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ACKNOWLEDGMENTS

Abstracted in part from a thesis submitted by J. A Plaizier-Vercammen to the Vrije Universiteit van Brussel in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors thank Mr. G. R. Bultinck for technical assistance.

Polymorphism of Spray-Dried Microencapsulated Sulfamethoxazole with Cellulose Acetate Phthalate and Colloidal Silica, Montmorillonite, or Talc

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Received January 8, 1981, from the *Gifu College of Pharmacy, Mitahora, Gifu 502, Japan.* Accepted for publication March 27, 1981.

Abstract □ Sulfamethoxazole was microencapsulated with cellulose acetate phthalate and talc, colloidal silica, or montmorillonite clay by a spray-drying technique. The surface topography of the products varied with the type of excipient used and the pH of the suspending medium. The products without the excipient were coated with flake-like crusts, while the products containing the excipient tended to become well-rounded spheres. In addition, the crystalline form of sulfamethoxazole converted from Form I to an amorphism and Form II during the spray-drying process. This polymorphic transformation was attributed to the interaction of cellulose acetate phthalate with sulfamethoxazole. Increasing the concentration of cellulose acetate phthalate in the formulation increased the attainment of amorphism. Form II was also obtained by freeze and vacuum drying. Talc was the only excipient that contributed to polymorphism, which occurred in the alkaline suspension medium. Montmorillonite products prepared from the acidic medium exhibited an exothermic differential scanning calorimetry thermogram, which might be interpreted in terms of adsorption of the fused sulfamethoxazole with the internal surface of montmorillonite.

Keyphrases □ Microencapsulation—sulfamethoxazole, spray drying with cellulose acetate phthalate and colloidal silica, montmorillonite, or talc, polymorphism □ Polymorphism—microencapsulation of sulfamethoxazole, spray drying with cellulose acetate phthalate and colloidal silica, montmorillonite, or talc □ Sulfamethoxazole—microencapsulated, polymorphism, spray drying with cellulose acetate phthalate and colloidal silica, montmorillonite, or talc

The appropriate selection of the most suitable polymorphic form of medicaments with high thermodynamic activities frequently is the key to improving bioavailability or preventing caking in an aqueous vehicle.

The polymorphic form of a compound depends on the nature of crystallization, *i.e.*, the type of solvent used, the temperature of crystallization, *etc.* It has been documented that polymorphism occurs during spray drying. Fell and Newton (1) produced spray-dried lactose that was a mixture of α-monohydrate, α-anhydrous, and β-lactose forms. Kawashima *et al.* (2) reported that spray-dried sodium salicylate was polymorphic, composed of normal crystals and amorphisms. Another study (3) showed that the crystalline form of spray-dried sulfamethoxazole with cellulose acetate phthalate converted from Form I to Form II and an amorphism.

The present study examined the effects of cellulose acetate phthalate and excipients such as colloidal silica, talc, and montmorillonite clay on polymorphism. Tests were performed by freeze drying and vacuum drying at 70° using the same formulations as for spray drying. Another microcapsule of sulfamethoxazole with cellulose acetate phthalate was prepared by the coacervation method of Merkle and Speiser (4) as a reference to test polymorphism.

EXPERIMENTAL

Preparations of Microcapsules and Agglomerates—Sulfamethoxazole[1] (50 g) and cellulose acetate phthalate[2] (10–50 g) were dis-

[1] Shionogi Pharmaceutical Co., Japan.
[2] Kishida Chemical Co., Japan.

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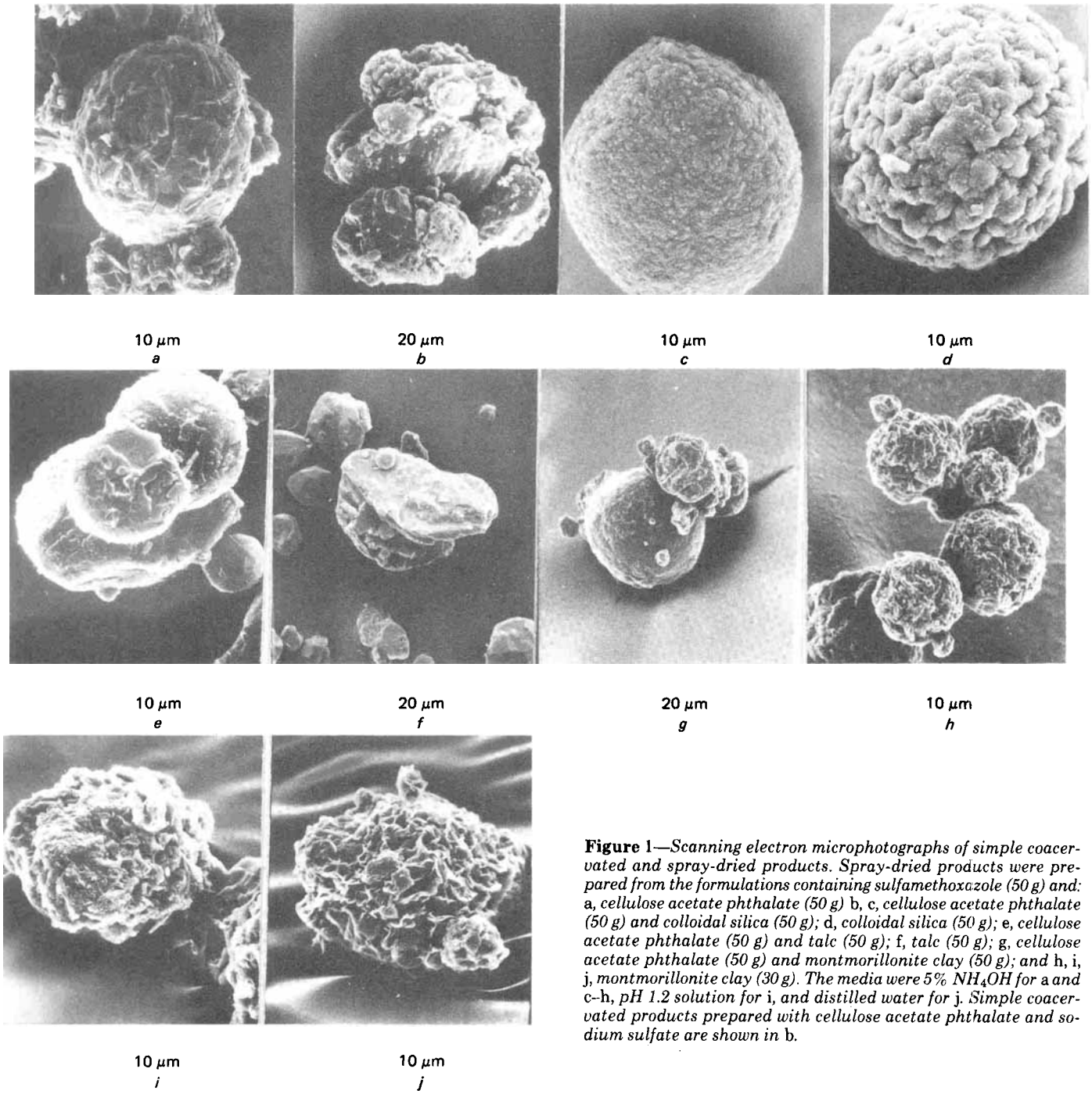

Figure 1—*Scanning electron microphotographs of simple coacervated and spray-dried products. Spray-dried products were prepared from the formulations containing sulfamethoxazole (50 g) and:* a, *cellulose acetate phthalate (50 g)* b, c, *cellulose acetate phthalate (50 g) and colloidal silica (50 g);* d, *colloidal silica (50 g);* e, *cellulose acetate phthalate (50 g) and talc (50 g);* f, *talc (50 g);* g, *cellulose acetate phthalate (50 g) and montmorillonite clay (50 g); and* h, i, j, *montmorillonite clay (30 g). The media were 5% NH_4OH for* a *and* c–h, *pH 1.2 solution for* i, *and distilled water for* j. *Simple coacervated products prepared with cellulose acetate phthalate and sodium sulfate are shown in* b.

solved in 1 liter of 5% NH_4OH. To this solution was added 0, 30, or 50 g of colloidal silica[3], talc[4], or montmorillonite clay[5]. The resultant slurries were supplied for spray drying. Formulations without cellulose acetate phthalate were also prepared to test the influence of excipients alone on polymorphism. These slurries or solutions were atomized into a drying chamber by a centrifugal wheel atomizer at 40,000 rpm[6]. The drying chamber was maintained at 140 ± 10°, and the dried products were collected by a cyclone collector.

The detailed formulations for spray drying were as follows.

Spray drying for microencapsulation involved sulfamethoxazole (50 g) as the medicament, cellulose acetate phthalate (50 g) as the wall material, colloidal silica and montmorillonite clay (0, 30, and 50 g) as the excipients, and 1 liter of 5% NH_4OH as the medium.

Spray drying for agglomeration involved sulfamethoxazole (50 g) as the medicament with colloidal silica, talc, and montmorillonite clay (30 and 50 g) in 1 liter of 5% NH_4OH; colloidal silica, talc, and montmorillonite clay (30 g) in 1 liter of pH 1.2 solution; and colloidal silica, talc and montmorillonite clay (30 g) in 1 liter of distilled water.

Evaporation at 70° in vacuum (20 mm Hg) or spray drying at 140 ± 5° involved sulfamethoxazole (50 g) as the medicament, cellulose acetate phthalate (10–50 g) as the additive, and 5% NH_4OH as the medium.

Cellulose acetate phthalate microcapsules of sulfamethoxazole were prepared by the coacervation method of Merkle and Speiser (4). Sulfamethoxazole (10 g) was suspended in 100 ml of aqueous solution (pH 7.5) containing 2 g of cellulose acetate phthalate and 0.74 g of dibasic sodium phosphate. The system was maintained at 60° and agitated at 620 rpm. Then 25 ml of 20% (w/w) aqueous sodium sulfate solution preheated at 60° was added in small portions. The system was slowly cooled to 20°, and the coacervates were separated and washed with water to remove noncoacervated cellulose acetate phthalate. The coacervate wall was hardened by 2% aqueous acetic acid.

Five grams of sulfamethoxazole and cellulose acetate phthalate were dissolved in 100 ml of 5% NH_4OH. The solutions were vacuum freeze

[3] Japan Aerosil Co., Japan.
[4] Matsumura Sangyo Co., Japan.
[5] Veegum-K, R. T. Vanderbilt Co.
[6] Iwai Kikai Kogyo Co., Japan.

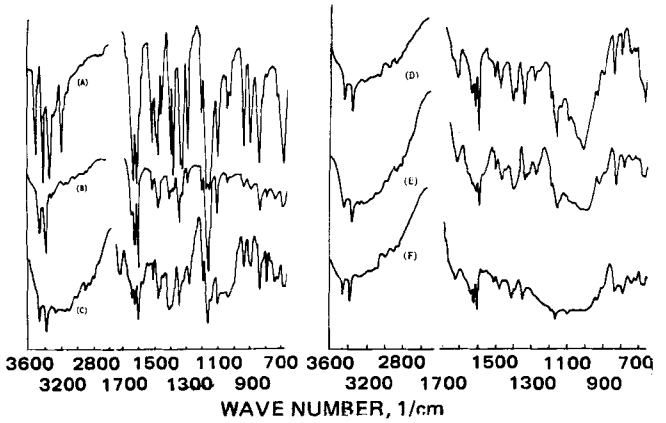

Figure 2—*IR spectra of original sulfamethoxazole and spray-dried products containing cellulose acetate phthalate. Key: A, Form I, original sulfamethoxazole, simple coacervated microcapsule; B, Form II; and C–F, spray-dried products prepared from the formulations containing 50 g of cellulose acetate phthalate (C), 50 g of cellulose acetate phthalate and 50 g of talc (D), 50 g of cellulose acetate phthalate and 50 g of montmorillonite clay (E), 50 g of cellulose acetate phthalate and 50 g of colloidal silica (F). The medium was 5% NH_4OH.*

dried at −20° (10^{-3} mm Hg) in a freeze dryer[7].

One hundred milliliters of 5% NH_4OH solution containing 5 g of sulfamethoxazole and cellulose acetate phthalate were evaporated at 70° in vacuum to remove ammonium hydroxide and water. The precipitated particles were supplied to test the crystalline form of sulfamethoxazole.

Measurement of Physicochemical Properties—The surface topography of the spray-dried particles coated with gold was investigated with a scanning electron microscope[8]. To determine the crystalline form of sulfamethoxazole, X-ray diffraction patterns, IR absorption spectra, and differential scanning calorimetry thermograms were obtained using an X-ray diffractometer[9], an IR spectrometer[10], and a differential scanning calorimetry calorimeter[11] run with a scanning rate of 5°/min, respectively.

RESULTS AND DISCUSSION

Surface Topography of Agglomerates and Microcapsules—Surface topography of the agglomerates and microcapsules was investigated using scanning electron microscopy. The microcapsules with cellulose acetate phthalate prepared by spray drying and coacervation are shown in Figs. 1*a* and 1*b*, respectively. The surfaces of spray-dried microcapsules were composed of flake-like crusts. The simple coacervated microcapsules were aggregated to form an agglomerate.

When the additives were introduced to the formulations for spray drying, the resultant microcapsules became well-rounded spheres without flakes but varied in some degree, depending upon the type of additive used (Figs. 1*c*, 1*e* and 1*g*). The surface topography of agglomerates prepared by spray drying with the formulations containing only sulfamethoxazole and the excipient are seen in Figs. 1*d*, 1*f*, and 1*h*–1*j*. The agglomerates took various forms, depending on the type of excipient and the pH of the vehicle. The latter factor strongly affected the topography of agglomerates with montmorillonite clay (Figs. 1*g*–1*j*).

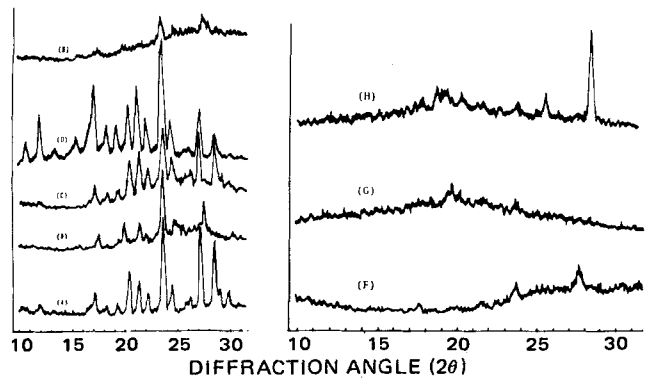

Figure 3—*X-ray diffraction patterns of original sulfamethoxazole, physical mixture, coacervated microcapsule, and spray-dried products with cellulose acetate phthalate. Key: A, Form I; B, Form II; C, physical mixture of sulfamethoxazole and cellulose acetate phthalate; D, simple coacervated microcapsule; and E–H, spray-dried products prepared from the formulations containing 50 g of cellulose acetate phthalate (E), 50 g of cellulose acetate phthalate and 50 g of colloidal silica (F), 50 g of cellulose acetate phthalate and 50 g of montmorillonite clay (G), and 50 g of cellulose acetate phthalate and 50 g of talc (H). The medium was 5% NH_4OH.*

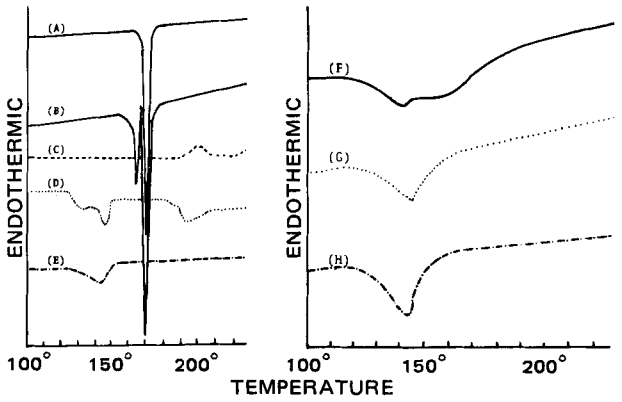

Figure 4—*Differential scanning calorimetric thermograms for original sulfamethoxazole, cellulose acetate phthalate, freeze-dried sulfamethoxazole, and spray-dried products containing cellulose acetate phthalate. Key: A, Form I; B, Form II; C, original cellulose acetate phthalate; E, freeze-dried sulfamethoxazole; and D and F–H, spray-dried products prepared from the formulations containing 50 g of cellulose acetate phthalate (D), 50 g of cellulose acetate phthalate and 50 g of colloidal silica (F), 50 g of cellulose acetate phthalate and 50 g of montmorillonite clay (G), and 50 g of cellulose acetate phthalate and 50 g of talc (H). The medium was 5% NH_4OH.*

Effects of Cellulose Acetate Phthalate on Polymorphism—The IR spectra of original sulfamethoxazole and spray-dried products with cellulose acetate phthalate are seen in Fig. 2. The crystalline form of original sulfamethoxazole was proved to be Form I by identification of its IR spectrum, characterized by intense bands at 3300 and 3150 cm^{-1} attributed to the amide N–H stretching vibration (5). Regardless of whether the excipients were included in the formulations, all spray-dried products with cellulose acetate phthalate exhibited the characteristic absorption bands of Form II in their IR spectra, *i.e.*, weaker bands than those of Form I at 3300 and 3150 cm^{-1} and additional bands at 1640, 1395, 1330, and 750 cm^{-1}.

Form II of sulfamethoxazole was prepared by recrystallizing its aqueous solution at dry ice–acetone temperature. It was also confirmed that the crystalline form of freeze- and vacuum-dried sulfamethoxazole always exhibited Form II when cellulose acetate phthalate was included. The sulfamethoxazole in the simple coacervated microcapsule proved to be Form I.

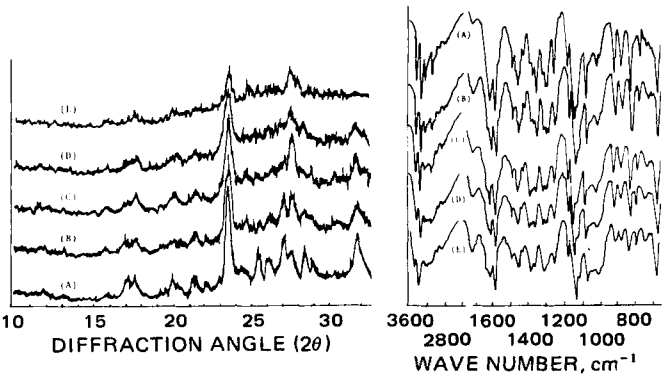

Figure 5—*IR spectra and X-ray diffraction patterns of spray-dried products with increasing amounts of cellulose acetate phthalate: A, 10 g; B, 20 g; C, 30 g; D, 40 g; and E, 50 g. The medium was 5% NH_4OH.*

[7] DC-35, Yamato Science Co., Japan.
[8] Nihon Denshi, JSM-S1.
[9] Nihon Denshi, JDX.
[10] Nihon Denshi, DS-403G.
[11] Rigaku, CN808521.

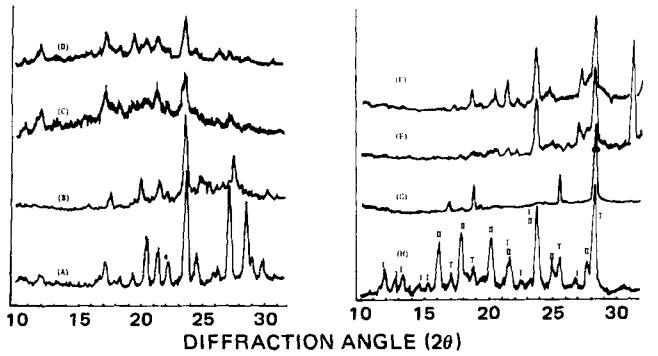

Figure 6—*X-ray diffraction patterns of original sulfamethoxazole and spray-dried products without cellulose acetate phthalate. Key: A, Form I; B, Form II; C–F and H, spray-dried products prepared from the formulations containing 30 g of colloidal silica (C), 30 g of montmorillonite clay (D), and 30 g of talc (E, F, and H); and G, original talc. Key for H: I, Form I; II, Form II; and T, talc. Media were 5% NH_4OH (C, D, and H), distilled water (E), and pH 1.2 solution (F).*

The peaks in X-ray diffraction patterns of the excipients were less intense than those of the original crystals (Fig. 3). This finding suggests that some sulfamethoxazole crystals in the spray-dried products converted to a disordered form due to the rapid evaporation. The pattern for sulfamethoxazole in the simple coacervated microcapsule coincided with that of Form I.

In the differential scanning calorimetric thermogram of Form II, sharp endothermic peaks appeared at 166 and 171° (Fig. 4), attributed to the transition temperature from Form II to I and to the fusion temperature of Form I, respectively. Spray- and freeze-dried products containing cellulose acetate phthalate exhibited a broad peak at 140–150° in the thermogram. This characteristic discrepancy in the thermograms suggests that some sulfamethoxazole in the spray-dried products exists in amorphic form as already described.

To investigate the effect of cellulose acetate phthalate on the crystalline form, spray drying was performed with various amounts of cellulose acetate phthalate contained in the formulations. With increasing cellulose acetate phthalate concentration, the characteristic IR bands of Form II at 1640, 1395, and 1330 cm^{-1} became more intense while the bands at 3300 and 3150 cm^{-1} became weaker (Fig. 5). The reduced intensities of the X-ray diffraction patterns of the product with a high cellulose acetate phthalate concentration indicated increased amorphism. These findings suggested that cellulose acetate phthalate in the formulation caused polymorphism to occur. It was reported (5, 6) that sulfonamide polymorphism might be due to the formation of intermolecular hydrogen bonds. Hydrogen bonding may occur between the acetyl and hydroxyl groups of cellulose acetate phthalate and the *p*-amino and sulfonyl groups

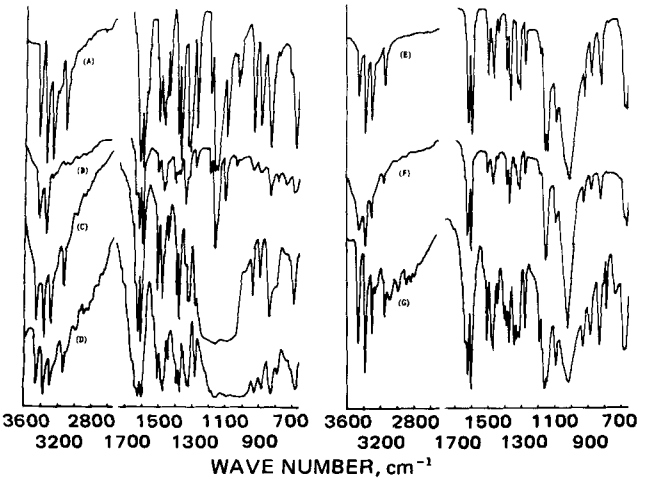

Figure 7—*IR spectra of original sulfamethoxazole and spray-dried products without cellulose acetate phthalate. Key: A, Form I; B, Form II; and C–G, spray-dried products prepared from the formulations containing 30 g of colloidal silica (C), 30 g of montmorillonite clay (D), and 30 g of talc (E–G). Media were 5% NH_4OH (C, D, and G), pH 1.2 solution (E), and distilled water (F).*

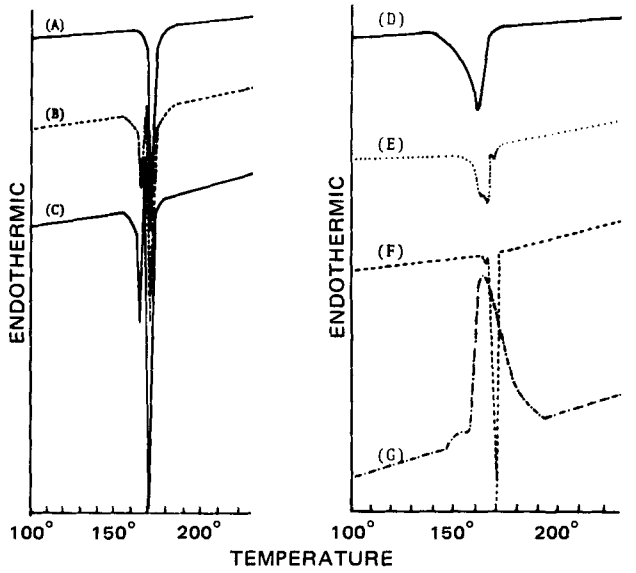

Figure 8—*Differential scanning calorimetric thermograms for original sulfamethoxazole and spray-dried products. Key: A, Form I; B, Form II; and C–G, spray-dried products prepared from the formulations containing 30 g of talc (C), 30 g of colloidal silica (D), and 30 g of montmorillonite clay (E–G). Media were 5% NH_4OH (C–E), distilled water (F), and pH 1.2 solution (G).*

of sulfamethoxazole. This phenomenon, and the steric hindrance of cellulose acetate phthalate, may restrict the intermolecular hydrogen bonding of sulfamethoxazole.

Effects of Excipients on Polymorphism—To examine the effects of excipients on the polymorphism of spray-dried sulfamethoxazole, cellulose acetate phthalate was excluded from the formulations. The X-ray diffraction patterns (Fig. 6) and IR spectra (Fig. 7) of the products with montmorillonite clay and colloidal silica suggested that the products were the polymorphic mixture of Form I and amorphisms. The products with talc exhibited a sharp X-ray diffraction pattern, characteristic of the patterns of Form I and talc (Fig. 6). Furthermore, the pattern varied with the type of medium (Fig. 6). IR spectra proved the crystalline forms of the products prepared from the aqueous and acidic slurries to be Form I. Peaks in the IR spectra and X-ray diffraction patterns of products prepared from the ammonium slurries were characteristic of both Form I and II, indicating a polymorphic mixture.

The mechanism of polymorphic transformation that occurred in the alkaline medium was not resolved in the present study. However, previous investigators (7) reported that anionic dyes were selectively adsorbed with talc from aqueous solution. In alkaline medium, the anionic form of sulfamethoxazole could be strongly adsorbed with talc, causing reduced intermolecular hydrogen bonding of sulfamethoxazole, and possibly converting crystals from Form I to Form II. In the aqueous medium, the silanol group of colloidal silica and montmorillonite clay should be hydrated, preventing the formation of hydrogen bonds between sulfamethoxazole and the silanol groups. Thus, the drug molecule adsorbed only physically might be disordered when crystallized by spray drying, leading to amorphism.

Differential scanning calorimetric thermograms of the spray-dried products were characteristic of the type of excipient and medium used. The thermogram of the talc-containing product prepared from ammonium slurries was characteristic of that of Form II (Fig. 8), thus supporting the polymorphic transformation suggested previously by X-ray and IR analyses. The product with colloidal silica exhibited a broad endothermic peak at 150–160° in the thermogram, suggesting the coexistence of amorphism.

Thermograms of the product with montmorillonite clay varied with the type of medium used. The product from distilled water was Form I since most sulfamethoxazole crystals were not dissolved but only suspended in water. With the ammonium slurries, a broad peak resembling that of the product with colloidal silica appeared in the thermogram. When the acidic medium was used, the thermogram changed to an exothermic pattern having a peak at 164°. Porubcan *et al.* (8) reported that the distance between the interlayers of montmorillonite clay in an acidic medium is larger than in an alkaline medium. Thus, when the product prepared from the acidic medium was heated, sulfamethoxazole might

interact with the internal surface of montmorillonite clay since the distance between the interlayers is wide enough for holding the molecule. This interaction might produce some heat, leading to the exothermic thermogram in Fig. 8.

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ACKNOWLEDGMENTS

The X-ray diffractometer and differential scanning calorimeter were used through the courtesy of Professor Otsuka at Meijyo University and Mr. Saito at Hokuriku Pharmaceutical Co., Japan.

This paper is Part X of studies on "Spray-Drying Agglomeration."

Extended Hansen Solubility Approach: Naphthalene in Individual Solvents

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Received January 30, 1981, from the **Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX 78712,* ‡*Abbott Laboratories, North Chicago, IL 60064,* §*Energy Center, University of California at San Diego, La Jolla, CA 92093,* and the ¶ *Department of Chemical Engineering, University of California, Berkeley, CA 94720.* Accepted for publication April 3, 1981.

Abstract □ A multiple regression method using Hansen partial solubility parameters, δ_D, δ_P, and δ_H, was used to reproduce the solubilities of naphthalene in pure polar and nonpolar solvents and to predict its solubility in untested solvents. The method, called the extended Hansen approach, was compared with the extended Hildebrand solubility approach and the universal-functional-group-activity-coefficient (UNIFAC) method. The Hildebrand regular solution theory was also used to calculate naphthalene solubility. Naphthalene, an aromatic molecule having no side chains or functional groups, is "well-behaved"; *i.e.*, its solubility in active solvents known to interact with drug molecules is fairly regular. Because of its simplicity, naphthalene is a suitable solute with which to initiate the difficult study of solubility phenomena. The three methods tested (Hildebrand regular solution theory was introduced only for comparison of solubilities in regular solution) yielded similar results, reproducing naphthalene solubilities within ~30% of literature values. In some cases, however, the error was considerably greater. The UNIFAC calculation is superior in that it requires only the solute's heat of fusion, the melting point, and a knowledge of chemical structures of solute and solvent. The extended Hansen and extended Hildebrand methods need experimental solubility data on which to carry out regression analysis. The extended Hansen approach was the method of second choice because of its adaptability to solutes and solvents from various classes. Sample calculations are included to illustrate methods of predicting solubilities in untested solvents at various temperatures. The UNIFAC method was successful in this regard.

Keyphrases □ Naphthalene—solubility study, extended Hansen, extended Hildebrand, and UNIFAC approaches compared □ Solubility—of naphthalene in various solvents, extended Hansen, extended Hildebrand, and UNIFAC approaches compared □ Extended Hansen solubility approach—compared with extended Hildebrand and UNIFAC approaches, naphthalene solubility in various solvents

The solubility parameter concept (1) was originally designed to describe nonpolar solvent–solute systems, although it recently has been extended to the realm of commercial paints, inks, plastics, insecticides, and pharmaceuticals, which may include highly polar solvents and solutes.

The problem of estimating the solubility of crystalline solids in various solvents has been particularly intractable. This report uses partial solubility parameters together with multiple regression analysis to obtain equations that predict solubilities within an error of <30% relative to experiment. Results using a partial parameter–multiple regression method, referred to here as the extended Hansen solubility approach, were compared with those obtained by the extended Hildebrand solubility approach (2) and the universal-functional-group-activity-coefficient (UNIFAC) method (3, 4).

The interaction of a solute and solvent follows either from weak van der Waals forces or from strong forces of a "chemical" nature, such as hydrogen bonding and Lewis acid–base interactions (5). For solutions of interest in the pharmaceutical and biological sciences, both physical and chemical forces are likely to be important.

THEORY

Partial Solubility Parameters—Burrell (6, 7) extended the original solubility parameter concept to estimate the solubility of coating materials (mainly polymers) in polar solvents of low, medium, and high hydrogen-bonding capacity. Hansen (8, 9) partitioned the cohesive energy density, $\Delta E/V$, for a species into contributions from dispersion forces, dipolar interactions, and hydrogen bonding:

$$\frac{\Delta E}{V} = \frac{\Delta E_D}{V} + \frac{\Delta E_P}{V} + \frac{\Delta E_H}{V} \qquad \text{(Eq. 1)}$$

or:

$$\delta^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \qquad \text{(Eq. 2)}$$

where:

$$\delta = (\Delta E^v/V)^{1/2} \cong \left(\frac{\Delta H^v - RT}{V}\right)^{1/2} \qquad \text{(Eq. 3)}$$

ΔE^v is the energy of vaporization of a liquid, ΔH^v is its enthalpy of vaporization, R is the gas constant, T is the absolute temperature, and V is the liquid molar volume. The quantity δ is the total solubility parameter, and δ^2 is the cohesive density for a solvent or solute. The term δ_D stands for the dispersion component of the total solvent or solute solubility parameter, δ_P is the polar component, and δ_H is the hydrogen-bonding component. These terms are the partial solubility parameters.

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