Diffuse Reflectance Studies of Solid–Solid Interactions IV: Interaction of Bishydroxycoumarin, Furosemide, and Other Medicinal Agents with Various Adjuvants

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Abstract □ Spectral information comparing the diffuse reflectance of drug–metallic-ion adjuvants with those of the isolated metallic chelates is presented. Various metallic-ion chelates of bishydroxycoumarin and furosemide were prepared and isolated, and their diffuse reflectance spectroscopy spectra were found to be comparable to those of drug–adjuvant equilibrated systems. This information, along with the color changes observed in both the chelate and the interaction product, and the new peaks observed in the UV and visible regions of the spectra suggest that these drug interactions due to chemisorption may proceed by a mechanism similar to that of chelation.

Keyphrases □ Solid–solid interactions—diffuse reflectance spectroscopy □ Drug–metal-ion adjuvants, drug–metal chelates—diffuse reflectance comparison □ Spectral changes, drugs—metal-ion adjuvants □ Diffuse reflectance spectroscopy—analysis □ IR spectrophotometry—identity

A number of articles have recently appeared in the literature which point out the existence of drug–excipient interactions in the solid state (1–5). Although drug–excipient interactions in pharmaceutical dosage forms have been recognized, very little information exists concerning the nature and degree of these physical and chemical surface interactions. Such solid–solid interactions may account, in part, for the discrepancies observed in drug availability of similar dosage forms.

This report represents a part of the continuing study of drug–excipient interaction and deals with mechanistic aspects of these drug–metallic-ion adjuvant interactions.

EXPERIMENTAL

Reagents—The following were used: dioxane-recrystallized bishydroxycoumarin, m.p. 288–289°;[1] alcohol-recrystallized furosemide, m.p. 215° dec.;[2] digoxin, m.p. 266° dec.;[3] indomethacin, m.p. 158°;[4] ergonovine maleate, m.p. 166° dec.;[3] chloramphenicol, m.p. 151°;[5] potassium bromide, spectroscopic grade; activated (basic) alumina (Woelm); magnesium oxide; magnesium trisilicate; calcium sulfate; magnesium carbonate; zinc stearate; zinc oxide; acacia powder; magnesium sulfate, A.R.; ferrous chloride, A.R.; ferrous sulfate, A.R.; aluminum chloride, A.R.; zinc sulfate, A.R.; talc; methanol, A.R.; ethanol USP; and 0.1 *N* NaOH.

Apparatus—The following were used: Beckman DU spectrophotometer with a diffuse reflectance attachment; constant-temperature water bath set at 30 ± 0.5° with rotating spindles; 150-ml. vials with caps sealed with Parafilm;[6] Frease-Precision Scientific vacuum oven; Beckman IR-5A infrared spectrophotometer; Pasadena Hydraulic bench press; and a capillary melting-point apparatus.[7]

[1] K and K Laboratories.
[2] Hoechst Pharmaceuticals.
[3] Burroughs Wellcome & Co.
[4] Merck Sharp and Dohme.
[5] Parke-Davis and Co.
[6] Marathon Co.
[7] Arthur H. Thomas Co.

PROCEDURES

Preparation of Sample—An exact amount of the drug (50 mg. of bishydroxycoumarin, 50 mg. of furosemide, 10 and 20 mg. of digoxin, 10 mg. of ergonovine maleate, and 30 mg. of indomethacin and chloramphenicol) is weighed for every 2 g. of adjuvant weighed. The powders are placed in 150-ml. vials, and 25 ml. of water is added as the dispersion medium. The vial is covered with Parafilm and capped. The sample is equilibrated for 8 hr. at 30 ± 0.5° to effect interaction. After equilibration, the sample is dried under vacuum at 40°. The percent reflectance of this sample is measured, using magnesium carbonate as the reference material.

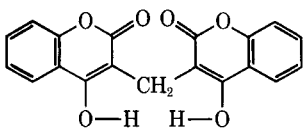
Preparation of Control—The same amounts of drug and of adjuvant are weighed as in the sample preparation and are physically mixed using a mortar and pestle. The percent reflectance of this control is measured, using magnesium carbonate as the reference material.

Preparation of Chelates—Approximately 3 g. of the drug (bishydroxycoumarin or furosemide) is accurately weighed and dissolved, using an equivalent amount of 1.0 *N* NaOH and the volume of the solution adjusted to 50 ml. with distilled water. A molar equivalent quantity of the metal-ion solution is added dropwise to the solution containing the drug while stirring continuously. The addition is continued until the pH drops to approximately 6; then the solution is filtered under vacuum and the insoluble complex is washed well with water to remove impurities and dried in a vacuum oven.

RESULTS AND DISCUSSION

Although no information in the literature describes metallic chelates of bishydroxycoumarin, previous diffuse reflectance spectroscopy (DRS) studies (6) in these laboratories dealing with bishydroxycoumarin–excipient interactions strongly suggested that the mechanism involved could be one of chemisorption due to surface chelation.

An examination of the structure of bishydroxycoumarin (Structure I) suggests that this compound could undergo chelate formation.



I

Attempts to study solution chelate formation of bishydroxycoumarin with metallic ions, based on the DRS information, by the solubility and continuous variation method were unsuccessful.

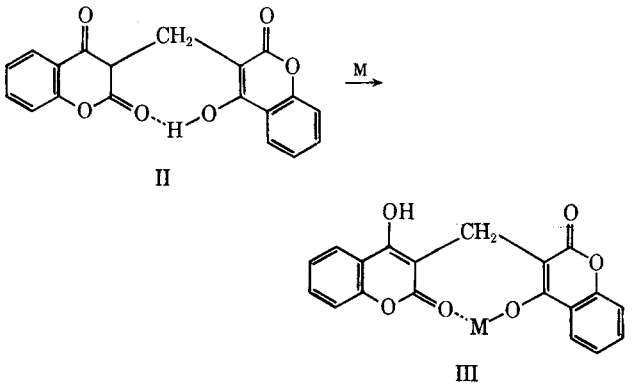
The use of potentiometric titrations, although not totally satisfactory since no significant pH changes were observed, did, however, give evidence of complexation, because visual observation of a precipitate was noted when sodium hydroxide titrant was added to a bishydroxycoumarin solution containing the metal ion under investigation. Since metal hydroxides were also formed in this method, the procedure was modified.

Bishydroxycoumarin was first solubilized by the addition of an equivalent amount of alkali and titrated with an aqueous solution of the metallic ion under investigation, resulting in the formation of highly colored precipitates and suggesting that chelate formation had occurred (Table I).

Table I—Bishydroxycoumarin–Metallic-Ion Chelates

Compound	Color
Bishydroxycoumarin	White
Mg(II) chelate	Light-yellow
Zn(II) chelate	Light-yellow
Fe(II) chelate	Gray
Fe(III) chelate	Brownish-red
Al(III) chelate	Light-yellow

The examination of the IR spectra of these isolated metallic chelates and of the pure bishydroxycoumarin indicated that apparently the accepted conformation (Structure I) of the drug is in disagreement with the present findings. The IR spectrum obtained for bishydroxycoumarin (Fig. 1) does not reveal a free O—H stretching band in the region of 3 μ, as would be expected. Although the spectral data are in agreement with the reported IR spectrum by Hayden *et al.* (7), these authors also fail to account for this in their listed structure. It is interesting to note that free O—H stretching in the 3-μ region is only evident in the chelate, for example, as seen in the zinc chelate (Fig. 2). This suggests that one hydroxyl group of bishydroxycoumarin, in the pure state, is strongly hydrogen bonded to the keto oxygen and that the hydroxyl group on the other coumarin ring would exist primarily in the keto form, which would account for the absence of free O—H stretching in this region. Data based on the IR spectra of the various isolated bishydroxycoumarin chelates indicate that the conformation of this drug and its chelates could be as shown in Scheme I.



Scheme I

Additional evidence supporting this line of reasoning was obtained using Dreiding models. The isolated metallic chelates were very insoluble in all solvent systems tested and, consequently, difficult to purify and characterize; they were highly colored, as listed in Table I.

The adjuvants used in the study of the solid–solid interactions with bishydroxycoumarin were chosen because of their importance in pharmaceutical formulations. In view of the fact that most of the adjuvants used exhibited reflectance values in excess of 100% throughout the wavelengths employed and, therefore, would not contribute to the absorption spectrum of the control or the equilibrated sample, their spectra are not shown.

Figure 3 represents the DRS spectrum of the interaction of magnesium oxide with bishydroxycoumarin. An examination of this figure does indicate a significant difference in the spectrum of the control and that of the equilibrated sample, as evidenced by the

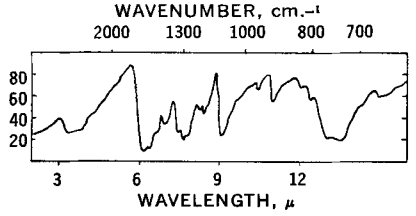


Figure 1—*IR spectrum of bishydroxycoumarin (KBr pellet).*

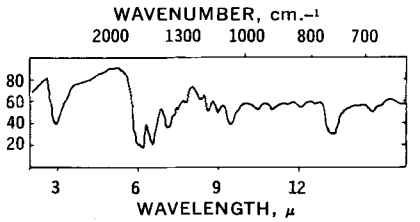


Figure 2—*IR spectrum of the zinc–bishydroxycoumarin chelate (KBr pellet).*

intensified absorption bands in the UV region. There also appear to be two new absorption peaks generated, one between 360 and 390 mμ and the other at approximately 450 mμ.

This band formation in the UV region may be explained as an interaction of the magnesium oxide with bishydroxycoumarin where the adsorption 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 oxide adsorbent. This is suggested in Fig. 4 where the transmittance curve of bishydroxycoumarin in basic medium shows that the $\lambda_{max.}$ at approximately 320 mμ lies in the same region as that obtained in the DRS spectrum. The appearance of two new bands at approximately 380 and 450 mμ in the visible region of the DRS spectrum in the equilibrated sample and their absence in the transmittance spectrum indicate the presence of a strong chemical surface interaction between bishydroxycoumarin and the magnesium oxide adsorbent. The high degree of interaction is further substantiated by the large intensity change and the significant bathochromic shift observed in the equilibrated sample as compared to that of the control. A comparison of this interaction DRS spectrum to that of the prepared and isolated magnesium chelate shows some interesting similarities. For example, the chelate also shows a new peak at 450 mμ. Both spectra show a hyperchromic effect throughout the UV region. The equilibrated magnesium oxide sample is light yellow in color, quite similar to the isolated magnesium chelate; in addition to the other similarities noted, this suggests that the mechanism involved in these interactions may be similar.

Other magnesium-ion metallic adjuvant–bishydroxycoumarin interactions, although not shown here, are somewhat similar to that of the magnesium oxide systems. In the magnesium carbonate system, there is a hyperchromic effect in the UV region and the possibility of new band formation, broad and distinct, between 375 and 390 mμ, indicative of strong interaction.

There is also a bathochromic shift of 80 mμ between 340 and 420 mμ in the equilibrated *versus* the control spectrum. The interaction of magnesium stearate with bishydroxycoumarin suggests a peak between 375 and 390 mμ, although it is indistinct and quite weak. A bathochromic shift of 40 mμ is observed between 360 and 400 mμ. The new band formation and bathochromic shifts are indicative of strong chemical interactions, and a mechanism similar to that of chelate formation seems reasonable for these interactions.

An examination of the spectrum of the zinc stearate interaction with bishydroxycoumarin (Fig. 5) reveals a slight hyperchromic effect in the UV region with this adjuvant, along with a $\lambda_{max.}$ at approximately 300 mμ.

No new peak formation was observed in the visible region as in the magnesium-containing systems. The DRS spectrum of the isolated zinc–bishydroxycoumarin chelate, however, does show

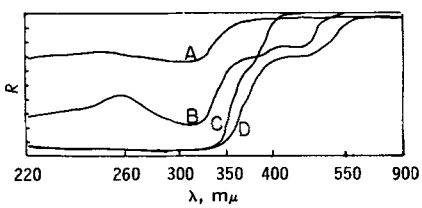


Figure 3—*DRS of bishydroxycoumarin (50 mg.) and magnesium oxide (2.00 g.). Key: A, control (physical mixture); B, equilibrated sample; C, bishydroxycoumarin, 100%; and D, magnesium–bishydroxycoumarin chelate, 100%.*

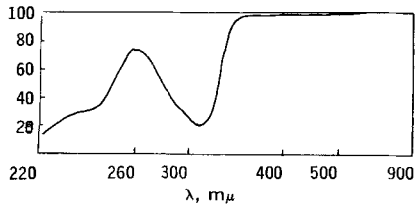


Figure 4—*Transmittance spectra of bishydroxycoumarin (10 mcg./ml.) in 0.1 N NaOH solution.*

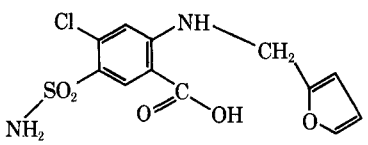
this new band at 450 mμ and a significant bathochromic shift as compared to the spectrum of the equilibrated sample. The absence of new peak generation in the visible region for the zinc stearate–bishydroxycoumarin system as compared to that of the isolated chelate indicates that the zinc in the zinc stearate molecule is less readily available for surface interactions. However, as with the magnesium-containing adjuvant, the degree of surface interactions will vary with other zinc-containing excipients.

Spectral data obtained for the alumina–bishydroxycoumarin interactions were quite similar to those seen with zinc stearate. Again, new peak generation at 450 mμ was observed only in the prepared chelate. It is possible that zinc stearate and alumina have very highly saturated surfaces and, thus, few active sites available for chemisorption.

Although the iron (II) and iron (III) bishydroxycoumarin chelates were prepared, a comparison of their DRS data to that of the equilibrated samples was difficult because of the highly adsorbing nature of the interaction products.

DRS of Furosemide Interactions and Comparison of Isolated Chelates—The interest in studying this drug was due in part to the color changes observed in certain tablet formulations and to the reported discrepancies in absorption when the drug was formulated with certain excipients.[8]

Furosemide (4-chloro-5-sulfamoyl-*N*-furfuryl anthranilic acid), an effective diuretic-saluretic agent (8–10), is similar chemically to the thiazide diuretics. Furosemide is a weak acid with a pKa of approximately 4.7. It forms salts easily with bases such as sodium hydroxide and has the structure shown in Structure IV.



IV

The large spectral and color changes observed in the diffuse reflectance spectrum of the furosemide–metallic-ion adjuvant interactions, as in the bishydroxycoumarin system, again suggest that this compound could undergo chelate formation in aqueous solution, although such chelates have not been previously reported.

Using the previously discussed modified method, the alkali-solubilized furosemide was titrated with a solution of the metallic ion under investigation. The highly colored isolated precipitate did indicate that interaction had occurred (Table II). An examination of the molecular structure using Dreiding models substantiates

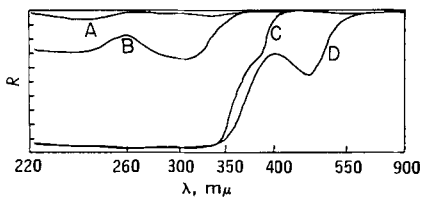


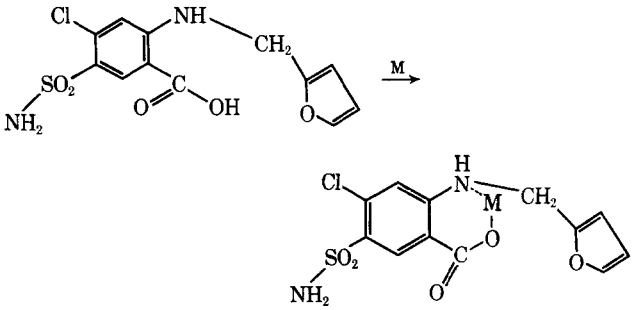
Figure 5—*DRS of bishydroxycoumarin (50 mg.) and zinc stearate (2.00 g.). Key: A, control (physical mixture); B, equilibrated sample; C, bishydroxycoumarin, 100%; and D, zinc–bishydroxycoumarin chelate, 100%.*

[8] Private communication.

Table II—Furosemide and Selected Chelates

Compound	Color	Melting Point
Furosemide	Off-white	215°
Mg(II) chelate	Light-yellow	300°
Zn(II) chelate	Yellow-brown	>360°
Fe(II) chelate	Light-cocoa	200°
Fe(III) chelate	Red-brown	>360°
Al(III) chelate	Yellow-gray	>360°

this line of reasoning, as illustrated in Scheme II.



Scheme II

As in the bishydroxycoumarin system, purification of the isolated chelates was extremely difficult due to their highly insoluble nature. Attempts to characterize these isolated chelates after repeated methanol washings in which the drug was relatively soluble were inconclusive because contamination due to the presence of metallic hydroxides was a problem.

Analysis for furosemide and metallic ion contained in the chelates by spectrophotometric, chelometric, and atomic absorption techniques generally indicated a 1:1 ratio, although a 2:1 ratio for the iron (III) system was suggested. Since the stoichiometric relationship is dependent on an exact metallic-ion determination and since trace amounts of metallic hydroxide contamination can result in a large change in this ratio, further purification studies are in progress to determine this ratio and to characterize the complexes. Although it is recognized that these isolated and methanol-washed chelates are not completely pure, results of an elemental analysis assuming a 1:1 ratio are listed in Table III.

In spite of the difficulties encountered in the purification and stoichiometric determination of these metallic chelates, it is of interest to note that this drug does undergo chelate formation in solution and this is reported here for the first time.

With respect to these solid–solid surface interactions, Fig. 6 represents the DRS of the furosemide–magnesium oxide interaction. Again, as seen in the bishydroxycoumarin–magnesium oxide interaction, equilibration of the furosemide with magnesium oxide results in the clarification of strong absorption bands at 230, 275, and 335 mμ; the bands are comparable to those seen in Fig. 7 which represents the transmittance spectrum of furosemide in methanol.

The clarification of absorption bands after the equilibration procedure indicates that a significant interaction has occurred. Comparable absorption peaks can be seen in the DRS spectrum of the isolated furosemide–magnesium chelate, although of signifi-

Table III—Percent of Various Elements Present in Furosemide Chelates Based on a Probable Stoichiometry of 1:1

Chelate	% Carbon		% Hydrogen		% Nitrogen	
	Theoretical	Actual	Theoretical	Actual	Theoretical	Actual
Mg(II)	40.6	39.53	2.84	3.1	7.92	7.27
Zn(II)	36.4	37.31	2.55	2.91	7.1	7.1
Fe(II)	37.36	41.69	2.61	3.2	7.26	8.03
Fe(III)	37.36	35.90	2.61	2.78	7.26	6.83
Al(III)	40.4	38.39	2.82	2.99	7.85	7.56

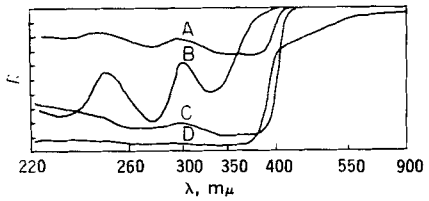


Figure 6—*DRS of furosemide (50 mg.) and magnesium oxide (2.00 g.). Key: A, control (physical mixture); B, equilibrated sample; C, furosemide, 100%; and D, magnesium–furosemide chelate, 100%.*

cantly less clarity, since high absorption results due to use of the pure chelate.

The hypochromic shift noted in the furosemide–magnesium oxide interaction to that of the pure drug and for the isolated chelate is also indicative of a strong surface interaction. This is in contrast to the bathochromic shift observed in the bishydroxycoumarin–magnesium oxide system. The spectral changes observed for furosemide–magnesium trisilicate, magnesium stearate, zinc stearate, and alumina and their isolated chelates are comparable to that of the magnesium oxide system and will not be discussed.

The importance of the strong surface interactions pointed out here cannot be overemphasized with respect to their effect on the therapeutic availability of furosemide. It is possible that these interactions could occur during the wet granulation process of tableting and in the compression of the tablet. The fact that these interactions may occur with different classes of compounds as well as with various adjuvants used in pharmaceutical dosage forms should be recognized, since they may contribute to discrepancies in blood levels and therapeutic efficacy of pharmaceutical dosage forms.

DRS of Interactions of Indomethacin, Digoxin, Chloramphenicol, or Ergonovine Maleate with Excipient—Since these drugs are in widespread use, it was felt that information concerning possible drug–excipient interactions would be of interest. Indomethacin, a recently introduced anti-inflammatory agent, exhibited a strong surface interaction with magnesium oxide and magnesium trisilicate. Figure 8, which illustrates the interaction of indomethacin with magnesium oxide, represents the type of interaction involved. Alumina and acacia exhibited slight interaction with indomethacin, since the DRS spectra of the control and equilibrated sample were comparable.

Due to space limitations, the DRS spectra of the interaction of chloramphenicol, ergonovine maleate, and digoxin with magnesium oxide and magnesium trisilicate are not given; however, a significant interaction was observed in these systems.

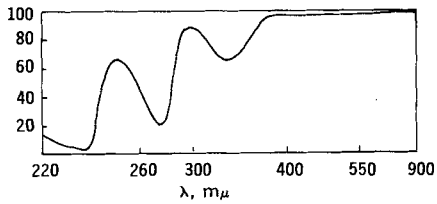


Figure 7—*Transmittance spectrum of furosemide (20 mcg./ml.) in methanol.*

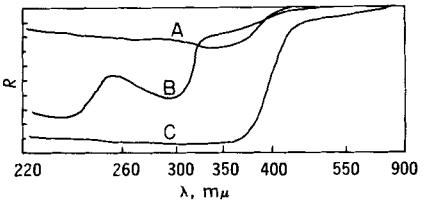


Figure 8—*DRS of indomethacin (30 mg.) and magnesium oxide (2.00 g.). Key: A, control (physical mixture); B, equilibrated sample; and C, indomethacin, 100%.*

SUMMARY

The spectral changes pointed out in this study strongly indicate that solid–solid interactions are not restricted to any particular class of drugs. Although the exact mechanisms of interactions may vary with different drugs, it is significant that they do occur and that they are more widespread than formerly realized.

The nature and strength of these interactions depend on the nature of the drug and of the adjuvant. The nature of adjuvant would include factors such as hydrogen bonding, van der Waals' forces, chemisorption, the amount of adsorbed moisture, and the availability of active sites on the surface of the adjuvant.

The knowledge concerning the availability of the active ingredient cannot be limited to therapeutic aspects but must also encompass the stability of the active ingredient. An awareness of the extent and variety of solid–solid interactions could lead to a more rational and scientific approach to dosage form design.

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