The effect of the presence of benzhydrol on the U.S.P. method for the assay of ergotamine, ergonovine, and dihydroergotamine is depicted in Fig. 2. In the absence of benzhydrol, ergonovine and ergotamine gave the same degree of color (and exhibited identical visible spectra). However, ergotamine was more reactive with benzhydrol than ergonovine since less color was formed with any given amount of benzhydrol. Thus, using a molar ratio of benzhydrol to ergot alkaloid of 3.5:1, only 30% of the usual color was developed with ergotamine, 44% with ergonovine, and 51% with dihydroergotamine. The interference was less in ethanolic hydrochloric acid, with 62, 69, and 79%, respectively, of the color being developed. As previously noted by Alexander (2), the relative intensity of the peaks at 610 and 575 mμ for ergonovine and ergotamine changes with increasing amounts of benzhydrol, and this feature may be utilized for estimating the amount of benzhydrol present.

Thin-layer chromatographic examination of the products of the reaction of five ergot alkaloids with benzhydrol showed that two reactions occurred. On treatment with acid, each ergot alkaloid through isomerization had given rise to three main compounds, each of which developed a blue color when sprayed with *p*-DMAB reagent. In the presence of benzhydrol, however, each of these isomerized alkaloids gave rise to a new product which no longer gave a blue color with the *p*-DMAB spray. The color observed was orange, of the same hue observed for the skatole–benzhydrol condensation product (VI). These results would therefore indicate that the interference shown by benzhydrol with ergot alkaloids is the same as that with skatole.

Although benzhydrol may arise from hydrolysis of cyclizine (1-diphenylmethyl-4-methylpiperazine) which is often formulated with ergot alkaloids, the more likely source in pharmaceutical dosage forms is the hydrolysis of benzhydryl chloride used in its manufacture. Formation of benzhydrol from cyclizine appears to be negligible under normal conditions, but increased temperature and acidity caused an increase in the rate of hydrolysis, as expected. The drastic conditions required for breakdown would therefore indicate that hydrolysis of cyclizine is not likely to occur within the tablet during storage and that benzhydrol may have been present as an impurity during synthesis of the drug. Indeed, Alexander (2) has examined several preparations of ergotamine with cyclizine and found no benzhydrol. Similarly, Caws and Lawrence (1) found benzhydrol in only certain instances. However, some benzhydrol could be formed during the assay procedure under strongly acidic conditions if the reaction medium is not kept at a low temperature, and thus affect the accuracy of the determinations.

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Diffuse Reflectance Studies of Solid–Solid Interactions

Interactions of Oxytetracycline, Phenothiazine, Anthracene, and Salicylic Acid with Various Adjuvants

By JOHN L. LACH and MICHAEL BORNSTEIN

Data are presented for oxytetracycline-, anthracene-, phenothiazine-, and salicylic acid-adjuvant systems indicating significant interactions in equilibrated samples and those prepared by compression techniques studied by diffuse reflectance spectroscopy. Spectral changes, both in the visible and ultraviolet regions, along with color changes, substantiate these interactions. Although the mechanism of these interactions is not fully understood, data presented indicate that these complexes are of the donor-acceptor variety.

ALTHOUGH relatively little work has been done in the field of diffuse reflectance, it is, nevertheless, a useful tool for the investigation of optical properties of adsorbed molecules. Here a beam of light penetrating into the sample, which is usually a finely divided powdered solid material, is scattered in many directions, is partially absorbed, and finally re-emerges to the surface. The light emerging from the sample is then

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collected by an integrated reflecting sphere and is focused onto a detector. This process is called diffuse in contrast to regular reflectance observed from a plane mirror-like surface where no absorbance takes place.

According to Kortum (1, 2) diffuse reflectance spectra (DRS) are greatly altered from transmittance spectra in solution. In the former, the bands are broader and less intense. Such changes have been attributed to effects of regular reflectance from small crystals altering the diffuse reflectance, since particle size has been shown to influence the regular reflectance.

A number of reflectance studies dealing with the adsorption of one solid onto another appear in the literature, but no reflectance work has been found directly related to pharmaceutical complexes. Zeitlin and co-workers (3–5) observed pronounced shifts in the spectra of Michler's ketone when an active adsorbent, such as alumina or silica gel, was substituted for the inactive diluent. Griffiths (6) and Kortum (7, 8) have studied diffuse reflectance spectra of iodide and other systems. Reflectance-fluorescence spectra using anthracene and related compounds have been investigated by Van Duuren (9).

The authors became interested in this work because very little attention has been given to this phenomenon although it has been recognized that many medicinal formulations in solid dosage forms may undergo interaction due to the adsorption of the active ingredient on the "inert material." This is partly because the methods employed to study these weak interactions did not readily lend themselves to the solid state. Using diffuse reflectance techniques, the authors were able to show clearly that such interactions do exist in the solid state and that, although they vary in variety and intensity, they may have significant effects with respect to the absorbability and availability of the medicinal agent in biological systems. The reason for studying a tetracycline derivative was due in part to a number of controversial articles appearing as references in a review article by Wagner (10) discussing the effects of adjuvants on adsorption on medicinal agents (11–14).

EXPERIMENTAL

Reagents

Recrystallized oxytetracycline (Pfizer & Co.), m.p. 182° dec.; alcohol recrystallized anthracene, m.p. 218°; toluene recrystallized phenothiazine N.F., m.p. 180°; recrystallized salicylic acid U.S.P., m.p. 159°; oxytetracycline HCl (Pfizer & Co.); magnesium trisilicate, magnesium oxide, magnesium hydroxide, activated (basic) alumina (Woelm); chloroform; 0.1 *N* NaOH; 0.1 *N* HCl.

Apparatus

All diffuse reflectance spectra (DRS) were measured on a Beckman DU spectrophotometer equipped with a tungsten and hydrogen lamp and a photomultiplier attachment to give the highest possible sensitivity. The diffuse reflectance attachment held two plastic, black-coated cells with a center circular hole 1 in. in diameter and $^1/_8$ in. deep. The powders were packed into cells (one being used for the $MgCO_3$ reference standard) with the aid of microscope slides. The glass slides were removed prior to reflectance readings. Variations in the slit width ranged from 0.04–1.8 mm. The solution spectra were obtained with the aid of a Beckman DK II spectrophotometer. An hydraulic bench press (Pasadena Hydraulics, Inc.) and a Stokes model E tablet press were used in the compression of powders. A constant-temperature water bath, set at 30 ± 0.5°, with rotating spindles, was used for the equilibration. Fifty- and 150-ml. vials with caps sealed with Parafilm (Marathon Co.) held the equilibrated samples. When chloroform was the equilibration medium, aluminum foil (Alcoa Wrap) was inserted between the vial and the cap to prevent leakage. A vacuum oven (Freas-Precision Scientific, model No. 524) was employed for the drying procedure.

Procedure

Equilibration Technique.—The general method of enacting these interactions involves equilibrating a weighed amount of adsorbent (5.0 Gm.) for 24 hr. with 75 ml. of distilled water using 150-ml. vials covered with Parafilm and capped. After equilibration, the dispersion medium is removed by vacuum at 115° for 0.5 hr.

Preparation of the Sample.—A specified amount (15–100 mg.) of active ingredient (oxytetracycline, oxytetracycline HCl, anthracene, phenothiazine, or salicylic acid) is weighed for every 2.00 Gm. of adsorbent used (unless otherwise indicated). The powders are then placed in a 50-ml. vial and 25 ml. of water is added as the dispersion medium (except in nonaqueous equilibrium which employs chloroform). The bottle is covered with Parafilm and capped. Then the bottle is equilibrated for 24 hr. (unless otherwise indicated) at 30 ± 0.5° in order to effect interaction. After equilibration, the suspension is filtered, and the powder is dried in a vacuum oven. The DRS of this sample is then measured using $MgCO_3$ as the reference standard.

Preparation of the Control.—Two grams of the previously equilibrated adsorbent is physically mixed with an indicated amount of dried active ingredient, using a mortar and pestle for the trituration. The DRS of this control is then measured using $MgCO_3$ as the reference standard.

Special Techniques

Washing the Sample.—The sample is equilibrated by the general procedure, filtered, and dried, and the DRS is taken. This powder is then placed in a 0 size Büchner funnel, and a specified amount of liquid (water or methanol) is added which is continuously being removed by filtration (this process removes some excess active ingredient adhering physically to the adsorbent while the chemically adsorbed material is not washed away). The resultant powder is then dried, and its DRS is measured.

Nonaqueous Equilibration.—In order to show that the liquid dispersion medium plays a minor role in this donor-acceptor solid–solid interaction, chloroform is substituted for distilled water as the dispersion medium; after equilibration, the solvent is removed by evaporation at room temperature in a vacuum desiccator. The DRS of this powder is then measured against a $MgCO_3$ reference standard.

Interaction by Compression.—Four grams of pure unequilibrated adsorbent under investigation was triturated with a specified amount of active ingredient with the aid of a mortar and pestle. Part of this physical mixture represents the control, while the remaining portion of powder is used in the preparation of the sample. The latter is prepared by compressing the physically mixed powder by the application of varying gauged amounts of pressures (5000–35,000 p.s.i.) using a Pasadena hydraulic bench press with a specially designed $^3/_4$-in. punch and dye or by using a Stokes model E tablet press. The tablet resulting from a 3-min. compression is then either used directly as the sample (in the case where the Stokes press is used) or, if the material tends to crack, the tablet may be crushed with a mortar and pestle, and the sample is read in the form of a powder. The DRS in tablet or powder form, of the compressed sample, give equivalent results within the limits of experimental error (approximately ±2%).

Transmittance Spectra.—In this technique the active ingredient is dissolved in the appropriate solvent, and the spectrum is obtained on a Beckman DK II spectrophotometer using quartz cells.

RESULTS AND DISCUSSION

Donor-Acceptor Solid–Solid Interactions Using Liquid Dispersion Media.—Since the theory and mechanistic aspects of solid–solid interactions are still controversial, in part because of the relatively small attention paid to this chemical phenomenon, the interpretation of data reported in this preliminary communication is of a qualitative nature. As additional information concerning this solid–solid interaction becomes available, quantitization of these data will be permissible. However, the authors do feel that the conformation and elucidation of such adjuvant–drug interaction are of pharmaceutical importance. Such an adjuvant–drug interaction is presented in Fig. 1, dealing with the complex formation between oxytetracycline and magnesium trisilicate. An examination of this figure shows that spectrum B, which represents an equilibrated oxytetracycline–magnesium trisilicate system, is significantly different from that of the physical mixture of the two components (Fig. 1, A, control) and also from the spectra of the individual components (Fig. 1, C and D). Physical evidence of this interaction was also manifested by color changes. The equilibrated mixture was straw yellow, while the physical mixture (consisting of a triturate of the individual components that had been equilibrated and dried prior to mechanical mixing) was white or faintly yellow. This color change correlates well, in that in an examination of the visible spectrum in the area of 400–700 mμ, a bathochromic shift, a new shoulder formation, as well as decreased reflectance were observed. This is strongly indicative of a chemical interaction as compared to a physical type. It was also observed that reflectance is decreased in the ultraviolet region which is accompanied by new band formation with a $\lambda_{max.}$ of 315 mμ. This new band formation in the near ultraviolet region may be explained as an interaction of the adsorbent with oxytetracycline where the adsorbent facilitates the clarification of an already existing peak in this region, or it may represent the actual reflectance spectrum of a film of the drug adsorbed onto the surface of the magnesium trisilicate adsorbent This is somewhat suggested by Fig. 2, A, where the transmittance curve of oxytetracycline in basic medium shows that the $\lambda_{max.}$ at 320 mμ lies in the same region in which the authors obtain new band formation in the solid state. It should be pointed out that the reflectance spectrum of oxytetracycline as seen in the solid control (Fig. 1, A) does not show absorbance or the characteristic maximum at this wavelength. However, after equilibration of this control, the formation of a band at this wavelength is evident, which is indicative of some type of interaction. It seems likely that chemisorption is operative in this reaction since spectral changes due to physical adsorption involving van der Waals forces or hydrogen bonding

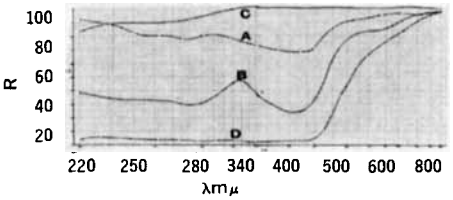

Fig. 1.– Diffuse reflectance spectra (DRS) of oxytetracycline (60 mg.) and magnesium trisilicate (2.00 Gm.). Key: A, control (physically mixed components); B, equilibrated sample; C, pure equilibrated magnesium trisilicate with no drug present; D, pure oxytetracycline with no adjuvant present.

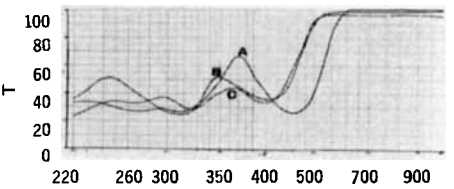

Fig. 2.—Transmittance spectra of aqueous solutions of oxytetracycline (17 mcg./ml.) in various solvents. Key: A, in 0.1 *N* NaOH solution; B, in 0.1 *N* HCl solution; C, in distilled water.

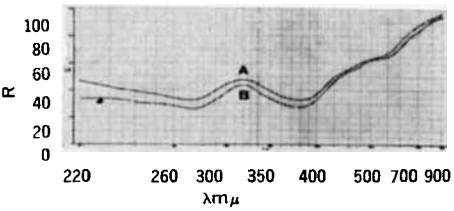

Fig. 3.—DRS of oxytetracycline (50 mg.) and magnesium trisilicate (2.00 Gm.) equilibrated for 12 hr., filtered, vacuum dried at 40° for 0.5 hr. (A), and washed with 200 ml. of anhydrous methyl alcohol, filtered, dried for 0.5 hr. at 115° (B). Key: A, unwashed sample; B, washed sample.

usually involve only minor shifts in the order of 5–10 mμ. In physical adsorption no chemical bonds are formed or broken, and the nature of the adsorbate is therefore unchanged. In chemical adsorption, however, the adsorbate does undergo chemical change, resulting in the dissociation of the molecule into independent fragments. This physical mixture, representing the control, can be compared to a pellet of pure KBr which is nonabsorbing in the I.R. region and in essence can be described as a preparation consisting of a series of holes. Here all the light is transparent and is therefore transmitted through these holes. However, after equilibration, a thorough dispersion of the sample is obtained resulting in a plugging of these holes with the adsorbate (oxytetracycline) as a result of chemical interaction. In this equilibrated mixture therefore, light no longer is totally transmitted; the result is a significant alteration of the spectrum as compared to that of the control. Consequently, the phenomenon of chemisorption may be of paramount importance in this interaction.

With respect to these interactions, there is no general agreement in the work that is reported as to what mechanisms chemisorption might proceed by, *i.e.*, $\pi \rightarrow \pi^*$ transitions, chelation, ionic acid–base interaction, carbonium ion mechanism, or charge transfer. It seems possible that each of the three main types of chemical bond: ionic, covalent, and coionic (charge transfer) may be formed in chemisorption (15).

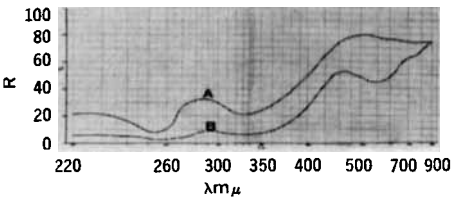

Fig. 4.—DRS of phenothiazine (100 mg.) and magnesium hydroxide (2.00 Gm.). Key: A, control; B, sample equilibrated for 12 hr.

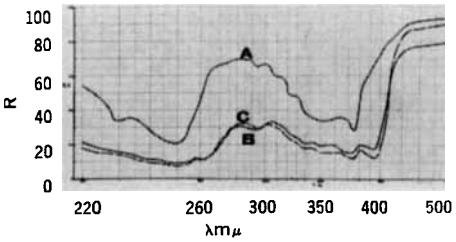

Fig. 5.—DRS of anthracene (100 mg.) and magnesium hydroxide (2.00 Gm.). Key: A, control; B, sample, equilibrated for 12 hr.; C, sample (B) washed with 1000 ml. of distilled water, dried, and the DRS read.

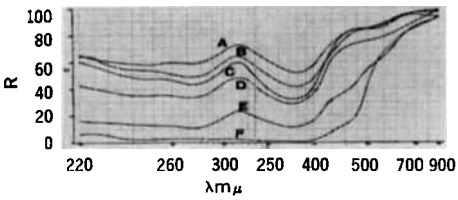

Fig. 6.—DRS showing the effects of varying oxytetracycline concentrations in equilibrated samples using 2.00 Gm. of magnesium trisilicate as the adsorbent. Key: A, 5 mg.; B, 15 mg.; C, 30 mg.; D, 60 mg.; E, 200 mg.; F, 2.00 Gm.

To elucidate more clearly the mechanisms involved in the oxytetracycline–adjuvant systems, aqueous spectra of oxytetracycline were prepared in protophilic (A), protogenic (B), and amphiprotic (C) solvents and are illustrated in Fig. 2. A plot of the transmittance against wavelength shows a maximum at 320 mμ and a minimum at 375 mμ for oxytetracycline in basic media. However, in acid media the weakly defined maximum is at 298 mμ, while the minimum occurs at 350 mμ. A comparison of the three spectra in the various solvents clearly illustrates the inconsistency of oxytetracycline transmittance curves. These spectral changes are, however, consistent in view of the multiplicity of functional groups present in the oxytetracycline molecule and the ability of the molecule to undergo acid–base interaction representing donor-acceptor (D–A) mechanisms. Since spectral changes in aqueous systems with acids and bases in solution are due to ionization, these are not comparable to interactions involved in solid–solid systems where ionization is negligible. However, in the solid–solid systems, the D–A theory is still applicable (16). For example, it was found that equilibrium of oxytetracycline and magnesium trisilicate in a nonaqueous chloroform media did not hinder this interaction. Bathochromic and hyperconjugative shifts obtained are comparable to those found with aqueous equilibrium of these insoluble materials.

Again, it is interesting to point out that spectral changes observed in the equilibration of soluble oxytetracycline hydrochloride with insoluble magnesium trisilicate are comparable to that obtained for the insoluble oxytetracycline free base with the same adjuvant. The removal of the oxytetracycline species from solution, in the formation of this complex, is indicative of the fact that the forces involved in the chemisorption process are greater than those forces involved in the formation of the soluble oxytetracycline HCl salt. Again, visual evidence of interaction was observed by the disappearance of the yellow color from the equilibrated filtrate (due to the soluble oxytetracycline hydrochloride salt), while the adsorbent (filtered material) concurrently acquired a straw-brown color. Attempts to elute the oxytetracycline from a water-equilibrated, vacuum-dried sample of an oxytetracycline–magnesium trisilicate complex with anhydrous methyl alcohol in which the oxytetracycline is quite soluble (Fig. 3) produced only minor changes in the spectral characteristics, indicating the strength and the high degree of interaction.

A comparison of the spectral data in Figs. 1 and 2 illustrates that a D–A mechanism or charge-transfer phenomenon is operative since one does find large bathochromic and hyperconjugative changes along with variations in color in the visible diffuse reflectance region of the oxytetracycline–adjuvant system, as compared to the physical mixtures. It is interesting to note that similarities do exist between the spectrum of oxytetracycline in basic solution (Fig. 2, A) and that of the oxytetracycline with the basic magnesium trisilicate (Fig. 1, B').

With respect to further investigation of the D–A mechanism, phenothiazine and anthracene systems equilibrated with magnesium hydroxide as the adjuvant (Figs. 4 and 5) also exhibit large shifts in the visible and ultraviolet regions. As was observed in other systems studied, a significant color change was also seen in the phenothiazine–magnesium hydroxide system indicative of a charge-transfer mechanism.

Concentration Effects.—The effect of varying concentrations of oxytetracycline on a fixed amount of adjuvant under investigation was studied in order to demonstrate that the decreased reflectances observed in the equilibrated samples were due primarily to chemisorption or complex formation. The data presented in Fig. 6 indicate that, with increased concentration, one initially obtains more interaction, as evidenced by an enlargement of the band at 315 mμ. After a maximum concentration is exceeded, however, it is seen that, although the reflectance of the equilibrated sample decreased somewhat with concentration, the clarity and definition of this band weakens. A concentration of oxytetracycline is eventually reached where the spectra of pure oxytetracycline (Fig. 1, D) and that of the sample (Fig. 6, F) are comparable. Data indicate here that the active sites of the adsorbent have undergone maximum interaction at a concentration of approximately 30 mg. of oxytetracycline per 2.00 Gm. of adsorbent, as evidenced by maximal reflectance changes and maximal shifts. Beyond this optimum drug concentration, however, further addition of oxytetracycline to the system results in physical adsorption onto the surface of the complex, as indicated by smaller shifts of reflectance as well as decreased band size with a limit approaching the spectrum of pure oxytetracycline (Fig. 1, D). A more detailed explanation of such a phenomenon is given by Trapnell (17).

The large spectral changes observed in the oxytetracycline–magnesium trisilicate system are certainly indicative of chemisorption since this interaction is due to forces other than those found in the van der Waals or hydrogen-bond type of interaction. As we have previously mentioned, spectral changes in the physical type of adsorption are in the order of 5–10 mμ. This type of interaction is illustrated in Fig. 7, where a salicylic acid–magnesium trisilicate system was interacted in a manner similar to that described for the oxytetracycline–magnesium trisilicate system. An examination of these spectra shows that no significant changes are obtained, except for a slight shift of the minimum to approximately 10 mμ. Along with the small bathochromic shift from 305 to 315 mμ, it is also found that the equilibrated sample exhibits increased reflectance resulting from the removal of part of the salicylic acid in the process of filtration prior to analysis of the sample. These results substantiate the data of Higuchi and Lach (18) in their study of weak salicylic acid complexes in solution. Additional evidence supporting this physical interaction in the salicylic acid–magnesium trisilicate system is presented in Fig. 8, which points out the fact that salicylic acid is easily removed from the magnesium oxide adsorbent by elution of the sample with water. This graph also shows a hypsochromic shift as well as a hypochromic change of the salicylic acid spectrum after washing. The net effect of washing this interacted sample is to obtain a spectrum which approaches that of the control. Equivalent results were obtained upon washing the equilibrated salicylic acid–magnesium trisilicate sample shown in Fig. 7, B, except that this magnesium trisilicate-containing system seems to exhibit a weaker retention capacity for the salicylic acid; subsequently, all of the drug is eluted and the spectrum approaches a reflectance of infinity after being washed. It is interesting to point out here that the oxytetracycline and anthracene systems (Figs. 3 and 5) did not demonstrate this reversible effect with elution, indicating a higher degree of interaction.

Oxytetracycline-Activated Alumina Systems.—Since a considerable amount of information is available in the literature dealing with activated alumina, it was of interest to us, therefore, to study the interaction of oxytetracycline with this adsorbent. Data involving the interaction of oxytetracycline with activated basic alumina are presented

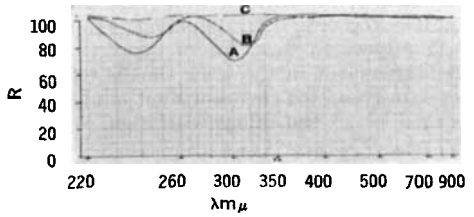

Fig. 7.—DRS of salicylic acid (30 mg.) and magnesium trisilicate (2.00 Gm.). Key: A, control; B, equilibrated sample; C, sample washed with 250 ml. of distilled water.

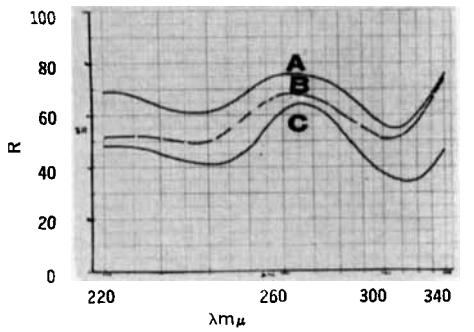

Fig. 8.—DRS showing the effects of aqueous washing of an equilibrated, dried sample of salicylic acid (25 mg.) and magnesium oxide (1.975 Gm.). Key: A, sample washed with 800 ml. of distilled water after filtering the water used as the dispersion media; B, control; C, equilibrated sample, filtered, and dried without washing.

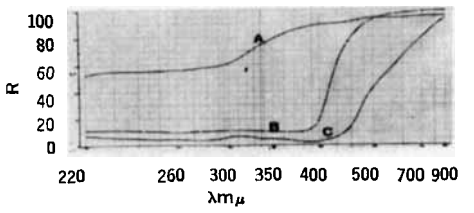

Fig. 9.—DRS of insoluble oxytetracycline (100 mg.) and basic chromatographic activated alumina (3.50 Gm.) using aqueous dispersion media. Key: A, pure equilibrated alumina without the presence of drug; B, control; C, equilibrated sample.

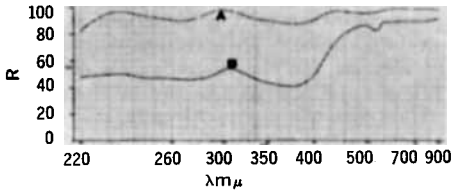

Fig. 10.—DRS showing the effects of compression (with a Stokes model E tablet press) on an unequilibrated mixture of oxytetracycline (10 mg.) and magnesium trisilicate (2.00 Gm.). Key: A, control (physical mixture); B, sample (compressed for 3 min.).

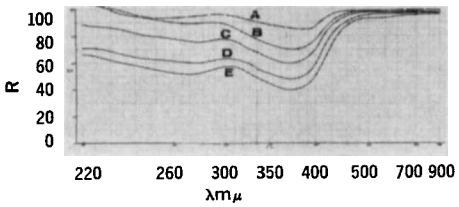

Fig. 11.—DRS showing the effects of varying compression pressures (with a Beckman hydraulic press using a specially designed punch and dye) on an unequilibrated mixture of oxytetracycline (20 mg.) and magnesium trisilicate (2.00 Gm.). Key: A, control (physical uncompressed mixture); B, 5000 p.s.i.; C, 10,000 p.s.i.; D, 20,000 p.s.i.; E, 30,000 p.s.i.

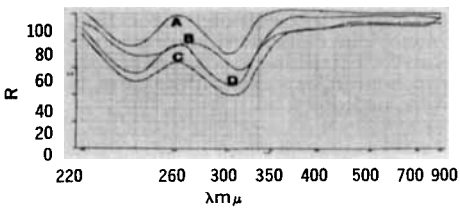

Fig. 12.—DRS showing the effects of interacting anthracene (100 mg.) with equilibrated magnesium trisilicate (2.00 Gm.) by compression using 30,000 p.s.i. of pressure with subsequent washing. Key: A, control; B, compressed sample measured in the form of a powder; C, compressed sample washed with 250 ml. of distilled water.

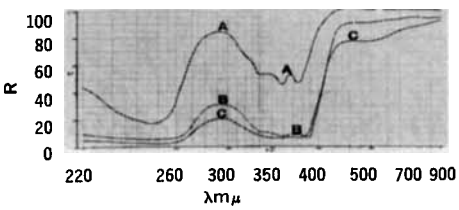

Fig. 13.—DRS showing the effects of varying compression pressures and changes due to washing in a salicylic acid (30 mg.) and magnesium trisilicate (2.00 Gm.) system. Key: A, control; B, compressed sample (35,000 p.s.i.) washed with 250 ml. of distilled water; C, compressed sample (35,000 p.s.i.) measured in the form of a tablet; D, compressed sample (15,000 p.s.i.) measured in the form of a tablet.

in Fig. 9. Here again, visual evidence of an interaction was observed. The physical mixture was faintly yellow in color as compared to the equilibrated sample which acquired a reddish-brown hue. An examination of these spectra does indicate a large bathochromic shift of approximately 75 mμ in the visible region. Such a change can certainly be attributed to chemical adsorption. Although some absorbance to the spectrum was contributed by the pure Al_2O_3, this absorbance did not significantly interfere with the spectrum of the equilibrated sample since this adjuvant's absorbance in the visible region, where the shift occurs, is negligible. As with the magnesium trisilicate adjuvant, soluble oxytetracycline HCl undergoes similar interaction with alumina in addition to the previously mentioned color change observed. This color change, along with the large bathochromic shift in the visible region, indicates that the mechanism involved is one other than that of physical adsorption. It is certainly apparent here that the types of spectral changes observed in such interactions are directly dependent on the type of adsorbent used. A comparison of the spectra obtained in the magnesium trisilicate *versus* the alumina system bears this out. With respect to the mechanisms of interaction involved, a consideration of the adsorbate and the adsorbent is necessary. For example Heftman (19), in his study of adsorption properties of alumina, points out the multiplicity of adsorption sites, either protophilic or protogenic, which may be available in this adsorbent.

Solid–Solid Interaction by Compression.—As previously pointed out, although a limited amount of information concerning these interactions in solution is available, no information is available concerning medicinal–adjuvant interaction in the solid state. The existence of such interactions is of paramount importance in tablet formulation in that such interactions would have significant effects not only on the stability of the medicinal in this dosage form, but also with respect to the availability of the drug in absorption. The possibility of solid–solid interaction in tablet formulation is certainly feasible in view of the high-compression pressures required to prepare this type of dosage form properly. Such interactions could be readily explained by the charge-transfer theory (20). In this study, solid–solid interaction under compression pressure is illustrated in Fig. 10. Since only minor diffuse reflectance variations were detected in the reflectance measurement of the compressed tablet and the triturated tablet, the form in which subsequent measurements were made varied, depending on the hardness of the tablet. It can be seen that the spectral changes resulting after compression of the sample, along with the usual color changes observed, are indicative of an interaction. It is also evident (Fig. 11) that increased pressures are directly proportional to the increased intensity changes observed. This can, in part, be explained by the fact that an increase in pressure facilitates the interaction of the drug on additional adsorption sites. Therefore, under compression pressures, sufficient energy is supplied to the system from an external force, resulting in chemisorption.

As with the oxytetracycline adsorbate, anthracene interacts strongly with magnesium trisilicate under compression pressure (Fig. 12) where subsequent

washing indicates little elution of the active ingredient as well as no hypsochromic effect. If salicylic acid is, however, substituted as the active ingredient as illustrated in Fig. 13, an interaction does result, but subsequent washing of the compressed sample causes the removal of part of the medicinal by the aqueous dispersion media. Substitution of salicylic acid as the active ingredient indicates that a greater degree of interaction is obtained by compression as compared to the previously discussed equilibrated salicylic acid system (Fig. 8). Here again, aqueous washing of the compressed sample (Fig. 13, B) results in partial removal of acid by the aqueous media. It is interesting to point out, however, that although the salicylic acid interaction is of a weaker variety, effects of varying compression pressures with respect to these complexes does result in proportional spectral changes; these are sufficiently greater than those observed as a result of particle size effects.

CONCLUSION

The data presented in this preliminary investigation indicate the presence of significant solid–solid interactions of medicinal agents studied with various adsorbents. Although the interactions are complex in nature, it is difficult at this time to assign a specific mechanism or mechanisms. However, generally speaking, these may be classified as a donor-acceptor type of interaction, although each system will have its individual spectral characteristics. Nevertheless, regardless of the mechanism(s) responsible for these complexes, the fact that they exist under equilibration, compression pressures, or other mixing conditions is of paramount importance. These interactions may certainly account for the discrepancies observed in blood levels and activities in various dosage forms. The reflectance technique, therefore, offers a means of confirming the existence of such interactions in solid dosage forms. Further studies are in progress in these laboratories concerning the interaction of various medicinal agents and adjuvants with respect to these solid–solid interactions.

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Reactions of a Secondary Amine in Chloroform

Implications for Drug Metabolism Studies

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Four new compounds were found to form in aged chloroform solutions of 1-(2-quinolyl)piperazine. Three of the compounds were identified, by comparison of thin-layer chromatographic behavior and infrared spectra with known compounds, as 1-formyl-4-(2-quinolyl)piperazine, 1-chlorocarbonyl-4-(2-quinolyl)piperazine, and 1,1′-oxomethylenebis[4-(2-quinolyl)piperazine]. Three new compounds were found to form in aged ethylene chloride solutions of 1-(2-quinolyl)piperazine, while only one new compound formed in aged methylene chloride solutions. It is concluded that the use of chlorinated hydrocarbons for extracting secondary amines from biological media should be approached with caution, especially if the extracts are allowed to stand for 24 hr. or longer.

THE COMPOUND, 1-(2-quinolyl)piperazine maleate (MA1291), is a new experimental oxytocic agent (1). During the course of thin-layer chromatographic experiments preliminary to studies of the biological disposition of the compound, it was found that chloroform solutions of the free base of MA1291 more than 1 day old contained from three to five components, depending on the age of the solution. In view of its potential significance, this phenomenon was investigated in an attempt to identify the new components and to gain some insight as to the reaction mechanisms. This report is presented to indicate the potential risk involved when chlorinated hydrocarbons are used to ex-

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