Another apparent disadvantage of these other methods is that the total bulk quantity of final dosage form required becomes prohibitive when the dose is of the order of 250 mg. The impracticality becomes evident when it is realized that a 1:9 drug–excipient ratio is frequently necessary to observe the increased rates. In the current study, a high drug–excipient ratio of 10:1 is indicated.

From the foregoing results, it is quite evident that the use of adsorbents can facilitate the dissolution process of relatively insoluble powders. Surface degradation is, however, a possibility with such systems (34, 35), but this aspect will be considered in the second article. The minuscular drug delivery system can be regarded as drug in a microparticulate form molecularly dispersed on the very extensive surface of fumed silicon dioxide. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the rate of solution of the drug.

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Use of Adsorbents in Enhancement of Drug Dissolution II

DONALD C. MONKHOUSE and JOHN L. LACH▲

Abstract □ Using the instrumental techniques of diffuse reflectance spectroscopy, differential thermal analysis, and X-ray analysis, it was possible to characterize the type of bonding forces involved in the minuscular drug systems prior to the dissolution process. Hydrogen bonding and van der Waals' forces accounted for the rapid desorption of the drugs from the adsorbent surface. A decrease in particle size was suggested as a major factor improving the dissolution rate of these equilibrated systems. Two polymorphic forms of indomethacin and probucol were identified as being present in the samples, the proportion of the metastable form being dependent on the percentage of fumed silicon dioxide added to the system.

Keyphrases □ Adsorbents—used to increase dissolution rates of drugs, characterization of drug–excipient binding □ Drug–excipient binding—dissolution characterization of micronized (minuscular) drug dispersed on adsorbents □ Diffuse reflectance spectroscopy—characterization of drug–excipient binding □ Differential thermal analysis—characterization of drug–excipient binding □ X-ray crystallography—characterization of drug–excipient binding □ Dissolution rates—micronized (minuscular) drug dispersed on adsorbents, characterization of binding forces

Reports in the literature in the last 5 years brought to light the importance of drug–excipient interactions. These interactions have been responsible in part for difficulties experienced in formulating pharmaceutical dosage forms. The most pertinent consequence associated with these interactions is often a decreased thera-

peutic action. This is most probably a result of altered stability, dissolution rate, and, ultimately, absorption of the drug.

These interactions could be eliminated if no excipients, or if only those excipients that show no interaction, were employed. However, since the official compendia demand a plethora of formulation variables in order to meet the specifications of disintegration time, dissolution rate, and physiological availability, the use of a number of excipients is usually required to prepare a satisfactory dosage form. If the likelihood of an interaction were suspected and subsequently detected in a preformulation procedure, many problems encountered later could be prevented. Until recently, available, effective, and dependable instrumentation was lacking for the study of interactions in the final dosage form.

Notwithstanding, new and established instrumentation is being applied to the study of individual drug–excipient interactions (1, 2). By applying the techniques of diffuse reflectance spectroscopy, differential thermal analysis, and X-ray crystallography in preformulation procedures, many of the problems associated with multicomponent dosage forms might be avoided.

Drug–adjuvant interactions in the solid state were investigated by Lach and Bornstein (1), Lach and Bighley (3), and McCallister *et al.* (4), using diffuse reflectance spectroscopy. The degree of strength of the interactions between drugs and adjuvants was interpreted from the observed spectral shifts.

In a continuing investigation into drug–excipient interactions, Wu *et al.* (5) and Wichman (6) examined the adsorption characteristics of various pharmaceutical adjuvants toward surface degradation of medicinals. In reviewing these latter investigations, as well as other studies currently in progress, it appears reasonable to generalize that those adjuvants that produce a peak atypical of the original molecule adsorbed onto them are most probably incompatible with that compound and are likely to catalyze its degradation in the solid state. This new peak is probably related to the chemisorption phenomenon, whereas physical adsorption produces very little change in the original transmittance spectrum of the neutral molecule.

Differential thermal analysis, a relatively old analytical tool, has recently gained favor in the study of compounds of interest to the pharmaceutical industry. Using thermal methods in their study of interactions between pharmaceutical compounds, Guillory *et al.* (2) ably demonstrated the use of differential thermal analysis, the cooling curve method, the thaw-melt method, and X-ray powder patterns to obtain data from which phase diagrams can be constructed for a number of binary systems. They showed differential thermal analysis to be a versatile technique, demonstrating several advantages over the more classical methods of thermal analysis in the prediction of drug–drug interactions. Systems in which interactions were detected and stoichiometries were determined included deoxycholic acid–menadione (2:1), quinine–phenobarbital (1:1), theophylline–phenobarbital (2:1), caffeine–phenobarbital (1:1), and atropine–phenobarbital (1:1).

Simon (7) was one of the first to utilize the technique of differential thermal analysis as a tool for the rapid evaluation of drugs with excipients in preformulation studies. He pointed out a possible interaction of triampyzine sulfate with magnesium stearate. In another study (8), differential thermal analysis was used to identify stearic acid as the inactivating component in an unstable formulation containing sodium dicloxacillin and several excipients. These results gave excellent correlation with those obtained in an 8-week 50° stability test.

The present study is the second part of an investigation into the dissolution characteristics of a new dosage type (9). Once it was established that the dissolution rate of drugs in the minuscular form was increased, it was then required that various techniques be utilized to help elucidate the mechanisms involved as well as to detect any drug–excipient interactions. Differential thermal analysis, diffuse reflectance spectroscopy, and X-ray crystallography permitted at least some detailed characterization of the systems previously reported prior to the dissolution process.

EXPERIMENTAL

Materials—The materials used were identical to the systems described previously (9).

Differential Thermal Analysis—A differential thermal analyzer, equipped with a standard cell attachment[1], was used. The finely powdered sample was placed in a 2-mm. diameter, capillary melting-point tube. The amount of sample varied from 2 to 5 mg. for each determination. Glass beads were used as the reference material, and the temperature was determined by the use of chromel–alumel thermocouples. A heating rate of 20°/min. was employed in all experiments[2].

A *y*-axis sensitivity setting of 1°/in. was used to measure the differential temperature. Experiments were carried out in a static air atmosphere to detect the possibility of oxidative decomposition.

Peak temperatures from the differential thermograms were taken as transition temperatures. These temperatures were corrected for the nonlinear temperature response of the chromel–alumel thermocouples.

Diffuse Reflectance Spectroscopy—Equilibrated samples containing 10 mg. of drug/g. of excipient were prepared in a manner similar to that previously described for the dissolution studies (9). Mechanical mix samples containing 20 mg. of drug/g. of excipient were prepared by geometrical dilution using a spatula technique or by light trituration with a mortar and pestle.

All diffuse reflectance spectra were measured using a spectrophotometer[3] with reflectance attachment. Recordings were made with a 25.4-cm. (10-in.) linear recorder[4]. The instrument was zeroed at 500 nm. and the spectrum was scanned from that point down to 200 nm. Special cells were constructed to hold the sample and reference powders. Each cell consisted of a 4.75-cm. (1.87-in.) square aluminum block, 0.63 cm. (0.25 in.) thick, with a 3.48-cm. (1.37-in.) hole machined through the center. A circular piece of quartz[5], 3.17 cm. (1.25 in.) in diameter and 0.15 cm. (0.06 in.) thick, was recessed into the face of the block covering the hole. An aluminum back cover was held in place by two thumb screws. The powder compartment between the quartz face and the back cover was therefore 0.46 cm. (0.18 in.) in depth.

The prepared sample was placed in the sample cell, and pure adjuvant was placed in the reference cell. Care was taken to use approximately the same quantity, by weight, of sample and reference material in their respective cells, since excessive packing can cause fluctuations in the percent reflectance. The pure adjuvant or adjuvant

[1] Dupont model 900.
[2] This relatively high rate of heating was necessary to obtain sharp intense endotherms. However, such a rate could lead to discrepancies between the observed transition temperatures and the literature values (*e.g.*, the reserpine melting point at 20°/min. is 280°, and at 10°/min. it is 270°; the Merck Index value is 265°).
[3] Beckman model DB-G.
[4] Beckman 10500.
[5] Suprasil.

treated identically to the sample (*e.g.*, washed with acetone, dried, and sieved) was used as the reference material to minimize the regular reflectance and keep the scattering coefficient relatively constant.

X-Ray Studies—Various combinations of the pure drug, mechanical mixtures, and equilibrated samples were analyzed by the X-ray powder diffraction method. A camera[6] with 114-mm. diameter was used, and Fe-K radiation was employed[7]. The powder patterns obtained in this study were reproduced elsewhere (10).

Miscellaneous Procedures—The IR spectra of the polymorphs were obtained from a spectrophotometer[8] by the KBr disk method.

TLC of indomethacin was accomplished using the method employed in a recent hydrolytic study (11). The pure and processed indomethacin samples were dissolved in acetone and spotted on silica gel microscope slides. The plates were developed in a solvent system of chloroform–acetic acid (95:5 v/v). Upon removal of the solvent, the spots were detected by exposure to iodine vapor.

The Form II polymorphs of indomethacin and probucol were prepared from the Form I compounds as follows. The mixed solvent systems employed were 50% aqueous acetone for indomethacin and 50% aqueous methanol for probucol. A sufficient amount of the commercial product was added to a suitable volume of the boiling mixed solvent until the system was saturated. A few drops of organic solvent were then added until complete solution resulted. This was filtered and allowed to cool very slowly to room temperature. The resulting crystals were then collected, washed with water, and dried at 70° in a heated vacuum desiccator.

RESULTS AND DISCUSSION

In all but a few exceptions (discussed later), the shifts in the maxima observed in the diffuse reflectance spectroscopy peaks of the equilibrated samples varied within the range of ±10 nm. from the same respective peaks observed for the diffuse reflectance spectroscopy of the physical mixes and the UV transmittance spectra. According to the theory of UV and visible spectroscopy, physical adsorption involving van der Waals' forces (0.5 kcal./mole) should result in spectral shifts of only 1–2 nm. and those involving hydrogen bonding (5–10 kcal./mole) should display spectral shifts of 5–10 nm. (1), whereas chemisorption of the donor-acceptor type (>40 kcal./mole) can exhibit spectral shifts (mainly bathochromic) of 10 nm. or greater and may be accompanied by a color change. Thus, from this information, it appears that van der Waals' and hydrogen bonding were the principal forces involved in the binding of these drugs to the silica surface. This conclusion is in agreement with the current theory on the type of bonding typical of silica compounds used for chromatography (12). In none of the systems studied was chemisorption conclusively identified.

During preparation of minuscular drug products, it can be presumed that the large excess of organic solvent (*e.g.*, methanol, acetone, or chloroform) containing the drug first displaces the water molecules and, upon evaporation of the solvent, the drug molecules present are selectively hydrogen bonded to the surface of the silica. However, as indicated from the dissolution studies, it can be postulated that addition of water to the drug powder results in desorption of the drug from the silica surface. This might be attributed to hydrogen-bond formation between the drug and water and between the silanol and water. Since these bonds are of stronger magnitude than those of the drug silanols, the drug is quickly displaced into the dissolution medium.

Figure 1 illustrates a diffuse reflectance spectroscopy pattern typical of the drug–fumed silicon dioxide systems investigated in this study. Very little spectral shift can be observed between the physical mixes and the equilibrated samples of hydrochlorothiazide. For comparative purposes, a system in which chemisorption has been indicated (4)—hydrochlorothiazide–magnesium oxide—is also included. Here, a hypsochromic shift of 15 nm. is evident from the equilibrated sample peak of 320 nm. to the physical mix peak at 335 nm.

In the reserpine system, an increase in the intensity of its characteristic yellow color was observed and was readily evidenced by the shape of the diffuse reflectance spectra (Fig. 2). In the

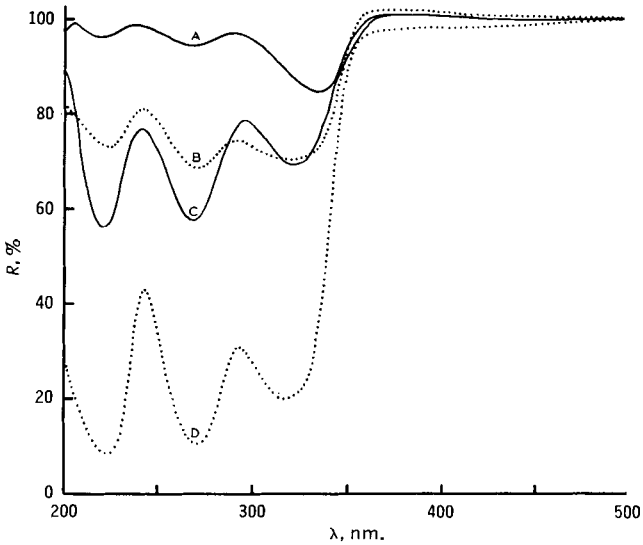

Figure 1—*Diffuse reflectance spectra of hydrochlorothiazide on fumed silicon dioxide and magnesium oxide. Key for fumed silicon dioxide: B, physical mixture; and D, equilibrated with acetone. Key for magnesium oxide: A, physical mixture; and C, equilibrated with acetone.*

solution spectrum, no peak in the visible region existed at low concentrations. In the physically mixed sample, a shoulder appeared at 400 ± 10 nm. in the diffuse reflectance spectrum. Upon equilibration, however, this shoulder developed into a well-defined peak at 396 nm. In a recent report (13), it was proposed that reserpine in chloroform solution is unstable and decomposes either *via* hydrolysis to reserpic acid, methanol, and trimethoxybenzoic acid or *via* oxidation to 3-dehydroreserpine. When solvents other than chloroform (*e.g.*, acetone and methylene chloride) were used to prepare the sample, the yellow coloration was still produced. This possibly indicates that the degradative reaction was surface catalyzed and that the coloration was independent of the solvent used to prepare the sample.

For the indomethacin system, a new shoulder appeared at about 460 nm. when the excipient was acidified silica gel. With the basified silica gel system, a bathochromic shift of 10 nm. was noted at 260 nm. and a new peak appeared at 227 nm. The results of the latter system are not entirely unexpected, because in basic solution the electronic structure of the molecule is perturbed, and increased conjugation would account for the observed effects. However, since decomposition of indomethacin was a possibility, TLC's were run

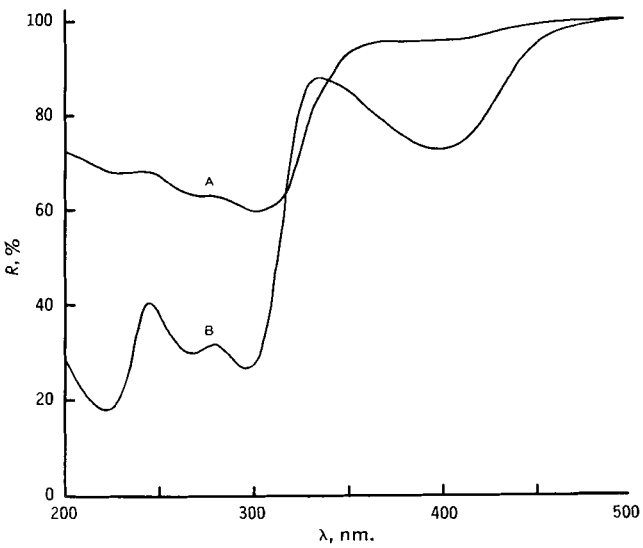

Figure 2—*Diffuse reflectance spectra of reserpine on fumed silicon dioxide. Key: A, physical mixture; and B, equilibrated with chloroform.*

[6] Debye-Scherrer.

[7] The authors thank Dr. Norman Baenziger of the Department of Chemistry, University of Iowa, for his assistance in obtaining and interpreting the powder patterns.

[8] Beckman model IR 10.

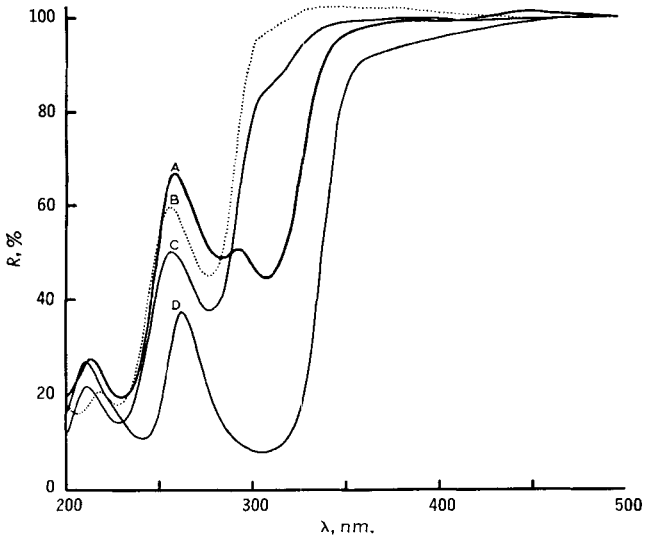

Figure 3—*Diffuse reflectance spectra of aspirin on fumed silicon dioxide. Key: A, equilibrated with acetone; B, equilibrated with methylene chloride; C, physical mixture; and D, physical mixture of fumed silicon dioxide and salicylic acid.*

on these samples. No spots were separated and the R_f value was identical to that of pure indomethacin. If decomposition was present, it would probably have occurred at the surface and it is highly possible that the TLC procedure was insensitive to any minor amounts of decomposition products present. At this stage, it seems as if the surface coating of indomethacin on acid- or base-treated surfaces is of practical potential in light of their influence on dissolution rates.

Figure 3 shows that when a fumed silicon dioxide–aspirin sample was prepared with the solvent methylene chloride, using minimal heat (40° for 1 hr.) to evaporate the solvent, the diffuse reflectance spectrum was identical to that of the physical mixture. This indicates that essentially no decomposition took place. When the sample was heated or prepared with acetone as the solvent (also evaporated at 70° for 1 hr. under vacuum), however, a new peak appeared at 305–315 nm. This peak is characteristic of salicylic acid, as verified by the diffuse reflectance spectrum of a physical mixture of salicylic acid and fumed silicon dioxide. Concurrent with the appearance of this new peak was the disappearance of the peak at 277 nm., which is characteristic of pure aspirin. At this juncture, the extent of degradation as detected in the figure is unknown. It is quite possible, however, that the total amount of degradation was relatively small, possibly situated only at the drug–excipient interface. Since other existing methods employed for studying the degradation of aspirin are

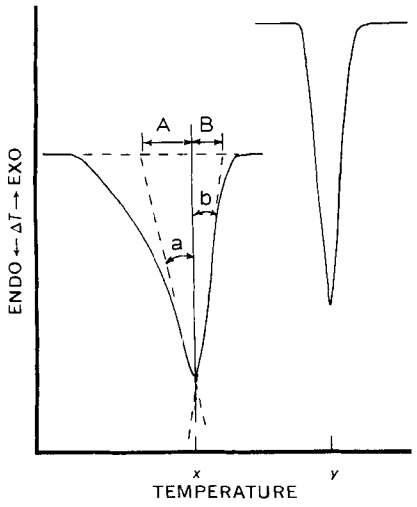

Figure 4—*Representative differential thermograms of a physically mixed* (y) *and an equilibrated* (x) *sample. The slope ratio = tan* a/*tan* b = A/B.

Table I—Transition Temperatures of Drugs Recorded in the Presence of Fumed Silicon Dioxide

Drug	Melting Point: Physical Mixture (y)	Melting Point: Equilibrated Mixture (x)	Depression ($y - x$)
Hydrochlorothiazide	268°	264°	4°
Aspirin	137°	134°	3°
Sulfaethidole	187°	184°	3°
Chloramphenicol	147°	145°	2°
Oxolinic acid	318°	316°	2°
Griseofulvin	220°	218°	2°
Reserpine	280°	274°	6°

inadequate in the detection of small quantities of decomposition products (14), this method does offer future possibilities for investigating the compatibility of aspirin with excipients in the solid state; such studies are presently underway in these laboratories.

For a given concentration of drug per fixed amount of fumed silicon dioxide, the equilibrated samples in this study invariably exhibited the greater reflectance at the peak position. This effect could be attributed to two factors: the physical adsorption phenomenon and a decrease in particle size. The percentage reflectance of the physically mixed sample could be varied by the amount of grinding to which the powder was subjected. This grinding process increased the amount of interaction and decreased the particle size; in other words, the drug covered a greater surface area and, consequently, more molecules were exposed to the path of the light beam of the spectrophotometer. Thus, the effective concentration per unit cross-sectional area was increased, resulting in a greater reflectance value. Once the sample was equilibrated, however, the value of its reflectance reached a maximum. This indicated both that the amount of physical interaction was maximal and that the drug in the minuscular form was indeed distributed upon the extensive surface of the silica excipient. Consequently, the drug's particle size had, in fact, been diminished and was in agreement with the rapid dissolution of these systems as previously reported (9).

A rather controversial aspect of differential thermal analysis has been the relationship of particle size to the resulting thermogram. It has been stated that finer particles release their heat more rapidly and that the increasing fineness of samples results in increasing area and peak intensity (15). Although there are no reports concerning medicinal compounds, most of the work accomplished in this connection has been performed with complex mineralogical and clay specimens (16, 17).

Representative thermograms of medicinal agents (minuscular drug and physical mix) employed in the present study are graphically illustrated in Fig. 4. From these diagrams the asymmetry of the equilibrated sample peak x is reflected by its high slope ratio. On the other hand, the symmetrical peak y of the physically mixed sample has a low valued slope ratio which approaches unity. In general, the thermograms of the pure compound as well as its physical mixture were very symmetrical, whereas the opposite was the case for the equilibrated samples. This pattern was followed by seven of the nine compounds investigated in this study. (The exceptions were indomethacin and probucol, and these will be discussed in detail later.)

These behavioral variations in peak symmetry may be explained in the following manner. The minuscular drug samples contain molecularly dispersed drug equilibrated on the surface sites of the silica adsorbents, the drug molecules being bound in various ways (*e.g.*, hydrogen bonding and van der Waals' forces) in a wide distribution of bond strengths. When heat is applied at a steady rate, some of the intermolecular forces between drug and adsorbent are disrupted and the bonds are broken. This allows the melting process to begin. As soon as the melting front reaches the larger intact drug particles, they are "dissolved" in the liquid melt already present. As a result, the transition temperature occurs early—anywhere from 0 to 6° below the observed melting point of the pure drug material. This depression is measured by the distance y–x as observed in Fig. 4 and listed in Table I.

In the physical mixture, however, the intact drug crystals are not bound but are, instead, mechanically distributed in the "inert" diluent; the constant thermal conductance of the diluents employed sharpens the thermographic minimum (18). It can be appreciated that the heat is conducted quickly and directly to the distinct crystal-

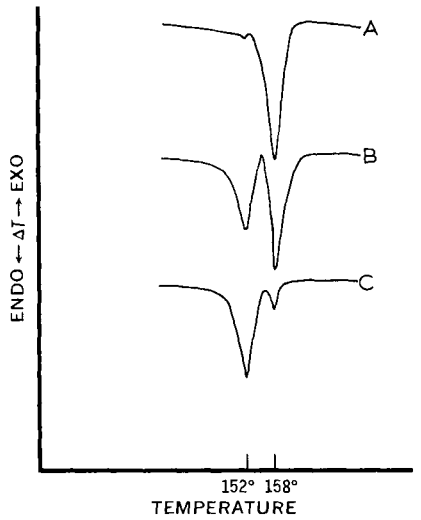

Figure 5—*Typical differential thermograms of indomethacin in the presence of fumed silicon dioxide. Key: A, pure indomethacin powder; B, indomethacin equilibrated with 10% fumed silicon dioxide; and C, indomethacin equilibrated with 20% fumed silicon dioxide.*

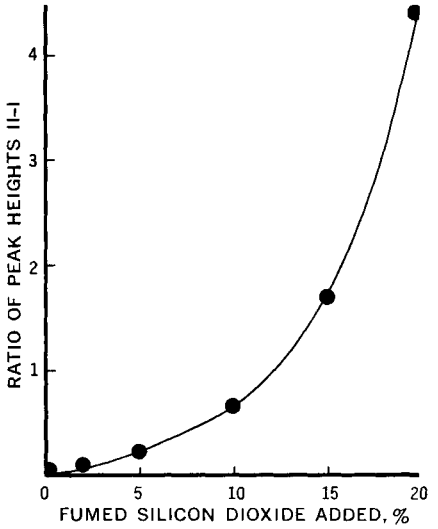

Figure 7—*Effect of percentage of fumed silicon dioxide added on the differential peak height on the indomethacin endotherms. Each point represents the ratio of the peak height of endotherm II to the peak height of endotherm I.*

line entities of drug particles. A characteristic heat of fusion is required to increase the interatomic and intermolecular distances in the individual drug, thus allowing melting to occur. In the physical mixture, therefore, the recorded transition point actually represents the melting point of the pure compound. The temperatures observed for the melting reactions of the seven drug-excipient systems are also listed in Table I.

In support of this discussion, it should be noted that after the melting process occurred and the samples were allowed to cool, their outward appearances were characteristic of their preparation. The physical mixture had a speckled appearance whereas the equilibrated sample exhibited a homogeneous color. This indicated that in the equilibrated system, the drug was uniformly deposited on the extensive surface of the fumed silicon dioxide; whereas the microheterogeneity of the mechanical mixture further confirmed that the crystals were individually dispersed.

From the data presented, it is evident that coating of the drug molecules on the surface of the adsorbent does result in a decreased particle size which, in turn, increases the percent reflectance, lowers the melting point, and enhances the release rate of the drug from the surface into the dissolution medium. As previously discussed, the drug silanol bonds are particularly weak (chemisorption was not detected in the systems investigated in this study) and this may explain the drug's relative ease of desorption.

Two of the systems that were studied, indomethacin and probucol, did not follow the trend as discussed previously. Instead, a new peak appeared below the observed melting point of the drug. The formation of a new peak suggested the presence of a new species, either a degradation product or a polymorphic form.

Typical endotherms of these new entities are illustrated in Figs. 5 and 6. As the fumed silicon dioxide concentration was increased, the intensity of the differential endotherms of the lower melting-point form also increased. As the intensity of this new peak increased, the intensity of the higher melting form decreased. Barrall and Rogers (18) stated that if all variables other than weight percent of active material are kept constant, the differential peak height may be used for quantitative work. By using this precedent with approximately equal sample weights, a relationship is seen to exist between the amount of fumed silicon dioxide added and the amount of lower melting form present. If the ratio of peak heights of the lower melting form to the higher melting form (tentatively desig-

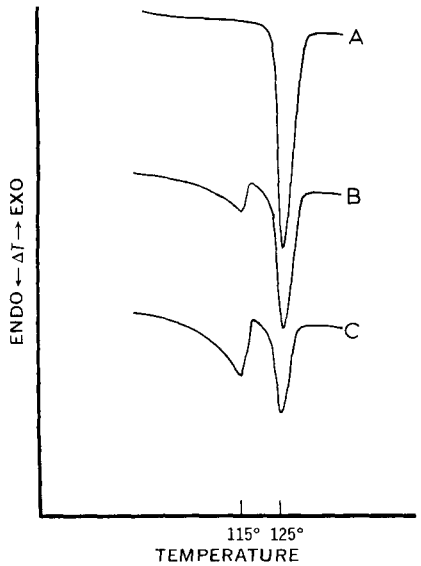

Figure 6—*Typical differential thermograms of probucol in the presence of fumed silicon dioxide. Key: A, pure probucol powder; B, probucol equilibrated with 10% fumed silicon dioxide; and C, probucol equilibrated with 20% fumed silicon dioxide.*

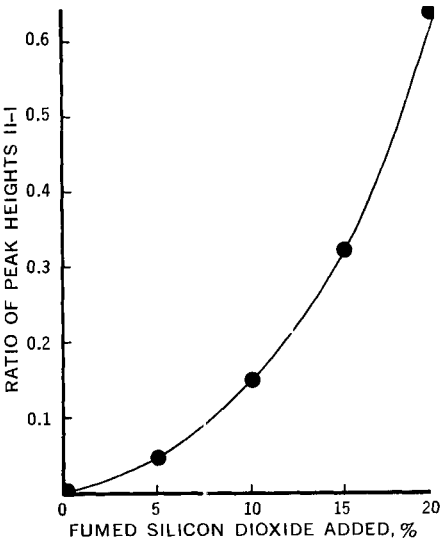

Figure 8—*Effect of percentage of fumed silicon dioxide added on the differential peak height of the probucol endotherms. Each point represents the ratio of the peak height of endotherm II to the peak height of endotherm I.*

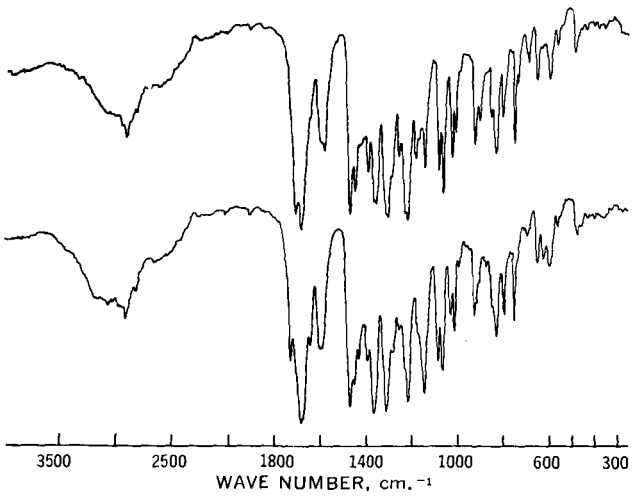

Figure 9—*IR spectra of two polymorphic forms of indomethacin. Key: upper spectrum, Form I; and lower spectrum, Form II.*

nated as II/I) is plotted *versus* the percent fumed silicon dioxide added, then curves of the type illustrated in Figs. 7 and 8 are obtained.

Since the transition of the differential thermal analysis curves did not shift with decreased heating rate (10°/min.), both transitions may have been due to reversible phase changes and not to chemical reaction (19). No separation of spots on the TLC of indomethacin samples was observed, which possibly rules out the presence of a decomposition product in the sample. No data were available on the decomposition of probucol.

By using an array of solvents, it was possible to duplicate the lower melting phenomenon in the absence of fumed silicon dioxide. The 152° form of indomethacin was crystallized from an acetone–water mixture, and the 115° form of probucol was crystallized from a methanol–water system. The C, H, and N analyses run on the two forms of each drug were found to be identical (*e.g.*, indomethacin calculated: C, 63.78; H, 4.51; N, 3.91; 152° form observed: C, 63.76; H, 4.52; N, 3.73; 158° form observed: C, 63.76; H, 4.44; N, 3.76; for probucol calculated: C, 71.98; H, 9.36; 125° form observed: C, 72.23; H, 10.05; and 115° form observed: C, 72.02; H, 10.12). The percentage of hydrogen for the probucol compounds was larger than "allowable" for both forms. Since they were almost identical to each other in both C and H, however, this internal consistency was regarded as satisfactory for this study. From Figs. 9 and 10, it can be observed that the IR spectrum of the higher melting form was significantly different from that of the lower melting form in each case.

It is apparent from the discussion thus far that the data presented are consistent for the phenomenon of polymorphism. This was indeed found to be the case and was confirmed when the chloroform

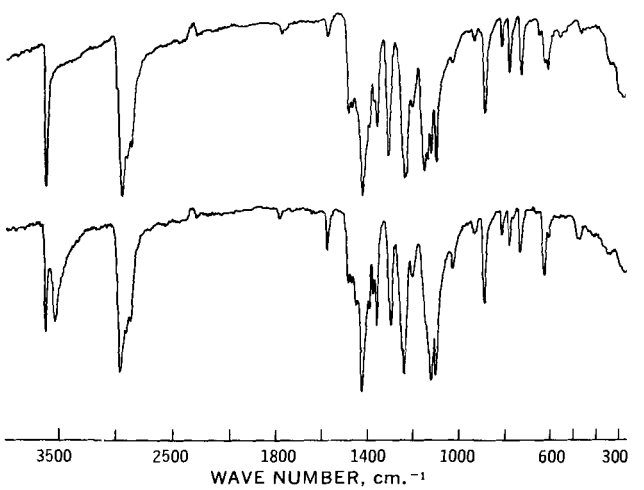

Figure 10—*IR spectra of two polymorphic forms of probucol. Key: upper spectrum, Form I; and lower spectrum, Form II.*

solution IR spectra were superimposable and the X-ray powder patterns were characteristic of each form (10). On the basis of these data, the lower melting entity was arbitrarily designated as Form II and the higher melting entity as Form I. To the authors' knowledge, such a polymorphic form for indomethacin has been only briefly mentioned prior to this study (20).

The samples of minuscular drug coated on the surface of fumed silicon dioxide were subjected to X-ray analyses (10). Fumed silicon dioxide by itself, or washed with organic solvent, did not display any crystallinity. With the equilibrated samples, however, it was possible upon careful examination, to discern lines characteristic of both polymorphic forms. The physical mixtures displayed only the patterns of the one form present which was originally added to the mixture. These data would seem to confirm the results obtained from the differential thermal analysis curves cited earlier in Figs. 5–8.

As previously noted, the percentage of Form II in the sample increased in proportion to the amount of fumed silicon dioxide added, which can be rationalized as follows. Upon addition of the organic solvent to fumed silicon dioxide, a gel structure is formed. The drug molecules may orient themselves in a position that is most stable in liquid (this form may or may not be the most stable in the solid state) *via* hydrogen bonding. As the solvent is evaporated, the drug commences to nucleate on the surface of the fumed silicon dioxide particles. This presumably results in microcrystals of Form II which are sterically fixed in the matrix of the fumed silicon dioxide surface. The particle size of these crystals will be very small because of the extremely high viscosity of the medium at the low temperature (evaporation of the solvent is exothermic), and the relatively short-time interval for the removal of the solvent. However, on the surface of the gel and on the sides of the beaker, there is a concomitant formation of Form I crystals.

As a result, a mixture of the two forms occurs. On this basis, it becomes quite understandable that as more fumed silicon dioxide is added, a greater proportion of Form II results in the final analysis.

During these thermal studies, some type of solvate or hydrate was detected for four of the systems. Sulfaethidole (crystallized from acetone–water) exhibited a very large endotherm centered at 95–105°; chloramphenicol (crystallized from acetone–water) exhibited a small endotherm at 95–105°; griseofulvin (crystallized from chloroform) exhibited a large endotherm at 130–140°; and indomethacin (crystallized from acetone–water) exhibited an endotherm immediately followed by an exotherm in the 80–100° range. Since these drugs were crystallized from mixed solvents, there was insufficient evidence to determine the exact type of solvate present. However, the normal heating process (70° under vacuum) used to prepare the samples was usually sufficient to remove these artifacts. The presence of these solvates may have been unexpectedly beneficial, since it has been postulated (21) that the lattice rearrangement to the solvate and back to the original compound prevents the growth of larger crystals and, consequently, offers an excellent method for the attainment of size reduction.

Once the existence of the polymorphic forms was substantiated, an investigation of the dissolution behavior of the isolated compounds was required. In both instances (indomethacin and probucol), it was found that the equilibrium solubility was the same as the original compound. Also, the dissolution rate did not vary significantly from that of the original pure compound. These results were not entirely unexpected. To measure slight differences between polymorphs requires the utilization of very refined techniques, usually including the measurements of absolute intrinsic dissolution rates and/or measurement of the rate of boundary movement of a single crystal edge with a special microscope. It is quite possible that the gross beaker procedure employed in this study was insensitive to such subtle differences.

SUMMARY

From the diffuse reflectance spectroscopy studies, physical adsorption was confirmed and chemisorption, if operative in these systems, was regarded as playing only a minor role. The mechanism of bonding was considered to involve mainly hydrogen bonding and van der Waals' forces. The ease of desorption reported in Part I (9) confirmed that the bonding forces are weak and reversible and, as a result, the drug molecules are easily displaced by dissolution media. The diffuse reflectance spectroscopy data also indicated that the selection of an excipient should be made with care because of the various surface catalytic effects which are generally overlooked.

A decreased particle size in these drug–excipient systems was confirmed by differential thermal analysis data; in most cases, a 2–3° depression in the melting point was observed. Hydrogen bonding in a gel matrix was apparently responsible for the formation of a metastable configuration in two systems: indomethacin and probucol. The polymorphic forms were first detected by differential thermal analysis and confirmed by X-ray and IR data. The existence of multiphase solids was a consequence of the presence of fumed silicon dioxide acting as a nucleating agent for the metastable crystals. Although the dissolution rates of the isolated polymorphs were found to be identical to those of the original compounds, it is quite possible that in the dispersed state the metastable form dissolved at a rate faster than the stable form.

Since drug–excipient interactions do readily occur in normal manufacturing procedures, and since these interactions not only alter the physical and chemical properties of the drug but also appreciably affect the physiological availability of the drug from the dosage form, it is highly desirable that such interactions be considered as a part of strict in-process quality control.

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GLC Determination of Chlormadinone Acetate in Plasma

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Abstract □ Plasma samples obtained from monkeys after oral administration of 0.5–2.0 mg. of chlormadinone acetate were extracted with hexane. The hexane extracts were washed, concentrated, and analyzed by GLC using a ^{63}Ni electron-capture detector. The analyses were performed on a 30.5-cm. (1-ft.) column packed with either 3.8% methyl silicone gum rubber on silanized diatomite or a mixed phase consisting of 3.0% methyl silicone gum rubber and 1.5% polyethylene glycol 20,000 on silanized diatomite. Levels as low as 1.0 ng. steroid/ml. plasma were detected by this procedure when 5-ml. samples of plasma were available.

Keyphrases □ Chlormadinone acetate—GLC analysis, plasma, monkeys □ GLC, electron capture—analysis, chlormadinone acetate in plasma, monkeys

Since the introduction of sequential oral contraceptives in the spring of 1965, chlormadinone acetate, 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate (I), has been used as a progestogen in one of these drug products (1). In 1967, Martinez-Manautou *et al.* (2) reported on the contraceptive efficacy of 0.5-mg. daily oral administration of chlormadinone acetate as a low-dose progestogen, free of estrogen. They considered the 0.5-mg. tablet an effective, remarkably benign oral contraceptive. During 1968, the 0.5-mg. tablet of chlormadinone acetate was introduced to the market in Mexico, France, and Argentina.

To demonstrate biological availability of chlormadinone acetate from tablets, it became necessary to develop a sensitive analytical method for the detection and quantitation of the drug in plasma. Work by Koons and Scroggs (3) and Donoho *et al.* (4), describing the determination of chlormadinone acetate in animal feeds and cattle tissue, was helpful in the development of such a method. The method described in these studies is based upon GLC using electron-capture detection. The initial studies were performed in monkeys using 0.5-, 1.0-, and 2.0-mg. doses of chlormadinone acetate. This method recently proved satisfactory for the monitoring of blood levels of this drug in humans (5).

EXPERIMENTAL

Reagents—Chlormadinone acetate, chlormadinone-C_1-^3H acetate, and chlormadinone caproate (II) were used[1]. Hexane and benzene were spectral quality while toluene and methanol were

[1] Supplied by Syntex, S. A., Mexico D. F., Mexico.