Diffuse Reflectance Studies of Solid–Solid Interactions III

Interaction Studies of Oxytetracycline with Metallic and Nonmetallic Adjuvants

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Spectral data are presented for chemisorption studies of oxytetracycline and oxytetracycline HCl with a number of metallic adjuvants containing aluminum, calcium, magnesium, zinc, and sodium ions as well as for some nonmetallic adjuvants including stearyl alcohol, cetyl alcohol, stearic acid, silica gel, starch, tannic acid, tragacanth, and polyethylene glycol 6000. The interactions, studied with equilibration, compression, and moisture techniques, indicate that a metal ion or polyfunctional adsorbent molecule is necessary for these charge transfer interactions.

In previous reports (1, 2), Lach and Bornstein have demonstrated that several drugs undergo chemisorption with a number of pharmaceutical adjuvants. Using diffuse reflectance spectroscopy (DRS), it was shown that salicylic acid, phenothiazine, anthracene, prednisone, and hydrochlorothiazide form complexes with a number of adsorbents commonly used in pharmaceutical dosage forms. Furthermore, it was pointed out that these reactions may occur either by compression techniques or equilibration of the components of the complex in aqueous or nonaqueous media. Interaction properties of oxytetracycline with magnesium trisilicate and activated alumina were also investigated, and results indicate that DRS of equilibrated or compressed samples produce large bathochromic shifts and intensity changes accompanied by significant visual color variation, indicative of charge transfer interactions.

The purpose of this investigation is to further study this oxytetracycline interaction with various metallic and nonmetallic adjuvants. Information from this investigation would give additional information as to the possible nature of the mechanism or mechanisms involved in this interaction.

EXPERIMENTAL

Reagents.—Recrystallized oxytetracycline, m.p. 182° dec. (Pfizer & Co.), oxytetracycline HCl (Pfizer & Co.), calcium phosphate (dibasic), calcium phosphate (tribasic), calcium hydroxide, calcium carbonate, calcium stearate, cetyl alcohol, stearyl alcohol, stearic acid, magnesium stearate, magnesium oxide, magnesium hydroxide, magnesium trisilicate, magnesium chloride, magnesium silicate,[1] magnesium carbonate, magnesium sulfate, talc, zinc stearate, aluminum hydroxide, silica gel, polyethylene glycol 6000,[2] starch, tannic acid, acacia, tragacanth, and dehydrated ethanol.

Procedure.—The routine experimental procedure for preparing the complexes and method of analysis have been described in a previous communication (1). All samples have been prepared by equilibration in 25 ml. of distilled water for 24 hr., except when otherwise indicated (2). The following is a special technique adopted for this study.

Moisture Effects.—This study involves the exposure of dried, physically mixed drug–adjuvant components to humidity conditions. The control is prepared by triturating a mixture of drug and adjuvant which were first individually vacuum dried for 0.5 hr. at 115°; the DRS of this physical mixture is then measured.

The moist sample is prepared by transferring a portion of this physical mixture onto an evaporating dish and placing it in a wax sealed desiccator in which water is substituted for the desiccant; the material is then allowed to stand in this humidity chamber for a designated period, after which time the moist sample is removed and its DRS is measured.

The above moist sample may also be vacuum dried for 0.5 hr. at 115° prior to DRS reading, in order to eliminate spectral moisture effects.

Past Work.—The complexes of interest in these studies vary in degree between the weaker van der Waal variety discussed by Higuchi and Lach (3), whose energy of reaction is derived mainly from dipole–dipole interactions, to the stronger intermolecular electron exchange mechanism described by McGlynn (4). These stronger charge transfer transitions of donor–acceptor complexes are often found as absorbancee bands in the near U.V. or visible region of the electromagnetic spectrum. According to Andrews and Keefer (5), this is often the case when acceptors are π acids.

Other pertinent reports in this area include com-

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[1] Marketed as Magnesol by the Waverly Chemical Co., Inc.

[2] Marketed as Carbowax 6000 by Carbide & Carbon Chemical Corp., New York, N. Y.

plex formation studies between adjuvants (6, 7) and various medicinal agents. Several examples may also be cited which deal with the complex formation of multivalent metallic cations, including Mg^{2+} and Ca^{2+}, with tetracyclines (8, 9). Other studies deal with the ability of magnesium, calcium, and aluminum (10–12) to alter the antibacterial action of various tetracyclines. In view of these developments, it is not surprising to find literature reports indicating significant gastrointestinal absorption differences between complexed and uncomplexed forms of tetracyclines (13, 14).

RESULTS AND DISCUSSION

Survey of Adjuvants with Oxytetracycline.—As has been pointed out, this investigation was undertaken to further study a number of oxytetracycline–adjuvant systems with respect to this interaction and the possible mechanism(s) involved. A number of representative spectral systems are presented and discussed. Other spectral data obtained in this study are not included in this report due to space consideration; however, they are included in the discussion.

Spectral data presented in Fig. 1 illustrate the interaction between oxytetracycline and aluminum sulfate. Here curve B represents an oxytetracycline–aluminum sulfate system, equilibrated in dehydrated ethanol, while the physical dry mixture (control) is represented by curve A. Spectra C and D (Fig. 1) represent curves of the individual aluminum sulfate and oxytetracycline components, respectively. An examination of these spectra reveals that the alcohol-equilibrated sample is significantly different from the physically mixed control and also from the spectra of the individual components. These differences include a large bathochromic shift of approximately 200 mμ in the visible region, accompanied by an intensity change in the U.V. region. Visual evidence of this interaction was also noted by a color change between the control and sample, where the physical mixture had a faint yellow color while the alcohol-equilibrated sample acquired an orange hue. These large spectral and physical differences are indicative of a strong charge transfer interaction (1, 2, 15). Similar spectral changes were also observed when equilibrating oxytetracycline with anionotropic and cationotropic alumina (1) in aqueous media. The nature of the solvent (aqueous or nonaqueous) apparently does not interfere significantly with this interaction, as has been previously pointed out (1), thus indicating a high degree of chemisorption. The presence of this strong interaction is further illustrated by the fact that the alcohol equilibrated oxytetracycline–aluminum sulfate sample (Fig. 1, B) produces a 200 mμ bathochromic shift, occurring at a higher wavelength than that for the reflectance spectrum of pure oxytetracycline (Fig. 1, D). This spectral observation further substantiates this strong interaction in that a summation of the drug-adjuvant spectrum would not result in this degree of change. It is of further interest to point out here that the addition of water to a mixture of oxytetracycline and alumina results in the release of a noticeable amount of heat along with the formation of bubbles, again indicating a large degree of interaction for this exothermic system.

Another aluminum-containing system, Fig. 2, represents spectra of aqueous equilibration of a dry physical mixture of oxytetracycline with aluminum hydroxide. Although the bathochromic shift is somewhat different from that of the aluminum sulfate interaction, the change in intensity is greater. This hyperchromic change in intensity is accompanied by a new band formation at 310 mμ. Possible reasons for this band formation have been previously discussed (1, 2).

In addition to the aluminum-containing adjuvants mentioned above, several calcium-containing systems were also investigated. These adjuvants also react with oxytetracycline producing the usual bathochromic shifts accompanied by significant hyperchromic changes, new band formation, as well as additional shoulder formation in the visible region. It should also be pointed out that visual color changes in calcium-containing systems were smaller than those described in the aluminum-containing adjuvants; here a color change from light yellow to a deeper more intense yellow was often noticed. Spectral data of oxytetracycline–calcium hydroxide equilibration, found in Fig. 3, point out some of these changes between the physically mixed control (A) and the equilibrated sample (B). An examination of this figure illustrates the fact that the bathochromic shift in this calcium hydroxide system is similar in magnitude to the aluminum hydroxide system found in Fig. 2. A difference between these two figures is evident, however, since the calcium-containing system has a smaller intensity change, especially in the region of 310–330 mμ where oxytetracycline–aluminum hydroxide band formation is more intense than that observed with the corresponding calcium hydroxide system. Nevertheless, calcium hydroxide does appear to react with oxytetracycline, as seen from various spectral changes in Fig. 3.

Other oxytetracycline systems producing similar spectral changes with aqueous equilibration to those described above include systems containing oxytetracycline with calcium carbonate, or calcium stearate, not shown in this communication due to space consideration.

Spectral data of aqueous equilibration of dibasic calcium phosphate or tribasic calcium phosphate with oxytetracycline are somewhat similar to that of calcium hydroxide with a bathochromic shift of 80 mμ and small band formation for oxytetracycline–$CaHPO_4$ while the oxytetracycline–$Ca_3(PO_4)_2$ system shows a 30 mμ bathochromic shift accompanied by intensity changes similar to those seen with the dibasic salt. Color changes from faint yellow to a deeper yellow were also observed in these calcium-containing systems. This interaction difference between $CaHPO_4$ and $Ca_3(PO_4)_2$ with oxytetracyline may be attributed to the fact that the former salt has a proton which could more easily provide an active site for interaction, because of its greater tendency to accept electrons from the adsorbate. It is also possible that a greater degree of hydrogen bonding is facilitated with $CaHPO_4$ systems as discussed in a previous report (2).

Another group of metal adjuvants investigated were those containing magnesium ions. Figure 4 represents spectra of an equilibrated and nonequilibrated oxytetracycline–magnesium hydroxide system. The changes observed after equilibration

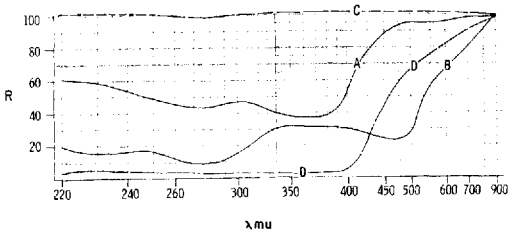

Fig. 1.—DRS of oxytetracycline (50 mg.) and aluminum sulfate (2.00 Gm.), equilibrated in dehydrated ethyl alcohol. Key: A, control (physical mixture); B, equilibrated sample; C, aluminum sulfate, 100%; D, oxytetracycline, 100%.

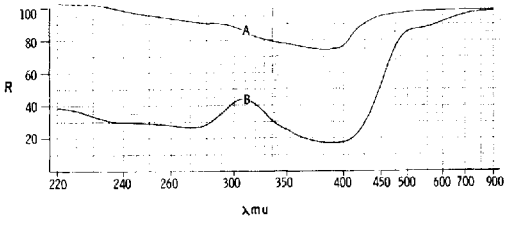

Fig. 2.—DRS of oxytetracycline (50 mg.) and aluminum hydroxide (2.00 Gm.). Key: A, control; B, sample.

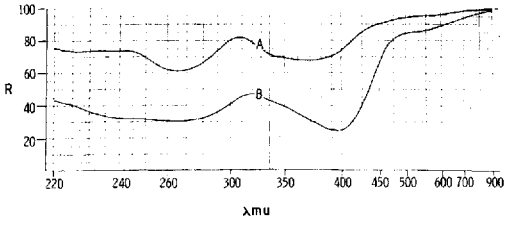

Fig. 3.—DRS of oxytetracycline (50 mg.) and calcium hydroxide (2.00 Gm.). Key: A, control; B, sample.

again include a bathochromic shift of about 50 mμ, a hyperchromic change, new band formation as well as a shoulder formation at 500 mμ. Similar spectral changes were observed with other oxytetracycline–magnesium-containing systems investigated. Included in this group are talc (native hydrated magnesium silicate), magnesium oxide, magnesium stearate, and synthetic magnesium silicate.[1] The interaction of oxytetracycline with synthetic magnesium silicate produces a bathochromic shift, intensity change, band formation, and shoulder formation to a greater degree than talc due to this material's high surface area, high porous structure, large internal surface, and high adsorption capacity. Similar changes were also observed on equilibrating oxytetracycline with zinc stearate, although the visual color change was not as pronounced.

Since data indicate that these interactions may be due primarily to the metallic ion in these systems, a study of nonmetallic adjuvants with respect to these interactions was undertaken. The interaction of oxytetracycline with stearyl alcohol or cetyl alcohol, shown in Fig. 5, illustrates this lack of interaction involved. An examination of this figure indicates that neither the stearyl alcohol, nor cetyl alcohol–oxytetracycline spectrum shifted to any appreciable degree after equilibration, as was expected. There is neither evidence of significant intensity variation, new band formation, shoulder formation, nor visual color change. The small variation in reflectance observed may be due to particle size difference, light scattering, or weak electrostatic attractions (2). Similar spectral results were also obtained on equilibrating oxytetracycline with stearic acid.

Since calcium stearate, magnesium stearate, zinc stearate, and other metal-containing adjuvants react strongly with oxytetracycline, as evidenced by large spectral changes, while stearyl alcohol, cetyl alcohol, and stearic acid do not, the interactions observed are primarily due to the metallic ion portion of the adjuvant. The other spectral and visible color observations previously indicated (1, 2) further suggest that this is a charge transfer chelation interaction.

It should be pointed out, however, that other nonmetallic adjuvants, containing polyfunctional groups, show spectral changes on equilibration with oxytetracycline, although these systems have inherently different spectral characteristics. An example of this type of change may be found in

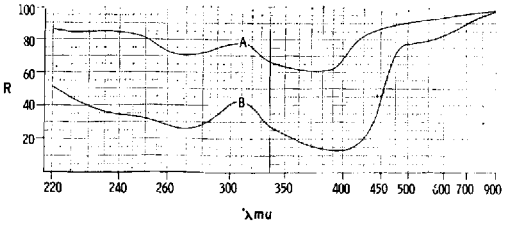

Fig. 4.—DRS of oxytetracycline (50 mg.) and magnesium hydroxide (2.00 Gm.). Key: A, control; B, sample.

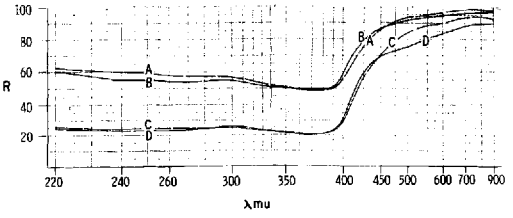

Fig. 5.—DRS of oxytetracycline (50 mg.) with stearic acid (2.00 Gm.) or with cetyl alcohol (2.00 Gm.). Key: A, oxytetracycline–stearic acid control; B, oxytetracycline–stearic acid sample; C, oxytetracycline–cetyl alcohol control; D, oxytetracycline–cetyl alcohol sample.

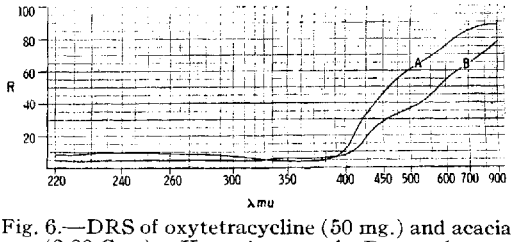

Fig. 6.—DRS of oxytetracycline (50 mg.) and acacia (2.00 Gm.). Key: A, control; B, sample.

Fig. 6, showing spectra of an equilibrated and non-equilibrated oxytetracycline–acacia system. Since acacia is a polyfunctional material, it is reasonable to assume that one or more of the functional groups may react with oxytetracycline by a donor–acceptor mechanism (16), producing the observed spectral change in the visible region. It should also be pointed out that other adjuvants, including tannic acid and starch, react with oxytetracycline to give similar changes; spectra of these systems are not presented due to space considerations. Figure 7 represents the spectra of an equilibrated and non-equilibrated oxytetracycline–polyethylene glycol 6000 system. The large bathochromic shift, hyperchromic effect, and visual color changes observed in equilibrating this system may again be attributed to an interaction between oxytetracycline and the ether linkage of the ethylene oxide units of the polyethylene glycol polymer. This observation is in agreement with published reports dealing with polyethylene glycol interactions in aqueous solution (3, 17). A bathochromic shift of similar magnitude, along with a visual color change from light yellow to a deep red-brown, was also observed on equilibrating oxytetracycline with silica gel.

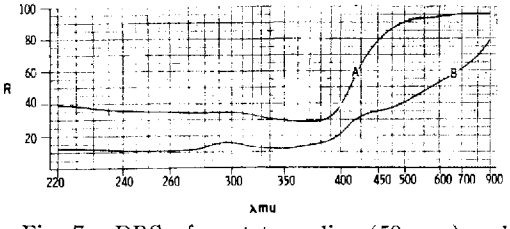

Fig. 7.—DRS of oxytetracycline (50 mg.) and polyethylene glycol 6000 (2.00 Gm.). Key: A, control; B, sample.

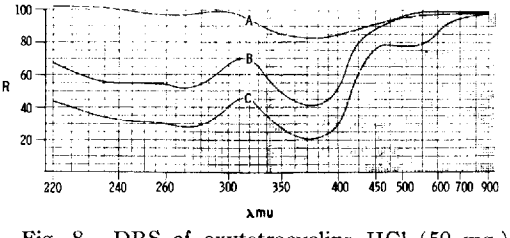

Fig. 8.—DRS of oxytetracycline HCl (50 mg.) and magnesium trisilicate (2.00 Gm.). Key: A, control (physical mixture); B, physical mixture left in moisture chamber for 24 hr. and vacuum dried; C, sample, equilibrated for 24 hr.

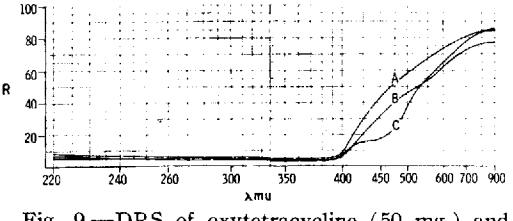

Fig. 9.—DRS of oxytetracycline (50 mg.) and sodium chloride (2.00 Gm.) study of moisture and drying effects. Key: A, control (physical mixture); B, physical mixture left in moisture chamber for 3 hr. and measured as the moist sample; C, spectrum of vacuum dried moist sample.

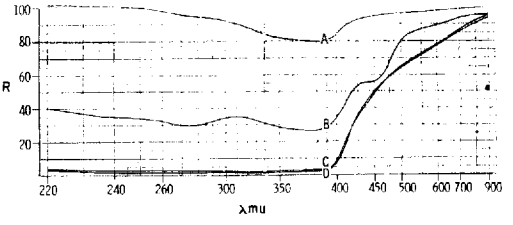

Fig. 10.—DRS of oxytetracycline (50 mg.) and magnesium sulfate (2.00 Gm.). Key: A, control; B, moist sample, remained in moisture chamber for 12 hr.; C, dry oxytetracycline, 100%; D, moist oxytetracycline, remained in moisture vessel for 12 hr., 100%.

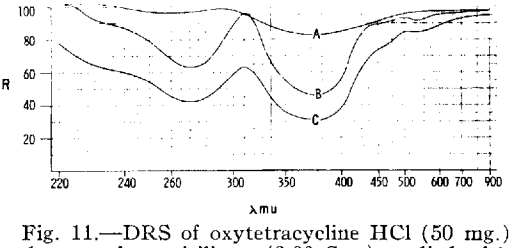

Fig. 11.—DRS of oxytetracycline HCl (50 mg.) and magnesium trisilicate (2.00 Gm.) studied with moisture effects and moisture effects followed by compression. Key: A, control (physical mixture); B, physical mixture left in moisture chamber for 30 hr. and measured as a moist sample; C, compression of the moist sample (B) at 30,000 p.s.i. for 5 min.

Particle-Size Variation.—Since particle size may produce variation in the reflectance spectrum (18), the authors' preliminary study dealing with this aspect indicates that some variation was obtained, although the changes are of a minor nature. For example, the spectrum of an equilibrated oxytetracycline–magnesium trisilicate complex was not altered to any significant degree when this equilibrated sample was subjected to reduction in particle size by homogenizing the powder for 0.5 hr. with the use of a Virtis blender. An examination of the filtered, vacuum dried sample's spectrum was comparable to that of the equilibrated control.

Although variation in particle size does have some effect on the regular reflection (1), the general characteristics of the control and homogenized sample spectra were essentially similar except for minor variations in the order of ±2%.

Moisture Effects.—Since solid pharmaceutical dosage forms involve the use of excipient materials such as fillers, binders, disintegrators, and lubricating agents, and since a certain percentage of moisture is necessary for the preparation of such dosage forms, as in the case of tablets, a preliminary investigation dealing with the effects of moisture was undertaken. Results presented thus far, dealing with drug–adjuvant interactions, were facilitated by compression or by equilibration techniques, either in aqueous or nonaqueous media. The present study involves the exposure of the dried, physically mixed drug–adjuvant components to humidity conditions for various time intervals.

Figure 8 illustrates this moisture effect with respect to spectral changes. Here curve A is the

diffuse reflectance spectrum of a dry physical mixture of oxytetracycline HCl and magnesium trisilicate and serves as the control. A portion of this dry physical mixture was then transferred onto an evaporating dish and placed in a wax-sealed desiccator in which water was substituted for the desiccant and allowed to stand for a period of 24 hr. This moist sample was then dried to eliminate moisture effects, and the DRS, represented by Fig. 8, curve B, was taken. Figure 8, C, represents the spectrum of physical mixture which has been equilibrated in water, filtered, and dried. An examination of curve B indicates that interaction does take place under moist conditions since this curve is comparable to the spectrum of the equilibrated sample (Fig. 8, C), except for an intensity change and the shoulder formation at 475 mμ. This greater intensity change, observed in the equilibrated sample, is probably due to a greater degree of interaction, since more surface area is exposed in equilibrating techniques. These spectral changes were accompanied by the usual color change from light yellow to a deep yellow color. It is of interest to note that the spectra of pure dry and moist oxytetracycline HCl or magnesium trisilicate, exposed to the same moist conditions, were similar in nature and did not vary by more than ±2%.

A similar effect is shown in Fig. 9, representing the interaction of oxytetracycline with sodium chloride. Spectrum A represents a physical mixture (control) of vacuum dried oxytetracycline and NaCl. A portion of this dried mixture was subjected to the moist humidity chamber previously described, and allowed to remain in this atmosphere for 3 hr. The DRS of this moist sample was then obtained and is represented by curve B. Figure 9, C, represents the spectrum of this moist sample which was vacuum dried. It is interesting to note that an interaction was observed with NaCl (Fig. 9, B), which cannot be totally attributed to a moisture effect, since drying of this moist sample does not cause a reversal in the spectrum back to the control, but instead, a higher degree of interaction results (Fig. 9, C). This may be explained on the basis that drying removes some of the surface water molecules from the adsorbent, producing additional reactive sites which facilitate the increased chemisorption or interaction.

Other adjuvant systems, investigated for oxytetracycline moisture effects, include anhydrous magnesium sulfate, magnesium chloride, and stearic acid. An examination of Fig. 10 again points out large spectral changes induced when a physical mixture of oxytetracycline and anhydrous magnesium sulfate is allowed to sit in a moisture chamber for 12 hr. Here curve A represents a physical mixture of individually dried oxytetracycline and magnesium sulfate, while curve B is the spectrum of a moist sample. These spectral changes along with an important color change from a whitish yellow to a deep yellow intensity are again indicative of a strong interaction. Similar spectral changes are also observed when subjecting an oxytetracycline–magnesium chloride mixture to a moist atmosphere. A difference between the sodium chloride and magnesium chloride reaction with oxytetracycline does exist, however, since the moisture exposed oxytetracycline–NaCl sample shifts, seen in Fig. 9, are of a magnitude of about 75 mμ while a bathochromic shift of about 150 mμ is observed with a corresponding oxytetracycline–magnesium chloride system. The greater spectral shift observed with the magnesium chloride system would be expected since magnesium chelates of oxytetracycline are known, and the interaction would be of a stronger variety than that produced by the sodium salt. It is interesting to point out again, however, that these changes are not observed between a physical mixture and moist sample of oxytetracycline and stearic acid. Spectral curves of the latter two systems have not been presented due to space considerations and chelation explanations for these differences have been discussed in previous sections.

Curves C and D (Fig. 10) represent spectra of dry and moist oxytetracycline, respectively. It is evident from these curves, and other adjuvant spectral data, that moisture effects of the individual components of these complexes are minor compared to the huge spectral differences when a physical drug–adjuvant mixture is allowed to remain in a moist environment.

The significance of such interactions can be easily applied to the area of tableting. The preparation of tablets usually requires that some moisture be present in the process of granulation, prior to tablet compression. Although such interactions, if they do occur, are already present in these granules, the effect of compression further accentuates this interaction. This effect is illustrated in Fig. 11, which represents the dry physically mixed control (curve A), the moist sample (curve B), and the compressed moist sample (curve C). An examination of the curves in this figure indicates that a greater degree of interaction may be obtained under compression pressures, as represented by the increased intensity and bathochromic change, even though the sample has already interacted due to moisture chamber equilibration. Furthermore, vacuum drying of these moisture equilibrated samples and subsequent compression does not destroy this interaction.

CONCLUSION

An examination of the large number of adjuvants which may react with oxytetracycline, together with the large spectral changes of specific systems, suggests the desirability of preliminary screening for the possible existence of such drug–adjuvant interactions in the formulation of dosage forms. Although no experimental data are available concerning the effect of these surface interactions with respect to dissolution and adsorption rates, it is felt that the possible existence of such interactions should be recognized. The literature does, however, contain information which strongly suggests that such interactions are responsible for the variation in blood level drug concentrations.

Since chemisorption primarily involves the surface area of the adjuvant, this type of interaction may not be of great therapeutic value when the drug to excipient ratio is sufficiently large, in that the chemisorbed unimolecular layer covering the surface of the adjuvant does not manifest itself until all the other physically adsorbed layers of the drug are removed. However, such drug–adjuvant interactions are extremely important when the ratio of the therapeutic drug to the amount of adjuvant or excipient is extremely low. In such ratios, the therapeutic agent primarily exists as the interacted

unimolecular layer and would be expected to significantly alter the dose response obtained. It is well to point out here that such interactions would not only manifest themselves in solid dosage forms, as in the case of tablets and capsules, but could also occur in suspensions and ointments, where drug–adjuvant ratios are usually low. 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.

Data presented in this study further illustrate the possibility that donor–acceptor interaction of many varieties play an important role in these drug–adjuvant interactions. This has been illustrated by different magnitudes of spectral shifts observed among aluminum, calcium, magnesium, zinc, and sodium-containing adjuvants as well as nonmetal-containing excipients represented by stearyl alcohol, stearic acid, cetyl alcohol, acacia, tragacanth, tannic acid, and polyethylene glycol. The degree of interaction observed further depends on the nature of the drug and the type of adjuvant used. For example, calcium-containing adjuvants interact strongly with oxytetracycline but show very little interaction tendency for anthracene.

Studies are currently in progress in these laboratories dealing with the effects of such interactions on various aspects of drug dosage formulation and absorption.

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LSD Analogs

N-Methyl-*N*-*p*-(and *m*-)methoxyphenyl-β-alanine Derivatives

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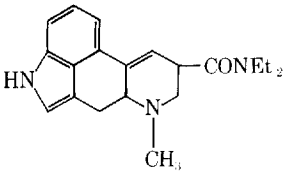
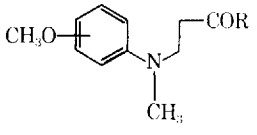
Patterned after a fragment of the LSD molecule, the ethyl esters, simple amides, and *N*,*N*-diethylamides of *N*-methyl-*N*-*p*-(and *m*-)methoxyphenyl-β-alanine were prepared for evaluation as psychotomimetics. Of five compounds tested, three exhibited some degree of antiserotonin activity in the isolated rat fundus preparation. One of these three appeared also to be anticholinergic.

ATTEMPTS HAVE been made to elucidate an active psychotomimetic moiety in the lysergic acid diethylamide (LSD) molecule (1, 2). In the present work, the *N*-methyl-*N*-phenyl-β-alanine fragment of LSD was selected for study; an electron-rich methoxy group *para* or *meta* on the ring was intended to approximate the contribution made by the pyrrole nitrogen.

The ethyl esters (R = OEt in β-alanine moiety



LSD



β-Alanine Moiety

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