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Solid particulates of drug–β-cyclodextrin inclusion complexes directly prepared by a spray-drying technique *

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Summary

Inclusion complexes of drugs (acetaminophen, indomethacin, piroxicam and warfarin) with β-cyclodextrin were experimentally prepared by using a spray-drying technique. The spray-dried products were evaluated by X-ray diffractometry, differential scanning calorimetry and IR spectroscopy. The micromeritic properties and dissolution behaviour of spray-dried products were examined. It was found that the spray-drying technique could be used to prepare the amorphous state of drug inclusion complexes. The flowability and compressibility of the spray-dried products were poor, due to the small particle size formed by the spray drying process. However, the dissolution rates of drugs from tablets made by the spray-dried products were faster than those of the pure drug and the physical mixture of drug and β-cyclodextrin. The enhanced dissolution rate of spray-dried products might be attributed to the decreased particle size, the high-energetic amorphous state and inclusion complex formation.

Introduction

Cyclodextrins have been reported in a number of studies in the pharmaceutical field to interact with many drug molecules to form inclusion complexes. These inclusion complexes have been extensively used to improve the solubility, stability and bioavailability of various drugs (Szejtli, 1982; Uekama, 1981). The preparation method of cyclodextrin inclusion complexes includes kneading, grinding, freeze drying, slow evaporation and coprecipitation (Czugler, 1981; Kikuchi, 1987; Uekama, 1983; Kurozumi, 1975). We have prepared the freeze-dried warfarin–cyclodextrin inclusion complex not only to improve the dissolution rate of warfarin (> 1000 fold) but also to prolong the prothrombin time of warfarin (Lin and Yang, 1986, 1987). We also found that acetaminophen was included in the cavity of β-cyclodextrin when prepared by the grinding method and formed an inclusion complex (Lin et al., 1988, 1989). However, these procedures were time-consuming and required multistage processing including initial reaction, recrystallization, filtration and drying. Some preparation methods use organic solvents as media. The residual organic

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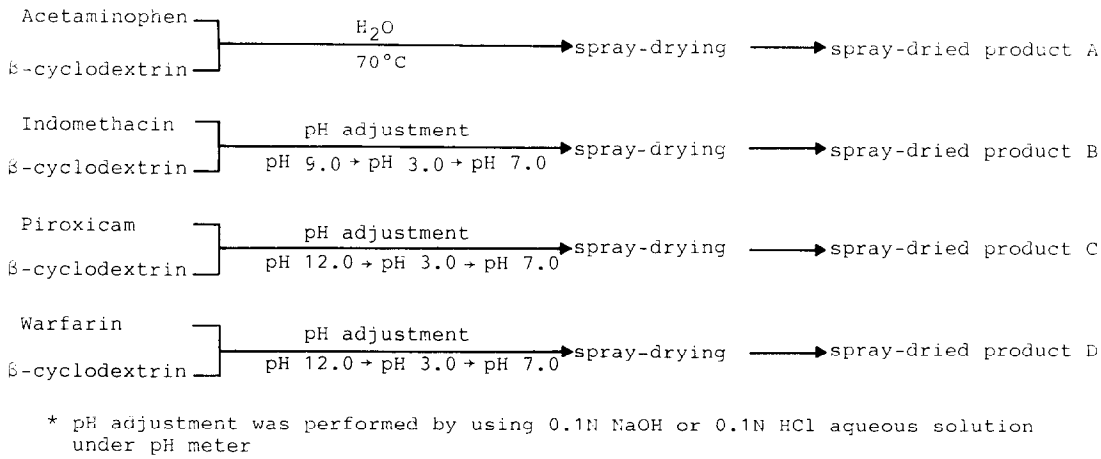

Chart I. Schematics for the preparation of spray-dried products.

solvent in the inclusion complexes, however, could be difficult to eliminate completely from the products.

Spray-drying offers significant versatility over other means of drying. One of the advantages of the spray-drying process, is the direct formation of solid particulates from droplets undergoing chemical reaction during drying (Abdul-Rahman and Crosby, 1973). Aminophylline, pyrabital and theophylline–phenobarbital complex have been directly prepared from aqueous droplets with the spray-drying technique by Kawashima et al. (1982, 1983a and b, 1984), which combined the synthesis, the drying and the agglomeration process into one process. This technique offers a one-step process with the advantage of reducing the preparation steps, saving time and cost, as well as better process control. Only few studies have used the spray-drying technique to prepare cyclodextrin inclusion complexes of drugs in order to improve the solubility of drugs (Tokumura et al., 1985; Kata and Wayer, 1985; Kata and Lukacs, 1986).

In our previous study, we found that acetaminophen molecules could be included into the cavity of β-cyclodextrin by a grinding process, resulting in an inclusion complex. On the other hand, indomethacin, warfarin and hydrocortisone acetate did not form an inclusion complex (Lin et al., 1988; Lin and Kao, 1987, 1988). In this study, the spray-drying technique was used to prepare drug inclusion complexes. The micromeritic properties of the spray-dried products were investigated. The physicochemical properties and dissolution behavior of the spray-dried products were also determined.

Materials and Methods

Materials

Acetaminophen, warfarin and indomethacin were purchased from Seven Star Pharm. Co. Ltd, Taiwan, Sigma Chem. Co., U.S.A., and Sumitomo Chem. Co. Ltd., Japan, respectively. Piroxicam was supplied by Standard Chem. & Pharm. Co. Ltd., Taiwan. β-Cyclodextrin was obtained from Chinoin Pharm. & Chem. Works Ltd., Budapest, Hungary. All the other materials were of analytical reagent grade.

Preparation of spray-dried products

The schematics for the preparation of 4 different drug systems of the spray-dried products is shown in Chart I. The same molar ratio of drug (acetaminophen, indomethacin, piroxicam or warfarin) and β-cyclodextrin was comixed in distilled water and their pH adjusted (according to the procedure of Chart I) by using 0.1 N NaOH or 0.1 N HCl aqueous solution. Acetaminophen was directly dissolved in distilled water by keeping the temperature above 70 °C. The other drugs were previously dissolved in alkaline aqueous media,

TABLE 1

Micromeritic properties of the spray-dried products and pure drugs

	Geometric mean diameter (μm)	Angle of repose	Parameters of Kawakita equation		Compressibility (%)	Yields (%)
			a	*b*		
Acetaminophen	21.3	52.2	0.2534	0.2097	30.36	–
Spray-dried product A	9.6	54.3	0.3989	0.0106	34.83	86.1
Indomethacin	10.7	49.7	0.2436	0.1104	27.59	–
Spray-dried product B	6.3	55.8	0.4302	0.0562	40.23	84.8
Piroxicam	12.8	54.7	0.3193	0.0401	32.50	–
Spray-dried product C	5.4	53.8	0.4256	0.0268	38.46	87.4
Warfarin	13.2	51.5	0.3723	0.0337	34.74	–
Spray-dried product D	7.6	54.8	0.4125	0.0203	35.59	86.9

Consolidation and packing parameter: *a*; packing velocity index: *b*.

and adjusted their pH from alkaline to acid, then neutral, according to the properties of drug. The solutions or uniform aqueous slurries were atomized into a drying chamber with a spray nozzle (A-64, 1626 μm). The spray-dryer (Pulvis Mini Spray GA-32, Yamato Sci. Co. Ltd., Tokyo, Japan) was operated under the following conditions: inlet temperature: 145 $\pm$ 1° C, outlet temperature: 75 $\pm$ 1° C, drying air flow rate: 0.37 m^3/min, atomizing air pressure: 1.0 kg/cm^2, sample feeding speed: 4.5 ml/min. The yields of all spray-dried products are $\geqslant$ 85%, as listed in Table 1. All the drugs remained stable throughout the spray-drying process by checking them with TLC on silica gel (Lin et al., 1988).

Particle size, shape and surface topography of spray-dried products

The particle sizes of the spray-dried products were measured by a photographic counting method using a particle size analyzer (TGZ-3, Karl Zeiss Co. Ltd, F.R.G.). The particle shape and surface topography of the spray-dried products were investigated by a scanning electron microscope (Hitachi S-550, Tokyo, Japan). The samples were mounted on a sample stub with double-sided adhesive tape and were vacuum coated with gold.

Powder flow properties of spray-dried products

The packing property of the spray-dried products was measured by a powder tapping method (Kawakita, 1964; Takenaka et al., 1980). The compressibility of the spray-dried products was also computed from powder density according to the following equation (Carr, 1965; Fiese and Hagen, 1986):

$$\text{Compressibility}\ (\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \qquad (1)$$

where ρ_t is the tapped bulk density and ρ_b is the initial bulk density. Angle of repose of the spray-dried products was determined by a fixed-funnel method.

Powder X-ray diffractometry

Powder X-ray patterns of the spray-dried products were carried out using an X-ray diffractometer (Rigaku Geigerflex D/Max-IIIA, Japan) with Ni-filtered Cu-K_α radiation.

Differential scanning calorimetry

The DSC patterns of the spray-dried products were measured with thermal analyser (Dupont DSC-1090, U.S.A.) at a scanning rate 10° C/min under N_2 gas stream from 40° C to 280° C.

Infrared absorption spectroscopy

Studies of the IR spectra of the spray-dried products were conducted with an IR spectrophotometer (Jasco IR-700, Tokyo, Japan) using the KBr disc method.

Dissolution rate determination

The samples used for dissolution rate studies were prepared by mixing the spray-dried products with microcrystalline cellulose at a weight ratio of 1 : 1. The powder blends were compressed into a flat-faced tablet, 10 mm diameter and 3 mm thickness, using a hydraulic press for KBr pellets under 300 kg/cm^2 for 1 min. The dissolution test was carried out in distilled water according to USP XXI, using the paddle method. The determinations were performed at a rotational speed of 50 rpm at a constant temperature of 37 °C.

Results and Discussion

Physicochemical properties of spray-dried products

In order to determine whether the spray-dried product resulted into an inclusion complex or a physical mixture of the drug with β-cyclodextrin, examinations were conducted using X-ray diffractometry, DSC thermograms and IR spectra.

Fig. 1 shows the X-ray diffraction patterns of pure drugs (a), β-cyclodextrin (b), physical mixture (c) and spray-dried product (d) of drug and β-cyclodextrin, where A belongs to acetaminophen

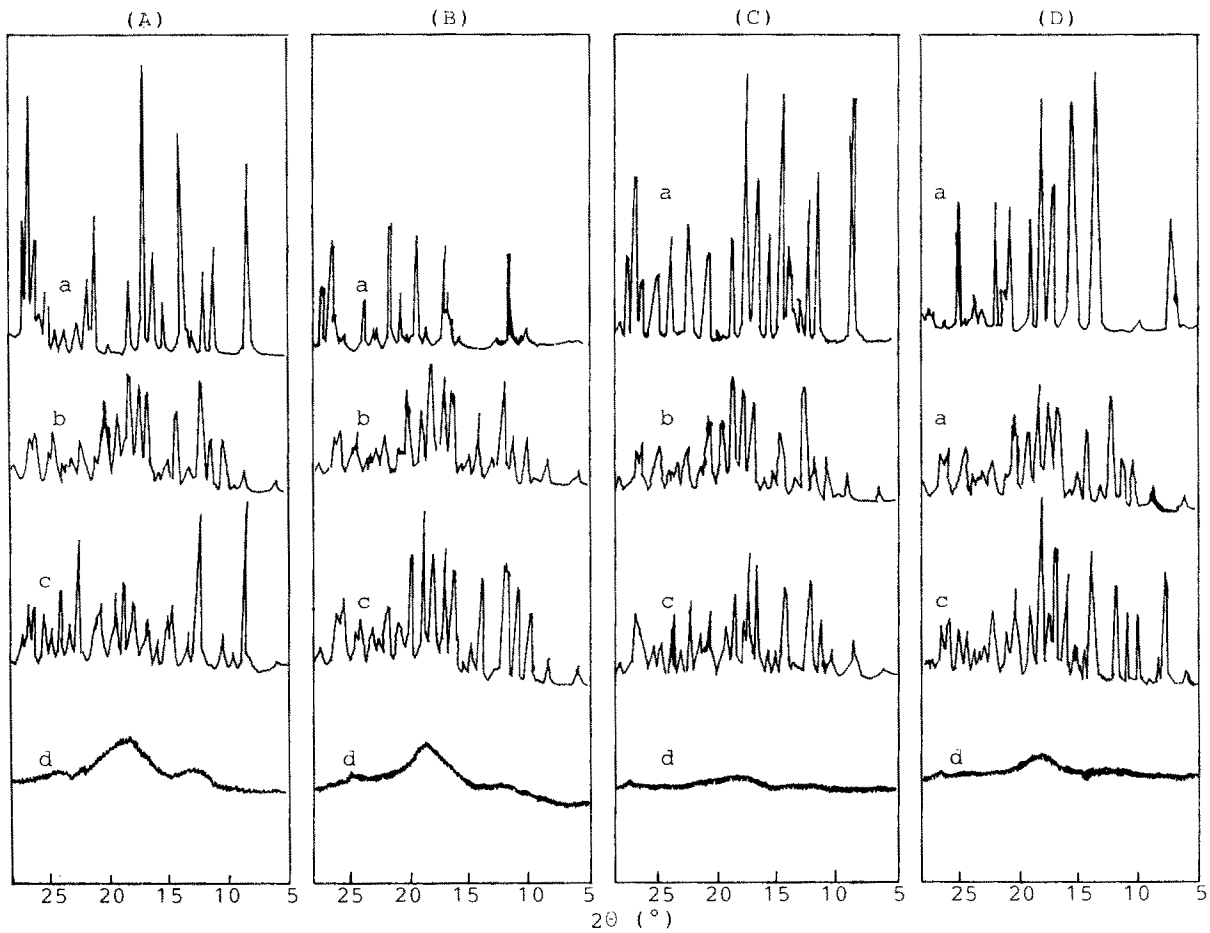

Fig. 1. X-ray diffraction patterns of pure drug (a), β-cyclodextrin (b), physical mixture (c) and spray-dried product (d) of drug with β-cyclodextrin. (A) acetaminophen series; (B) indomethacin series; (C) piroxicam series; (D) warfarin series.

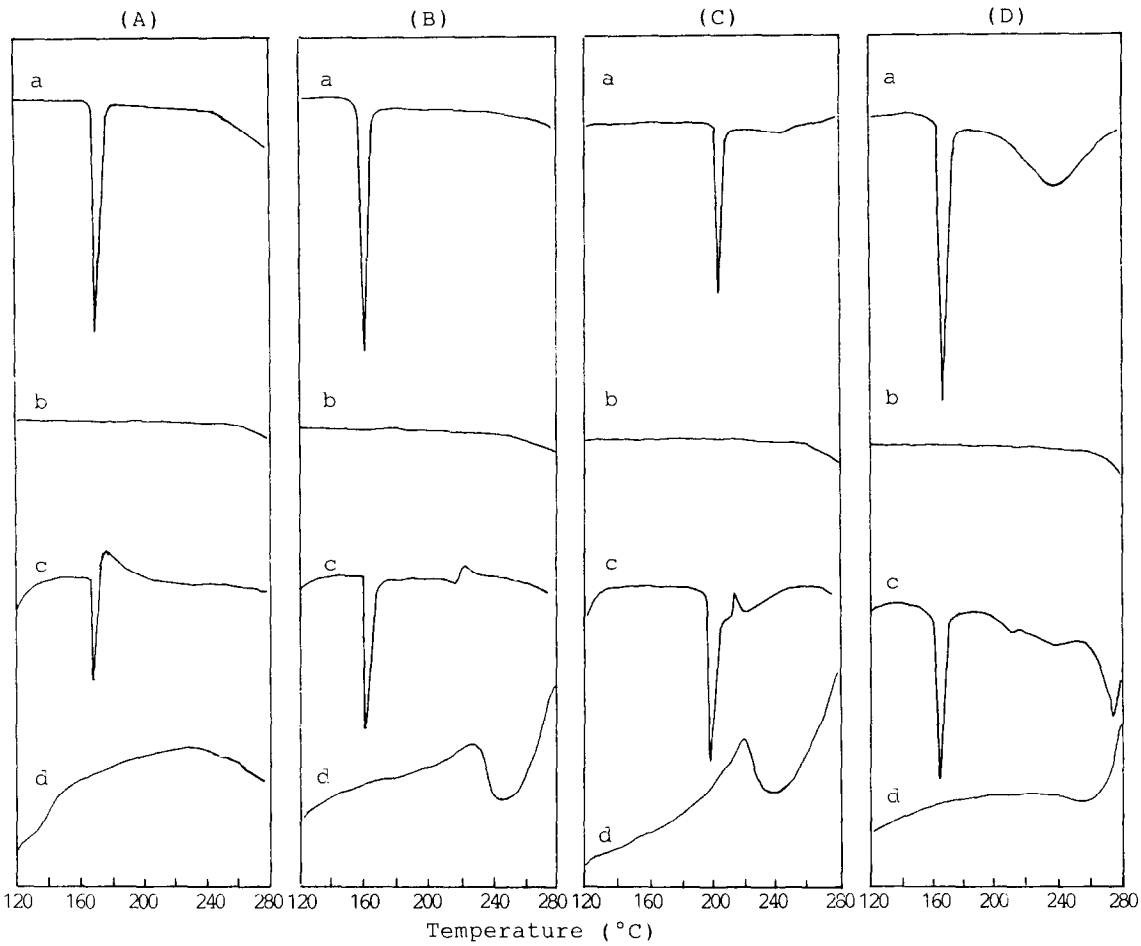

Fig. 2. DSC thermograms of pure drug (a), β-cyclodextrin (b), physical mixture (c) and spray-dried product (d) of drug with β-cyclodextrin. (A) acetaminophen series; (B) indomethacin series; (C) piroxicam series; (D) warfarin series.

series, B is indomethacin series, C is piroxicam series and D is warfarin series. It is obvious that pure drugs (A-a, B-a, C-a and D-a) β-cyclodextrin (A-b, B-b, C-b and D-b) and physical mixtures (A-c, B-c, C-c and D-c) of drug with β-cyclodextrin exhibited crystalline characteristics. All the spray-dried products (A-d, B-d, C-d and D-d) showed an amorphous state by spray-drying the physical mixture of drug with β-cyclodextrin from solutions or slurries. The peaks in the X-ray diffraction patterns of the spray-dried products were less intense than those of the original crystals. Moreover, we also found that if the spray-dried products without β-cyclodextrin exhibited more intense X-ray diffraction peaks than the spray-dried products with β-cyclodextrin. This finding indicated that drug crystals were converted to a disordered form, which might be attributed to the rapid crystallization in the presence of β-cyclodextrin.

DSC thermograms of pure drug (a), β-cyclodextrin (b), physical mixture (c) and spray-dried product (d) of drug with β-cyclodextrin are shown in Fig. 2. The endothermic peaks of drugs (a,c) due to the fusion of drug crystals disappeared in DSC thermograms for the spray-dried products (d). Here, the disappearance of endothermic peaks of the spray-dried products may be attributed to the amorphous state or inclusion complex formation or both.

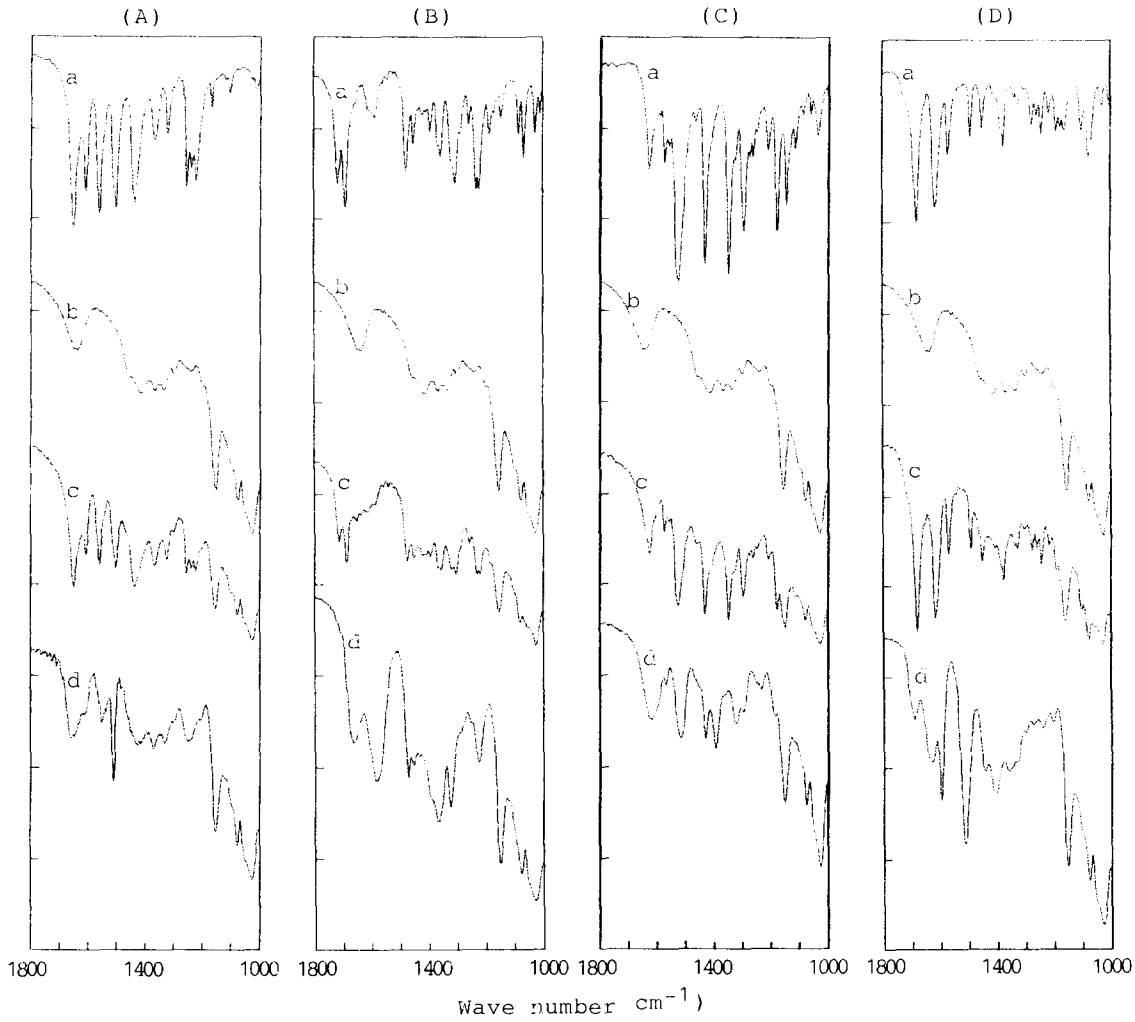

Fig. 3. IR spectra of pure drug (a), β-cyclodextrin (b), physical mixture (c) and spray-dried product (d) of drug with β-cyclodextrin. (A) acetaminophen series; (B) indomethacin series; (C) piroxicam series; (D) warfarin series.

Fig. 3 also shows the IR spectra of drug-β-cyclodextrin systems. It is apparent that some of IR absorption peaks in each spray-dried product were different from that of physical mixture of drug and β-cyclodextrin, due to the inclusion complex formation. The band at 1568 cm^{-1} belongs to the amido C = O of acetaminophen, which was shifted to 1555 cm^{-1} by intermolecular hydrogen bonding in spray-dried products. The band at 1716 cm^{-1} is due to the carbonyl C = O of indomethacin, this band was shifted to 1666 cm^{-1} due to the formation of intermolecular hydrogen bonding between indomethacin and β-cyclodextrin. The phenolic OH at 1180 cm^{-1} for piroxicam was also changed to 1154 cm^{-1} by intermolecular hydrogen bonding in spray-dried products. The carbonyl strengthening band of warfarin shifted from 1688 cm^{-1} to 1697 cm^{-1}, suggesting the dissociation of the intermolecular hydrogen bonds of warfarin molecules by inclusion complexation.

From the above results, it is suggested that the

spray-drying technique can be used to prepare the amorphous state of drug-β-cyclodextrin inclusion complexes.

Micromeritic properties of spray-dried products

The spray-dried products were observed to be fairly spherical particles under an optical microscope. Their sizes varied from 3 to 40 μm and their distributions were described by a logarithmic plot. The geometric mean diameter of the products is listed in Table 1. All the spray-dried products show smaller size in particles.

The packing process of the spray-dried products in a tapped graduated cylinder can be described by the following equation (Kawakita, 1964).

$$N/c = 1/ab + N/a \quad (2)$$

$$c = (V_0 - V_n)/V_0 \quad (3)$$

where a and b are constants representing the proportion of consolidation at the closest packing attained and packing velocity index, respectively. 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. Therefore, a low value a implies a better flowability and packability of powder. The param-

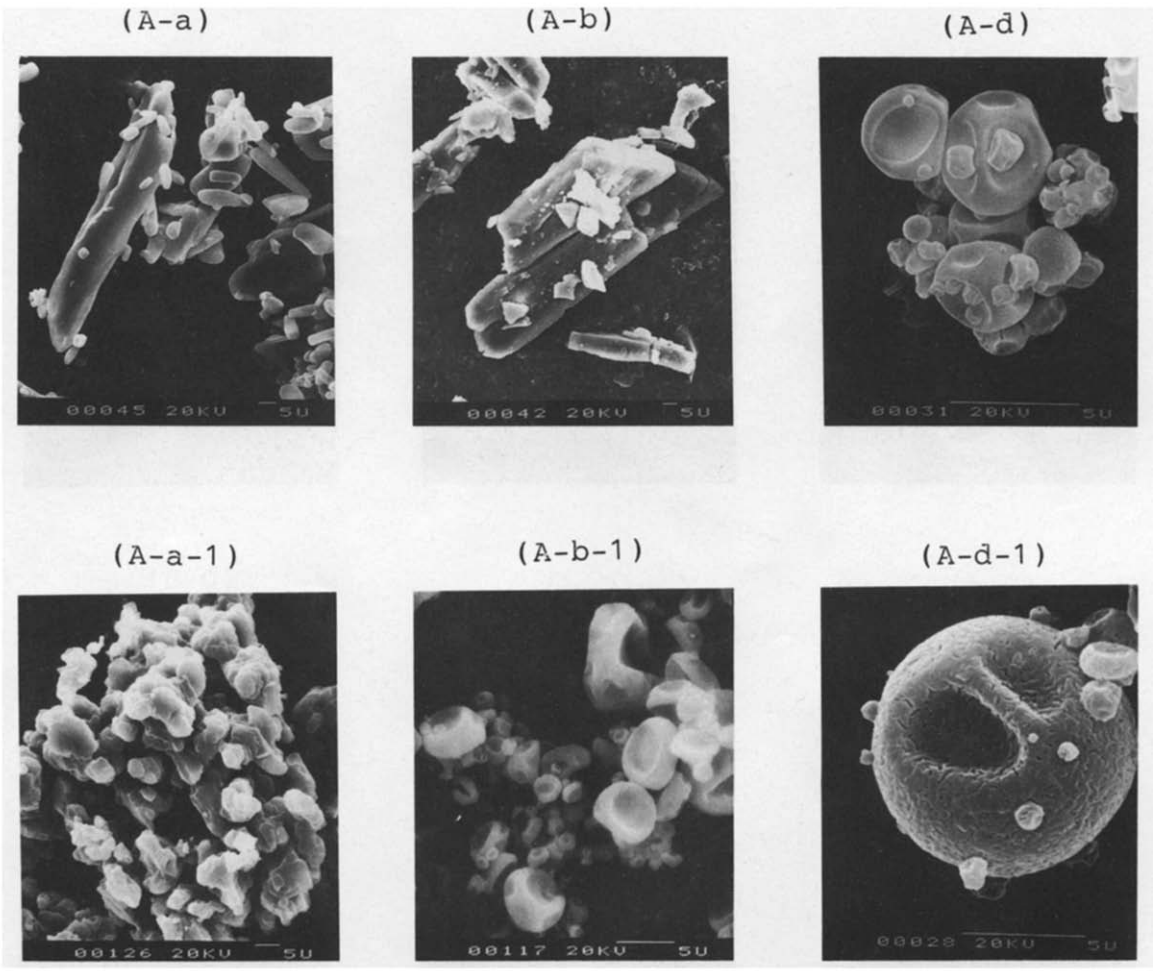

Fig. 4. Scanning electron microscopic photographs of pure drug, β-cyclodextrin and spray-dried products. (A-a) acetaminophen; (A-a-1) spray-dried acetaminophen; (A-b) β-cyclodextrin; (A-b-1) spray-dried β-cyclodextrin; (A-d) spray-dried product A; (A-d-1) spray-dried product A.

eter a in Eqn. 2 for the spray-dried products was found to be larger than that of the original drug crystals, as shown in Table 1. The result indicates that the particles of the spray-dried products might be packed more loosely than those of the original drug crystals. This might be due to the small particle size of spray-dried products, which results in higher porosity and poor flowability.

Compressibility of powder, as computed from Eqn. 1, is also related to the flowability of a free-flowing powder. The more the flowability of powder the smaller the value of compressibility. A compressibility value smaller than 20% suggests excellent flowability of powders (Carr, 1965; Fiese and Hagen, 1986). Table 1 shows that the compressibility value of original drug crystals was smaller than that of the spray-dried products, indicating that the spray-dried powder has poor flowability due to the smaller particle size.

The angle of repose of original drug crystals and of the spray-dried products was determined by a fixed-funnel method, as tabulated in Table 1. All the spray-dried products and original drug crystals have a repose angle of approximately $> 50°$. It has been concluded that values for angle of repose $< 30°$ generally indicate a free-flowing material and angles $> 40°$ suggest a poorly flowing material (Pilpel, 1964). From the above data, the spray-dried products exhibited very poor flowability due to the formation of many smaller

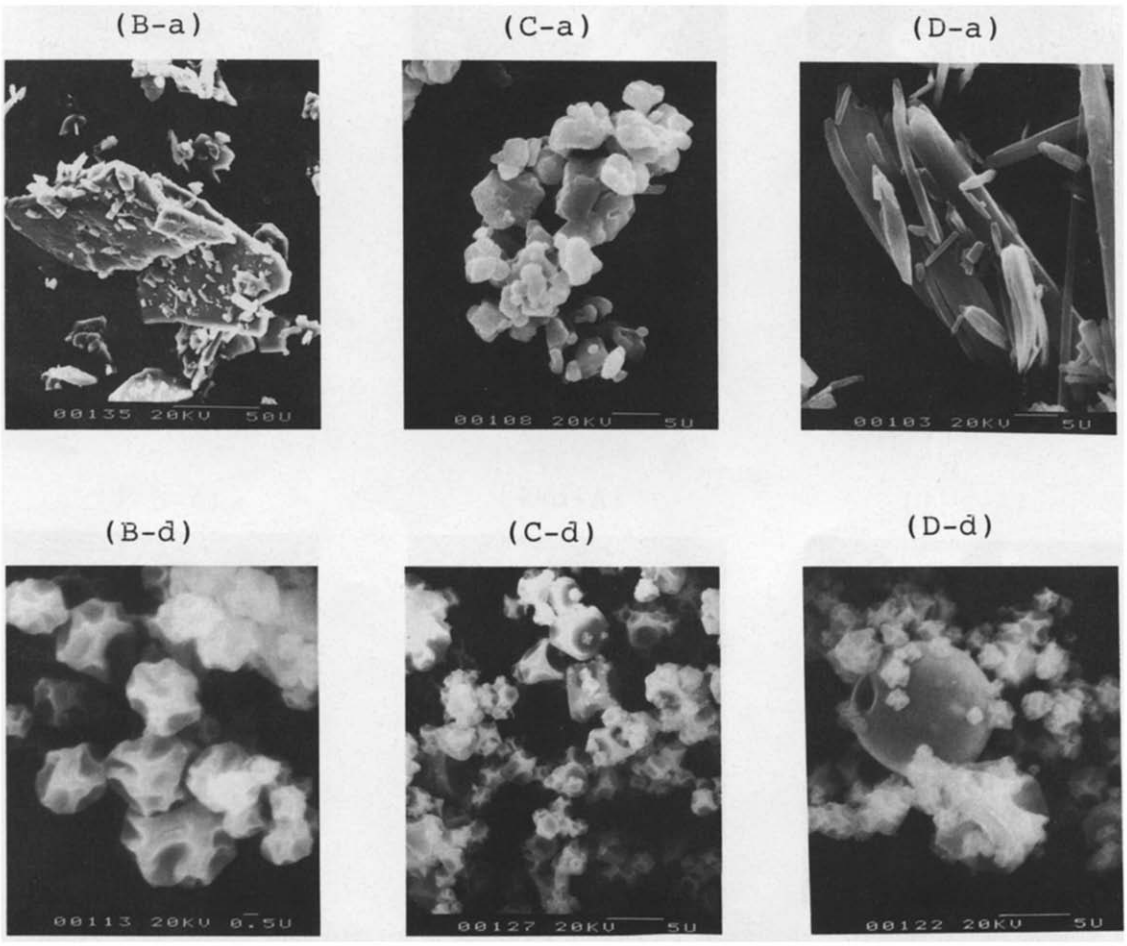

Fig. 5. Scanning electron microscopic photographs of pure drug and spray-dried products. (B-a) indomethacin; (B-d) spray-dried product B; (C-a) piroxicam; (C-d) spray-dried product C; (D-a) warfarin; (D-d) spray-dried product D.

particles (Table 1). Poor flowability can be improved by the use of glidants (Kawashima, 1983).

Scanning electron microscopic photographs of the spray-dried products are shown in Figs. 4 and 5. The shape and surface topographs of acetaminophen crystals and the spray-dried acetaminophen without β-cyclodextrin were different from each other (Figs. 4 A-a and A-a-1). It is apparent that the microcrystalline forms of acetaminophen were obtained by the spray-drying process, which was different from the original acetaminophen crystals. β-Cyclodextrin crystals (Fig. 4 A-b) dissolved in water and then spray dried show a spherical, folded and invaginated surface (Fig. 4 A-b-1). On the other hand, the spray-dried products containing acetaminophen and β-cyclodextrin exhibited a smooth surface with some fissures in the coating layer (Fig. 4 A-d). Moreover, a few spray-dried products also possessed a characteristically folded and invaginated surface. Another different appearance of the spray-dried products containing acetaminophen and β-cyclodextrin was also observed (Fig. 4 A-d-1). Evidence of large fissured surface and invagination was noted. Fig. 5 also indicates that the shape and surface appearance of the spray-dried products containing drugs (indomethacin, piroxicam or warfarin) and β-cyclodextrin, which was similar to that of the spray-dried products of acetaminophen and β-cyclodextrin, although the topograpy of the original drug crystals was different. A smooth surface with a folded and invaginated structure was also observed. The result indicates that small and spherical particles with some invaginations were obtained by spray-drying drug formulations containing β-cyclodextrin.

Dissolution behavior of tabletted spray-dried products

Dissolution patterns of the tablets made from the spray-dried products in distilled water were determined using the USP XXI paddle dissolution method, as shown in Fig. 6. It is evident that the dissolution rate of the spray-dried products of

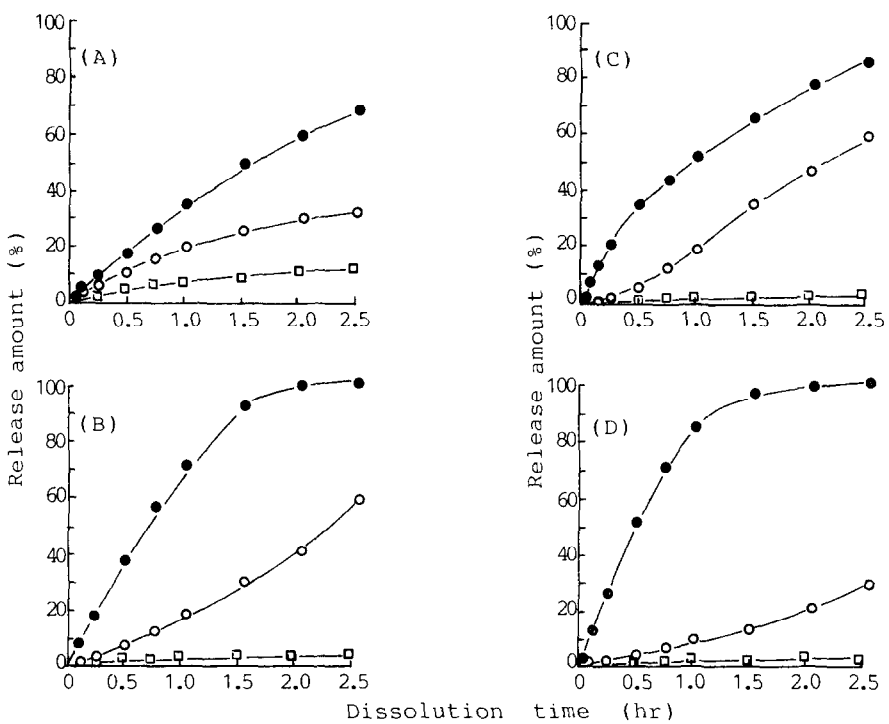

Fig. 6. Dissolution patterns of pure drug (□), physical mixture (○) and spray-dried product (●) of drug with β-cyclodextrin. (A) acetaminophen series; (B) indomethacin series; (C) piroxicam series; (D) warfarin series.

drug with β-cyclodextrin was faster than that of the physical mixture and pure drug. This might be due to the high energetic amorphous state of spray-dried products, resulting in a faster dissolution rate. Furthermore, β-cyclodextrin has surfactant-like properties which can reduce the interfacial tension between water-insoluble drugs and the dissolution medium, leading to a higher dissolution rate. The smaller particle size produced by the spray-drying process might increase with surface area of spray-dried particles, also resulting in a higher dissolution rate. Thus, the enhanced dissolution rate of the spray-dried products might be due to a decrease in crystallinity and particle size, and formation of an inclusion complex.

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