ylacetyl chloride, were chromatographed over 3% SP2401 (9) (Scheme II). Using this system good separation of diastereomers was achieved (Fig. 1). Retention times of derivatized (+)-norketamine and (−)-norketamine were 13.5 and 14.9 min, respectively. These compounds failed to show a parent ion (m/z = 439) using electron impact mass spectroscopy, but when subjected to chemical ionization conditions, both displayed significant M + 1 ions. Fragmentation patterns also were consistent with the structures. When purified enantiomers were derivatized and subjected individually to GLC analysis, no contamination from the other stereoisomer could be detected, indicating that the resolution procedure had resulted in highly stereochemically pure norketamine.

The enantiomers were converted into either hydrochloride or bisuccinate salts. The former proved to be quite hygroscopic making the bisuccinate salts more convenient for subsequent studies. The signs of optical rotation were the same for both salts. The free bases were not highly purified to permit accurate measurements of their optical rotations, but using partially purified samples, it was determined that the signs of rotation for the free bases and the salts were the same. This observation is in contrast to reported optical rotations of ketamine (10). The free bases and hydrochloride salts for this compound show opposite signs of rotation.

Initial pharmacological evaluation revealed that intraperitoneally injected dextrorotatory norketamine bisuccinate caused a greater duration of loss of righting reflex in mice than the levorotatory isomer (Table I). At doses of 100 mg/kg (calculated on free base content) the levorotatory isomer failed to induce loss of righting reflex, whereas this same dose appeared to be near the ED_{50} value for the dextrorotatory form. At 200 mg/kg all animals lost righting reflex with the dextrorotatory compound, producing a significantly greater duration of loss (Table I). These preliminary studies also suggested that levorotatory norketamine bisuccinate may cause greater amounts of central excitation than the dextrorotatory form. This is based on the observation that animals receiving the levorotatory drug appeared to show greater amounts of spontaneous locomotor activity than those receiving the dextrorotatory isomer.

Similar actions as to loss of righting reflex and central excitation have been reported for the ketamine enantiomers (3). Also, it has been shown that racemic norketamine and ketamine are qualitatively similar with regard to central nervous system depressant effects and posthypnotic excitation (5). Because of the these findings, it is tempting to speculate that the levorotatory salts of ketamine and norketamine have identical stereochemical configurations; the same being true for the dextrorotatory forms. However, additional studies will be needed to establish the exact stereochemical relationships between these compounds as well as the pharmacological significance of the norketamine enantiomers.

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Preparations of Solid Particulates of Theophylline–Ethylenediamine Complex by a Spray-Drying Technique

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Received May 27, 1981, from the **Gifu College of Pharmacy, Mitahora, Gifu 502, Japan* and the ‡*Ichimaru Company, Matsuhora, Takatomi, Gifu 502-21, Japan.* Accepted for publication November 3, 1981.

Abstract □ Aqueous solutions of ethylenediamine and theophylline were spray dried to obtain solid particulates of theophylline–ethylenediamine complex to improve solubility of theophylline. Packing and flow properties of the spray-dried products were much improved when compared with those of original theophylline particles, due to their spherical shapes which were confirmed by a scanning electron microscope. The solubility of theophylline in the resultant products was found to be three to five times higher than that of original theophylline. The solubilities of the products decreased with increasing drying temperature and rotation speed of the atomizer, which was interpreted in terms of the contents of ethylenediamine in the products. The products were confirmed to be a mixture of aminophylline, α-aminophylline, and theophylline by X-ray analysis and NMR spectroscopy. The logarithm of the relative intensity of the X-ray diffraction peak of α-aminophylline to that of theophylline decreased linearly with drying temperature and rotation speed of the atomizer. Thermal decomposition of the spray-dried products involved liberations of crystal water at 100° and ethylenediamine between 110 and 127°. Liberation of ethylenediamine occurred *via* three steps for aminophylline, but with different steps for the spray-dried products.

Keyphrases □ Complexation—theophylline–ethylenediamine, preparations, spray-drying technique, solid particulates □ Theophylline—complexation with ethylenediamine, preparations, solid particulates, spray-drying technique □ Ethylenediamine—complexation with theophylline, preparations, solid particulates, spray-drying technique

The spray-drying technique has been accepted as a favorable method for drying a variety of heat-sensitive materials, such as foods, pharmaceuticals, enzymes, *etc.* The preparation of particulate solids from liquid droplets by chemical reaction during drying is one of the recent uses of this technique. Microcapsules of barbituric acid and phenobarbital with a tensioactive precondensate of the hexamethylolmelamine type, which form macromolecules under the influence of heat, have been prepared previously (1, 2). An ammonium sulfate sphere has been produced by the reaction of a single drop of phosphoric acid with gaseous ammonia (3).

The objective of the present study was to prepare solid particulates of the theophylline–ethylenediamine complex (*e.g.*, aminophylline) by a spray-drying technique. The manufacturing method of aminophylline referred to in the

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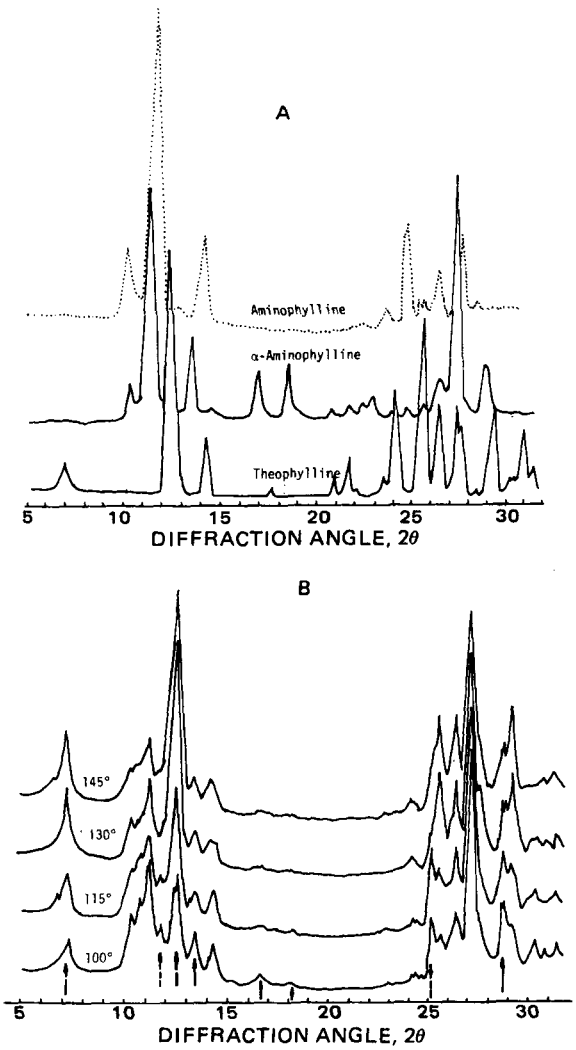

Figure 1—*(A) X-ray diffraction patterns of references; (B) the spray-dried products prepared at various spray-drying temperatures.*

Japanese Pharmacopeia (JP) involves a multistage process including reaction, filtration, drying, *etc.* In addition, the reaction takes several hours. The process of the present study offers the advantage of reducing the preparation steps, which can save time and cost. Another objective was to investigate the spray-drying conditions affecting the composition of the products. Thermal decomposition of spray-dried products by thermal analysis was also investigated.

EXPERIMENTAL

Materials—Theophylline[1] and ethylenediamine[1] used were chemical reagent grade. Aminophylline[1] (JP) and another theophylline–ethylenediamine complex, α-aminophylline, were used as a reference for identifying the spray-dried products. α-Aminophylline was produced by a method (JP) modified previously (4). Ethylenediamine purified by distillation (11.47 ml) was dissolved in 100 ml of absolute alcohol. Theophylline (30.82 g) was stirred into the resulting solutions. After agitation for several hours, the resultant precipitates were filtered and dried at 5–7° immediately after filtration without washing. The X-ray diffraction pattern of the products, *i.e.*, α-aminophylline, was different from that of aminophylline (JP) as shown in Fig. 1A. α-Aminophylline contained 13.9% ethylenediamine, 85.9% theophylline, and 0.2% water, which suggested the composition of α-aminophylline with 2 moles of theophylline, 1 mole of ethylenediamine, and small amounts of water.

[1] Nakarai Chemical LTD, Japan.

Table I—Micromeritic Properties of Spray-Dried Products

Drying Temperature	Rotation Speed of Atomizer, rpm	Dg[a], μm	σ,g[b]	ρ,g/cm³[c]	Solubility of Theophylline, mg/ml[d]
100	20,000	13.0	1.31	1.31	43.0
115	20,000	10.1	1.57	1.32	40.0
130	20,000	11.5	1.38	1.30	30.7
145	20,000	12.0	1.41	1.31	29.6
115	10,000	14.2	1.48	1.37	40.4
115	20,000[e]	10.1	1.57	1.32	40.0
115	40,000	9.8	1.34	1.39	29.0

[a] Geometric mean diameter. [b] Geometric standard deviation. [c] Particle density, the particle density of aminophylline is 1.43. [d] The solubilities of theophylline and aminophylline (JP) in water are 8.74 and 49.4 mg/ml, respectively, at 30°. [e] The parameters (*a*,*b*) in Eq. 1 of spray-dried products, original theophylline, and spray-dried theophylline are (0.16, 0.064), (0.23, 0.062), and (0.31, 0.036), respectively.

Spray-Drying Technique—Theophylline (53.5 g) and ethylenediamine (23.0 ml) were dissolved in 500 ml of water. The solutions were atomized in a drying chamber by a centrifugal wheel atomizer at rotations of 10,000, 20,000, or 40,000 rpm. The drying chamber was maintained at 100, 115, 130, or 145 ± 5°. The dried products were collected by a cyclone. As a reference, 500 ml of aqueous suspensions containing 53.5 g of theophylline was spray dried at 115° with an atomizer rotation speed of 20,000 rpm.

Measurement of Micromeritic Properties—The sizes of the spray-dried products were measured by a photographic counting method using a particle size analyzer[2]. The packing properties of the products were investigated by a tapping method. The true densities of the products were measured with a helium–air comparison pycnometer[3]. The surface topographs of the products coated with gold were investigated by a scanning electron microscope[4]. The solubilities of the products were measured in water at 30°.

Measurement of Physicochemical Properties—The contents of ethylenediamine and theophylline in the products were measured by a neutralization titration method with 0.1 *N* HCl and spectrophotometrically at 270 nm, respectively. Water contents were measured by the Karl Fischer method[5]. To analyze the crystalline form of the products, X-ray diffraction patterns were obtained by an X-ray diffractometer[6]. Thermal decomposition of the products was examined using a differential scanning calorimeter[7] with heating rate at 10°/min. Thermal analysis of the products treated with heating at 110 or 120° for 30 min was also carried out in a muffle to investigate the process of the thermal decomposition. NMR spectra of ethylenediamine, aminophylline, α-aminophylline, theophylline, and the spray-dried products were obtained in dimethyl sulfoxide using an NMR spectrometer[8].

RESULTS AND DISCUSSION

Micromeritic Properties of Spray-Dried Products—Size distribution of the spray-dried products was described in log-normal form. The geometric mean diameters of the products varied from 9.8 to 14.2 μm, and were independent of the drying temperature, but dependent on the rotation speed of the atomizer. The sizes of products decreased with an increase of the rotation speed, since the diameters of the spray droplets were reduced by enhancing the rotation speed. The geometric standard deviations of diameters of the products were 1.31–1.57 (Table I).

The scanning electron photographs of the original and the spray-dried theophylline and spray-dried products with ethylenediamine are exhibited in Fig. 2. The surface of the spray-dried theophylline was rough compared with that of the original crystal. A number of small spherical-sized products, which adhered to the crystals, yielded from the atomized solution of theophylline, are shown in Fig. 2B. Spray-dried products prepared from the formulation containing ethylenediamine yielded spheres covered with thin flake crusts, as shown in Figs. 2C and D. Loose internal texture of the products could be predicted from the characteristic surface topography. This was confirmed by the lower particle densities of the spray-dried products than original theophylline and aminophylline (JP) as tabulated in Table I.

[2] Karl Zeiss TGZ-3.
[3] Model 1302, Micromeritics Instrument Co.
[4] Nihon Denshi, JMS-SI, Japan.
[5] Kyoto Electronics Manufacturing Co., Japan.
[6] Nihon Denshi, JDX, Japan.
[7] Rigaku CN 80852, Japan.
[8] R-20B, Hitachi, High Resolution NMR Spectrometer, Japan.

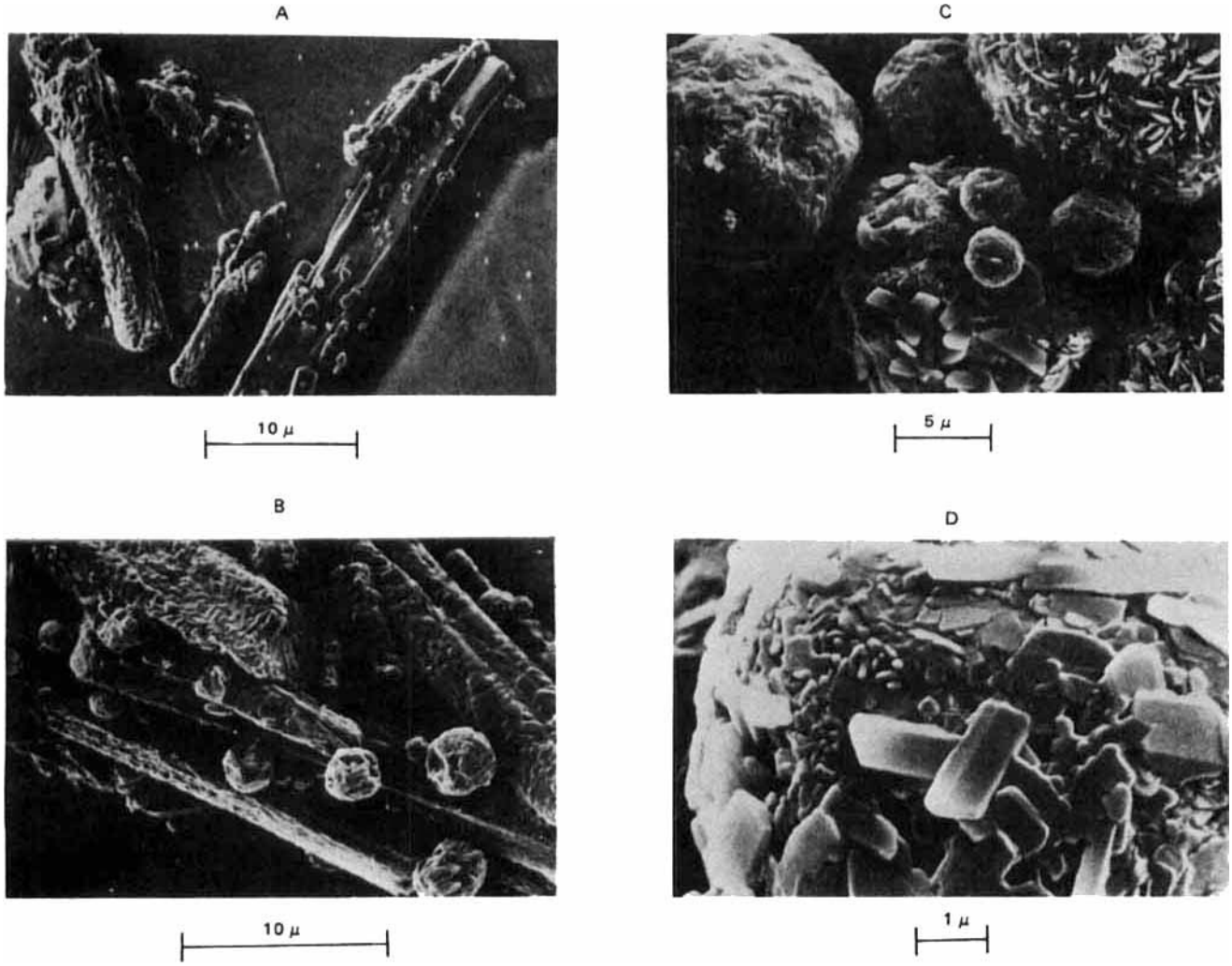

Figure 2—*Scanning electron microscopic photographs of spray-dried products. Key: (A) original theophylline; (B) spray-dried theophylline; (C) and (D) spray-dried products prepared at 115°, 20,000 rpm with the formulation containing ethylenediamine (20 ml) and theophylline (53.5 g).*

Packing and flow properties of the spray-dried products were much improved compared with those of original theophylline particles due to their spherical shapes. The packing process by tapping was described by the Kawakita equations (5, 6):

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

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

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. Parameter a in Eq. 1 for the spray-dried products was found to be smaller than that of original theophylline (Table I), which indicated that packing properties of the spray-dried products were improved.

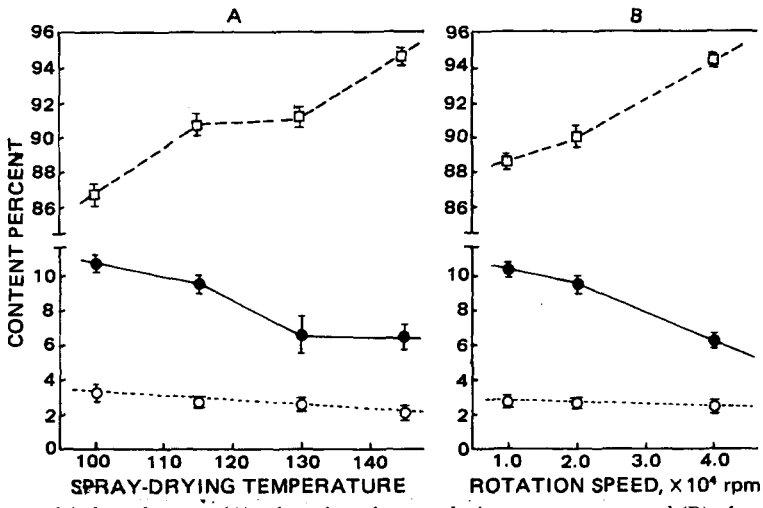

Figure 3—*Composition of the spray-dried products as (A) a function of spray-drying temperature and (B) of rotation speed of the atomizer. Key: (□) theophylline; (●) ethylenediamine; and (○) water.*

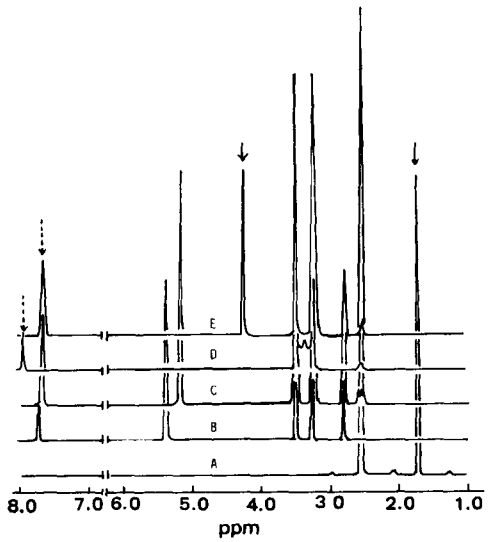

Figure 4—*NMR spectra of (A) ethylenediamine, (B) aminophylline, (C) α-aminophylline, (D) theophylline, and (E) the spray-dried products prepared at 115°, 20,000 rpm with the formulation containing ethylenediamine (20 ml) and theophylline (53.5 g). Key: (→) amino group protons of ethylenediamine; (- - -→) proton at position 8 of theophylline.*

The solubility of the spray-dried products with ethylenediamine was found to be three to five times higher than that of original theophylline, but lower than that of aminophylline (JP). However, no improvement in the solubility of the spray-dried theophylline without ethylenediamine was found. The solubilities of the products with ethylenediamine decreased with increase of both the drying temperature and the rotation speed of the atomizer. This finding could be interpreted in terms of the contents of ethylenediamine in the products, which decreased with an increase in the drying temperature and the rotation speed of the atomizer.

Physicochemical Properties of the Spray-Dried Products—The contents of theophylline in the products increased with increasing temperature of the drying chamber, whereas ethylenediamine contained in the products decreased with the temperature, as shown in Fig. 3. The ethylenediamine content in the products dropped sharply by raising the drying temperature higher than the boiling point of ethylenediamine (117°) but >6% ethylenediamine still remained. This finding suggested that ethylenediamine contained in the products did not exist as a free form adsorbed on the surface of the products but as a chemically bonded form, which resulted in preventing evaporation of ethylenediamine. This speculation was proven by NMR spectra of the spray-dried products in Fig. 4, which almost coincided with those of aminophylline and α-aminophylline. The signal of amino group protons of ethylenediamine in the product shifted to lower field (chemical shift, δ = 4.3 ppm) compared with that of ethylenediamine (δ = 1.7 ppm), which might be due to intermolecular hydrogen bondings. The hydrogen bondings might be attained by the interaction between the hydrogens of NH_3^+ of ethylenediamine formed by a proton migration from =NH of theophylline, and C=O at position 6 and $=N^-$ of theophylline (4, 7). The signal of the proton at position 8 of aminophylline and the spray-dried products shifted to a higher field compared with that of theophylline, as shown in Fig. 4, which support the migration of a proton from =NH of theophylline to NH_2 of ethylenediamine. Water content of the products decreased gradually with increased temperature.

Theophylline contents in the products increased with increased rotation speed of the atomizer, while the contents of ethylenediamine and water decreased with rotation speed (Fig. 3). An increase in the rotation speed of the atomizer reduced the diameters of resultant spray droplets by which evaporation speed was accelerated (Table I); therefore, this action was equivalent to raising drying temperature.

The X-ray diffraction patterns of the products prepared at various drying temperatures are exhibited in Fig. 1B. In the pattern of the spray-dried products, the characteristic peaks of theophylline appeared at 7.2 and 12.5°, of aminophylline at 11.8 and 25.2°, and of α-aminophylline at 11.2, 13.5, 16.7, 18.1, and 28.8°. These were confirmed by the references in Fig. 1A. The described X-ray diffraction analysis suggested that the spray-dried products were a mixture of these three compounds. The X-ray diffraction pattern varied with the drying temperature. The

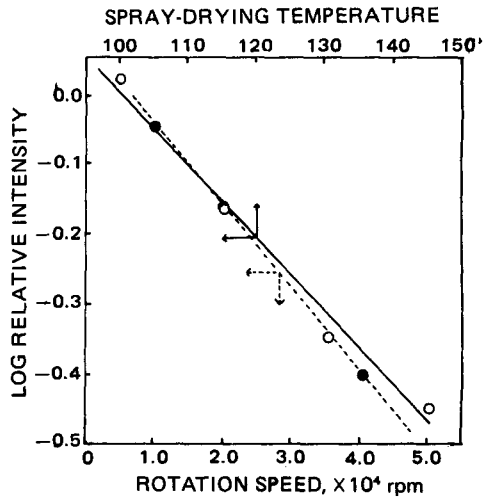

Figure 5—*Relative intensities of X-ray diffraction peak of α-aminophylline to theophylline as a function of spray-drying temperature (○) and of rotation speed of the atomizer (●).*

intensities of characteristic diffraction peaks of aminophylline at 25.2° and of α-aminophylline at 11.2, 16.7, and 18.1° decreased with the increasing drying temperature, whereas those of theophylline at 7.2, 12.5, and 29.3° increased strongly (Figs. 1A and B).

This relation can be described quantitatively in Fig. 5. The relative intensities (*RI*) of α-aminophylline to theophylline defined by Eq. 3 are plotted against drying temperature on a semilogarithmic graph:

$$RI = \frac{I(11.2°) - I(20.0°)}{I(12.5°) - I(20.0°)} \qquad \text{(Eq. 3)}$$

where I(11.2°) and I(12.5°) are the relative intensities of diffraction peaks of α-aminophylline and theophylline to that of sodium chloride at 31.7° used as an internal standard material, respectively, and I(20.0°) is the relative intensity of the base line to that of sodium chloride. The logarithm of the relative intensity correlated improportionately to the drying temperature. A similar correlation was found between the rotation speed of the atomizer and the logarithm of the relative intensity (Fig. 5).

Thermal Decomposition of the Spray-Dried Products—Differential scanning calorimetry and thermogravimetric thermograms of the references of aminophylline, α-aminophylline, and theophylline are exhibited in Fig. 6A by solid and dotted lines, respectively. On the differential scanning calorimetric curve of aminophylline, endothermic peaks at 100–103, 110, 120, 127, and 271° appeared. The endothermic peak at 100° was caused by releasing water, where the weight loss (4%) detected by thermogravimetric analysis corresponded to 1 mole of water. The endothermic peaks which appeared in the 110–127° range might have been caused by liberation of ethylenediamine, since the thermogravimetric curve revealed the weight loss corresponding to 1 mole of ethylenediamine. These findings indicate that ethylenediamine of aminophylline may be liberated by heating *via* three stages. The endothermic peak at 271° corresponds to the melting point of theophylline. The differential scanning calorimetric thermogram of α-aminophylline revealed two endothermic peaks at 116 and 271°. No endothermic peak at 100° caused by releasing water appeared on the thermogram, which was predicted by the Karl Fischer analysis described in the experimental section. The decomposition of α-aminophylline was completed up to 125°, at which point the weight loss reached 12%, equivalent to ~1 mole of ethylenediamine.

The differential scanning calorimetric thermograms of the spray-dried products are displayed as a function of drying temperature and of rotation speed of atomizer in Figs. 6B and C, respectively. On the differential scanning calorimetric curve of the product prepared at the relatively low drying temperature (*e.g.*, 100°), endothermic peaks appeared at 100, 116, and 271°. Liberation of ethylenediamine from the product was assumed to occur at 116°, because the endothermic peaks at 100 and 271° correspond to the releasing point of water and the melting point of theophylline, respectively. When the drying temperature was increased, the endothermic peak at 116° became weak, while another peak appeared at 127°, as seen on the thermogram of the products prepared at 115°. This finding indicates that the bond strength of ethylenediamine with theophylline in the products was affected by the drying temperature employed for spray drying. The latter peak became intense, whereas the former

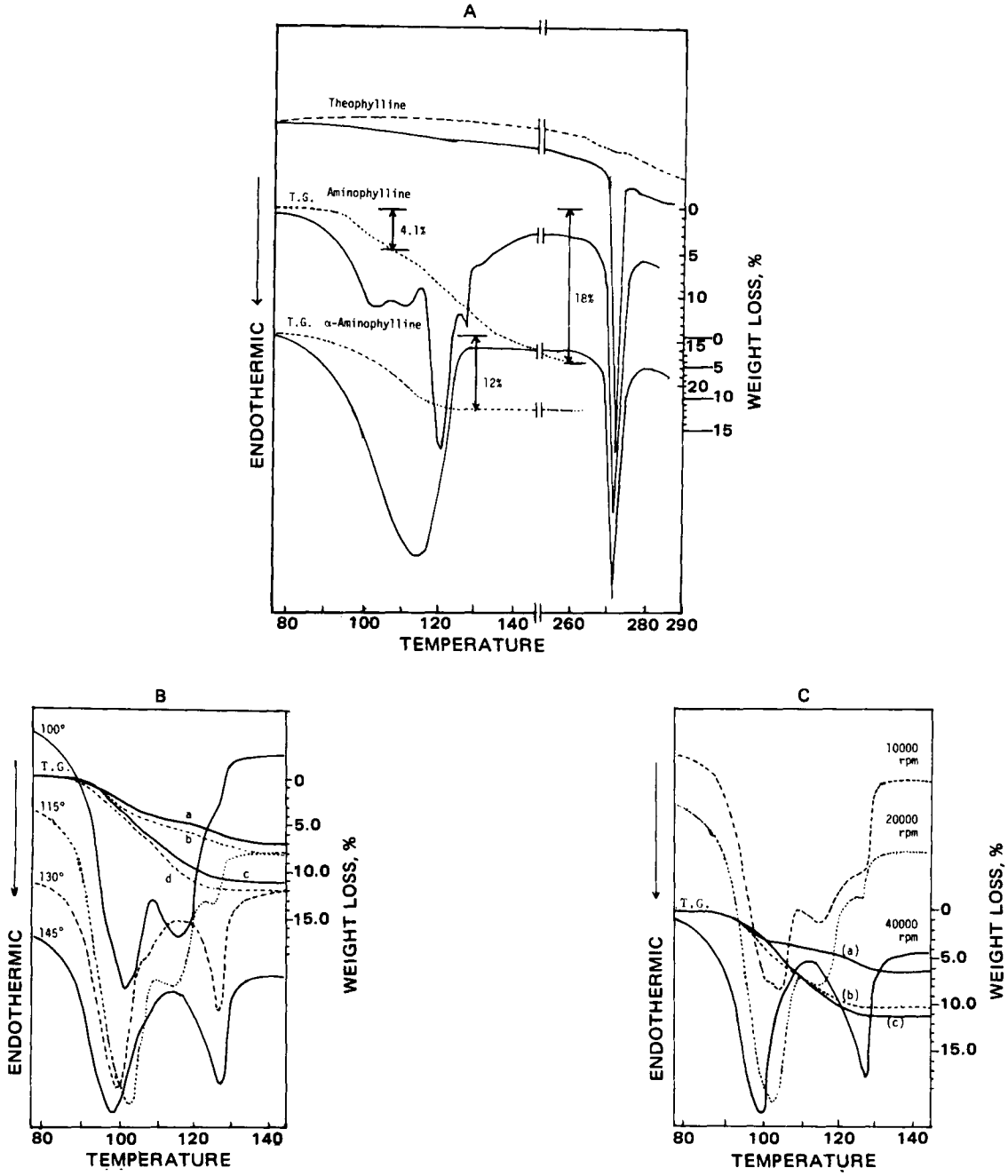

Figure 6—*Differential scanning calorimetric and thermogravimetric thermograms of (A) references; (B) the spray-dried products prepared at various spray-drying temperatures; and (C) rotation speed of the atomizer. Key: thermogravimetric curves in (B): (a) 145°; (b) 130°; (c) 115°; (d) 100°; thermogravimetric curves in (C): (a) 40,000 rpm; (b) 20,000 rpm; (c) 10,000 rpm.*

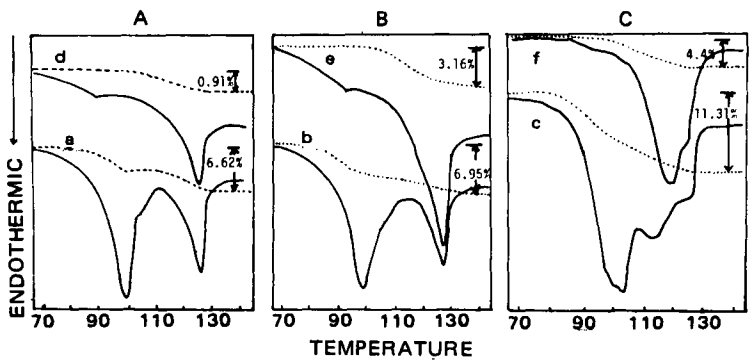

Figure 7—*Changes in differential scanning calorimetric and thermogravimetric thermograms of the spray-dried products by heat treatment. Key: spray-drying condition, a, b, c; (drying temperature, rotation speed of atomizer) and heat-treatment condition, d, e, f; (temperature, time) (A): a (115°, 40,000 rpm); (B): b (145°, 20,000 rpm); (C): c (115°, 10,000 rpm); d (120°, 30 min); e (120°, 30 min); f (110°, 30 min).*

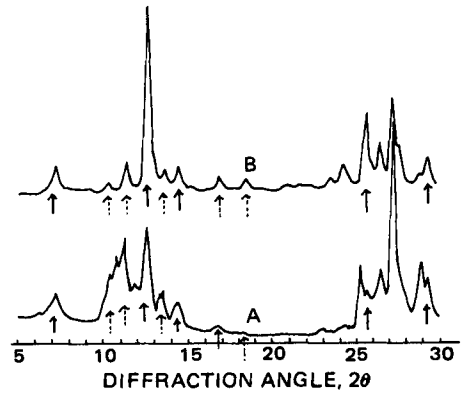

Figure 8—*Changes in X-ray diffraction patterns of the spray-dried products caused by heat-treatment. Key: (A) spray-dried products prepared at 115°, 10,000 rpm; (B) products treated at 110°, 30 min; (→) theophylline; (- - -→) α-aminophylline.*

peak disappeared when the drying temperature was >130°. The weight loss indicated by thermogravimetric curves in Fig. 6B corresponded approximately to the contents of water and ethylenediamine contained in the products as indicated in Fig. 3. The weight loss detected by thermogravimetric analysis decreased with an increase in the drying temperature as shown in Fig. 6B, as predicted from the findings in Fig. 3.

The changes in differential scanning calorimetry and thermogravimetric thermograms, with the rotation speed of the atomizer, are displayed in Fig. 6C. The thermal behaviors of the product prepared with high (low) rotational speed of the atomizer resembled those of the products prepared at high (low) drying temperature. As expected, the weight loss which appeared on the thermogravimetric curve decreased with increasing rotation speed of the atomizer.

Differential scanning calorimetric and thermogravimetric thermograms of the products treated with heating were compared with those of the products prior to the treatment in Fig. 7. After treatment by heating, the endothermic peak at 100° for water releasing disappeared from the thermogram. No weight loss on the thermogravimetric curve at 100° also indicated that the products treated by heating contained no crystalline water. However, an endothermic peak at 127° of the products prepared by spray drying at high temperature or with high rotation speed of the atomizer still remained even after heat treatment at 120°. The products prepared at low drying temperature or at low atomizing speed revealed an endothermic peak at 120° on the thermograph after heat treatment at 110°. The weight loss detected at 127 or 120° by thermogravimetric analysis suggested that some ethylenediamine still remained in the products even after heat treatment.

The X-ray diffraction pattern of the products treated with heating revealed characteristic peaks of theophylline and α-aminophylline at 7.2, 12.5, 14.2, 25.7, 29.3° and 10.2, 11.2, 13.5, 16.7, 18.1°, respectively. The peaks for theophylline strengthened, but no diffraction peaks for aminophylline appeared on the pattern in Fig. 8. These findings proved that the endothermic peak at 116 or 127°, that appeared on the thermogram of the spray-dried products, was caused by the liberation of ethylenediamine contained in a theophylline–ethylenediamine complex.

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ACKNOWLEDGMENTS

The authors thank Prof. A. Otsuka, Meijyo University, Nagoya, Japan, for use of the X-ray diffractometer and the differential scanning calorimeter.

Bioavailability of Regular and Controlled-Release Chlorpheniramine Products

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Received May 8, 1979, from the **Biological Availability Group Studies Laboratory, School of Pharmacy, University of Georgia, Athens, GA 30602*, the ‡*Food and Drug Administration, Rockville, MD*, and the §*Baxter Travenol Laboratories, Morton Grove, Ill.* Accepted for publication November 3, 1981.

Abstract □ The bioavailability of chlorpheniramine regular-release *versus* controlled-release products was compared using 15 human subjects. The dosage forms evaluated were an 8-mg barrier coated-bead capsule, an 8-mg repeat action tablet, two 4-mg tablets, and 4- and 8-mg syrups. Single doses of each product were administered orally in a 5-way crossover study, plasma samples were collected at specific time intervals, and chlorpheniramine levels assayed by HPLC. Pharmacokinetic analysis was based on a two-compartment open model. The average plasma elimination half-life of chlorpheniramine was calculated to be ~18.3 hr. The controlled-release products gave a higher C_{max} than the 4-mg syrup, but <two 4-mg tablets. The controlled-release products also extended the time necessary to attain peak drug levels compared to the 4- and 8-mg syrups. The area under the curve (*AUC*) data for the controlled-release products was not equivalent to equal amounts of the regular-release products. The study indicated that while the controlled-release chlorpheniramine products were successful in prolonging the time course of absorption, this was at the expense of incomplete bioavailability of the drug.

Keyphrases □ Chlorpheniramine—bioavailability of regular and controlled-release products □ Bioavailability—regular and controlled-release chlorpheniramine products □ Controlled-release products—bioavailability of chlorpheniramine

Chlorpheniramine maleate is commonly used in the treatment of various allergic conditions. The different dosage forms of chlorpheniramine maleate marketed include regular- (or immediate) release and controlled- (or sustained) release products.

Little comparative information is currently available

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