Laser Raman Investigation of Drug–Polymer Conjugates: Sulfathiazole–Povidone Coprecipitates

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Abstract □ Laser Raman spectroscopy is used for the investigation of the drug-polymer conjugates, sulfathiazole-povidone. Specifically, Raman spectra, both in the lattice vibration and the intramolecular vibration regions, are used to characterize various polymorphic forms of sulfathiazole. It is found that sulfathiazole exists in two unsolvated forms, untreated sulfathiazole and another form grown from propanol. The crystals grown from ethanol include varying amounts of ethanol depending on the growth condition. The nature of the povidone-sulfathiazole coprecipitates of various compositions are studied. We find no evidence of any new polymorphic form of sulfathiazole in these coprecipitates. The coprecipitates are found to consist of one of the unsolvated forms of sulfathiazole.

Keyphrases □ Sulfathiazole-conjugate with povidone, laser Raman spectroscopy □ Povidone-conjugate with sulfathiazole, laser Raman spectroscopy

The potential of a polymer matrix to produce a high-energy form of a drug has been realized for a long time. Interest in drug-polymer conjugates stems from the fact that the bioavailability of a drug, and therefore its therapeutic utility, can be increased. The strength and the specificity of interactions between a drug and a polymer play important roles in determining the lattice energy of the drug-polymer conjugate and, thus, the dissolution rate of the drug. The dissolution rate of one drug-polymer conjugate, sulfathiazole-povidone, has been studied by Simonelli *et al.* (1, 2). Povidone produced a high-energy form of the drug which exhibited much faster dissolution than the previously known polymorphic forms of sulfathiazole. When a drug is present in a polymer matrix, its enhanced dissolution rate may be derived from any of the following: (*a*) chemical attachment to the polymer; (*b*) existence of a metastable form of the drug stabilized by specific interactions with polymer; (*c*) the reduction of particle size and crystallinity due to the presence of the polymer. For the sulfathiazole-povidone conjugate, the drug does not appear to chemically bond with the polymer (2). The nature and the effect of the sulfathiazole–povidone interaction on enhancement of dissolution rates is not fully understood.

In this paper we present the investigation of the sulfathiazole-povidone conjugate by the technique of laser Raman spectroscopy. Raman spectroscopy provides spectra of both lattice vibrations (phonons) and intramolecular vibrations (3-5). Phonon spectra provide valuable information on the crystalline interactions; they are used to characterize the crystalline modifications and the effect of various external perturbations (including interactions with a matrix). The intramolecular vibrations are used to study the chemical stability of the various forms (5). These probes are based on the principle that a physical transformation in the solid state shows a dominant effect on the phonon motions but only a small effect on the intramolecular vibrations. On the other hand, a chemical change leads to a change both in the phonon spectra and in the spectra of intramolecular vibrations (6).

Laser Raman spectroscopy was used for the following investigations of sulfathiazole and sulfathiazole-povidone conjugates: (*a*) to identify and characterize the various polymorphic forms of sulfathiazole; (*b*) to determine if povidone produces a high-energy polymorphic form of sulfathiazole that is different from the known polymorphic forms; (*c*) to study the nature and strength of interaction between the drug and the polymer.

EXPERIMENTAL SECTION

Sulfathiazole was grown from ethanol solution by using two different procedures: slow growth at room temperture to generate large crystals, or rapid growth from a warm ethanol solution. The latter method was used by Higuchi *et al.* to produce their polymorphic form I (7). Sulfathiazole was also grown from 1-propanol[1] (80°C and room temperature) and 2-butanol[2] (room temperature) solutions as well as from the melt. The sulfathiazole-povidone[3] conjugates were prepared by the alcohol-evaporation method described by Simonelli *et al.* (1).

Raman spectra were obtained using a double monochromator[4] and the 514.5-nm line of a coherent radiation argon ion laser. Spectra were taken at room temperatures. Direct current detection was used.

RESULTS AND DISCUSSIONS

Polymorphic Forms of Sulfathiazole—Higuchi *et al.* have reported two polymorphic forms of sulfathiazole (7). The recrystallization of sulfathiazole from a warm ethanol solution gave form I. The second form of sulfathiazole was obtained either from the melt, or from a 1-propanol or 2-butanol solution. The room temperature Raman phonon spectra of four sulfathiazole samples are shown in Fig. 1. The phonon spectra obtained were for untreated sulfathiazole (A), rapidly recrystallized from warm ethanol (B), slowly recrystallized from ethanol (C) and recrystallized from 1-propanol (D), respectively. Sulfathiazole B phonon spectra appear to correlate with the phonon spectra of the untreated sulfathiazole. But there are some notable differences. The weak band at 82.0 cm^{-1} of sulfathiazole A splits into a doublet at 81.5 and 89.5 cm^{-1} in the sulfathiazole B spectrum. Additionally, the doublet at 135.0 and 145.0 cm^{-1} in the sulfathiazole A spectrum shifts to 134.5 and 139.5 cm^{-1} for the ethanol-grown sample. We carefully compared the intramolecular vibrations of sulfathiazole A and sulfathiazole B. In the 200–650 cm^{-1} and 900–1600 cm^{-1} regions, the vibrational spectra of sulfathiazole B were essentially similar to that of sulfathiazole A. However, the spectral region 650–900 cm^{-1} showed the following changes (Fig. 2): an extra band was observed at 878.5 cm^{-1} in the sulfathiazole B spectrum; the 681.5, 733.0, and 838.0 bands of pure sulfathiazole shifted to 684.5, 730.0, and 842.5 cm^{-1}, respectively, in the sulfathiazole B spectrum. The observed internal vibration at 878.5 cm^{-1} was identified as belonging to the solvent, ethanol. When frequency shifts are small (<3 cm^{-1}) the interaction between two components is generally weak and of a van der Waals type. In the ethanol-grown sulfathiazole, the observed shifts were ≥3 cm^{-1}. These results may indicate specific interaction between the solvent and some functional group of the drug, *i.e.*, hydrogen bonding. Our analysis was not able to detect the O—H stretching of the ethanol due to its broad and weak nature. However, we found these ethanol-sulfathiazole crystals to be stable for >6 months.

The third phonon spectrum (Fig. 1C) is of sulfathiazole grown slowly from ethanol. New bands were observed at 22.0, 24.5, 27.5, 64.0, and 126.5 cm^{-1}. In addition to these extra features, a comparison of the 30–70 cm^{-1} region for the sulfathiazole B and the sulfathiazole C samples reveal shifts to higher frequencies in the sulfathiazole C spectrum. Again, an inspection of the intramolecular vibrations for the sulfathiazole C sample shows the ethanol band (~878 cm^{-1}) and shifting of bands in the spectral region from 650 to 900

[1] J. T. Baker Co.
[2] Aldrich Chemical Co.
[3] Mol. wt. 10,000; GAF Corp.
[4] Model 14018; Spex.

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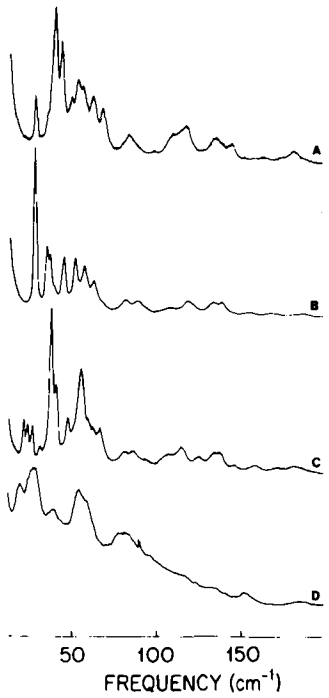

Figure 1—*Room temperature phonon spectra of four sulfathiazole samples. Key: (A) untreated sulfathiazole; (B) sulfathiazole rapidly recrystallized from warm ethanol; (C) sulfathiazole slowly recrystallized from ethanol; (D) sulfathiazole recrystallized from 1-propanol.*

cm^{-1}, similar to what was observed in the sulfathiazole B spectrum. We have also found that some ethanol-grown crystals exhibit phonon features which are in between that observed for sulfathiazole B and sulfathiazole C (*i.e.*, smaller shifts and fewer peaks than the sulfathiazole C spectrum). The ethanol band (~878 cm^{-1}) was present in all spectra of sulfathiazole grown from ethanol.

The results indicate that sulfathiazole incorporates the solvent (ethanol) into its crystal lattice and thus forms a solvate. The differences we observed in the phonon spectra of the various ethanol solvates may be due to varying intake of the solvent by the drug lattice. In other words, sulfathiazole and ethanol do not crystallize in one fixed stoichiometry.

The phonon spectrum of sulfathiazole grown from the 1-propanol solution is also shown (Fig. 1D). The phonon spectrum of this polymorph is distinctly different from the phonon spectra of sulfathiazole A or the ethanol solvates. Only five broad features are observed in the 10–100-cm^{-1} region. Identical broad phonon spectra were also obtained for crystals grown from the 2-butanol solution and from the melt. The intramolecular region 200–1600 cm^{-1} of the sulfathiazole D crystals were compared with that observed for sulfathiazole A. Some notable differences were observed: two new bands were observed at

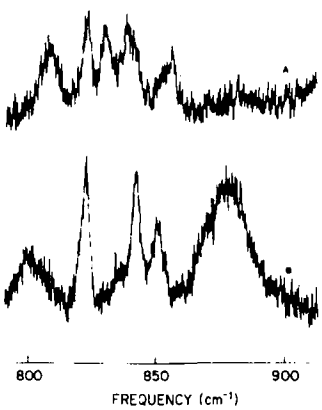

Figure 2—*The 800–900 cm^{-1} internal vibration regions are compared for the untreated sulfathiazole (A) and the sulfathiazole sample rapidly recrystallized from warm ethanol (B). In spectrum B, the broad peak at 878.5 cm^{-1} belongs to the solvent, ethanol.*

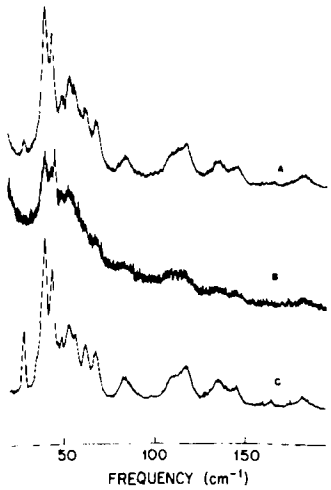

Figure 3—*Phonon spectra of the conjugates having sulfathiazole–povidone weight ratios of 10:1 (A) and 1:1 (B) are compared with the phonon spectra of untreated sulfathiazole (C).*

552.0 and 1502.0 cm^{-1} in the sulfathiazole D spectrum; the 304.0 and 649.5 cm^{-1} bands of pure sulfathiazole shifted to 288.0 and 656.5 cm^{-1} in the sulfathiazole D spectrum; the doublet, 632.5 and 638.5 cm^{-1}, in pure sulfathiazole shifted to 630.0 and 635.5 cm^{-1}. The extra features at 552.0 and 1502.0 cm^{-1} were also present in the 2-butanol-grown sulfathiazole spectra and in some of the drug–polymer conjugates (see next section) that were grown from ethanol. Thus, we do not attribute these new features to the solvent, 1-propanol. The appearance of new features and the shifting of peaks are believed to result from the formation of a different polymorph of sulfathiazole. From the broad nature of phonon bands, it appears that this polymorphic form is more disordered than the ethanol solvate.

Sulfathiazole–Povidone Conjugates—The phonon and the intramolecular vibrational spectra at room temperature were obtained for conjugates having sulfathiazole–povidone weight ratios of 10:1, 5:1, 3:1, 1:1, and 1:2. The phonon spectra of the conjugates 10:1, 1:1, and the sulfathiazole A sample are shown in Fig. 3. The phonon spectra of the 10:1 and 5:1 conjugates were essentially identical with that of sulfathiazole A. The only observable change is that the 27.5-cm^{-1} phonon band decreases in intensity as the weight ratio of sulfathiazole to povidone decrease. A decrease in the weight ratio of sulfathiazole to povidone appears to decrease the resolution of the phonon bands. This can be seen with the phonon spectrum of the 1:1 weight ratio. The 27.5 cm^{-1} transition is no longer visible. This poorly resolved spectrum still correlates with the spectrum of sulfathiazole A. The intramolecular vibrations of the 5:1 and 1:1 conjugates consisted of essentially unperturbed sulfathiazole bands. Also, the ethanol band (~878 cm^{-1}) was not present in either spectra. Therefore, we find no evidence of any chemical interaction between the drug and the polymer. Sulfathiazole appears in an unsolvated form even though the conjugate was precipitated from ethanol.

The phonon spectra of the conjugates 3:1, 1:2, and that of sulfathiazole grown from 1-propanol are shown in Fig. 4. The broad phonon features of the 3:1 conjugate correlates with those observed in the sulfathiazole D spectrum. The intramolecular vibrations of the 3:1 conjugate also correlate with the sulfathiazole D internal vibrations. Thus, sulfathiazole is present in the 3:1 conjugate as the polymorph grown from propanol. Again, no specific interactions between the polymer and the drug were observed.

The phonon spectrum of the 1:2 conjugate (Fig. 4) has a broad transition at 48 cm^{-1} and a weak broad feature at 57 cm^{-1}. While the phonon region of povidone is not shown in Fig. 4, the phonon spectrum of the 1:2 conjugate correlates with that of povidone. Thus, at ratios ≥1:2, the phonon spectra are dominated by povidone. With the lower ratios of sulfathiazole to povidone, the intermolecular vibrations of sulfathiazole were so weak that even the most intense vibrations were barely visible. No correlation of the 1:2 conjugate spectrum could be made. A 1:1 conjugate was prepared by rapidly cooling a sulfathiazole–povidone solution. The phonon spectrum of this conjugate was also dominated by povidone. However, the intramolecular vibrations were observed. Sulfathiazole was present in the 1:1 conjugate as the polymorphic form obtained from 1-propanol.

Simonelli *et al.* have correlated the dissolution rates of sulfathiazole–povidone conjugates to povidone weight fractions (2). They found two plateaus at low povidone weight fractions. They concluded that the lower plateau (lower dissolution rate) resulted from form I (sulfathiazole grown from warm ethanol) being present in the drug–polymer conjugates. Our results of the phonon

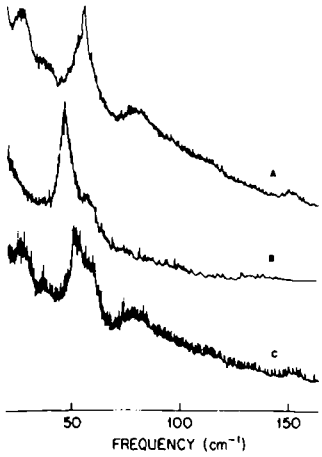

Figure 4—*Phonon spectra of the conjugates having sulfathiazole–povidone weight ratios of 3:1 (A) and 1:2 (B) are compared with that of sulfathiazole grown from propanol (C).*

and intramolecular vibrations have shown that at low povidone weight fractions (10:1, 5:1, and 1:1 conjugates), sulfathiazole was not present as the ethanol solvate but as the unsolvated sulfathiazole. In the sulfathiazole–povidone conjugate region 3:1–1:1.5, a second (higher dissolution rates) plateau was observed. Simonelli *et al.* postulated that the initial rate of dissolution exhibited at the higher plateau could rise from the presence of a new higher energy form of sulfathiazole. However, this higher energy form of sulfathiazole exhibited much faster dissolution than the previously known polymorphic forms of sulfathiazole. In the sulfathiazole–povidone region 3:1–1:1, we observed two different kinds of phonon and intramolecular spectra, one belonging to the sulfathiazole A form and the other being the polymorphic form obtained from propanol. The method of preparation (*i.e.*, temperature and/or concentration of solution) probably determines which of the two forms of sulfathiazole is present in the conjugates with drug–polymer ratios of 3:1–1:1.5. No other crystalline forms of sulfathiazole were observed in the drug–polymer conjugates. We therefore attribute the higher dissolution rate observed to arise from the particle size reduction of the drug in the presence of the polymer, whereby the increased effective surface area leads to an enhanced dissolution rate.

REFERENCES

(1) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **58,** 538 (1969).

(2) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **65,** 355 (1976).

(3) J. C. Bellows, F. P. Chen, and P. N. Prasad, *Drug Dev. Ind. Pharm.*, **3,** 451 (1977).

(4) D. E. Resetarits, K. C. Cheng, B. A. Bolton, P. N. Prasad, E. Shefter, and T. R. Bates, *Int. J. Pharm.*, **2,** 113 (1979).

(5) B. A. Bolton and P. N. Prasad, *J. Pharm. Sci.*, **70,** 789 (1981).

(6) P. N. Prasad, J. Swiatkiewicz, and G. Eisenhardt, *Appl. Spectrosc. Rev.*, **18,** 59 (1982).

(7) W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, *J. Pharm. Sci.*, **56,** 200 (1967).

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Electrostatic Effects in Acylation of Hemoglobin by Aspirins

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Abstract □ Carboxylate substituents added to the salicylate ring increase the effectiveness of a variety of aspirins and diaspirins in acylating hemoglobin. Even more effective are a series of monoesters of dicarboxylate derivatives. Bis(5-carbomethoxysalicyl)fumarate and -succinate at 5 mM concentrations modify ~100% of the hemoglobin in solution and should alter the aggregation behavior of sickle hemoglobin.

Keyphrases □ Diaspirin—hemoglobin, sickle cell anemia, carboxylate substituents □ Hemoglobin—carboxylate-substituted diaspirins, acylation, sickle cell anemia

Previous studies have shown that aspirin and its analogues are capable of acylating hemoglobin (1). Acetylsalicylate, the prototype monoester, tends to transfer its acetyl group largely to the βLys[1] 59 and βLys 144 residues. These are in areas of the protein with a high local concentration of cationic side chains; *e.g.*, βLys 59 is part of a surface constellation constituted of βLys residues 59, 61, 65, and 66. The double-headed bissalicylates, in turn, preferentially go to the β-cleft of hemoglobin. In this canyon, both β chains contribute their βVal 1, βHis 2, βLys 82, and βHis 143 residues to provide a highly cationic environment.

In view of these observations, it seemed likely that even greater acylation of hemoglobin might be achieved with salicylate esters carrying additional negative charges. Furthermore, different structural dispositions of anionic charges on the reagents might lead to alternative specificities in binding to and acylation of Lys residues in hemoglobin. These might be directed toward placing substituents near βVal 6 or near βPhe 85 or βLeu 88 of hemoglobin S, residues evidently at a contact interface in sickled hemoglobin (2, 3). Therefore, several aspirin analogues with added substituents, particularly anionic ones, have been prepared. These substances are members of different classes of compounds: substituted monosalicylates [substituted carboxyphenyl acetates (I–V)]; substituted bissalicylates of succinic acid [bis(substituted carboxyphenyl)succinates (VI, VII, X, and XI)], of fumaric acid [bis(substituted carboxyphenyl)fumarates (VIII and IX)], or of anhydromethylene citric acid [bis(substituted

[1] Key: (Lys) lysine; (Val) valine; (His) histidine; (Phe) phenylalanine; (Leu) leucine.

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