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POLYMORPHISM AND DRUG RELEASE BEHAVIOR OF SPRAY-DRIED MICROCAPSULES OF SULFAMETHOXAZOLE WITH POLYSACCHARIDE GUM AND COLLOIDAL SILICA

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ABSTRACT

Sulfamethoxazole microcapsules with polysaccharide gum, i.e. xanthan gum and guar gum, were prepared by employing a spray drying technique. The aqueous or the ammonium hydroxide solution of the gum containing the drug with or without colloidal silica was atomized with a centrifugal wheel atomizer rotated at 40000 rpm into a drying chamber held at 140±10°C. By formulation with colloidal silica, particle size of the resultant product increased, leading to improve the flowability and packability for the tableting. Polymorphic sulfamethoxazole mixture of Form I, II and III was produced in the formulation with cellulose acetate

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phthalate. Xanthan gum product prepared from both aqueous and ammonium hydroxide solution and guar gum product from ammonium hydroxide solution also contained the polymorphic mixture. In the formulations with colloidal silica, the crystalline form of all the products was Form I. A dissolution test of the product compressed into a tablet with microcrystalline cellulose was undertaken using a disintegration apparatus and a flow-type GI tract simulator. The product prepared from the aqueous solution had prolonged drug release rate, while the product prepared from ammonium hydroxide solution exhibited rapid drug release due to improve tablet disintegration. Colloidal silica in the product enhanced the drug dissolution rate of the product from the aqueous solution, but decreased that from the product made from the ammonium hydroxide solution. In the flow-type simulator, the drug release from the product was pH independent.

INTRODUCTION

Spray drying techniques have been used widely for drying heat-sensitive foods, pharmaceuticals, and other substances. Recently, interests have been paid on the polymorphism of drugs occurred during spray drying[1-3], because the characteristic of pharmaceutical preparation compounded with the resultant dried products is

frequently determined by their crystalline forms as well as micromeritic properties such as diameter, density and etc.

In the previous studies [4-5], the authors found that cellulose acetate phthalate compounded in the formulation specifically caused to polymorphism of sulfamethoxazole during spray drying. The objective of the present study was to investigate polymorphism of the spray-dried sulfamethoxazole with polysaccharide gum, i.e. xanthan gum and guar gum, cellulose acetate phthalate and colloidal silica which are widely used as a binder or an excipient for cosmetics and pharmaceuticals. Drug release test of the tablet prepared from the resultant product was also conducted with a disintegration apparatus and a flow type GI tract simulator developed previously [4]. Investigation of the effect of colloidal silica compounded into the spray drying formulation on the micromeritic property of the resultant products and on the drug release behavior of the tablet was another objective.

MATERIALS AND METHODS

Spray Drying Technique

Sulfamethoxazole (Shionogi Pharmaceutical Co., Japan) was used as received as a model drug for microencapsulation. The polysaccharide gums used as a wall material for the microcapsule were guar gum and

xanthan gum. Five grams of the gum was dissolved in 1 ℓ of distilled water or 5 % ammonium hydroxide solution. To the solution, the drug (50 g) and an excipient (colloidal silica (30 g) (Japan Aerosil Co., Japan) or cellulose acetate phthalate (5 g) (Kishida chemical Co., Japan)) were dissolved or dispersed uniformly. As a reference, a feeding liquid for spray drying without the excipient was also prepared.

The slurries of solutions were atomized into a drying chamber by a centrifugal wheel atomizer (Iwai Kikai Co., Japan) at 40000 rpm. The drying chamber was maintained at 140±10°C. The dried products were collected by a cyclone collector.

Measurement of Physicochemical Properties

Particle size of the spray-dried products was measured by a photographic counting method using a particle size analyzer (TGZ-3, Karl Zeiss, West Garmany). Packing property was measured by a tapping powder method. Angle of repose and particle density were measured by a pouring powder method on a circular plate and with a helium-air comparison pycnometer (Model 1302, Shimadzu-Micromeritics Instrument Co., Japan) respectively. The specific surface area of the products were measured by an air permeability apparatus (Model SS-100, Shimadzu Manufacturing Co., Japan). Surface topography of the spray-dried particles coated with gold was investigated with a scanning electron microscope

(JMS-SI, Nihon Denshi Co., Japan). To analyze the crystalline form of sulfamethoxazole in the spray-dried products, their X-ray diffraction patterns (JDX, Nihon Denshi Co., Japan) and IR spectra (DS-403G, Nihon Denshi Co., Japan) were obtained.

Dissolution Test of the Tablets Prepared from the Spray-dried Products

An equal mixture of each spray-dried product and microcrystalline cellulose (Avicel-101, Asahi Kogyo Co., Japan) was tableted using a single-punch tablet machine. Hardness and friability of the tablet were measured by a hardness tester (Kyowa Seiko Co., Japan) and a friability tester (Erweka -G.m.b.H. Frankfurt am Main, Germany), respectively.

Dissolution test of the tablet was undertaken using a JP X disintegration apparatus in the specified disintegration test solution (pH 1.2) at 37°C. The test was also conducted with a new in vitro release simulator devised by the present author [4] with 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 that tablets would experience when exposed to the GI tract. An aliquot of 2 ml of the dissolution medium was sampled at prescribed intervals through a pipet plugged with cotton and was filtered through a filter (TM-2, Membrane Filter (0.45 μm), Toyo Roshi Co. Ltd., Japan). An aliquot of distilled water (same volume and

temperature) was added immediately to the dissolution apparatus to maintain constant volume. The concentration of dissolved sulfamethoxazole in the medium was determined spectrophotometrically at a suitable UV region using a double-beam spectrophotometer (Model 556, Hitachi Manufactory Co., Japan).

RESULTS AND DISCUSSION

Micromeritic Properties of Spray-dried Products

The size distribution of the spray-dried products was described in log-normal form. The geometric mean diameter ranged from 4.3 to 13.0 μm. The average diameter of the product with colloidal silica was larger than that of the product without it as shown in Table 1.

Scanning electron microscopic photographs of the products are displayed in Fig. 1. Film-forming capability of xanthan gum seemed to be superior to that of guar gum as indicated in Fig. 1-(a) and (b). Without colloidal silica the surface of the xanthan gum product was fairly smooth in contrast with that of the guar gum product, on which several numbers of fine crystals were adsorbed as shown in Fig. 1-(b). Introduction of colloidal silica or cellulose acetate phthalate into the formulation for spray drying made the resultant product surface more smooth but a few macro pores remained on the surface as shown in Fig. 1-(c), (d), (e) and (f).

TABLE 1

Micromeritic Properties of Powdered and Tableted Spray-dried Products

Wall material	Guar Gum (5g)					Xanthan Gum (5g)				
Medium (1ℓ)	H_2O		5% NH_4OH			H_2O		5% NH_4OH		
Excipient	-	Colloidal silica(30g)	-	Colloidal silica(30g)	CAP(5g)	-	Colloidal silica(30g)	-	Colloidal silica(30g)	CAP(5g)
ρ (g/cm^3)	1.50	1.53	1.46	1.66	1.39	1.42	1.75	1.48	1.55	1.61
D (μm)	12.5	13.0	4.7	8.0	5.6	5.1	9.5	4.3	5.8	6.5
Sw(cm^2/g)	4702	10575	4382	8970	2928	5582	9363	5871	6277	10001
Θ (°)	58	43	56	48	52	59	41	57	48	57
a	0.230	0.164	0.189	0.191	0.143	0.232	0.116	0.239	0.221	0.256
b	0.057	0.060	0.056	0.022	0.068	0.038	0.037	0.057	0.035	0.021
Polymorphism	I	I	I+II+III	I	I+II+III	I+II+III	I	I+II+III	I	I+II+III
H (Kg)	3.29	4.95	1.74	4.95	4.11	3.00	8.08	3.99	9.09	3.96
F (%)	0.09	0.26	3.63	0.04	0.14	0.05	0.47	1.35	0.12	1.07

Key: ρ, true density D, geometric mean diameter Sw, specific surface area Θ, angle of repose
a and b, parameter in Kawakita equation H, hardness of tablet F, friability of tablet

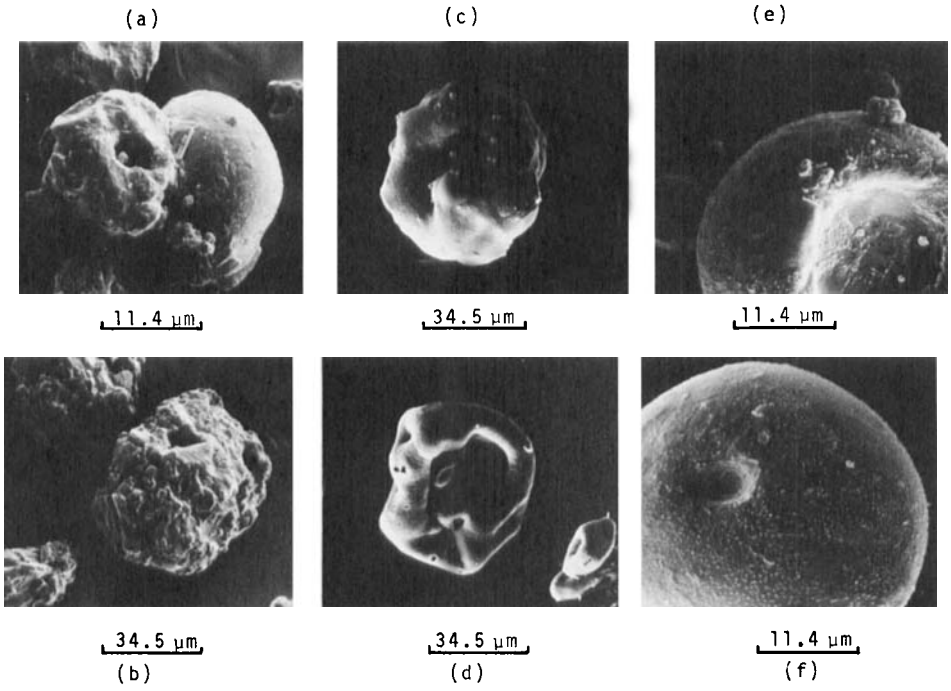

FIGURE 1

Scanning Electron Microphotographs of Spray-dried Products

Key: Spray-dried products were prepared from the formulations containing sulfamethoxazole (50 g) and (a), xanthan gum (5 g); (b) guar gum (5 g) ; (c), xanthan gum (5 g) and colloidal silica (30 g) ; (d), guar gum (5 g) and colloidal silica (30 g) ; (e), xanthan gum (5 g) and cellulose acetate phthalate (5 g) ; (f), guar gum (5 g) and cellulose acetate phthalate (5 g)

The spray drying medium was distilled water for a, b, c, d and 5 % ammonium hydroxide solution for e, f.

Flow properties of the resultant product was improved by introducing colloidal silica into the spray drying formulation, as revealed by the decreased angle of repose in Table 1. Packing property of the product with colloidal silica was also improved to some extent as suggested by the decreased parameter "a" in Eq. (1) as shown in Table 1. Equation (1) represents packing process of powder in a tapped graduated cylinder [6].

$$n/c = 1/ab + n/a \quad \cdots\cdots\cdots (1)$$

$$c = (V_o - V_n)/V_n \quad \cdots\cdots\cdots (2)$$

Where b is a constant , n is the number of taps, V_o is the volume of powder in a measuring cylinder at the loosest packing, and V_n is the volume after the n-th tapping. The parameter "a" corresponds to the proportion of consolidation at the closest packing attained. Therefore, a lower value "a" implies a better flowability and packability of powder. The hardness of tablet prepared directly by compressing the product with colloidal silica was stronger than the other tablets. Whereas the friability of the tablet was not affected by introducing colloidal silica into the formulation as shown in Table 1.

Polymorphism of Spray-dried Products

The IR spectra of original sulfamethoxazole and spray-dried products are seen in Fig. 2. The crystalline form of the original sulfamethoxazole was proven to be Form I by identification of its IR spectrum,

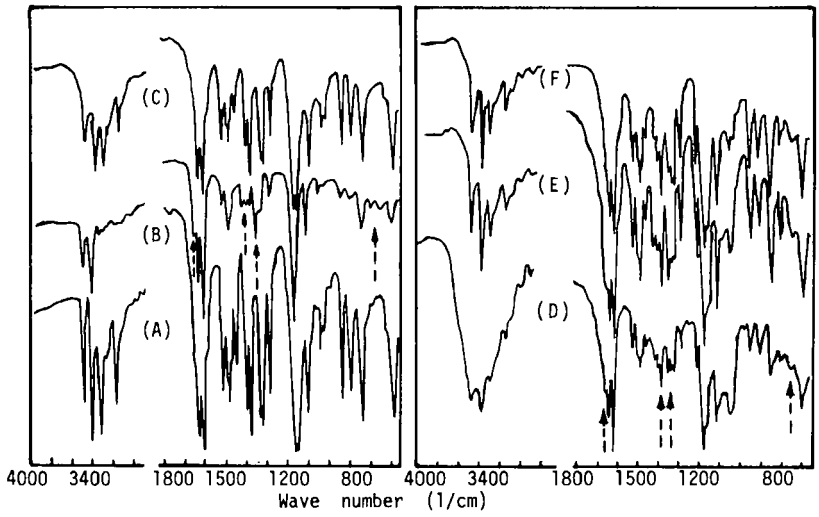

FIGURE 2

IR Spectra of Original Sulfamethoxazole and Spray-dried Products

Key: A, Form I, original sulfamethoxazole;
B, Form II, and C-G, spray-dried products prepared from the formulations containing 5 g guar gum (C), 5 g xanthan gum and 5 g cellulose acetate phthalate (D), 5 g xanthan gum (E) and (F)

The spray drying medium was distilled water for (C) and (F) and 5 % ammonium hydroxide solution for (D) and (E).
----▶ ; characteristic peaks for Form II

characterized by intense bands at 3150 and 3300 cm^{-1} attributed to the amide N-H stretching vibration[7]. Irrespective of the type of gum in the spray-dried products, the product with cellulose acetate phthalate exhibited the additional characteristic absorption bands of Form II in their IR spectra at 1640, 1395, 1330 and 750 cm^{-1}. As a reference, Form II of sulfamethoxazole was prepared by recrystallizing from an aqueous solution at

dry ice-acetone temperature. It was also found that the gum products without excipient were polymorphic mixtures of Form I and II , but except the guar gum product prepared from the aqueous solution used as a dispersing medium. The sulfamethoxazole crystalline form in the product with colloidal silica was found to be Form I, irrespective of the gum type, i.e. xanthan gum or guar gum.

The polymorphism of the spray-dried products was also investigated by X-ray diffraction analysis. Because it was difficult to distinguish Form III from Form I by IR analysis, owing to the spectra of Form III resembling that of Form I [7]. In the pattern of the product assumed as a polymorphic mixture of Form I and II from their IR spectra, several additional diffraction peaks from those of Form I and Form II appeared at diffraction angle, 11.7, 12.6, 17.3, 25.5 and etc. as shown in Fig. 3. These peaks were identified with those of Form III . The Form III was prepared by pouring a saturated aqueous solution of the original sulfamethoxazole into 150 ml of water at room temperature. In conclusion, all the products with cellulose acetate phthalate, xanthan gum product without colloidal silica and guar gum product prepared from the ammonium hydroxide solution without colloidal silica were found to be a polymorphic mixture with Form I, II and III (Table 1).

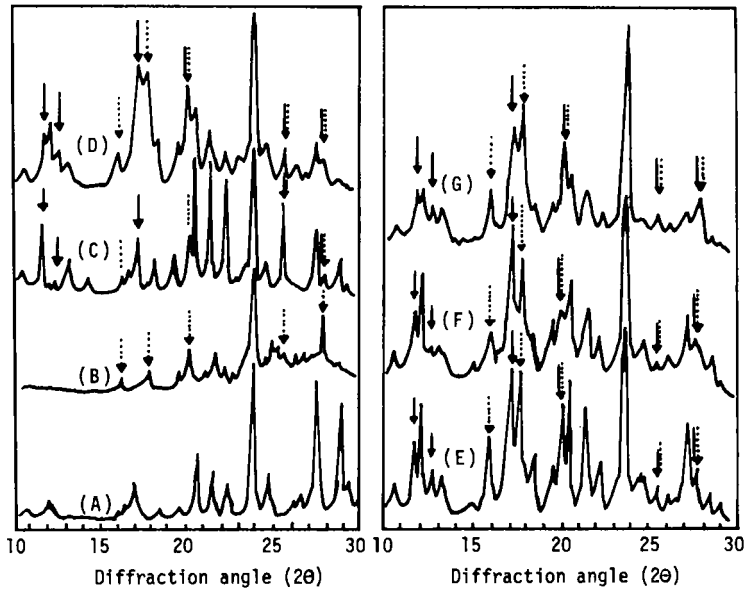

FIGURE 3

X-ray Diffraction Patterns of Original Sulfamethoxazole and Spray-dried Products

Key : A, Form I; B, Form II ; C, Form III ; and D-G, Spray-dried products prepared from the formulations containing 5 g guar gum (D), 5 g xanthan gum (E) and (F), 5 g xanthan gum and 5 g cellulose acetate phthalate (G)

The spray drying medium was distilled water for (E) and 5 % ammonium hydroxide solution for (D), (F) and (G)
——▶ ; characteristic peaks for Form II
----▶ ; characteristic peaks for Form III

Drug Release Behavior of Tablet Prepared from Spray-dried Product and Microcrystalline Cellulose

The drug release pattern from the tablet in acidic solution is displayed in Fig. 4. When drug release mechanism from the tablet obeys the Higuchi model [8], percent of the drug dissolved (Cr) is represented by

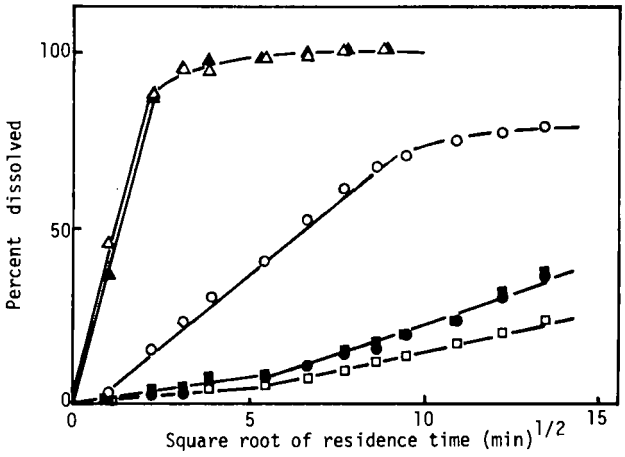

FIGURE 4

Drug Released Percent as a Function of the Square Root of the Residence Time with Microcrystalline Cellulose in pH 1.2 Dissolution Medium

Key : Formulation containing 5 g xanthan gum (○), (△); 5 g guar gum (●), (▲); 5 g xanthan gum and 30 g colloidal silica (□); 5 g guar gum and 30 g colloidal silica (■).

The spray drying medium was distilled water for (○), (●) and 5 % ammonium hydroxide solution for (△), (▲), (□), (■).

equation (3), when the solubility of the drug in the external phase of the matrix (Cs) is extremely smaller than the total amount of drug present in the matrix per unit volume[9].

$$Cr = 100 \cdot Sv(2DCst/A)^{1/2} \quad \ldots\ (3)$$

Where D is the diffusion constant, and Sv is the specific surface area. Based on equation (3), the released drug (%) in the acidic solution (pH 1.2) was plotted as a function of the square root of residence time in Fig. 4.

The tablets of both products with xanthan gum or guar gum prepared from the aqueous solution released drug linearly with residence time. The tablet did not disintegrate and the surface was covered with a gel-like film. At the beginning, a reduced release period, i.e. induction period, appeared. During this stage, the solvent might penetrate into the tablet and dissolved the drug. Thereafter, the dissolved drug diffused to the outer surface of the tablet. In the course of dissolution, the gum in the tablet gelled, and reduced the drug release rate at the later stage for the xanthan gum product. It was found that prolonged release action of guar gum was greater than that of xanthan gum. This finding might be interpreted in terms of the higher solubility of xanthan gum than that of guar gum in acidic solution [10-11]. When 5 % ammonium hydroxide solution was used as a dispersing medium for spray drying, the prolonged release action of resultant product changed drastically as shown in Fig. 4, which was characterized by an increased release rate. The drug release rate enhancement might be interpreted in terms of disintegration of the tablet during the course of the dissolution test. This finding suggested that denaturalization of the gum due to spray drying with ammonium hydroxide solution adversely affected the gel formation of the gum in the tablet. This was not the case in the presence of colloidal silica in the

formulation for spray drying. The tablet prepared from the product with colloidal silica exhibited a fairly prolonged release pattern like a matrix type.

Another drug release test was undertaken using a flow-type simulator to simulate the pH change during transit in the GI tract. Release patterns of the tablet prepared from the product with guar gum exposed to a medium whose pH changed continuously from 1.2 to 7.0 is shown in Fig. 5. It was found that the release pattern of the product without colloidal silica prepared from the aqueous solution was also almost linear all through the residence time. This finding indicated that the drug release from the tablet was pH-independent and a fairly prolonged drug release in the GI tract was anticipated. This prolonged release action was owing to the fact that the tablet did not disintegrate. When colloidal silica was compounded in the formulation for spray drying, the resultant product tablet exhibited a dramatic change in the drug release pattern, characterized by a fast release rate. This finding might be interpreted in terms of hydrophilic property of colloidal silica contained in the product, promoting a penetration of the dissolution medium into the tablet. This explanation was rationalized by the fact that the tablet disintegrated during the dissolution test. The action of colloidal silica on the tablet dissolution behavior of the product prepared from an ammonium hydroxide solution contrasted

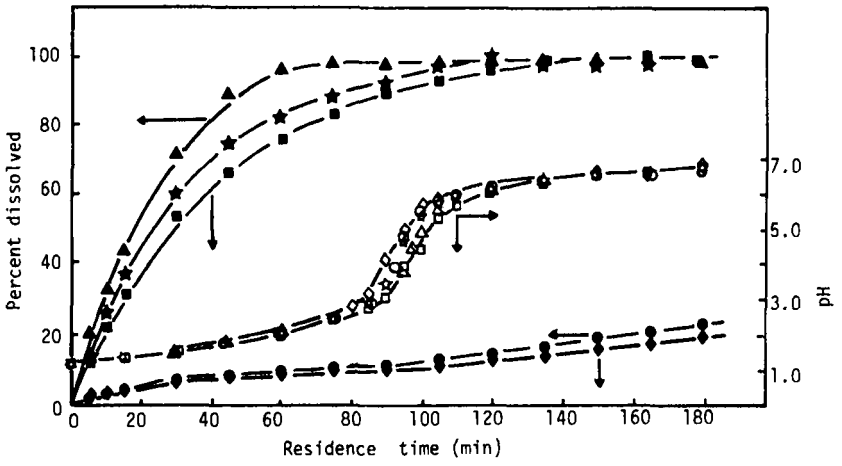

FIGURE 5

Drug Release and pH Change Patterns in a Flow-type Simulator for Spray-dried Products Containing Guar Gum

Key : Formulation containing 5 g guar gum (●, ○; ▲, △); 5 g guar gum and 30 g colloidal silica (■, □; ◆, ◇); 5 g guar gum and 5 g cellulose acetate phthalate (★, ☆)

The spray drying medium was distilled water for (●, ■) and 5 % ammonium hydroxide solution for (▲, ◆, ★).
The solid and open symbols represent drug release and pH change patterns respectively.

with that of the product prepared from the aqueous solution. The drug release rate from the product with colloidal silica was drastically reduced. in the aqueous solution, the drug were partly dissolved in the medium, but mostly were suspended. While in the ammonium hydroxide solution, all of the drug dissolved in the medium. The dissolved drug adsorbed strongly into the pore of colloidal silica. Therefore, the drug was firmly caught in the pore of colloidal silica involved in the

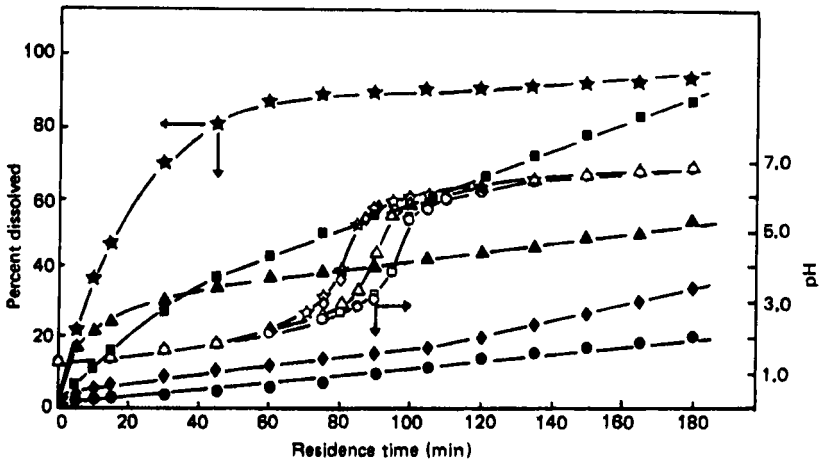

FIGURE 6

Drug Release and pH Change Patterns in a Flow-type Simulator for Spray-dried Products Containing Xathan Gum

Key : Formulation containing 5 g xanthan gum (●, ○; ▲, △);
5 g xanthan gum and 30 g colloidal silica (■, □; ◆, ◇);
5 g xanthan gum and 5 g cellulose acetate phthalate (★, ☆).

The spray drying medium was distilled water for (●, ■) and 5 % ammonium hydroxide solution for (▲, ◆, ★).

resultant spray-dried products. Such a characteristic texture of the product might cause to delaying the drug release rate significantly.

The drug release rate of the tablet of the product with xanthan gum in the flow-type simulator is shown in Fig. 6. Colloidal silica compounded in the products affected similarly on the drug release from the xanthan gum products to that from the guar gum products. Cellulose acetate phthalate in the both gum products

little reduced the drug release rate in the lower pH range of dissolution medium (Figs. 5 and 6), contrasted to the finding in the previous study[4] . This was partly due to the fact that concentration of cellulose acetate phthalate in the formulation was insufficient for it. Mainly it might be due to the fact that the denaturalization of the gums in the ammonium hydroxide solution during spray drying caused to disintegration of the tablet as described previously.

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