Diffuse Reflectance Studies of Dye-Adjuvant Chemisorption

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A number of pharmaceutical adjuvants were screened by means of diffuse reflectance spectroscopy for possible solid–solid interaction with certified Red No. 3, Blue No. 1, and Yellow No. 5 dyes. Results indicate that a metallic or polyfunctional adsorbent molecule is necessary for these interactions. Furthermore, it was generally observed that the order of metallic adjuvant interaction with these dyes is $Mg^{2+} > Ca^{2+} > Zn^{2+} \backsim Al^{3+}$. Spectral and visual color changes, elution studies, and accelerated fading techniques support the reflectance data presented.

SEVERAL ARTICLES have recently appeared in the literature which point out drug–adjuvant interactions (1, 2) and the need for prescreening of the excipients used in the preparation of solid dosage forms. Since such interactions may be responsible for the various therapeutic discrepancies reported in related formulations, these interactions may also be of significant importance in color and drug stability.

EXPERIMENTAL

Reagents—FD&C Red No. 3 dye and aluminum lake (National Aniline), FD&C Blue No. 1 dye (National Aniline), FD&C Yellow No. 5 dye and aluminum lake (Warner-Jenkinson Mfg. Co.), acacia, aluminum hydroxide, aluminum stearate, calcium hydroxide, cellulose acetate phthalate, citric acid, lactose, magnesium citrate, magnesium hydroxide, pectin, polyethylene glycol 6000 (Carbide and Corton Chemical Corp.), starch U.S.P., titanium dioxide, zinc oxide, zinc sulfate.

Apparatus—Beckman DU spectrophotometer with a diffuse reflectance attachment, constant-temperature water bath set at 30 ± 0.5° with rotating spindles (1), assorted round amber bottles from 30 to 200 ml. with caps, Parafilm (Marathon Co.), aluminum foil (Reynolds), vacuum oven (National Appliance Co.), glass desiccator, lyophilizer (National Research Corp.) attached to a refrigeration system (Webber Refrigeration).

PROCEDURES

Equilibration Technique—The general method of studying these interactions involves equilibrating a weighed amount of adsorbent for 24 hr. with distilled water or an organic equilibration medium. After equilibration the dispersion medium is removed either by vacuum filtration followed by vacuum drying at 35° for 24 hr., by vacuum evaporation from a glass desiccator, or by freezing the aqueous media with the aid of a dry ice–methanol mixture and lyophilization for 24 hr. The particular drying method used is described under *Results and Discussion*.

Preparation of the Sample—A specified amount of pre-equilibrated dye and adsorbent (pharmaceutical adjuvant) are weighed. The powders are then placed in a suitable amber bottle and 20 ml. of the dispersion media is added. The bottle is covered with Parafilm or aluminum foil, capped, and equilibrated for 24 hr. at 30 ± 0.5° in order to effect interaction. After equilibration, one of the following three techniques is employed in order to dry the samples.

Vacuum Filtration and Drying—Used for samples with aqueous dispersion media reported in Tables I and II. The suspension is vacuum filtered after equilibration and the powder is dried in a vacuum oven at 35° for 24 hr. The resulting dry powder is then triturated, and its diffuse reflectance (DRS) measured using a magnesium carbonate reference standard.

Evaporation by Vacuum—The equilibrated solution or suspension is placed in an evaporation dish and placed in a vacuum desiccator. The organic solvent is removed at room temperature, and the resulting powder is triturated and its DRS measured.

Drying by Lyophilization—This process is used exclusively in all the samples reported in Table II. The equilibrated aqueous solution or suspension is frozen in a dry ice–methanol mixture and lyophilized for 24 hr. The resulting powder is triturated and its DRS measured.

Preparation of the Control—A specified weight of the previously equilibrated and dried adsorbent is physically mixed with an indicated amount of pre-equilibrated and dried adsorbate using a mortar and pestle. The DRS of this control is then measured using a magnesium carbonate reference standard.

SPECIAL TECHNIQUES

Washing the Sample—The dry powdered sample is placed in a 51-mm. Büchner funnel and 200 ml. of distilled water is added and removed by vacuum filtration. The resultant powder is dried and its DRS measured.

Accelerated Light Studies—The powder under study is packed into an inverted 4-cm. diameter bottle cap and placed into an Envira-Lite cabinet (Thermal Research, Inc.) which houses 10 Westinghouse F-40 CW/RFL fluorescent lamps and 4 GE lumiline No. L60 IF/T8 incandescent lamps and is

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TABLE I—FD&C RED NO. 3 DYES OR LAKES: DYE OR LAKE REACTIONS WITH PHARMACEUTICAL ADJUVANTS USING AN EXCESS OF COLORING MATTER

Dye or Lake + Adjuvant	Concn., Dye:Adjuvant	Equilibration Media	Method of Solvent Removal	Relative Size of Spectral Changes	Visual Color Changes (Control to Sample)
Dye + TiO_2	200 mg.:4.00 Gm.	EtOH	Vacuum evaporation	No significant change	White to off white
Dye + TiO_2	200 mg.:4.00 Gm.	H_2O	Vacuum filter, wash and dry	Medium change	White to white
Dye + starch	100 mg.:4.00 Gm.	Dil. EtOH (1:1)	Vacuum evaporation	Small change	Light pink to pink
Lake + starch	100 mg.:4.00 Gm.	Dil. EtOH (1:1)	Vacuum evaporation	No significant change	Light pink to light pink
Dye + lactose	200 mg.:4.00 Gm.	EtOH	Vacuum evaporation	No significant change	Light pink to light pink
Dye + CAP	200 mg.:4.00 Gm.	H_2O	Vacuum filter, wash and dry	Small change	Lavender with white specks to fire engine red (heterogeneous)
Dye + CAP	200 mg.:4.00 Gm.	EtOH	Vacuum evaporation	Small change	Lavender with white specks to fire engine red, solid mass
Dye + PEG 6000	200 mg.:4.00 Gm.	Acetone	Vacuum evaporation	Small change	Light violet to deep, fluorescent red

TABLE II—FD&C YELLOW NO. 5 DYES OR LAKES: DYE OR LAKE REACTIONS WITH PHARMACEUTICAL ADJUVANTS USING AN EXCESS OF COLORING MATTER

Dye or Lake + Adjuvant	Concn., Dye:Adjuvant	Equilibration Media	Method of Solvent Removal	Relative Size of Spectral Changes	Visual Color Changes (Control to Sample)
Dye + Al stearate	200 mg.:2.00 Gm.	H_2O	Vacuum filter, wash and dry	No significant change	Heterogeneous whitish pink to light yellow
Dye + $ZnSO_4$	100 mg.:4.00 Gm.	EtOH	Vacuum evaporation	Small change	Orange to intense yellow
Dye + ZnO	200 mg.:4.00 Gm.	H_2O	Vacuum filter, wash and dry	No significant change	Off white to off white
Dye + Mg citrate	100 mg.:4.00 Gm.	$CHCl_3$	Vacuum evaporation	Large change	Light peach to intense yellow
Dye + citric acid	100 mg.:4.00 Gm.	$CHCl_3$	Vacuum evaporation	Small change	Orange to yellow-gold
Dye + TiO_2	200 mg.:4.00 Gm.	H_2O	Vacuum filter, wash and dry	No significant change	White with red specks to white
Dye + starch	100 mg.:4.00 Gm.	Dil. EtOH (1:1)	Vacuum evaporation	Medium change	Pink to bright yellow
Lake + starch	100 mg.:4.00 Gm.	Dil. EtOH (1:1)	Vacuum filtration	Small change	Pink to bright yellow
Dye + lactose	200 mg.:4.00 Gm.	EtOH	Vacuum evaporation	No significant change	Orange to heterogeneous orange with dark pink crystals
Lake + CAP	100 mg.:4.00 Gm.	H_2O	Vacuum filter, wash and dry	No significant change	Yellow to yellow
Dye + PEG 6000	200 mg.:4.00 Gm.	$CHCl_3$	Vacuum evaporation	Increased reflectance	Heterogeneous light orange to orange
Dye + PEG 6000	200 mg.:4.00 Gm.	Acetone	Vacuum evaporation	No significant change	Heterogeneous light orange to deep yellow
Dye + acacia	100 mg.:4.00 Gm.	EtOH	Vacuum evaporation	Medium change	Heterogeneous light orange to intense orange
Lake + acacia	50 mg.:4.00 Gm.	EtOH	Vacuum evaporation	No significant change	Yellow to yellow
Dye + pectin	100 mg.:4.00 Gm.	Dil. EtOH (1:1)	Vacuum evaporation	Increased reflectance	Golden yellow to golden yellow

equipped with a rheostat dimmer and fan. The light intensity used throughout this study was 2,000 foot candles (f.c.) and the temperature within the cabinet was 32 ± 3°.

RESULTS AND DISCUSSION

Although it is generally acknowledged that the most common type of dye instability in pharmaceutical and cosmetic systems is due in part to light and thermal rearrangements, it is possible that some of these color changes occurring in solid dosage formulations may be due to dye–excipient interactions (1). During the past 10 years some attention has been given to color stability in pharmaceutical dosage forms (3, 4). A number of reports have appeared in the literature dealing with studies to elucidate the nature of this interaction, the effect of excipients with respect to fading, and methods employed to retard such an interaction (5–8). Since most of the reported investigations dealing with this dye–adjuvant interaction have been studied in solution, very little information is available concerning the degree of this interaction observed with diffuse reflectance techniques.

Since diffuse reflectance spectroscopy (DRS) has been shown to be a useful tool for interaction studies in the solid state (1), this technique was employed to further study dye–adjuvant interactions.

In this present study, various certified dyes were screened with a large group of adjuvants for the existence of such interactions. The dyes, FD&C Red No. 3, Blue No. 1, and Yellow No. 5, were selected either on the basis of their chemical structure, light instability, or use in pharmaceuticals. The adjuvants were chosen on the basis of the metal fraction or polyfunctional groups they contain (8) or because of their use in medicinal dosage forms.

As has been pointed out in previous communications (9–11) the adsorbate/adsorbent ratio must be carefully considered in order to observe these solid–solid interactions; if an excess of adsorbate is used, the monomolecular chemisorption occurring at the surface of the adsorbent is masked by subsequent

physical layers of the adsorbate, and the DRS spectrum approaches that of the pure dye under investigation. In this preliminary dye–adjuvant interaction study, 50 to 200 mg. of dye was used with 4.00 Gm. adjuvant samples. The controls, reported in Tables I and II, were prepared by physically mixing the dye with pre-equilibrated and vacuum dried adjuvants; the samples represent the result of equilibrating dye–adjuvant combinations in the designated equilibration media, followed by either vacuum evaporation of the solvent at room temperature or removal of the solvent by vacuum filtration, washing of this sample, and vacuum drying at about 35° for 24 hr.

An examination of the data reported in Tables I and II suggests that these dyes either undergo little interaction or that the dye–adjuvant ratio was such as to completely mask any effects due to chemisorption (unimolecular layer). The absorbance behavior of multilayers of the dye on these excipient particles becomes similar to that of the pure dye (1).

The spectral changes observed with Red No. 3 dye after equilibration with various adjuvants (see Table I) were small and correlate well with the lack of visual color changes observed. It is interesting to point out, however, that the spectral changes observed as a result of equilibrating Yellow No. 5 dye with starch or magnesium citrate did produce significant spectral and visual color changes at these high dye–adjuvant concentration ratios, suggesting chemisorption. Figure 1 illustrates this Yellow No. 5 dye–starch interaction. It is clearly seen that the absorbance and visual color change of the sample (see Table II) along with a new band formation at 315 mμ is indicative of a strong interaction. It is also interesting to note here that the interaction of the corresponding Yellow No. 5 lake with starch is much smaller, suggesting that a number of the adsorption sites are not available in the aluminum lake.

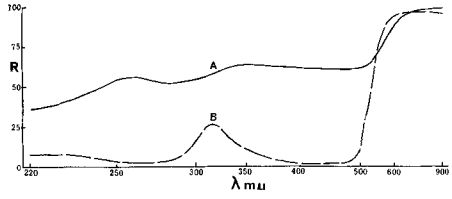

Fig. 1—DRS of FD&C Yellow No. 5 dye (100 mg.) and starch (4.00 Gm.). Key: A, *control;* B, *sample equilibrated in 30 ml. dilute ethanol (1:1).*

As has already been mentioned, spectral changes due to chemisorption are readily seen when a single layer of the dye is chemisorbed onto the surface of the adsorbent (8,9). Since the dye–adjuvant ratios employed in the initial phase of this investigation were high, these interactions were again studied, using lesser quantities of the dye. Dye concentrations of 30 mg./10.00 Gm. of adjuvant were found suitable in exhibiting this chemisorption effect.

In order that all experimental conditions be kept constant, the controls in this phase of study were prepared by separately equilibrating the dye and adjuvant in distilled water for a period of 24 hr., followed by lyophilization to remove the solvent media. The appropriate concentration of dye and adjuvant was then weighed and physically mixed by geometric dilution, and the diffuse reflectance spectrum (DRS) of this control was measured, using a magnesium carbonate reference standard. Interacted samples were prepared by placing a weighed amount of pre-lyophilized dye and adjuvant in a suitable container, adding distilled water, and equilibrating the mixture for 24 hr. This interacted sample was then lyophilized and triturated and its DRS was obtained. Although the degree of spectral change depends on both the dye and excipient under investigation, "no significant change," reported in the tables, will be defined as spectral intensity changes of 10 reflectance units (RU) or less. A "small change" will generally indicate intensity changes of 10–30 RU, whereas a "medium change" implies a spectral change of about 30–60 RU; a "large change" indicates hyperchromic changes of 60 or more reflectance units at the maximum wavelength. It is interesting to point out that the aqueous solvent serves as a dispersion medium in order to facilitate maximal interaction with the sites available. These interactions will also occur in the solid unequilibrated state in the presence of moisture (10).

Tables III, IV, and V summarize the data obtained in this study, using the structurally different certified Red No. 3, Blue No. 1, and Yellow No. 5 dyes. The spectral changes observed in these low dye concentration systems again correlate well with visual color changes observed. Typical interaction spectra of several Red No. 3–adjuvant systems are presented in Figs. 2–4. An examination of these figures certainly illustrates the high degree of interaction as evidenced by the large absorbance and other spectral differences of the equilibrated sample as compared with the control. The strength of these interactions with various adjuvants can also be demonstrated with the use of an elution technique. For example, the dye in the Red No. 3–$Al(OH)_3$ or Red No. 3–ZnO system exhibiting small or medium-sized spectral changes (Fig. 4) was readily eluted with water. In comparison, starch or $Mg(OH)_2$ interactions with this same dye, presented in Figs. 2 and 3, did not undergo significant spectral changes after the sample was washed with distilled water, indicating a stronger interaction.

It should be pointed out, however, that in spite of the fact that a dye can be readily desorbed from an excipient, indicating a relatively weaker adsorption, the interaction is nevertheless important since the color stability of the intact dosage form may be affected by this weaker interaction. In contrast, desorption of a medicinal agent from an adjuvant material is extremely important in that the therapeutic availability of this agent is directly related to this desorption phenomenon or chemical interaction.

The strength of these interactions was sometimes further correlated by subjecting the equilibrated sample to accelerated light fading conditions. For example it is seen that under these conditions, the color intensity of a Red No. 3–$Al(OH)_3$ equilibrated sample undergoes 61% increased reflectance. This change occurs at the $\lambda_{max.}$ after a 42-hr. exposure to 2,000 f.c. artificial light. On the other hand, the Red No. 3–$Mg(OH)_2$ equilibrated sample exhibits approximately 17% increased reflectance under the same conditions. This slower rate of fading or dye decomposition in the dye–$Mg(OH)_2$ system may be indicative of a stronger chemisorbed system. This is

TABLE III—FD&C RED NO. 3 DYE: DYE REACTIONS WITH PHARMACEUTICAL ADJUVANTS (CONCENTRATION: 30 mg. DYE/10.00 Gm. ADJUVANT)

Red No. 3 Dye + Adjuvant	Relative Size of Spectral Changes	Visual Color Changes (Control to Sample)	Effect of Washing Sample with 200 ml. Water	Sample Exposure to Artificial Light, 2,000 f.c.	
				42 hr.	184 hr.
$Al(OH)_3$	Small to medium change	Light pink to light pink	Eluted; spectrum approaches adjuvant	Increase of 21 RU or 61% fading[a]	Increase of 34 RU or 95% fading
$Ca(OH)_2$	Medium to large change	Light pink to pink	No elution	Increase of 16 RU or 22% fading	
$Mg(OH)_2$	Large change	Light pink to lavender	No elution	Increase of 12 RU or 17% fading	Increase of 29 RU or 41% fading
ZnO	Medium change	Faint pink to sharp pink	Eluted		
$ZnSO_4$	No significant change	Light pink to light pink			
Mg citrate	Small change	Pink to reddish-pink			
Citric acid	No significant change	Light pink to whitish pink			
Starch	Large change	Light pink to pink	No elution	Increase of 27 RU or 42% fading	Increase of 49 RU or 78% fading
Lactose	Medium change	Light pink to rosy red			Increase of 2 RU or 4% fading
Acacia	Small to medium change	Light pink to pink			

[a] % Sample fading at $\lambda_{max.} = \frac{R_{faded\ sample} - R_{sample}}{R_{control} - R_{sample}} \times 100$.

TABLE IV—FD&C BLUE NO. 1 DYE: DYE REACTIONS WITH PHARMACEUTICAL ADJUVANTS (CONCENTRATION: 30 mg. DYE/10.00 Gm. ADJUVANT)

Blue No. 1 Dye + Adjuvant	Relative Size of Spectral Changes	Visual Color Changes (Control to Sample)	Effect of Washing Sample with 200 ml. Water	Sample Exposure to 42 hr. Artificial Light at 2,000 f.c.
$Al(OH)_3$	Medium change	Powder blue to bluish-gray	Eluted	Increase of 14 RU or 31% fading
$Ca(OH)_2$	Medium change	Gray to light lavender	Eluted	Increase of 12 RU or 30% fading
$Mg(OH)_2$	Large change	Faint blue to deep blue	Little elution	Increase of 3 RU or 3% fading
ZnO	Medium to large change	Powder blue to blue	Eluted	
$ZnSO_4$	Large change	Light blue to sky blue		
Mg citrate	Large change	Light blue to dark blue-green		
Citric acid	No significant to small change	Light blue to powder blue		
Starch	Large change	Light blue to blue	Little elution	Increase of 1 RU or 1% fading
Lactose	Large change	Light blue to blue-green		
Acacia	Large change	Gray to deep blue		

TABLE V—FD&C YELLOW NO. 5 DYE: DYE REACTIONS WITH PHARMACEUTICAL ADJUVANTS (CONCENTRATION: 30 mg. DYE/10.00 Gm. ADJUVANT)

Yellow No. 5 Dye + Adjuvant	Relative Size of Spectral Changes	Visual Color Changes (Control to Sample)	Effect of Washing Sample with 200 ml. Water	Sample Exposure to 42 hr. Artificial Light at 2,000 f.c.
$Al(OH)_3$	Medium change	Off white to yellow	Eluted; spectrum approaches adjuvant	No significant change
$Ca(OH)_2$	Medium change	Off white to yellow	About $^2/_5$ eluted	Increase of 7 RU or 11% fading
$Mg(OH)_2$	Large change	Off white to golden yellow	No significant elution evident	No significant change
ZnO	Medium change	Off white to yellow	Eluted	
$ZnSO_4$	Medium change	Faint yellow to light orange-yellow		
Mg citrate	Large change	Faint yellow to canary yellow		
Citric acid	Small to medium change	Light pink to intense gold		
Starch	Large change	Faint yellow to darkish yellow	Little elution	No significant change
Lactose	Large change	White to deep yellow		
Acacia	Large change	Off white to bright yellow		

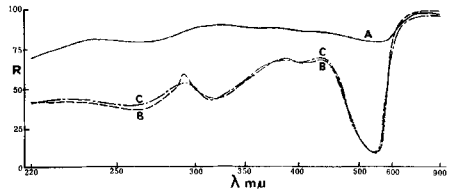

Fig. 2—DRS of FD&C Red No. 3 dye (30 mg.) and magnesium hydroxide (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample washed with 200 ml. distilled water.*

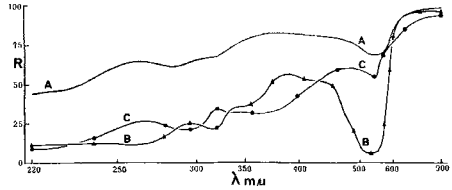

Fig. 3—DRS of FD&C Red No. 3 dye (30 mg.) and starch (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample exposed to 184 hr. artificial light at 2,000 f.c.*

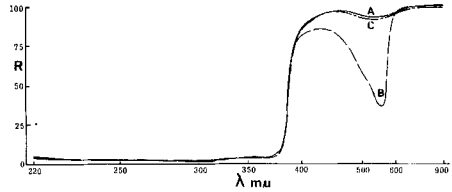

Fig. 4—DRS of FD&C Red No. 3 dye (30 mg.) and zinc oxide (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample washed with 200 ml. distilled water.*

clearly substantiated in the comparison of Blue No. 1 dye fading of starch and $Ca(OH)_2$ equilibrated samples presented in Figs. 5 and 6 and Table IV. These results indicate the Blue No. 1 fades about 1% in a dye–starch chemisorbed sample as compared to 30% fading in the dye–$Ca(OH)_2$ equilibrated sample, exposed to similar accelerated light conditions.

It is also interesting to note that although lactose shows comparable spectral interaction changes with the dyes to that of starch, its fading characteristics are somewhat different. For example, Fig. 7C, which represents an equilibrated Red No. 3–lactose system, shows little fading tendency even after 184-hr. exposure to artificial light at 2,000 f.c.; a Red No. 3–starch sample fades extensively under the same conditions, as illustrated in Fig. 3C. These differences show the complexity of these interactions and the need for individual dye–excipient study.

Although the structure of the dyes is quite different, suggesting different binding sites, it is nevertheless of interest to point out that the interaction obtained is dependent on both the dye and adjuvant employed. For example, Figs. 8 and 9 as well as Tables III, IV, and V illustrate that zinc sulfate reactions are markedly different with the dyes studied. Equilibration of this excipient with Red No. 3 dye, containing a sodium salt of a carboxyl group, but lacking phenylsulfonic acid functional groups,

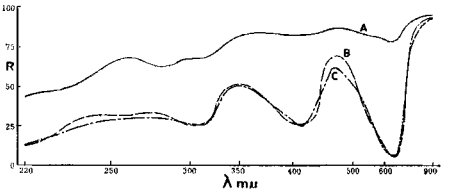

Fig. 5—DRS of FD&C Blue No. 1 (30 mg.) and starch (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample exposed to 42 hr. artificial light at 2,000 f.c.*

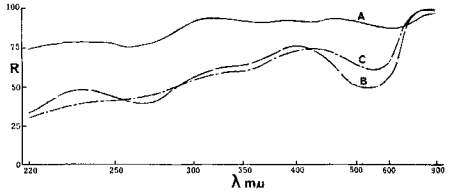

Fig. 6—DRS of FD&C Blue No. 1 dye (30 mg.) and calcium hydroxide (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample exposed to 42 hr. artificial light at 2,000 f.c.*

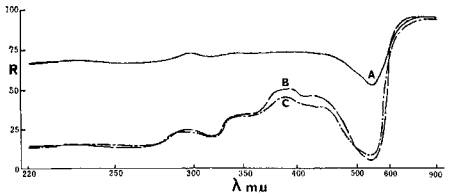

Fig. 7—DRS of FD&C Red No. 3 dye (30 mg.) and lactose (10.00 Gm.). Key: A, *control;* B, *sample;* C, *sample exposed to 184 hr. artificial light at 2,000 f.c.*

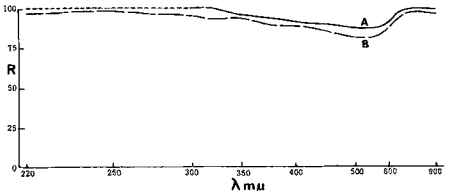

Fig. 8—DRS of FD&C Red No. 3 dye (30 mg.) and zinc sulfate (10.00 Gm.). Key: A, *control;* B, *sample.*

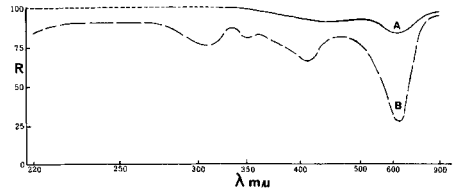

Fig. 9—DRS of FD&C Blue No. 1 dye (30 mg.) and zinc sulfate (10.00 Gm.). Key: A, *control;* B, *sample.*

found in the other two dyes under investigation, results in only very minor spectral changes, as seen in

Fig. 8. In contrast, $ZnSO_4$ does react to a large extent with Blue No. 1 dye, containing three phenylsulfonic acid groups, as well as with FD&C Yellow No. 5 which also contains a phenylsulfonic acid group, one carboxyl, and one hydroxyl functional group. These phenylsulfonic acid groups may therefore be involved in the observed chemisorption.

Furthermore, the same dye has been shown to react differently, depending on the excipient under investigation. For example, the strength of $Mg(OH)_2$, $Ca(OH)_2$, and $Al(OH)_3$ interaction with Yellow No. 5 dye is markedly different as observed in Figs. 10, 11, and 12, as well as Table V. An examination of these figures indicates that dye–$Mg(OH)_2$ equilibration facilitates a large decreased reflectance of about 74 units at the $\lambda_{max.}$ of 435 mμ as reported in Fig. 10B; the strength of this large interaction is further supported with the aid of elution studies presented in Fig. 10C. Although $Ca(OH)_2$ equilibration with this yellow dye does produce a 59 reflectance unit decrease at the $\lambda_{max.}$ of 410 mμ, seen in Fig. 11B and Table V, aqueous washing of this sample indicates that about 40% of the dye can be eluted. It is also interesting to point out that although Yellow No. 5 dye equilibration with $Al(OH)_3$ also produces a 47 reflectance unit decrease at the $\lambda_{max.}$ of 400 mμ, Fig. 12, this dye is eluted to a much greater extent from the surface of the adsorbent with aqueous washing of the sample. The above bathochromic and hyperchromic spectral changes again indicate that reactivity differences of the metallic ion present in these hydroxide adjuvants is $Mg^{2+} > Ca^{2+} > Al^{3+}$.

With regard to these interactions, although some systems may not exhibit visual color changes after equilibration, the spectral changes observed in the ultraviolet region may be significant in the photodecomposition of a particular dye.

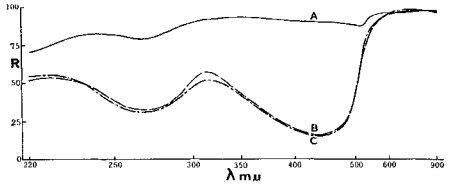

Fig. 10—DRS of FD&C Yellow No. 5 dye (30 mg.) and magnesium hydroxide (10.00 Gm.). Key: A, control; B, sample; C, sample washed with 200 ml. distilled water.

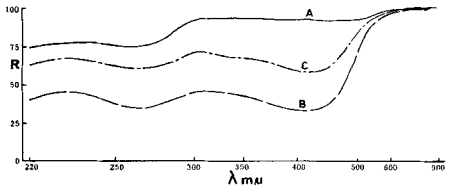

Fig. 11—DRS of FD&C Yellow No. 5 dye (30 mg.) and calcium hydroxide (10.00 Gm.). Key: A, control; B, sample; C, sample washed with 200 ml. distilled water.

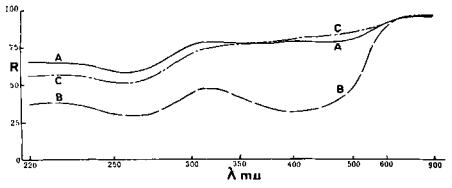

Fig. 12—DRS of FD&C Yellow No. 5 dye (30 mg.) and aluminum hydroxide (10.00 Gm.). Key: A, control; B, sample; C, sample washed with 200 ml. distilled water.

CONCLUSION

The data presented here indicate that the "inert" materials, including starch, lactose, and acacia, do undergo significant interactions with the dyes investigated. Furthermore, various metal-containing adjuvants also chemisorb with certified dyes; the order of chemisorption capacity of the metallic adjuvants with certified dyes was as follows: $Mg^{2+} > Ca^{2+} > Zn^{2+} \backsim Al^{3+}$. These dye–adjuvant interactions may be responsible for the various color problems encountered in solid pharmaceutical formulations.

It appears that the mechanism involved in these interactions is a combination of a chelation type of interaction and one of chemisorption. This is particularly true where the excipient material does not undergo ionization. It is apparent that these solid–solid interactions are of importance, not only in drug–adjuvant studies, but also in the investigation of color and drug stability.

These studies and those previously conducted with respect to drug–excipient interactions point out the need for incompatibility studies of drug or dye–adjuvant interactions in conjunction with other considerations in the formulation of pharmaceuticals.

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