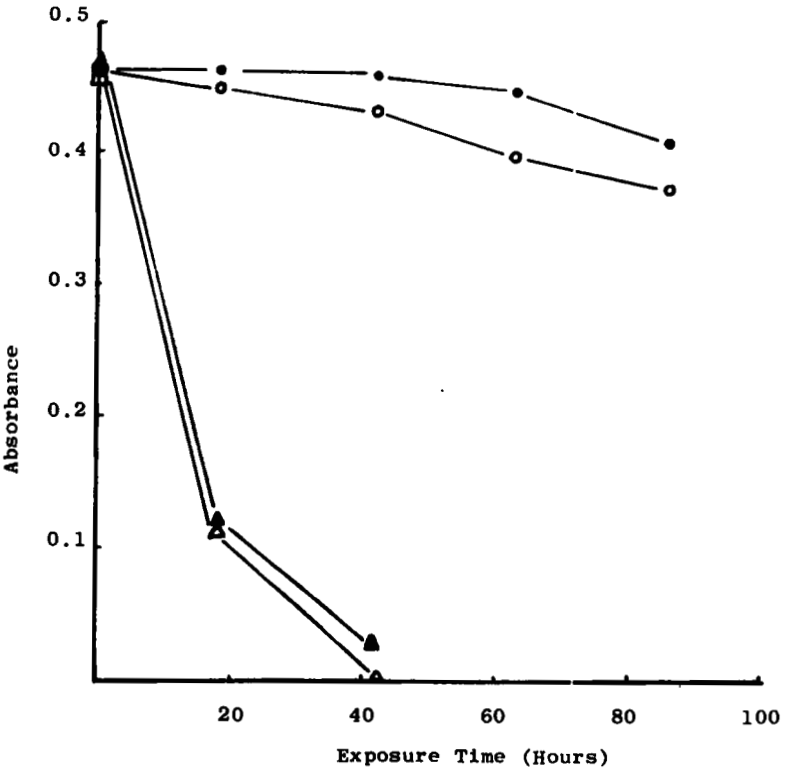

FIGURE 8. Photostabilizing Effect of Uric Acid for FD&C Blue No. 2 Solution Containing Tartaric Acid

o Dye Solution without Uric Acid

● Dye Solution with Uric Acid

Δ Dye Solution Containing Tartaric Acid

▲ Dye Solution Containing Tartaric Acid and Uric Acid

(8) found that citric acid caused a rapid fading of the indigo carmine solution. The acceleration of fading of FD&C Blue No.2 by such hydroxy acids may be

attributed OH^- groups acting as electron donor in the degradation mechanism of the dye. The presence of uric acid appears to have practically little or no effect on stabilizing the dye solution containing tartaric acid.

REFERENCES

(1) A. Asker and A. Collier, This Journal, 7, 563 (1981).

(2) R. Kuramoto, L. Lachman, and J. Cooper, J. Am. Pharm. Ass., Sci. Ed., 47, 175 (1958).

(3) C.A. Brownley, Jr., and L. Lachman, J. Pharm. Sci., 52, 86 (1963).

(4) A. Krause and B. Stasinski, J. Roczinki Chem., 28, 359 (1954); through C.A., 49, 7946f.

(5) A.K. Dmitriev, Zhur. Obshchei Khim., 22, 545 (1952); through C.A. 46, 8477 a.

(6) H.J. Kauffmann, J. Am. Chem. Soc., 69, 899 (1947).

(7) M.W. Scott, A.J. Goudie, and A.J. Huetteman, J. Am. Pharm. Ass., 49, 467 (1960).

(8) P. Turi, R.A. Tausendfreund, A.F. Michaelis, and C. Steren, J. Pharm. Sci., 63, 1309 (1974).

(9) H. Waibel, Mitt. Chem. Forschungsinst. Wirtshe Österr., 9, 34 (1955).

(10) C. R. Kowarski, J. Pharm. Sci., 58, 360 (1969).

(11) R. Barkman and R. Ortengren, J. Mondial Pharm., 315, 26 (1959).

(12) G.B. West and T.D. Whittet, J. Phar. Pharmacol. Suppl., 12, 113T (1960).

(13) R.A. Anderson and J.W. Maudson, Australasian J. Pharm., 44, S 24 (1963).

(14) Z. Parafinska, Acta Polon. Pharm., 20, 395 (1963).

(15) R.G. Coombe and J.J. Roxon, Australasian J. Pharm., 44, S 34 (1963).

(16) H. Toenjes and H. Poetter, Ger. Pat. 1,182,389, VEB Arzneimittelwirk, Dresden, Germany; through C.A. 62, 10301 g (1956).

(17) D.E. Griffith, J. Pharm. Sci., 56, 1197 (1967).

(18) N. A. Hodges and P.G. Walton, ibid., 70, 960 (1981).

(19) S. Green, A. Mazur, and E. Shorr, J. Biol. Chem., 220, 237 (1956).

(20) J. Morch, " Proceedings of the 17th Congress on Pharmaceutical Sciences" Leiden, The Netherlands, 1957; through T.D. Whittet, Pharm. Acta. Helv., 34, 489 (1959).

(21) J. A. Clements, K. Hasson, and G. Smith, J. Pharm. Pharmacol., 32, 50P (1980).

(22) G. Oster and N. Wotherspoon, J. Am. Chem. Soc., 79, 4836 (1957).

(23) G. Straus and W. Nickerson, ibid., 83, 3187 (1961).