Dye–Polyethylene Glycol 6000 Interactions in Filmcoating Solutions and Their Effect on Color Uniformity

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The objective of this study was to evaluate the problems of uneven coloration in tablets filmcoated with solutions utilizing polyethylene glycol (PEG 6000) and cellulose acetate phthalate (CAP) in a solvent system consisting of 65 per cent acetone and 35 per cent absolute alcohol. It was hypothesized that to obtain uniform color the dye needed to be brought into solution due to interaction between it and one of the other ingredients in the solution. Attention was focused on CAP, PEG 6000, and titanium dioxide. The procedures included the following steps: (*a*) study of the interaction between dyes, and PEG 6000; (*b*) study of interaction between dyes and CAP; (*c*) testing of the hypothesis stated above in filmcoating operations; (*d*) study of the function of titanium dioxide in filmcoating solutions. The results show that the interaction of PEG 6000 with the solid dye results in the solubilization of the latter and this is significant in producing uniform color. No interaction was observed between CAP and the dyes. Titanium dioxide was found to act purely mechanically in preventing the aggregation of dye particles.

One type of filmcoating solution that is frequently used utilizes a combination of cellulose acetate phthalate (CAP) and polyethylene glycol 6000 (PEG 6000) as the film former in a solvent system consisting of acetone (65%) and absolute alcohol (35%). Such a filmcoating solution was described by Gross and Endicott in 1960 (1). While the formula for such a solution consists of a variety of auxiliary agents such as flavoring agents, sweeteners, etc., the basic ingredients are as follows:

CAP	6%
PEG 6000	14%
Dye	0.05%
Titanium dioxide	2%
Solvent system (acetone 65%, absolute alcohol 35%)	*q.s.* to 100%

The dyes used in this formula are essentially insoluble in the solvent system, and it has been noted that their action is often unpredictable with respect to the uniformity of color deposition. In certain concentrations some of the dyes produce coatings with a mottled appearance, particularly when the filmcoating solution is not rendered opaque by the titanium dioxide.

The objective of this investigation was to study the cause of the lack of uniformity in the color deposition. It was hypothesized that to obtain a uniform color coverage the dye must be brought into solution. This could be achieved only by interaction between the dye and some ingredient in the filmcoating formulation causing the formation of a soluble complex.

Since it was observed that titanium dioxide played some role in obscuring the mottled appearance of the filmcoated tablets, its function in a filmcoating formulation was also investigated.

The procedure adopted in this investigation consisted of the following steps: (*a*) study of any interaction between several dyes and PEG 6000; (*b*) study of any interaction between several dyes and CAP; (*c*) testing of the hypothesis presented above by the use of the interaction data of two of the dyes in actual filmcoating operations; (*d*) study of the function of titanium dioxide in a filmcoating formulation.

EXPERIMENTAL PROCEDURE[1] AND RESULTS

The materials used in this study included the following: dyes (provided by Abbott Laboratories): FD&C Blue No. 1 (brilliant blue), FD&C Yellow No. 5 (tartrazine), FD&C Red No. 1 (Ponceau 3R), FD&C Red No. 2 (amaranth red), FD&C Red No. 4 (Ponceau SX); CAP (Eastman Kodak Co.); PEG 6000 (Union Carbide Chemicals Co.); and titanium dioxide (Fisher Scientific Co.).

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[1] All spectrophotometric analyses were conducted on a Beckman DB recording spectrophotometer.

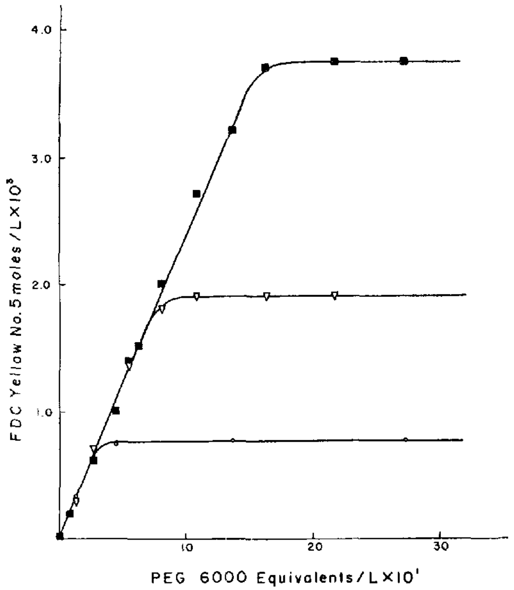

Fig. 1.—Interaction between dye FD&C Yellow No. 5 and PEG 6000. Key: ■, 50 mg.; ∇, 25 mg.; O, 10 mg.

Interaction Studies Between PEG 6000 and Dyes

In this study the following dyes were used: FD&C Yellow No. 5 (mol. wt. = 534.39), FD&C Blue No. 1 (mol. wt. = 792), FD&C Red No. 2 (mol. wt. = 604.49), FD&C Red No. 1 (mol. wt. = 494.46), and FD&C Red No. 4 (mol. wt. = 480).

General Procedure.—All interaction studies between PEG 6000 and dyes were carried out by the phase solubility method (2). A certain amount[2] of the dye under consideration was placed in each of a series of 100-ml. glass-stoppered volumetric flasks. Several stock solutions of PEG 6000 in the solvent system were made. The concentrations of the stock solution were varied, depending on the requirements of a particular experiment. Different volumes of PEG 6000 stock solutions representing different amounts of PEG 6000 were added to each flask. Then, with the aid of a buret, sufficient amounts of the solvent system were added to make up the volume to 25 ml. in each flask. Solutions were shaken in a mechanical shaker at a constant temperature of 25° for 24 hr. to establish dynamic equilibrium. Solutions were then filtered using Whatman No. 2 filter paper, analyzed spectrophotometrically, and the concentrations of the dye were determined from the Beer's law plots.

Three sets of studies using 10 mg., 25 mg., and 50 mg. of dye, respectively, were carried out with FD&C Yellow No. 5 and FD&C Reds No. 1, No. 2, and No. 4. In the case of FD&C Blue No. 1 the amounts of the dye used in the three studies were 200 mg., 250 mg., and 350 mg.

The results of the interaction studies between FD&C Yellow No. 5 and PEG 6000 are shown in Fig. 1. (The interaction between FD&C Blue No. 1 and PEG 6000 gave a similar plot and hence is not illustrated.)

The results of the interaction studies between FD&C Red No. 2 and PEG 6000 are shown in Fig. 2. (The interactions between FD&C Reds No. 1 and No. 4 and PEG 6000 gave similar plots and hence are not illustrated.)

Interaction Studies Between CAP and Dyes

No interaction was noted between CAP and any of the dyes tested.

Filmcoating Studies.—Two of the dyes were selected for this study: FD&C Yellow No. 5 and FD&C Red No. 2. Their selection was based on the fact that they showed two different types of interaction.

Preparation of the Test Tablets.—The test tablets containing equal amounts of sodium bicarbonate and lactose were prepared. Starch paste was used as the granulating agent and magnesium stearate (0.75%) as the lubricant. The tablets were compressed on a Stokes B-2 machine using 7/16-in. standard concave punches to a pressure of 8–10 Strong-Cobb units. The weight of each tablet was 650 mg. (±5%). The average thickness of the tablets was 5.10 mm.

Preparation of the Filmcoating Solution.—The basic filmcoating formula used in all these studies was:

CAP		6%
PEG 6000		14%
Acetone	65%	*q.s.* 100%
Absolute ethanol	35%	

The filmcoating solutions used with the various dyes are presented in Table I (FD&C Yellow No. 5) and Table II (FD&C Red No. 2) and were the modification of the above basic formula.

The test formulations presented above were designed to be of the following two main types.

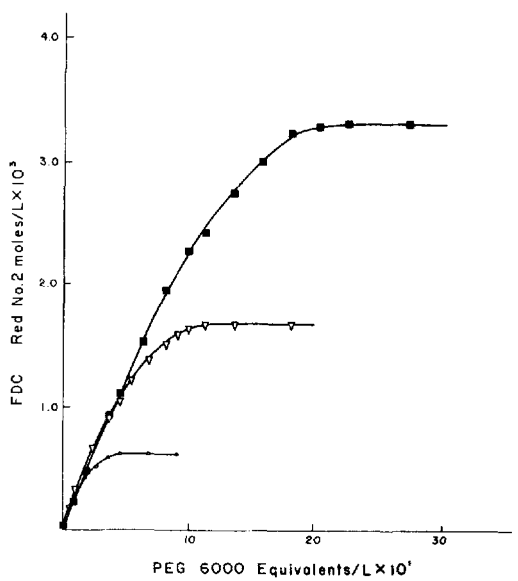

Fig. 2.—Interaction between dye FD&C Red No. 2 and PEG 6000. Key: ■, 50 mg.; ∇, 25 mg.; O, 10 mg.

[2] The amounts used for each dye were chosen on the basis of (*a*) solubility of the dye and (*b*) knowledge of the amount of the dye generally used in the filmcoating formulations.

TABLE I.—COMPOSITION OF TEST FILMCOATING FORMULATIONS USING FD&C YELLOW NO. 5 AND THE OCCURRENCE OF MOTTLING ON THE TABLETS COATED BY THEM

	Formulation No. YI	YII	YIII	YIV
Dye	0.875 Gm.	7 Gm.	0.875 Gm.	7 Gm.
CAP	30 Gm.	30 Gm.	30 Gm.	30 Gm.
PEG 6000	70 Gm.	70 Gm.	70 Gm.	70 Gm.
Titanium dioxide	...	...	10 Gm.	10 Gm.
Acetone, 65%, Absolute ethanol, 35% } q.s.	500 ml.	500 ml.	500 ml.	500 ml.
Occurrence of mottling	No	Yes	No (Final color lighter than YI)	No (Final color lighter than YII)

TABLE II.—COMPOSITION OF TEST FILMCOATING FORMULATIONS USING FD&C RED NO. 2 AND THE OCCURRENCE OF MOTTLING ON THE TABLETS COATED BY THEM

	Formulation No. RI	RII	RIII	RIV
Dye	0.675 Gm.	5.4 Gm.	0.675 Gm.	5.4 Gm.
CAP	30 Gm.	30 Gm.	30 Gm.	30 Gm.
PEG 6000	70 Gm.	70 Gm.	70 Gm.	70 Gm.
Titanium dioxide	...	...	10 Gm.	10 Gm.
Acetone, 65%, Absolute ethanol, 35% } q.s.	500 ml.	500 ml.	500 ml.	500 ml.
Occurrence of mottling	No	Yes	No (Final color lighter than RI)	No (Final color lighter than RII)

(*a*) Those containing 4 times (a large excess) the amount of dye that could be solubilized by PEG 6000; *i.e.*, formulation No. YII, YIV, RII, and RIV. (*b*) Those containing half the amount of dye that could be solubilized by PEG 6000; *i.e.*, formulation No. YI, YIII, RI, and RIII.

The determination of the amount of dye used in each formulation was based on the dye–PEG 6000 interaction studies. A typical calculation is shown in the illustration for FD&C Yellow No. 5 (Fig. 1).

On an average, 0.91 equivalents[3] of PEG 6000 (40 Gm.) would completely solubilize 0.0018 equivalents of the dye (1 Gm.). Therefore, 140 Gm. (the amount used per liter of a typical filmcoating formulation) of PEG 6000 would solubilize 3.5 Gm. of the dye.

The two dye concentrations used were $3.5 \times 4 = 14$ Gm./L. (excess dye in suspension) and $3.5/2 = 1.75$ Gm./L. (dye completely solubilized).

In formulations YI, YII, RI, and RII the method of preparation was carried out in the following steps. (*a*) The requisite amount of dye was milled for 24 hr. with 200 ml. of solvent system in a ball mill. (*b*) This mixture was transferred to a bottle containing a solution of 30 Gm. of CAP and 70 Gm. of PEG 6000 in 200 ml. of the solvent system. (*c*) The volume was made up to 500 ml. with the solvent system.

In formulations YIII, YIV, RIII, and RIV, the method of preparation was carried out in the following steps. (*a*) The requisite amounts of dye and titanium dioxide were milled for 24 hr. with 200 ml. of solvent system in a ball mill. (*b*) This mixture was transferred to a bottle containing a solution of 30 Gm. of CAP and 70 Gm. of PEG 6000 in 200 ml. of the solvent system. (*c*) The volume was made up to 500 ml. with the solvent system. All the solutions were kept in a water bath at 55–60°.

[3] Equivalents of PEG 6000 were calculated on the basis of oxyethylene linkages (44 Gm. per equivalent).

Filmcoating Procedure

The filmcoating was carried out using a pear-shaped copper pan of 16 in. maximum diameter with a panload of 5 lb. Four tape-baffles were used to improve the rolling character of the tablets.

Initially a mixture of 50 ml. of the filmcoating solution diluted with 50 ml. of the solvent system was used. This diluted solution was poured in a series of 5 to 10-ml. portions in a thin stream over the tumbling tablets and was added as quickly as possible, making sure that the tablets were perfectly dry between each addition. Then 75 ml. of filmcoating solution (undiluted) was added in a series of 2 to 5-ml. portions. Then the tablets were removed and the pan was washed and dried. The pan was recharged and another 100 ml. of the filmcoating solution (undiluted) was added in a series of 2 to 5-ml. portions. Then the coated tablets were dried and samples were taken.

The results obtained using the various formulations are also shown in Table I (FD&C Yellow No. 5) and Table II (FD&C Red No. 2). It can be seen that mottling occurred only in the tablet coats which contained an excess of the dye and did not contain titanium dioxide. It was also noted that the final color of the tablets coated with formulations containing titanium dioxide was lighter than that of the tablets on which a corresponding formulation without titanium dioxide was used.

Study of the Function of Titanium Dioxide in the Filmcoating Formulation

The following two approaches were used in this study to determine if the presence of titanium dioxide altered the interaction phenomenon between dye and PEG 6000. This study was carried out using FD&C Yellow No. 5 and FD&C Red No. 2.

A.—A constant amount (excess) of the dye under consideration was placed in a series of 100-ml. glass-stoppered volumetric flasks. Amounts of titanium dioxide varying from 0 to 750 mg., in 125-mg. increments, were also placed in the series of flasks. Twenty-five milliliters of the 14% PEG 6000 solution was added to each flask. The solutions were shaken in a mechanical shaker at a constant temperature of 25° for 24 hr. to establish dynamic equilibrium. Solutions were then filtered using Whatman No. 2 filter paper and analyzed spectrophotometrically.

B.—A constant amount (excess) of the dye under consideration was placed in a series of 100-ml. volumetric flasks. Twenty-five milliliters of 14% PEG 6000 solution was added to each flask. The solutions were shaken in a mechanical shaker at a constant temperature of 25° for 24 hr. to establish dynamic equilibrium. Amounts of titanium dioxide varying from 0 to 750 mg., in 125-mg. increments were added to the series of solutions and again the solutions were shaken for another 24 hr. at a constant temperature of 25°. The solutions were then filtered using Whatman No. 2 filter paper and analyzed spectrophotometrically.

The results obtained using the above two approaches were identical to those obtained from experiments conducted under similar conditions without the addition of titanium dioxide.

DISCUSSION

Interaction Studies Between PEG 6000 and Dyes

Interaction Studies Between Dye FD&C Yellow No. 5 and PEG 6000.—The type of interaction between FD&C Yellow No. 5 and PEG 6000 may be explained on the basis of an adsorption phenomenon. It is postulated that there exists an equilibrium between the solid dye, PEG 6000 in solution, and the adsorbed species. Then the adsorbed species goes into solution. The possible scheme of interaction can be represented as:

$$Y + P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} YP_s \xrightarrow{k_2} YP_l$$

where

Y = FD&C Yellow No. 5,
P = PEG 6000,
YP_s = adsorbed species (solute P adsorbed on solid Y),
YP_l = adsorbed species in solution.

Various approaches were tried to substantiate the existence of the adsorption phenomena mentioned above. These include the use of Freundlich's isotherm (3) and elemental and infrared spectral analysis of the residues from different regions of the interaction curves.

The use of the isotherm could not be applied in the case of FD&C Yellow No. 5 because a method of direct determination of the weight of the solute adsorbed on the dye surface or indirect determination from analyzing the solution at a particular instant for PEG 6000 content was too cumbersome and hence could not be established.

The results obtained from the two analyses did not prove to be definitive and, hence, these experiments neither proved nor disproved the existence of the adsorption phenomenon.

It is observed from Fig. 1 that as the concentration of PEG 6000 is increased, the amount of dye being constant, the curve levels off at some concentration of PEG 6000. Since such a plateau would occur when all the dye molecules are coated by PEG 6000 molecules resulting in the solubilization of the dye, the amount of PEG 6000 (expressed in terms of equivalents of oxyethylene linkages) required to solubilize a mole of dye could be obtained from Fig. 1. For example, in Fig. 1 (10 mg. dye) 4.0×10^{-1} equivalents per liter of PEG 6000 (the point where the curve starts leveling off) are required to solubilize 0.76×10^{-3} moles/L. of dye. Thus,

$$\frac{\text{PEG in equivalents/L.}}{\text{dye in moles/L.}} = \frac{4.0 \times 10^{-1}}{0.76 \times 10^{-3}} = 5.26 \times 10^2$$

Similarly, the ratios of 5.26×10^2 and 5.20×10^2 are obtained from 25 mg. dye and 50 mg. dye plots in Fig. 1, respectively. Thus, the average ratio,

$$\frac{\text{PEG in equivalents/L.}}{\text{dye in moles/L.}} = 5.24 \times 10^2$$

That is, on an average, 524 equivalents of oxyethylene linkages are required to solubilize 1 mole of FD&C Yellow No. 5.

Interaction Studies Between Dye FD&C Blue No. 1 and PEG 6000.—The type of interaction between FD&C Blue No. 1 and PEG 6000 observed was similar to that observed between FD&C Yellow No. 5 and PEG 6000, and could be explained on a similar basis.

It was found that on an average, 51 equivalents of oxyethylene linkages are required to solubilize 1 mole of FD&C Blue No. 1.

Interaction Studies Between Dye FD&C Red No. 2 and PEG 6000.—The type of interaction between FD&C Red No. 2 and PEG 6000 could also be explained on the basis of adsorption phenomenon and may be represented schematically as:

$$A + P \overset{1}{\rightleftharpoons} AP_s$$

$$AP_s + nP \overset{2}{\rightleftharpoons} AP_{ns} \rightarrow AP_{nl}$$

where

A = FD&C Red No. 2,
P = PEG 6000,
AP_s = primary adsorbed species (solute P adsorbed on the solid A),
AP_{ns} = secondary adsorbed species,
AP_{nl} = secondary adsorbed species in solution.

FD&C Red No. 2 differs from FD&C Yellow No. 5 and FD&C Blue No. 1 in that a shift in the phase solubility curve to the right is observed (Fig. 2) as the initial amount of the dye is increased. Because of this observation the interaction of FD&C Red No. 2 with PEG 6000 was studied in greater detail as shown in Fig. 3. This shift was seen to occur in all the studies shown in this figure. Such a shift indicates that as the dye concentration is

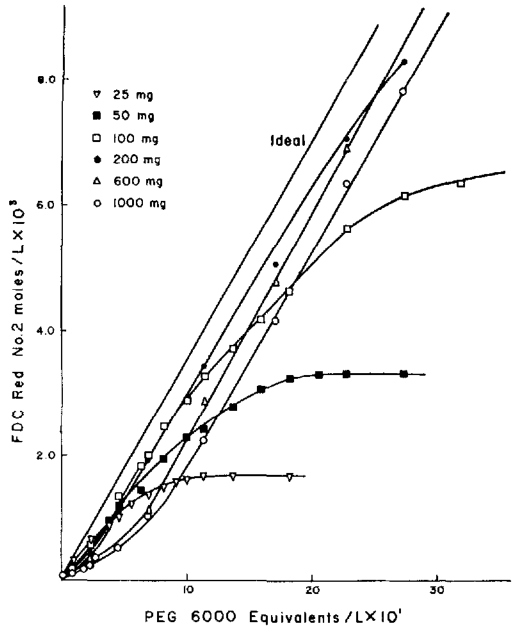

Fig. 3.—Interaction between dye FD&C Red No. 2 and PEG 6000.

increased under conditions in which the PEG 6000 concentration is kept constant, less dye actually enters into solution. This phenomenon could be explained on the basis of the relative insolubility of the primary adsorbed species AP_s (step *1* in the interaction scheme). A greater initial amount of the dye would adsorb more PEG 6000 from its solution forming the insoluble species in relatively larger amounts. Thus a smaller amount of PEG 6000 would be available to form the secondary adsorbed species AP_{ns} (step *2* in the interaction scheme) which leads to solubilization (step *3* in the interaction scheme).

At a lower initial amount of the dye, since less PEG 6000 is required for primary adsorption, more PEG 6000 would be available for secondary adsorption, and, hence, the higher solubility of the dye is observed. It is assumed here that AP_s is practically insoluble and the concentration of dye read at the absorption maximum at any instant is directly proportional to the amount of AP_{nl} in solution.

To substantiate the hypothesis that an adsorption phenomenon (adsorption of solute PEG 6000 from solution onto the solid dye) from solution occurs, the empirical isotherm suggested by Freundlich (3) mentioned earlier may be applied here.

An ideal line, *i.e.*, the line representing no shift due to adsorption phenomenon, is drawn (Fig. 3) passing through the initial point (point representing the saturation solubility of the dye in the absence of PEG 6000) and parallel to the interaction lines in the higher concentration region of PEG 6000.

To apply the Freundlich isotherm, the weight of PEG 6000 adsorbed on the dye is first determined. An illustration to calculate the values of x is as follows:

$$x = x_t - x_i$$

where

x = weight of PEG 6000 (in equivalents per liter) adsorbed,

x_t = weight of PEG 6000 (in equivalents per liter) taken,

x_i = weight of PEG 6000 (in equivalents per liter) required to solubilize the same amount of dye if no shift in the curves occurred.

Referring to Fig. 3 (1000 mg. dye curve which represents the dye in a concentration of 1 Gm./25 ml. or 40 Gm./L.), when $x_t = 0.5$, $x_i = 0.15$, then $x = 0.35$.

Since the plot of log x/m against log C (Fig. 4) yields a straight line, the experimental results conform to the Freundlich expression indicating the existence of adsorption phenomenon.

In the lower concentration region of PEG 6000 and when the amount of dye present is large, the primary adsorption phenomenon would be predominant. However, as the concentration of PEG 6000 in solution is increased, the secondary adsorption and solubilization phenomenon would come into predominance. Approaching the plateau region of the curves, the solubilization process would be predominant in nature.

In case of FD&C Red No. 2 also, the residues from ten different regions of the interaction curves after dynamic equilibrium was established were collected and dried. Here also no definite conclusions could be drawn either from elemental (C, H, N) analysis or infrared spectra (using KBr pellet method) of the residues. The above analyses did not prove or disprove the existence of the adsorption phenomenon. The ratio

$$\frac{\text{PEG in equivalents/L.}}{\text{dye in moles/L.}}$$

for FD&C Red No. 2 is calculated in the same manner as shown with FD&C Yellow No. 5. On an average 721 equivalents of oxyethylene linkages are required to solubilize 1 mole of FD&C Red No. 2.

Interaction Studies Between Dye FD&C Red No. 1 and PEG 6000 and FD&C Red No. 4 and PEG 6000.—These interactions were similar to that ob-

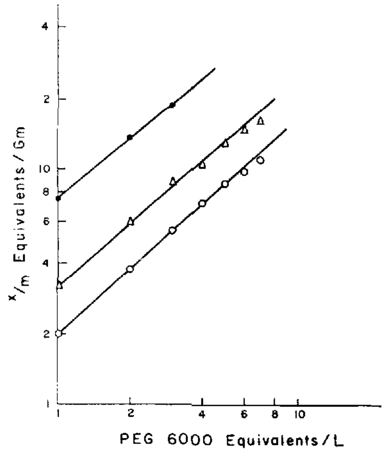

Fig. 4.—Adsorption isotherms for PEG 6000. Key: ●, 200 mg.; △, 600 mg.; ○, 1000 mg.

served between FD&C Red No. 2 and PEG 6000, and can be explained similarly on the basis of adsorption phenomenon. On an average, 700 equivalents of oxyethylene linkages are required to solubilize 1 mole of FD&C Red No. 1, and 450 equivalents to solubilize 1 mole of FD&C Red No. 4.

Filmcoating Studies.—The relative uniformity of color produced by formulations YI (FD&C Yellow No. 5) and RI (FD&C Red No. 2) contrasted with the highly mottled appearance produced by formulations YII (FD&C Yellow No. 5) and RII (FD&C Red No. 2) substantiates the hypothesis presented earlier that to achieve uniform color coverage the dye must be brought into solution. However, the results shown by formulations YIV (FD&C Yellow No. 5) and RIV (FD&C Red No. 2) do not substantiate this hypothesis. Although here the amount of dye is in excess (same as in YII and RII, respectively), the presence of titanium dioxide helps to prevent the expected mottled appearance of the tablets.

Study of the Function of Titanium Dioxide in the Filmcoating Formulation.—The results obtained in the study designed to evaluate the function of titanium dioxide in the filmcoating formulation showed no change in the adsorption curve patterns obtained for PEG 6000–dye interactions. Hence, it is concluded that titanium dioxide does not act as an adsorbent for the dye or PEG 6000 and thus does not aid in preventing mottling by an adsorption process. Furthermore, the studies show that the titanium dioxide does not act in any way to affect the interactions between the dyes and PEG 6000. However, the results in the filmcoating studies show that even when the dye was not completely solubilized by PEG 6000, the mottling was considerably reduced by the addition of titanium dioxide to the filmcoating formula. Therefore, it is concluded that the presence of titanium dioxide promotes color uniformity simply due to "mechanical effect" of its bulk; that is, the larger number of titanium dioxide particles present tends to mechanically prevent the aggregation of the dye particles.

CONCLUSIONS

The results of the present investigation have demonstrated: (*a*) PEG 6000 interacts with the dyes tested (FD&C Red No. 1, 2, and 4; FD&C Yellow No. 5; and FD&C Blue No. 1). The interaction (adsorption of PEG 6000 onto the solid dye) results in solubilization of the dyes which are almost insoluble in the solvent system used (65% acetone and 35% absolute ethanol). (*b*) No interaction is observed between CAP and the dyes tested. (*c*) Presence of titanium dioxide does not alter or affect the adsorption of PEG 6000 onto dyes.

Thus, in a typical basic filmcoating formulation containing dye, PEG 6000, CAP, and titanium dioxide in the nonaqueous solvent system, the interaction between PEG 6000 and dyes plays a significant role in affecting the uniformity of color. In order to assure maximum color uniformity, the amount of dye in a filmcoating formulation should not exceed the amount capable of being brought into solution by PEG 6000. The purely mechanical effect of titanium dioxide in preventing the aggregation of dye particles also plays a significant role in achieving color uniformity.

The information provided by this study gives some insight into methods that may be employed in formulating filmcoating solutions on the basis of scientific data rather than by the use of purely empirical techniques.

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Experiences in Development of Directly Compressible Tablets Containing Potassium Chloride

By JACK LAZARUS and LEON LACHMAN

The influence of particle size distribution, particle shape, apparent bulk density, moisture content, additives, and punch shape on the directly compressible characteristics of potassium chloride were investigated. The relative weight and drug variability of hydrochlorothiazide–potassium chloride tablets prepared by direct compression were compared with those prepared by customary wet granulating techniques.

According to the literature (1, 2) it should be possible to directly compress crystals belonging to the cubic system into conventional flat-faced or biconvex tablets. Potassium chloride crystals fall under this classification and can normally be directly compressed into such tablets. However, when the tablet shape is altered, not all batches of U.S.P. potassium chloride crystals obtained from different suppliers could be directly

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