Preparation of Enteric-Coated Microcapsules for Tableting by Spray-Drying Technique and *In Vitro* Simulation of Drug Release from the Tablet in GI Tract

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Abstract □ Improved methods were developed for the preparation of enteric-coated microcapsules for tableting by a spray-drying technique, and the drug release behavior from the tableted microcapsules was investigated using a disintegration apparatus and a new *in vitro* method of simulating the GI tract. As a model system, ammonium solutions of sulfamethoxazole and cellulose acetate phthalate were spray dried using a centrifugal wheel atomizer at 140°. Additives such as colloidal silica, montmorillonite clay, and talc were included in the formulations for spray drying. The influence of the additives on the particle diameter, density, packing properties, and compressibility of the product and on the release characteristics of the resultant tablet *in vitro* were investigated. The additives in the formulations greatly improved the flow properties of the spray-dried products, which could be tableted easily. Products from the nonadditive formulations could not be tableted due to their poor flowability. The hardness and disintegration rate of the tablet increased with increasing concentration of additives in the formulations. X-ray analysis and IR spectroscopy confirmed that the crystals of sulfamethoxazole in the spray-dried microcapsules with cellulose acetate phthalate were converted from Form I to Form II. *In vitro* release characteristics of the tablets were studied using a disintegrator (JP) in buffer solutions (pH 1.2 and 7.5) and distilled water. Enteric action of the spray-dried products was proved by comparison with the original nontreated powders. The additives in the tablet increased the release rate at the initial stage in all dissolution media used. A new *in vitro* release simulator was devised consisting of a flow-type dissolution container in which the pH of the medium was changed continuously from 1.2 to 7.0 to simulate the pH change of tablets exposed to the GI tract.

Keyphrases □ Microcapsules—preparation of enteric-coated microcapsules for tableting by a spray-drying technique, drug release from tableted microcapsules □ Tablets—preparation of enteric-coated microcapsules for tableting, drug release from tableted microcapsules □ Dissolution—tableted enteric-coated microcapsules

Spray-drying techniques have been used widely for drying heat-sensitive foods, pharmaceuticals, and other substances because of the rapid evaporation of the solvent from the droplets. Interest has been renewed in this technique for the preparation of agglomerates or microcapsules of pharmaceuticals. Speiser *et al.* (1) prepared microcapsules of barbituric acid employing a spray polycondensation method. Kawashima and Takenaka (2) produced sustained-action antacid tablets by compressing spray-dried microcapsules of magnesium carbonate. The successful results from these studies encouraged further development of this technique for preparation of a new dosage form.

One objective of the present study was to prepare enteric-coated microcapsules of sulfamethoxazole efficiently by a spray-drying technique instead of by a phase separation method (3). Proper formulation and spray-drying conditions were sought for producing microcapsules with enteric action that meet the requirement for tableting. Another objective was to devise a new *in vitro* simulator for the GI tract to evaluate the enteric action of the tablet prepared by compressing the spray-dried products.

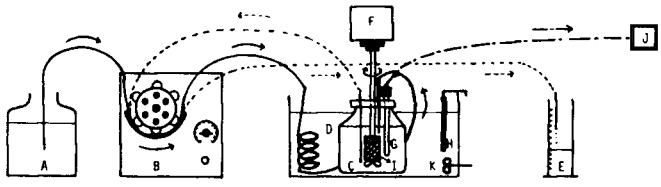

Figure 1—*Apparatus for a new* in vitro *release simulator. Key: A, alkaline solution supplier; B, roller pump (1.27 ml/min); C, modified dissolution apparatus; D, water bath (37°); E, receiving reservoir; F, motor (94 rpm); G, pH electrode; H, heater; I, USP basket modified by attaching four-blade propeller; J, pH meter; K, stirrer; and — and ---, polyethylene tube plugged with cotton at initial points.*

EXPERIMENTAL

Spray-Drying Technique—Sulfamethoxazole[1] was used as received as a model pharmaceutical for microencapsulation or agglomeration. Sulfamethoxazole and cellulose acetate phthalate[2] (50 g each) were dissolved in 1 liter of 5% NH_4OH. To this solution were added 0, 30, and 50 g of colloidal silica[3], montmorillonite clay[4], and talc[5]. Formulations without cellulose acetate phthalate also were prepared as a reference for testing the enteric action.

The slurries or solutions were atomized into a drying chamber by a centrifugal wheel atomizer at 40,000 rpm. The drying chamber was maintained at 140 ± 10°. The dried products were collected by a cyclone collector.

Measurement of Physicochemical Properties—The particle size of the spray-dried products was measured by a photographic counting method using a particle-size analyzer[6]. Packing properties and particle density were measured by a tapping powder method and with a helium–air comparison pycnometer[7], respectively. The surface topography of the spray-dried particles coated with gold was investigated with a scanning electron microscope[8]. To analyze the crystalline form of sulfamethoxazole in the spray-dried products, X-ray diffraction patterns[9] and IR spectra[10] were obtained.

Dissolution Test of Tablets Prepared from Spray-Dried Products—Spray-dried products with additives and the mixtures with microcrystalline cellulose[11] (1:1) were tableted using a single-punch tablet machine. The dimensions and weights of 10 tablets were measured. The hardness of the tablets was measured by a moving platen-type hardness tester[12]. Tablet hardness is presented as average values.

The dissolution test of a tablet was undertaken using the JP IX disintegration apparatus and the specified disintegration test solutions (pH 1.2 and 7.5) and distilled water at 37°. Tests also were conducted with a new *in vitro* release simulator (Fig. 1) with a flow-type dissolution container in which the pH of the medium was changed continuously to simulate the pH change on the surface of the tablets exposed in the GI tract.

[1] Shionogi Pharmaceutical Co., Japan.
[2] Kishida Chemical Co., Japan.
[3] Japan Aerosil K.K., Japan.
[4] Veegum-K, R. T. Vanderbilt Co.
[5] Matsumura Sangyo Co., Japan.
[6] Karl Zeiss TGZ-3.
[7] Model 1302, Micromeritics Instrument Co.
[8] Nihon Denshi JMS-S1.
[9] Nihon Denshi JDX.
[10] Nihon Denshi DS-403G.
[11] Asahi Kasei Kogyo K.K., Japan.
[12] Kyowa Seiko K.K., Japan.

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Table I—Micromeritic Properties of Powdered and Tableted Spray-Dried Products [a]

Property	Montmorillonite Clay		Colloidal Silica		Talc		No Additive
			With Cellulose Acetate Phthalate				
Weight of additive, g	30	50	30	50	30	50	—
D_{av}, μm	8.8	12.8	12.8	15.9	13.4	9.9	22.2
S_w, cm^2/g	4947	3386	3190	2498	2986	4126	2159
ρ, g/cm^3	1.38	1.39	1.50	1.50	1.50	1.50	1.25
a	0.29	0.32	0.14	0.06	0.36	0.31	0.37
b	0.05	0.08	0.07	0.12	0.05	0.05	0.07
ϵ	0.12	0.05	0.07	0.07	0.19	0.16	—
H, kg	3.7	24.2	2.2	12.4	1.1	2.3	—
			Without Cellulose Acetate Phthalate				
Weight of additive, g	30		30	50	30	50	
D_{av}, μm	8.1		7.1	3.6	3.5	8.8	
S_w, cm^2/g	4619		5093	9898	10,988	3940	
ρ, g/cm^3	1.61		1.66	1.68	1.55	1.72	
a	0.31		0.13	0.16	0.39	0.45	
b	0.06		0.13	0.07	0.07	0.09	
ϵ	0.21		0.63	0.45	0.31	0.32	
H, kg	8.7		45	—	2.27	3.77	

[a] Key: D_{av}, geometric mean diameter; S_w, specific area measured by air permeability method; ρ, porosity of tablet; and H, hardness of tablet.

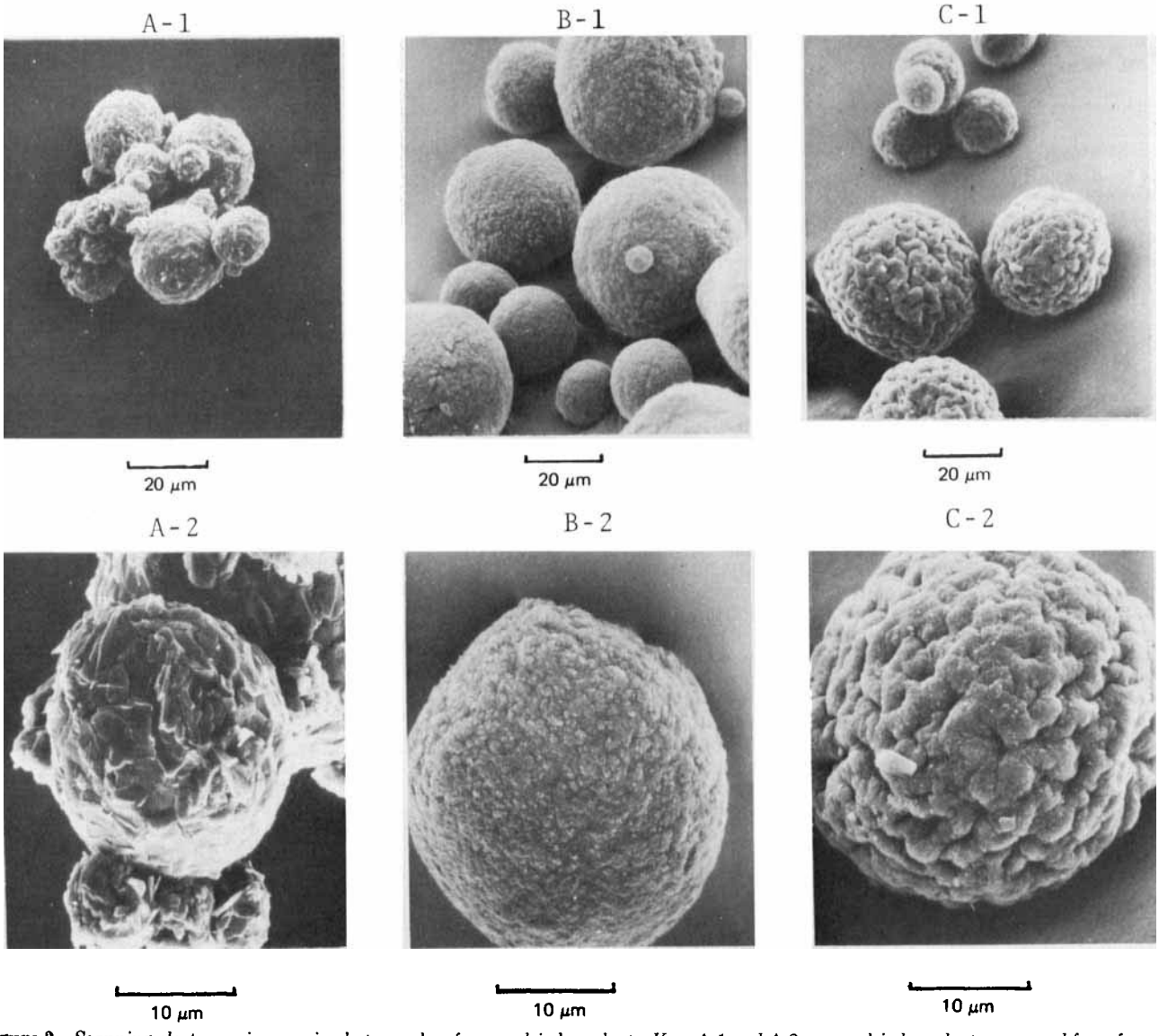

Figure 2—*Scanning electron microscopic photographs of spray-dried products. Key: A-1 and A-2, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g); B-1 and B-2, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g) and colloidal silica (50 g); and C-1 and C-2, spray-dried products prepared from formulations containing colloidal silica (50 g).*

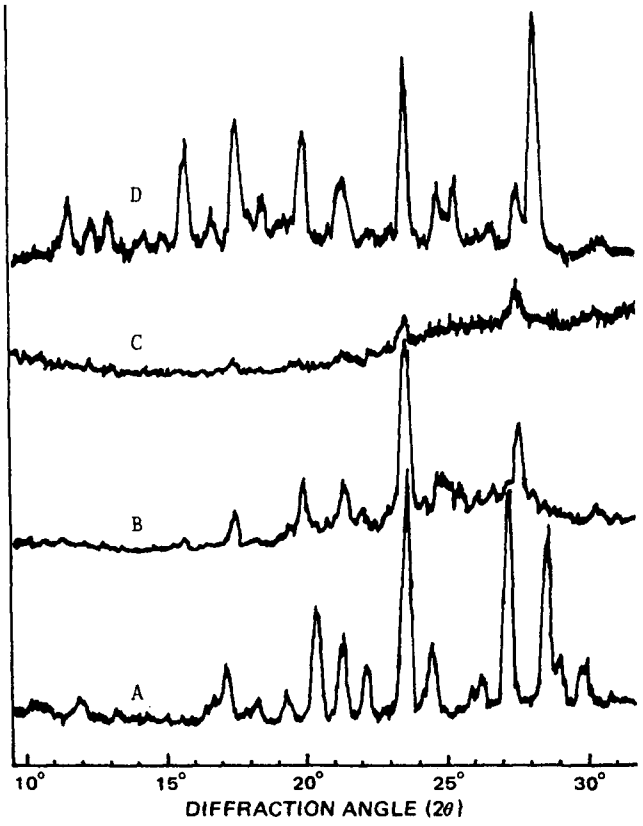

Figure 3—*X-ray diffraction patterns of original and spray-dried sulfamethoxazole. Key: A, Form I, original sulfamethoxazole; B, Form II, sulfamethoxazole recrystallized in water at dry ice–acetone temperature; C, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g) and colloidal silica (50 g); and D, spray-dried products prepared from formulations containing talc (50 g).*

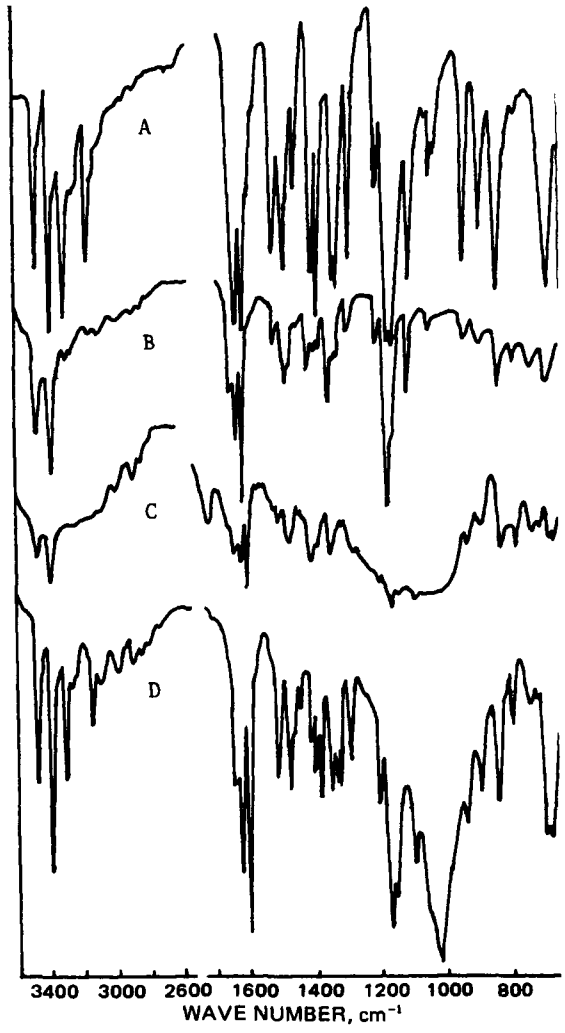

Figure 4—*IR spectra of original and spray-dried sulfamethoxazole. Key: A, Form I, original sulfamethoxazole; B, Form II, sulfamethoxazole recrystallized in water at dry ice–acetone temperature; C, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g) and colloidal silica (50 g); and D, spray-dried products prepared from formulations containing talc (50 g).*

The test was carried out by placing a tablet in the basket specified in the USP dissolution apparatus, which was modified by attaching a four-blade propeller. This basket was set 1.0 ± 0.2 cm from the bottom of the container and was rotated at 94 rpm. The pH 1.2 medium (300 ml) was introduced into the dissolution apparatus, followed by the addition of the alkaline medium (pH 7.5) at a rate of 1.27 ml/min. Simultaneously, the agitated dissolution medium was removed at the same rate to a reservoir using a rotating-type pump[13]. With this technique, the volume of medium in the container was held to 300 ml and the pH of the medium was changed continuously from 1.2 to 7.0. This pH change corresponds to that of the GI tract. The pH change in the dissolution medium was monitored by a pH meter placed in the dissolution medium.

Aliquots of 2 ml of the dissolution medium in the apparatus and the reservoir were sampled at prescribed intervals through a pipet plugged with cotton and were filtered through a Millipore filter (0.3 μm). Aliquots of distilled water (same volume and temperature) were added immediately to the dissolution apparatus to keep the volume of the dissolution medium in the container constant during the test. The concentration of dissolved sulfamethoxazole in the medium was determined spectrophotometrically at a suitable UV region using a double-beam spectrophotometer[14].

RESULTS AND DISCUSSION

Physicochemical Properties of Spray-Dried Products—The size distribution of the spray-dried particles was described in log-normal form. The geometric mean diameter ranged from 3.6 to 22.0 μm. The formulations including cellulose acetate phthalate and the additives yielded smaller products than the formulations without the additives. The products prepared from the formulations with the additives alone became smaller compared to the others (Table I).

Scanning electron microscopic photographs of the spray-dried products are shown in Fig. 2. The surfaces of the products prepared from the nonadditive formulations were covered with flake-like crusts (Fig. 2A). When the additives were added to the formulations, no flakes appeared, and the surface had an orange peel texture (Fig. 2B). Figure 2C shows an

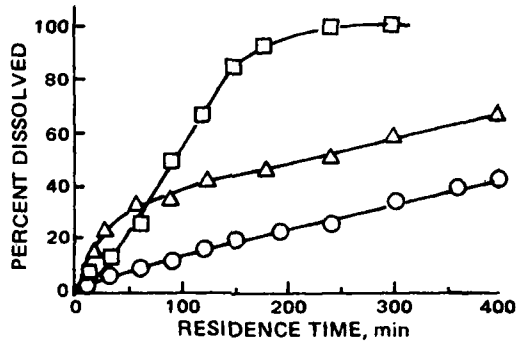

Figure 5—*Release patterns of tablets without microcrystalline cellulose in various media. Key: ○, distilled water; △, pH 1.2; and □, pH 7.5. The additive was 30 g of colloidal silica.*

[13] Furue Science Co., Japan.
[14] Hitachi model 556.

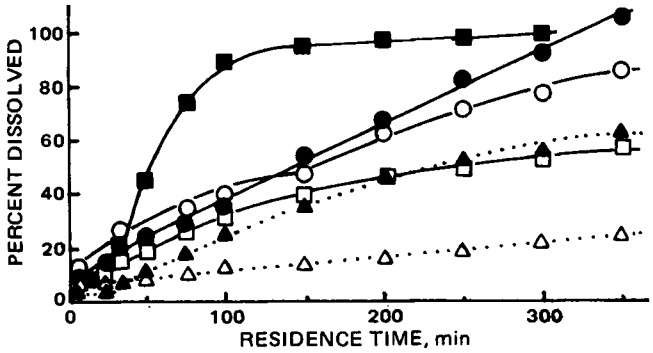

Figure 6—*Drug release patterns of tablets without cellulose acetate phthalate and microcrystalline cellulose and with varying amounts of colloidal silica in various dissolution media. Key: ●, 30 g, pH 1.2 medium; ○, 50 g, pH 1.2 medium; ■, 30 g, pH 7.5 medium; □, 50 g, pH 7.5 medium; ▲, 30 g, distilled water; and △, 50 g, distilled water.*

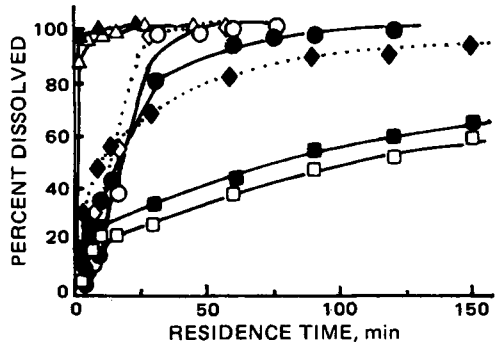

Figure 8—*Drug release patterns of tablets containing microcrystalline cellulose with varying amounts of colloidal silica in various dissolution media. Key: □, 0 g, pH 1.2 medium; ■, 30 g, pH 1.2 medium; ○, 0 g, pH 7.5 medium; ●, 30 g, pH 7.5 medium; ◇, 0 g, distilled water; and ♦, 30 g, distilled water. The original powder also was dissolved in pH 1.2 (△) and 7.5 (▲) media.*

image of the product with the additives alone, which seems to be an agglomerate composed of lobes. Many sulfamethoxazole crystals apparently are adsorbed onto the surface.

The characteristic bulkiness of the spray-dried product from the formulations with cellulose acetate phthalate alone (Fig. 2A) suggests that their particle density and packing property differ from those of the other formulations. It was assumed that these products might be lighter than those with the additives. This assumption was proved by the particle density data given in Table I. The products including the additives alone had a higher particle density. The packing process of the spray-dried products in a tapped graduated cylinder was represented by (4):

$$n/c = 1/ab + n/a \quad \text{(Eq. 1)}$$

$$c = (V_0 - V_n)/V_n \quad \text{(Eq. 2)}$$

where b is a constant, n is the number of taps, V_0 is the volume of powder in a measuring cylinder at the loosest packing, and V_n is the volume after the nth tapping. The parameter a in Eq. 1 for the products without additives was found to be larger than that of the particles with montmorillonite clay and colloidal silica. This finding indicates that the particles with the additives might be packed more easily since a corresponds to the proportion of consolidation at the closest packing attained.

Tablets could not be made directly by compressing the products without the additives due to their poor flowabilities. The products including the additives were tableted easily. Compressibility of the spray-dried products including the additives was improved with increasing amounts of the additives, as indicated by their greater hardness and smaller porosity. This trend clearly appeared with the tablets containing colloidal silica and montmorillonite clay (Table I).

The crystalline forms of the spray-dried products were investigated by X-ray diffraction analysis and IR spectroscopy. The IR spectra and X-ray diffraction patterns of the untreated original sulfamethoxazole used in the present study identified the crystals as Form I, as defined previously (5). The peaks in the X-ray diffraction patterns of the spray-dried products were less intense than those of the original crystals (Fig. 3). This finding indicated that some sulfamethoxazole crystals were converted to a disordered form due to rapid crystallization.

In the patterns of the products with cellulose acetate phthalate, regardless of whether the additives were included, fairly characteristic peaks of Form II appeared. Form II was prepared as a reference by recrystallization in water at dry ice–acetone temperature (Fig. 3). The X-ray diffraction patterns of the products with colloidal silica and montmorillonite clay proved that they were Form I. The patterns of the products with talc exhibited peaks of both Forms I and II, indicating that they were a mixture.

The polymorphic forms of the spray-dried products also were confirmed by their IR spectra (Fig. 4). The spray-dried products with cellulose acetate phthalate exhibited the characteristic bands of Form II at 3080, 2990, and 1640 cm^{-1}, which did not appear in the spectrum of Form I. Differences in the spectra from Form I also were found at 1395, 1330, 1150, and 750 cm^{-1}. When cellulose acetate phthalate was excluded from the formulations, the spectra of the spray-dried products changed to those of Form I. Spectra of the products with talc exhibited the intense bands at 3300 and 3150 cm^{-1} and several characteristic bands of Form II. This result suggests that the products with talc contain Forms I and II.

It has been suggested that polymorphism in sulfonamides may be

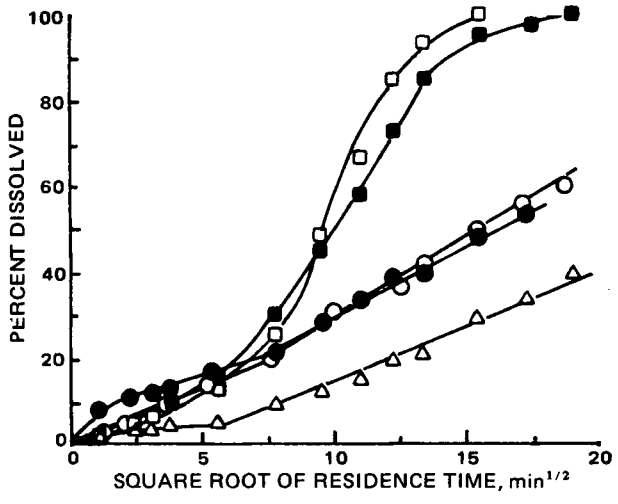

Figure 7—*Percentage of drug release as a function of the square root of the residence time with and without cellulose acetate phthalate, without microcrystalline cellulose, and with varying amounts of colloidal silica in various dissolution media. Key for formulations with cellulose acetate phthalate: ●, 50 g, pH 1.2 medium; □, 30 g, pH 7.5 medium; ■, 50 g, pH 7.5 medium; and △, 30 g, distilled water; ○ represents a formulation without cellulose-acetate phthalate and containing 50 g of colloidal silica in a pH 7.5 medium.*

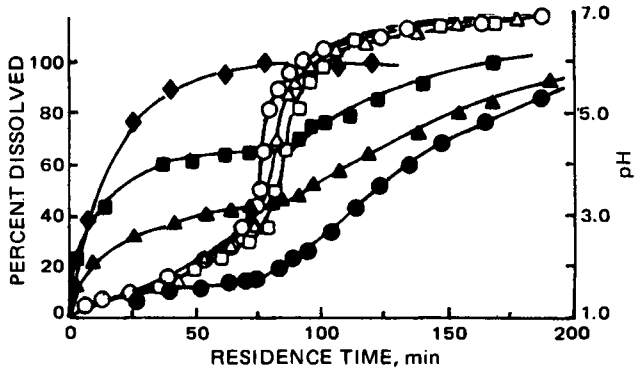

Figure 9—*Drug release (closed symbols) and pH change (open symbols) patterns in a flow-type simulator for formulations containing varying amounts of colloidal silica. Key for formulations containing cellulose acetate phthalate: ●, ○, 0 g; ▲, △, 30 g; and ■, □, 50 g. The formulation without cellulose acetate phthalate and containing 50 g of colloidal silica is represented by ♦.*

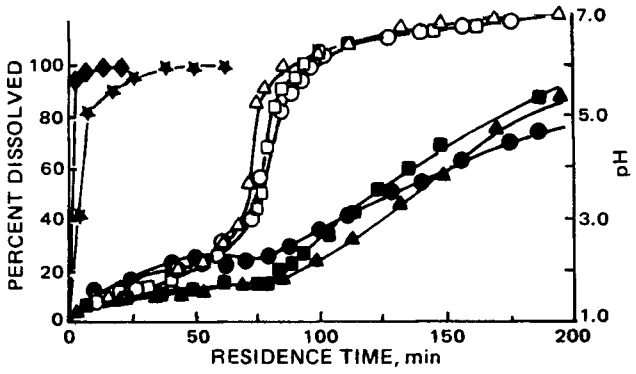

Figure 10—*Drug release (closed symbols) and pH change (open symbols) patterns in a flow-type simulator for formulations containing varying amounts of additives. Key for formulations with cellulose acetate phthalate: ●, ○, 50 g of talc; ▲, △, 50 g of montmorillonite clay; and ■, □, no additive. Key for formulations without cellulose acetate phthalate: ★, ☆, 30 g of talc; and ♦, ◇, 30 g of montmorillonite clay.*

brought about due to the intermolecular hydrogen bonding (6, 7). Hydrogen bonding in the alkaline solutions used might be attained mainly by the interaction between the hydrogen of the *p*-amino group and the oxygen of the S–O group in the sulfamethoxazole molecule. Furthermore, cellulose acetate phthalate molecules might influence the way in which the sulfamethoxazole molecules associate in the solution. This effect was confirmed by the fact that the products from the simple formulations without cellulose acetate phthalate or the additives exhibited Form I but not Form II. Such a polymorphism might make the drug metastable, but it could improve solubility.

Dissolution Behavior of Tablets in Disintegration Apparatus—Dissolution patterns of the tablets of the spray-dried products with colloidal silica and cellulose acetate phthalate in the disintegration test solutions (pH 1.2 and 7.5) and distilled water were determined using a disintegration apparatus (Fig. 5). The dissolution curves in the alkaline solution were distinguished by their much faster release rate from those in the other media used due to the enteric-coating action of the cellulose acetate phthalate contained in the tablet. Although the initial release rate in the acidic solution was faster than in distilled water, the slope of the release curve became almost identical at the later stage. In the alkaline solution, the tablets were gradually disintegrated to fine particles and a few small pieces; in the acidic media, disintegration did not occur, and only the size of the tablet slowly decreased during the dissolution process.

The dissolution behavior of the tablets prepared from the formulations with colloidal silica but without cellulose acetate phthalate is shown in Fig. 6. There was less variation in the rate in the three dissolution media used. The colloidal silica may have acted as a disintegrating agent due to its wettability, which might have resulted in an increased release rate. However, when the concentration of colloidal silica in the tablet was increased, the release rate was decreased significantly, which might have been due to a matrix-like structure of the tablet binding strongly with colloidal silica.

These differences in the release behavior of the tablets were explained by plotting the data on a semisquare root graph (Fig. 7). In the acidic solution and distilled water, all release patterns of the tablets, regardless of the formulation, became fairly straight lines after enhanced dissolution periods. This finding indicates that the release process at the later stage obeys the Higuchi model (8) represented by:

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad \text{(Eq. 3)}$$

where Q is the amount dissolved per unit area of exposure at time t, A is the total amount of drug present in the matrix per unit volume, C_s is the solubility of the drug in the external phase of the matrix, and D is the diffusion constant. When $C_s \ll A$, Eq. 3 can be transformed to a more convenient form to exhibit the release patterns described in Fig. 7 (9):

$$C_r = 100[S_v(2DC_s t/A)^{1/2}] \quad \text{(Eq. 4)}$$

where C_r is the percent of the drug dissolved and S_v is the specific surface area. In alkaline solution, the release patterns of the tablets with and without cellulose acetate phthalate exhibited sigmoid curves and straight lines, respectively.

When microcrystalline celluloses were mixed into the spray-dried products in a 1:1 ratio, tablets could be made even if the products without the additives were used. However, the hardness of the tablet was insufficient for practical use compared with the tablets containing the additives. The dissolution rate of the tablets containing microcrystalline cellulose became faster than that of the tablets without it in all dissolution media due to their rapid disintegration. The distinct discrepancies of the release patterns depended on the type of dissolution medium used (Fig. 8). The prolonged release in the acidic medium was clearly evident when compared to the mixtures of microcrystalline cellulose and original sulfamethoxazole. Thus, the effectiveness of the enteric coating of the spray-dried products containing cellulose acetate phthalate is proved in Figs. 7 and 8.

In the alkaline medium and in distilled water, the dissolution rate was delayed when the additives were included in the formulations. In the acidic solution, the release rate of the tablet with the additives was faster than for those without them. This result might have been due to the fact that the additives included in the discrete microcapsules could promote penetration of the solvent.

Dissolution Behavior of Tablet Containing Various Additives in a Flow-Type Simulator—Gastric contents do not become alkaline merely as a result of passing through the pylorus. The upper small intestine is more likely to be slightly acidic. Thus, to simulate *in vivo* action, it may be desirable to conduct the enteric test in a dissolution medium whose pH is changed continuously from 1.2 to 7.0 rather than in a medium fixed at pH 7.0 or above. Release patterns of tablets prepared from the mixtures of microcrystalline cellulose and the spray-dried products containing various additives exposed to a medium whose pH changed continuously from 1.2 to 7.0 are shown in Figs. 9 and 10. The pH change of the medium with residence time followed a sigmoid curve which varied slightly from batch to batch, although the patterns were almost identical.

The release rate of the tablets with cellulose acetate phthalate was relatively fast at the initial stage, followed by a stage with a decreased rate. After the residence time of 70–90 min at pH 3.5–5.5, the release rate increased rapidly again, which caused an inflection on the release curve. It is reasonable to assume that this point corresponds to the starting point of the enteric action. By increasing the concentration of colloidal silica, the release rate at the initial stage (pH values of <3.5–4.0) increased due to enhancement of the solvent penetrating action by colloidal silica (Fig. 9).

The release patterns of the tablets without cellulose acetate phthalate were characterized by a smooth convex curve without an inflection point. With talc and montmorillonite clay, similar enteric action of the tablets containing cellulose acetate phthalate was observed; however, some solvent penetration appeared at the lower concentrations of these additives. At the later stage (pH > 5.0), the release rate was more delayed compared to that of the additive-free tablets. This result might have been due to the fact that the drug was adsorbed firmly in the pores of the additives, forming a matrix-like structure.

From these results, it is concluded that the enteric-coating behavior of the tablets was more clearly demonstrated by using the flow-type simulator and a medium whose pH changed continuously than by studying dissolution and disintegration at constant pH values. By this technique, it also was possible to detect the pH above which the enteric action was overcome.

REFERENCES

(1) P. Speiser, H. P. Merkle, and L. Schibler, Ger. Offen. 2,233,428 (1973).

(2) Y. Kawashima and H. Takenaka, *J. Pharm. Sci.*, **63**, 1546 (1974).

(3) H. P. Merkle and P. Speiser, *ibid.*, **62**, 1445 (1973).

(4) K. Kawakita, *Zairyo*, **13**, 421 (1964).

(5) S. S. Yang and J. K. Guillory, *J. Pharm. Sci.*, **61**, 26 (1972).

(6) S. S. Yang, *Diss. Abstr.*, **30**, 585 B (1969).

(7) R. J. Mesley and E. E. Houghton, *J. Pharm. Pharmacol.*, **19**, 295 (1967).

(8) T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).

(9) H. Takenaka, Y. Kawashima, and S. Y. Lin, *Chem. Pharm. Bull.*, **27**, 3054 (1979).

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