Diffuse Reflectance Studies of Solid–Solid Interactions II

Interaction of Metallic and Nonmetallic Adjuvants with Anthracene, Prednisone, and Hydrochlorothiazide

By MICHAEL BORNSTEIN* and JOHN L. LACH

Spectral information is presented on chemisorption-diffuse reflectance studies of metallic and nonmetallic adjuvant interaction with anthracene, prednisone, and hydrochlorothiazide. The systems investigated indicate that the primary mechanism responsible for the bathochromic, hyperchromic, and visual color changes is that of charge transfer chelation.

THIS COMMUNICATION is the second in a series in which diffuse reflectance spectra (DRS) of chemisorbed systems of pharmaceutical importance are examined. In the first report (1), the complexing properties of oxytetracycline, phenothiazine, anthracene, and salicylic acid have been investigated in order to verify the existence of such solid–solid interactions in pharmaceutical systems. Based on these data and theoretical considerations, it was felt that these interactions probably exist in other drug–adjuvant systems.

The purpose of this study was to continue this investigation in order that additional information be obtained concerning the nature of these interactions. Complexing data for anthracene, prednisone, and hydrochlorothiazide, with a number of metallic and nonmetallic adjuvants, is presented along with a discussion of probable mechanisms involved.

EXPERIMENTAL

Reagents.—Alcohol recrystallized anthracene, m.p. 218° (Eastman Organic Chemicals); prednisone U.S.P., m.p. 233–235° dec. (American Roland); hydrochlorothiazide, m.p. 273–275° (Merck, Sharp and Dohme); acid (anionotropic) alumina (Woelm); basic (cationotropic) alumina (Woelm); aluminum hydroxide, magnesium borate (K & K Laboratories); talc, attapulgite (colloidal) (Minerals and Chemicals Phillip); kaolin (colloidal), calcium carbonate, dibasic calcium phosphate, zinc stearate, stearic acid; anhydrous methyl alcohol.

Procedure.—The routine experimental procedure for preparing the complexes and method of analysis have been described in a previous report (1). All samples were prepared by aqueous equilibration in 25 ml. of distilled water for a period of 24 hr.

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RESULTS AND DISCUSSION

It has been shown in our previous publication (1) that large spectral shifts involved in the 400 mμ region, along with significant color changes observed, indicate that these interactions are of the donor–acceptor or charge transfer type. Spectral data dealing with anthracene, prednisone, and hydrochlorothiazide further indicate that these interactions are of a charge transfer variety.

ANTHRACENE–ADJUVANT SYSTEMS

The first group of systems to be discussed is the anthracene–adjuvant interactions. Anthracene was selected in that our preliminary studies, together with various literature reports, suggest that it undergoes various donor–acceptor interactions. For example, Aalbersberg *et al.* (2), in discussing complexes of aromatic hydrocarbons with strong Lewis acids, show electronic absorbance spectra from solution between basic anthracene (M) and such Lewis acids (A) as BF_3, PF_5, $SbCl_5$, and SO_3 and imply that these complexes may be covalent, MA, or contain M^+ ions. Solution MA spectra resemble those of MH^+, suggesting addition of A and H^+ at the same C atom in the —CH_2 bridges. Leonhardt and Weller (3), in studying proton–donor effects of hydrated cations with aromatic hydrocarbons, found that the order of proton donor capacity of metallic ions was as follows.

$Mg^{2+} > Ca^{2+} > Ba^2 > Li^+ > Na^+$. Perkampus and Kranz (4) studied anthracene complexes of Al_2O_3 with the aid of U.V. spectroscopy and found that the complexes do not fulfill the laws of normal electron donor–acceptor complexes and concluded that these were not charge transfer complexes. Rooney and Pink (5), in the EPR study of anthracene adsorption of a silica–alumina catalyst, compared the color of his complexes with spectra of anthracene dissolved in 98% H_2SO_4 and found that the color of the adsorbed species was identical to the corresponding H_2SO_4 solution, indicating that the adsorbed species is a radical resulting from the transfer of a single electron from the aromatic molecule to a hole in the surface, probably located at a Lewis acid site. Bhaltacharya (6) measured charge transfer interaction energies of I complexes with anthracene and other hydrocarbons in CCl_4 and found that the charge transfer energy was not

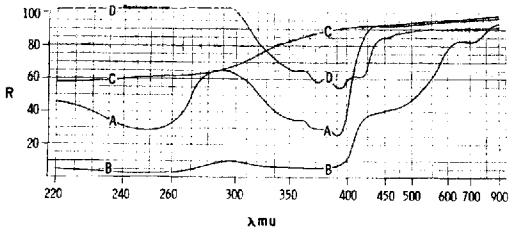

Fig. 1.—Diffuse reflectance spectra (DRS) of anthracene (100 mg.) and acidic alumina (3.50 Gm.). Key: A, control (physically mixed components); B, equilibrated sample; C, pure equilibrated acidic alumina, with no anthracene present; D, pure anthracene with no adjuvant present.

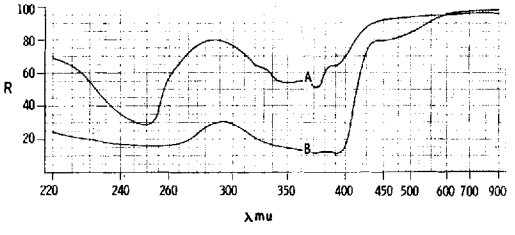

Fig. 2.—DRS of anthracene (100 mg.) and magnesium borate (2.00 Gm.). Key: A, control; B, sample.

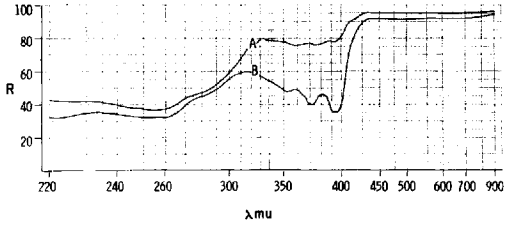

Fig. 3.—DRS of anthracene (100 mg.) and talc (2.00 Gm.). Key: A, control; B, sample.

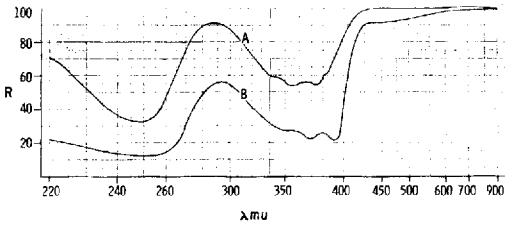

Fig. 4.—DRS of anthracene (100 mg.) and magnesium carbonate (2.00 Gm.). Key: A, control; B, sample.

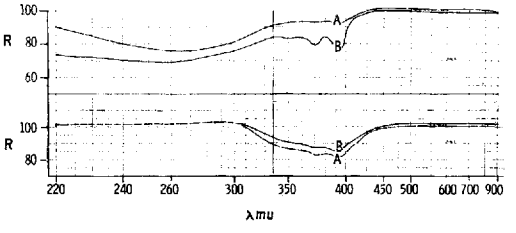

Fig. 5.—DRS of anthracene (100 mg.) and dibasic calcium phosphate (2.00 Gm.). Key: A, control; B, sample. (Top.) DRS of anthracene (100 mg.) and calcium carbonate (2.00 Gm.). Key: A, control; B, sample. (Bottom.)

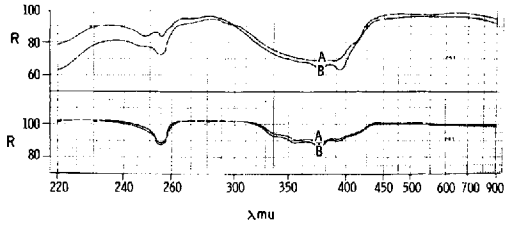

Fig. 6.—DRS of anthracene (50 mg.) and stearic acid (2.00 Gm.). Key: A, control; B, sample. (Top.) DRS of anthracene (200 mg.) and zinc stearate (0.750 Gm.). Key: A, control; B, sample. (Bottom.)

appreciably affected by the change in the dielectric constant of the medium, and, therefore, postulated that charge transfer must take place between the molecule, held together by forces other than electrostatic.

The adjuvants chosen for this study were selected on the basis of the metal fraction they contain or because of their usage in pharmaceutical formulation. Several of the adjuvants included in this study have also been investigated with respect to their effects on the absorption of various phenothiazine derivatives (7, 8).

This type of drug–adjuvant interaction, presented in Fig. 1, deals with the complex formation between anthracene and acid (anionotropic) alumina. It becomes apparent in examining this figure that Fig. 1,B, representing an equilibrated anthracene–alumina system, is significantly different from that of the physical mixture (1,A) and from the spectra of the individual components (1,C and 1,D). Upon interaction, a visual color change was evident; the physical mixture was white in color while the interacted sample acquired a reddish-tan hue. Along with the color change, a huge bathochromic shift is observed in the 400 mμ region along with a new shoulder formation and decrease in reflectance. It might also be pointed out that, in this system, the spectrum of the control is somewhat similar to that of pure anthracene, but the interacted sample loses some spectral fine structure in the region of 350–400 mμ. Furthermore, not only are significant spectral changes observed in the visible region, but a large change also occurs in the U.V. region of the spectrum. The absorbance peak observed at 290 mμ in the control is almost absent in the equilibrated sample, suggesting the complexity of this chemisorption phenomenon and the probable existence of a number of mechanisms. The individual spectrum of pure anthracene and pure alumina, in the region of 425–900 mμ, show no absorption while the interacted sample strongly absorbs in the visible region. The large bathochromic shift observed in the equilibrated sample occurs at a higher wavelength than that which would be produced by

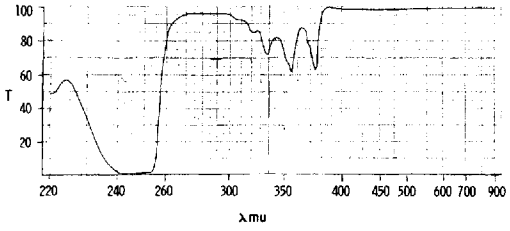

Fig. 7.—Transmittance spectrum of anthracene (5 mg./L.) in anhydrous methyl alcohol.

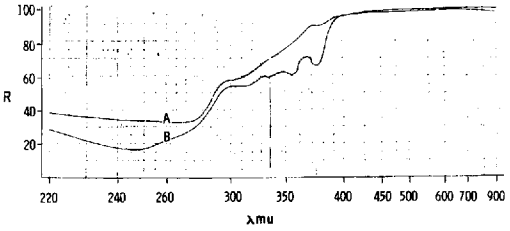

Fig. 10.—DRS of prednisone (100 mg.) and magnesium borate (2.00 Gm.). Key: A, control; B, sample.

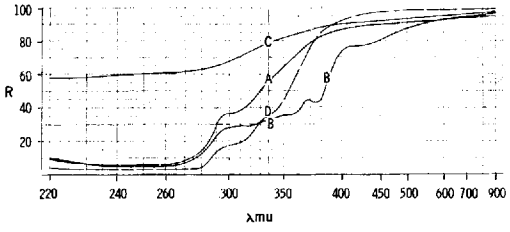

Fig. 8.—DRS of prednisone (100 mg.) and acidic alumina (3.50 Gm.). Key: A, control; B, sample; C, acidic alumina, 100%; D, prednisone, 100%.

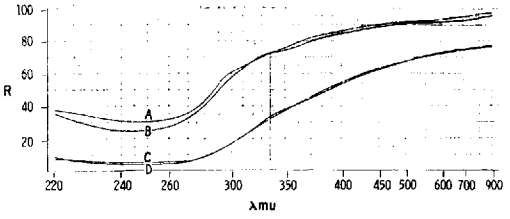

Fig. 11.—DRS of prednisone (100 mg.) with kaolin (2.00 Gm.) or with attapulgite (2.00 Gm.). Key: A, prednisone–kaolin control; B, prednisone–kaolin sample; C, prednisone–attapulgite control; D, prednisone–attapulgite sample.

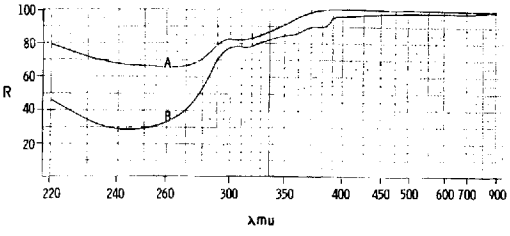

Fig. 9.—DRS of prednisone (100 mg.) and aluminum hydroxide (2.00 Gm.). Key: A, control; B, sample.

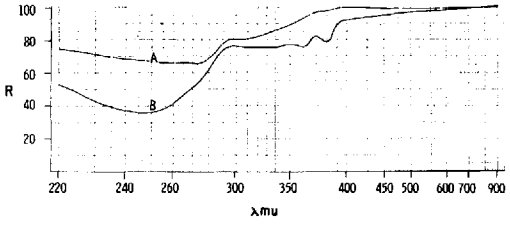

Fig. 12.—DRS of prednisone (100 mg.) and magnesium carbonate (2.00 Gm.). Key: A, control; B, sample.

a summation of the individual spectra of anthracene and alumina. Such a bathochromic shift along with the inability to elute the interacted anthracene sample with a large volume of water (1) further indicates the chemical nature of this strong interaction.

Although the spectra of an anthracene-basic alumina system are not shown due to space consideration, this system does exhibit similar spectral changes after equilibration, but to a lesser extent. Although a bathochromic shift and decreased reflectance were apparent, they were not as pronounced as the anthracene–acidic alumina system shown in Fig. 1. Since the shifts occur with both protophilic and protogenic excipients, it is suggested that anthracene may function either as an electron donor or acceptor, depending on the adjuvant available for interaction. Since greater shifts were observed in the acid alumina system, under the same experimental conditions, it may be reasoned that either less energy is required for the activation of the anthracene–acid alumina system or that fewer Lewis base sites were available for chemisorption with the anthracene. Similar changes were also observed when equilibrating anthracene with aluminum hydroxide. In this system, however, a white to orange visual color change was observed along with a slightly smaller shift in the visible region, but greater intensity increase in the area of 270–340 mμ.

In addition to the aluminum-containing systems mentioned above, a group of magnesium-containing adjuvants were also investigated. Results of magnesium trisilicate and magnesium hydroxide interactions have been previously reported (1). Figure 2 represents an anthracene–magnesium borate system. Here again, the usual bathochromic shift, loss of fine structure, and decreased reflectance associated with such an interaction, are found in the interacted sample. An anthracene–talc system may be found in Fig. 3. Talc, defined as native hydrous magnesium silicate, with a small portion of aluminum silicate, shows relatively little interaction affinity for anthracene, as seen in the small

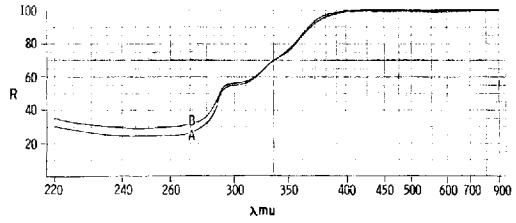

Fig. 13.—DRS of prednisone (100 mg.) and calcium carbonate (2.00 Gm.). Key: A, control; B, sample.

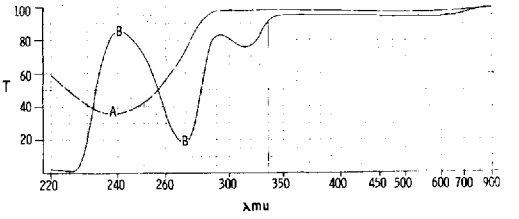

Fig. 16.—Transmittance spectra of prednisone and hydrochlorothiazide solutions. Key: A, spectrum of prednisone (10 mg./L.) in anhydrous methyl alcohol; B, spectrum of hydrochlorothiazide (10 mg./L.) in anhydrous methyl alcohol.

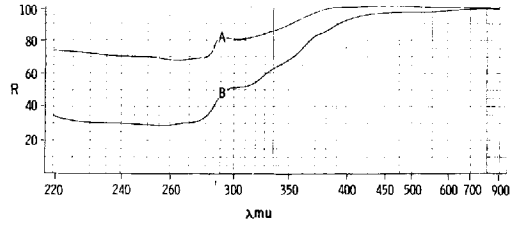

Fig. 14.—DRS of prednisone (200 mg.) and zinc stearate (1.00 Gm.). Key: A, control; B, sample.

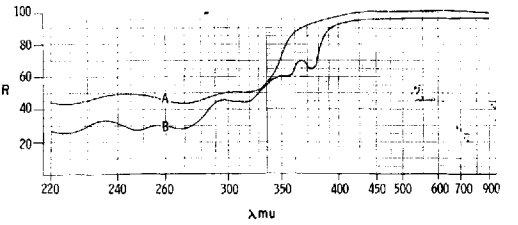

Fig. 17.—DRS of hydrochlorothiazide (100 mg.) and basic alumina (3.50 Gm.). Key: A, control; B, sample.

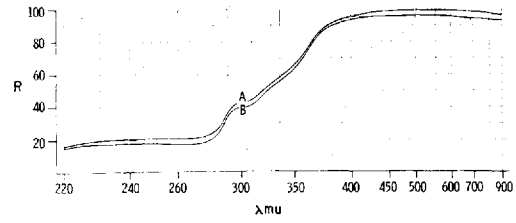

Fig. 15.—DRS of prednisone (100 mg.) and stearic acid (2.00 Gm.). Key: A, control; B, sample.

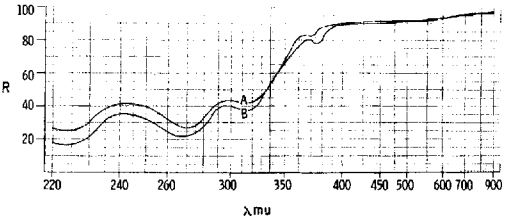

Fig. 18.—DRS of hydrochlorothiazide (100 mg.) and acidic alumina (3.50 Gm.). Key: A, control; B, sample.

spectral changes, both in the 220–300 mμ as well as in the 425–900 mμ regions. A larger change does occur, however, between 310–400 mμ. This change probably indicates some interaction of the metallic ion with the adsorbate since analogous changes were observed with attapulgite, which is hydrous magnesium aluminum silicate, and with kaolin which is hydrous aluminum silicate. The magnitude of anthracene–adjuvant change was found to be of the following order: kaolin > attapulgite > talc.

The difference in spectral changes of metal-containing anthracene–adjuvant systems may reside in the fact that although the magnesium or other ions may be present in talc and other metal-containing systems, they may be held tightly by the anionic fraction of the adjuvant and are, therefore, unavailable for interaction. This metal "attraction" difference exists between adjuvants since many surfaces are more saturated than others and the valency requirements of their surface atoms may be thought to be more fully satisfied by bonding with nearby atoms, therefore facilitating less chemisorption. Another cause for differences in saturation between metallic adjuvants may be the result of different amounts of hydration in adjuvant systems. For example, talc (primarily native hydrous magnesium silicate) may have a large portion of its active sites unavailable for charge transfer interaction since these sites are occupied by water molecules, resulting in the weaker electrostatic forces which may include hydrogen bonding.

An additional magnesium-containing system, found in Fig. 4, represents an anthracene–magnesium carbonate interaction. On equilibration, one again sees the usual bathochromic shift, along with decreased reflectance.

In addition to the aluminum and magnesium-containing adjuvants, anthracene interactions were also studied with calcium carbonate and dibasic calcium phosphate. The spectra of the anthracene–calcium carbonate system, shown in Fig. 5, indicate that the degree of interaction was minor, since the spectra of the equilibrated and nonequilibrated mixtures are comparable. The slight increased reflectance observed in curve 5,B (bottom) is attributed to the loss of small amounts of anthracene in the equilibrating procedure. The lack of any significant interaction with this calcium-containing adjuvant, as compared to the large changes observed in the magnesium and aluminum-containing systems,

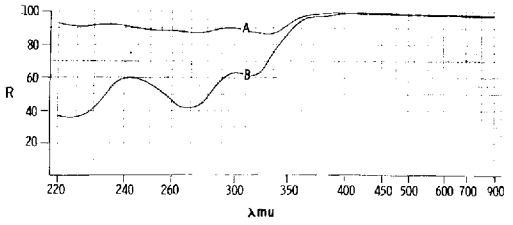

Fig. 19.—DRS of hydrochlorothiazide (100 mg.) and aluminum hydroxide (2.00 Gm.). Key: A, control; B, sample.

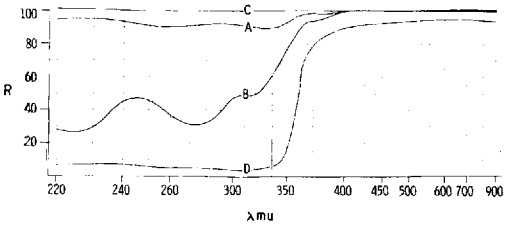

Fig. 20.—DRS of hydrochlorothiazide (100 mg.) and magnesium carbonate (2.00 Gm.). Key: A, control; B, sample; C, magnesium carbonate, 100%; D, hydrochlorothiazide, 100%.

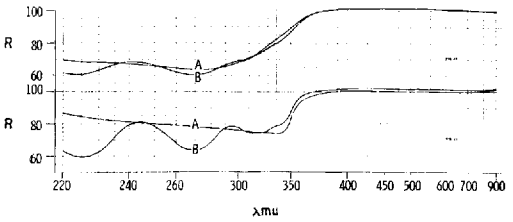

Fig. 21.—DRS of hydrochlorothiazide (100 mg.) and dibasic calcium phosphate (2.00 Gm.). Key: A, control; B, sample. (Top.) DRS of hydrochlorothiazide (100 mg.) and calcium carbonate (2.00 Gm.). Key: A, control; B, sample. (Bottom.)

suggests that the mechanism of paramount importance in this chemisorption process is one of chelation. This lack of calcium adjuvant–anthracene interaction is further illustrated in Fig. 5 (top), which again shows minor changes in the anthracene–$CaHPO_4$ system. However, since $CaHPO_4$ does show some decreased reflectance as compared to the $CaCO_3$ system, one may attribute this difference to proton site interactions, resulting from hydrogen-bond interaction rather than chelation. The lack of a color change in the calcium-containing adjuvant systems is in good agreement with the spectral data. As with the calcium-containing adjuvants, zinc stearate showed very little interaction tendency with anthracene, as illustrated in Fig. 6. Although other zinc-containing adjuvants were not studied, it is felt that the zinc ion would show low interaction tendencies with this anthracene system. It is further interesting to note that stearic acid itself shows no important interaction affinity for anthracene and the minor changes observed in the spectrum, Fig. 6, may be due to van der Waal or hydrogen-bond type of interactions.

With respect to the general mechanism of chemisorption, there is no specific agreement by what mechanism(s) this phenomenon proceeds. Weiss (9) suggested that all molecular complexes essentially have an ionic structure, B^+A^-. He points out that a low ionization potential for the base, B, and a high electron affinity for the Lewis acid, A, should give a stable complex. Here the color of molecular complexes, as in quinones or nitro compounds with unsaturated hydrocarbons, is described as being essentially of ionic character formed from the two components by an electron transfer from unsaturated hydrocarbon or its derivative (A), to the quinone or polynitro compound (B). Matsen and associates (10), in discussing charge transfer adsorption on metals, describe the metals as Lewis acids. In a similar manner, one might expect the unsaturated anthracene, due to its "basic" character, to transfer electrons to Al^{3+} or Mg^{2+} due to their acidic sites.

Mulliken (11) suggests that molecular complexes are a union of a Lewis acid (electron acceptor) and a Lewis base (electron donor) resulting in the formation of charge transfer complexes. Here, the electron of the adsorbate absorbs a quantum of radiation and is excited, not to a higher energy level of this molecule, but rather to one of the vacant high energy levels of the adsorbent. Therefore, in addition to absorption in the ground state (N), the molecule may combine to an excited state (E), resulting in an intense absorption band $\lambda N \rightarrow \lambda E$. This probability often accounts for the color changes observed when molecular complexes are formed. Similarly, in the anthracene–adjuvant systems presented in this communication, the large increase in intensity observed in the U.V. region (290 mμ), Fig. 1, may be attributed to a charge transfer complex between the Lewis base, anthracene, and the Lewis acid, Al^{3+}. Akamatu (12) has suggested, however, that in some anthracene chemisorption complexes, the metallic components transfer electrons to hydrocarbons, which in this case serve as acceptors rather than donors. This is probably the case when using the basic (cationotropic) alumina adsorbent discussed above.

It is interesting to compare Figs. 3, 4, and 6, containing anthracene equilibrated with magnesium carbonate, talc, and stearic acid, respectively; here bathochromic shifts and intensity differences also decrease respectively as one compares the three systems. These differences could be explained by

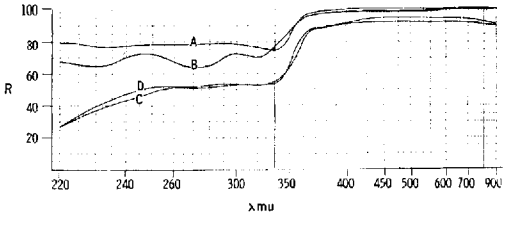

Fig. 22.—DRS of hydrochlorothiazide with zinc stearate or stearic acid. Key: A, hydrochlorothiazide (200 mg.) zinc stearate (0.750 Gm.) control; B, sample; C, hydrochlorothiazide (100 mg.)—stearic acid (2.00 Gm.) control; D, sample.

stating that the larger shifts are related to donor–acceptor forces which represent a charge transfer interaction along with the weaker hydrogen bonding, while in the talc and stearic acid, the weaker electrostatic forces predominate. It is also probable that some small spectral differences do result from regular reflection (1) and particle-size variations.

On further examination of the anthracene system, it is observed that aqueous equilibration of the anthracene–adjuvant mixture (Fig. 1,B) results in the disappearance of the band maxima at 290 mμ along with a loss of fine vibrational structure in the 350–400 mμ region. This band and fine structure also exist in anthracene solution spectra as seen in Fig. 7, as well as in the anthracene–adjuvant unequilibrated physical mixture (Fig. 1,A). In contrast to such a change, the equilibrated oxytetracycline–adjuvant system previously reported (1), show the formation of a new reflectance band at 320 mμ. It is further interesting to note that the maximum absorbance band is also present in transmittance spectra of oxytetracycline solutions but absent in the unequilibrated oxytetracycline–adjuvant mixture. Although no explanation is offered at this time, it nevertheless does illustrate the complexity of these interactions and the probability of a change of mechanism involved.

Based on the spectral data and visual color changes presented and already discussed, it is highly likely that the major mechanism involved in this anthracene chemisorption interaction, with various type adjuvants, is one of chelation since the metallic ions do show a specificity with respect to the degree of interaction. For example, aluminum and magnesium interactions were significantly larger than those observed with calcium and zinc-containing adjuvants. It is, therefore, difficult to make generalizations regarding such interactions in that the nature and the degree of interaction will vary with the type of drug and adjuvant employed.

PREDNISONE–ADJUVANT SYSTEMS

Since a number of reports have appeared in the literature dealing with the possible inactivation of prednisone by excipient-type materials used in solid dosage forms (13, 14) and since prednisone represents a polyfunctional steroidal molecule used in milligram quantities in therapeutics, an investigation of this drug with various adjuvants was undertaken. Although no color change was observed on equilibration of prednisone with acidic alumina, Fig. 8, an examination of the spectral data does indicate that prednisone undergoes a significant interaction. In addition to the usual bathochromic shifts observed, the presence of the equilibrated prednisone–adjuvant spectrum at a higher wavelength than that of the physical mixture or the pure prednisone, further supports this high degree of reactivity. Equilibration of prednisone with basic alumina results in similar spectral changes, but to a lesser extent.

A comparison of prednisone–aluminum hydroxide interaction, Fig. 9, with the above alumina system clearly illustrates the spectral changes possible with the use of different adjuvants. In an aluminum hydroxide system, no significant bathochromic shifts are observed, but a large hyperchromic change occurs in the U.V. region, suggesting the variety of mechanisms possible in such interactions.

This is further observed in magnesium-containing adjuvants, as illustrated in Fig. 10. In this prednisone–magnesium borate system, equilibration facilitates small intensity changes in the U.V. region, along with a new band formation between 350–400 mμ and a smaller bathochromic shift. The use of magnesium trisilicate as the adjuvant results in comparable spectral changes, accompanied by a larger intensity increase in the U.V. region.

Furthermore, even though ions may be present in such adsorbents as talc, attapulgite, and kaolin, their interaction tendencies with prednisone are minor, as illustrated in Fig. 11. As was previously pointed out in the anthracene–adjuvant systems, the degree of saturation of individual adjuvants varies, resulting in different reaction potentials. This difference in availability or reaction potential of these ions is shown in the prednisone–magnesium carbonate interaction, illustrated in Fig. 12. Here again, large intensity and bathochromic changes in the U.V. and near the U.V. region are observed.

A comparison of prednisone–calcium carbonate equilibration, Fig. 13, indicates a lack of interaction of this drug with calcium, as seen from the minor intensity changes in the U.V. region. Equilibration of prednisone with $CaHPO_4$ produced spectral changes of similar nature to the calcium carbonate system, except for a slightly greater hyperchromic effect. This change in reactivity between $CaHPO_4$ and $CaCO_3$ may again be attributed to proton site interactions possible in the $CaHPO_4$ system.

In addition to aluminum, magnesium, and calcium-containing adjuvants, prednisone was also equilibrated with zinc stearate. Spectral data presented in Fig. 14 indicate a strong reactivity of prednisone for this adjuvant. In the previously discussed anthracene system, however, the same adjuvant showed very little interaction tendency. This difference in reactivity of prednisone and anthracene for the zinc stearate adjuvant, along with the lack of any interaction of prednisone with stearic acid, shown in Fig. 15, illustrates the chemical specificity of these charge transfer reactions.

The above information presented on these prednisone–adjuvant systems again indicates that although no visible color differences are observed on equilibration, large spectral changes do suggest strong interactions with various characteristics, depending on the adjuvant studied. Although the control and equilibrated sample's reflectance spectra somewhat resemble the prednisone transmittance spectrum in solution (Fig. 16,A) solid–solid interaction often facilitates the elucidation of new vibrational structure in the near U.V. region, not present in the prednisone solution spectra. Furthermore, the spectral changes of prednisone complexes differ from anthracene systems since aluminum-containing adjuvants appear to facilitate a greater degree of interaction with anthracene, while zinc ions play an important role in prednisone–adjuvant chemisorption.

HYDROCHLOROTHIAZIDE–ADJUVANT SYSTEMS

This medicinal agent has been selected for the study of these drug–adjuvant interactions due to its unique polyfunctional chemical nature and because of its widespread use as a therapeutic agent.

As in the prednisone–adjuvant interactions, although no color change was observed on equilibration of hydrochlorothiazide with basic alumina, an examination of Fig. 17 indicates that this system does undergo important interaction.

A somewhat different spectral graph was obtained on equilibrating hydrochlorothiazide with acidic alumina, Fig. 18, as compared to that of the basic alumina, since the usual bathochromic shift was absent and an intensity change of only 5% was observed. A possible explanation for this lack of reactivity in the hydrochlorothiazide–acid alumina system may be due to the presence of stronger electron-donating sites in hydrochlorothiazide, represented by the dioxide or sulfamoyl groups. Since hydrochlorothiazide and acidic alumina both function as Lewis bases, their lack of significant interaction, Fig. 18, is reasonable. However, hydrochlorothiazide does react strongly with basic alumina (cationotropic) or aluminum hydroxide, Fig. 19, which function as Lewis acids.

In addition to the aluminum-containing adjuvants, hydrochlorothiazide was also equilibrated with a group of magnesium-containing excipients. Figure 20, B, dealing with a hydrochlorothiazide–magnesium carbonate interaction, indicates that although no visible color change was observed in this, or any other hydrochlorothiazide system investigated, large intensity changes are seen in the U.V. region; these hyperchromic changes are also accompanied by important shoulder formation, not found in the pure hydrochlorothiazide reflectance spectrum (Fig. 20,D), in the physical drug–adjuvant control (Fig. 20,A), in the pure adjuvant's spectrum (Fig. 20,C), but present in the solution transmittance spectrum (Fig. 16,B). Similar spectral changes were also seen on equilibrating hydrochlorothiazide with magnesium borate or magnesium trisilicate adjuvants.

In contrast to these adjuvants, talc, attapulgite, or kaolin produced only minor intensity changes on equilibration with hydrochlorothiazide, again indicating minor interaction tendency for this drug. Hydrochlorothiazide shows different spectral changes with calcium adjuvant equilibration, as seen in Fig. 21. An examination of this figure indicates that equilibration of hydrochlorothiazide with $CaCO_3$ facilitates the formation of new bands, although the usual bathochromic shift seen with aluminum and magnesium systems was absent. This drug was also equilibrated with dibasic calcium phosphate. In the anthracene and prednisone systems, $CaHPO_4$, functioning as the adjuvant, showed somewhat greater interaction tendencies than observed with calcium carbonate. However, the interaction of $CaCO_3$ in the hydrochlorothiazide system was found to be in reverse, Fig. 21, indicating the $CaCO_3$ functions as a stronger Lewis acid (electron acceptor) in this system.

The interaction data presented and discussed indicate that a donor–acceptor chelation mechanism is operative in these systems and is further supported in the zinc stearate, stearic acid interaction differences with hydrochlorothiazide, as shown in Fig. 22, again pointed out the greater interaction tendency of the metal-containing adjuvants.

CONCLUSION

Chemisorption interaction data have been presented for anthracene, prednisone, and hydrochlorothiazide with a number of metallic and nonmetallic adjuvant systems. Although minor spectral contributions may be attributed to van der Waal and hydrogen bond-type interactions, particularly in nonmetallic adjuvants studied, the large bathochromic and hyperchromic spectral changes observed on equilibration are primarily the result of strong charge transfer chelation interactions.

Results indicate that anthracene and prednisone function mainly as Lewis acids in alumina systems, while hydrochlorothiazide primarily exhibits Lewis base properties. The interactions observed are, therefore, highly dependent on the chemical properties of the adsorbate and the adsorbent.

Although these surface chemisorption phenomena exist as a unimolecular film and may be of no great consequence when physically adsorbed multilayers of the drug exist, particularly when the ratio of the therapeutic agent to adjuvant is high, they do become significant when the drug–adjuvant ratio is low. In such systems, where the medicinal agent is primarily chemisorbed as a unimolecular layer, one would expect to find large deviation in dissolution rates and blood levels in biological systems. It is of significant interest to point out here that one cannot overlook the distinct possibility of the excipient itself existing as a chemisorbed layer covering the surface of the drug resulting in similar alterations of the physical or biochemical behavior of the medicament in dosage forms where the drug–adjuvant ratios are high. Diffuse reflectance spectroscopy therefore provides a simple means of studying the possible existence of such interactions in solid dosage forms.

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