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EFFECT OF MOISTURE ON CRYSTALLIZATION OF THEOPHYLLINE IN TABLETS

Hidenobu Ando, Masaaki Ishii, Masanori Kayano and Hiroshi Ozawa

Pharmaceutical Development Research Laboratories,
Eisai Co., Ltd., Kawashima-cho, Hashima-gun,
Gifu 501-61, Japan

ABSTRACT

Needle-like crystals appeared on the surface of theophylline tablets containing anhydrous theophylline, hygroscopic materials such as potassium, and other formulation ingredients, when stored under conditions of high relative humidity. X-ray powder diffraction studies on these crystals showed that anhydrous theophylline was converted to the hydrate.
Crystal growth was accelerated by increased moisture uptake in tablets containing the hygroscopic materials polyethylene glycol 6000 or sodium chloride. The appearance of needle-like crystals on the surface of tablets resulted in a decrease in the rate of release of theophylline.

INTRODUCTION

An investigation into needle-like crystal growth has been carried out for caffeine, ethenzamide, salicylic acid, sodium valproate, carbamazepine, lactose and manitol (1-8). These phenomena of crystallization can result in a decrease in powder flowability, caking, cracking, and change in appearance (9). We have reported the formation of needle-like crystals, indentified as theophylline hydrate, on the surface of tablets to be due to a similar phenomenon (10).

This paper reports on X-ray diffraction studies carried out on needle-like crystlas, and the influence of moisture uptake on crystal growth in the presence of hygroscopic materials. The physico-chemical properties of the crystallized tablets were investigated through dissolution studies.

EXPERIMENTAL

Material

JP-grade crystalline cellulose (Asahi Kasei Kogyo, Japan), polyethylene glycol 6000 (Nihon Yushi Ltd., Japan), and carboxy methylcellulose calcium (Nichirin Chemical Industries, Ltd., Japan) were used. Anhydrous theophylline, potassium acetate and sodium chloride were supplied by Wako Pure Chemical Industries, Japan, and silicic acid (Syloid 244) was supplied by Fuji-Davison Chemicals, Japan. Anhydrous theophylline, supplied by Shiratori Pharmaceutical Co., Ltd., Japan, was used for sample E.

Preparation of Sample

Table 1 shows various formulations. The batch size was 50 g. Potassium acetate, polyethylene glycol 6000 and sodium chloride

TABLE 1

SAMPLE FORMULATION

Ingredient	Sample				
	A	B	C	D	E
Theophylline	20	20	20	20	20
Potassium acetate	10	-	-	-	10
Polyethylene glycol 6000	-	10	-	-	-
Sodium chloride	-	-	5	10	-
Silicic acid	50	50	50	50	47
Crystalline cellulose	20	20	25	20	20
Carboxy methylcellulose calcium	-	-	-	-	3
Total	100	100	100	100	100

The table shows the ratio of ingredients in each sample formulation. The batch size for each sample was 50 g.

were dissolved separately in 50 ml of distilled water. Using a 1-L Henshel-type mixer, silicic acid and crystalline cellulose, were blended for 3 minutes, following which all samples were granulated for approximately 5 minutes with an aqueous solution of potassium acetate, polyethylene glycol 6000 or sodium chloride and 10 ml of distilled water. After drying at 60°C for 24 hours, samples were passed through a no. 32 JP mesh screen and then blended with anhydrous theophylline and carboxymethylcellulose calcium according to the ratios shown in the formulations in Table 1 for 3 minutes in a 1-L Henshel-type mixer.

Tablet Compression Procedure

Granule from the five formulations, A to E, were compressed into 200 mg flat-faced tablets, 7.98 mm in diameter, at a pressure of 2000 kg/cm^2.

Storage Conditions

The tablets were stored in a chamber maintained at a relative humidity (RH) of 59, 75, or 90 %, and a temperature of 37°C. These relative humidities were maintained using saturated solutions of cobalt chloride, sodium chloride, and potassium nitrate, respectively (chemicals were obtained from Wako Industries).

X-ray Powder Diffraction

The crystalline forms of theophylline were determined by X-ray diffraction. (Diffractometer JDX-7E, Nihon Denshi, Tokyo, JAPAN) with nickel-filter CuKα radiation.

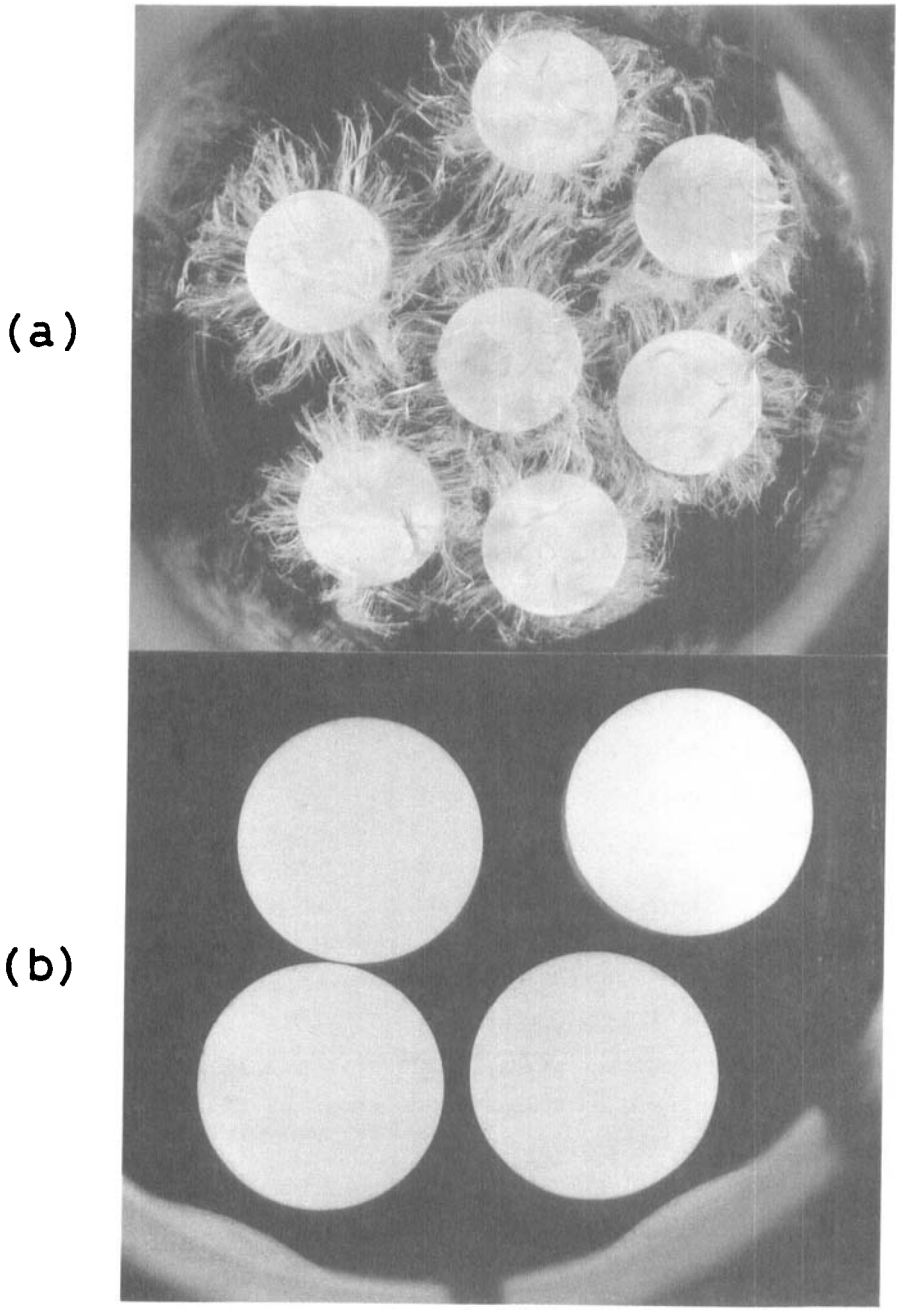

FIGURE 1

Photographs of Sample A Stored under 75 and 90% Relative Humidity (RH) at 37°C for 1 Year. Key: (a)Sample A, 90% RH; (b)Sample B, 75% RH.

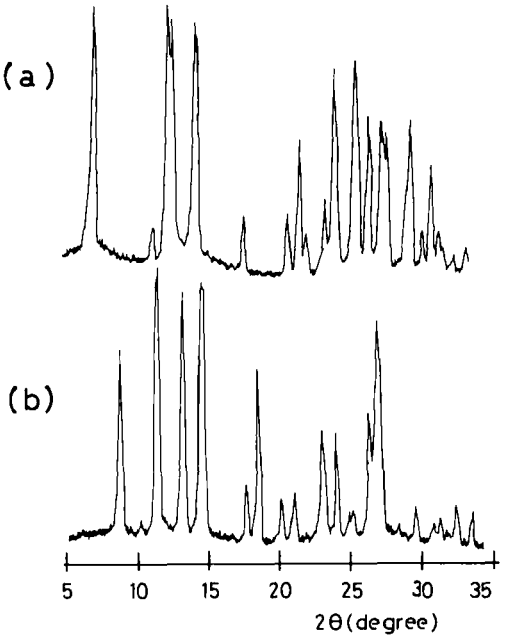

FIGURE 2

X-ray Diffraction Patterns of Anhydrous Theophylline and Sample A Stored under 90% Relative Humidity at 37°C for 1 Year. Key: (a) Anhydrous Theophylline, (b)Sample A.

Crystal Observation

The crystals found forming on the surface of the tablets were observed with an Akashi Seisakusho scanning electron microscope (Model MSM-7).

Photographs were taken using a PENTAX SP camera. The Nikon microscope was connected to Nikon FX-35A camera.

Dissolution Test

The dissolution testing was performed in 900 ml of distilled water at 37°C using the paddle method (U.S.P.XXII) at a rotational speed of 50 rpm.

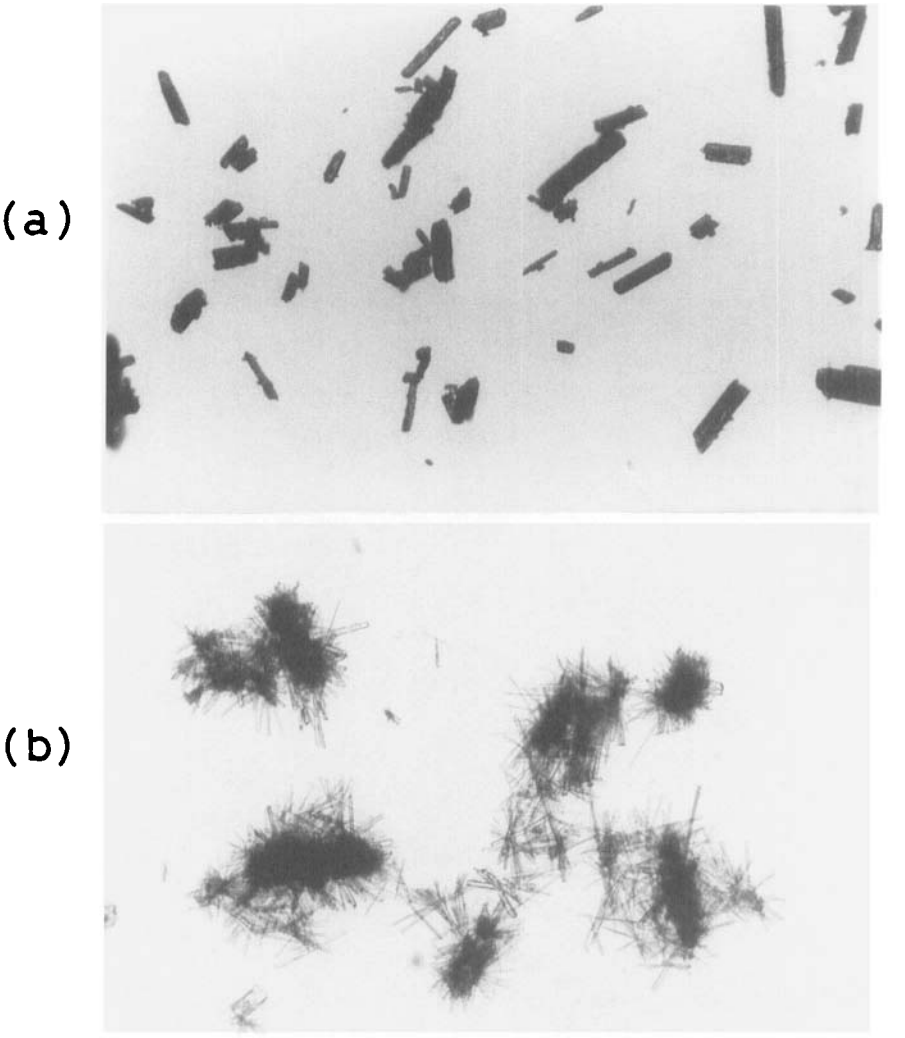

FIGURE 3

The Crystallization of Theophylline Hydrate. Key: (a)Intitial Situation; Thophylline Anhydrous Particles; (b)after 15 Minutes: the Growing Process of Needles of Theophylline Hydrate in Aqueous Suspension.

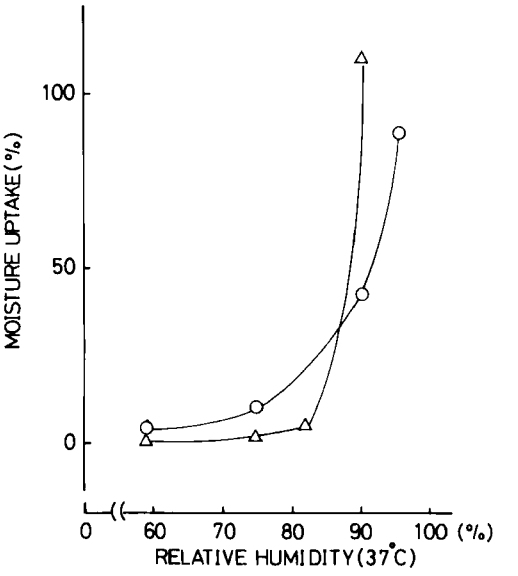

FIGURE 4

Percent Moisture Uptake at a Variety of Relative Humidities at 37 °C for 4 Weeks. Key: (△)Polyethylene Glycol 6000; (○)Sample B.

Samples were taken frequently and absorbance was measured at 271 nm.

RESULTS AND DISCUSSION

Sample A was stored at 37°C 75% RH, and 37°C 90% RH for 1 year. During storage, crystals growth was observed on the surface of samples stored at 90% RH (Fig.1). X-ray powder diffraction showed similar traces to those observed for theophylline hydrate (Fig.2). This confirms that the crystal growth of theophylline hydrate from tablets occurred by solvent-mediated transformation (11-12). This phenomenon of crystal growth was similar to the formation of theophylline hydrate crystals from anhydrous theophylline in suspension (Fig.3)(13-15). On this

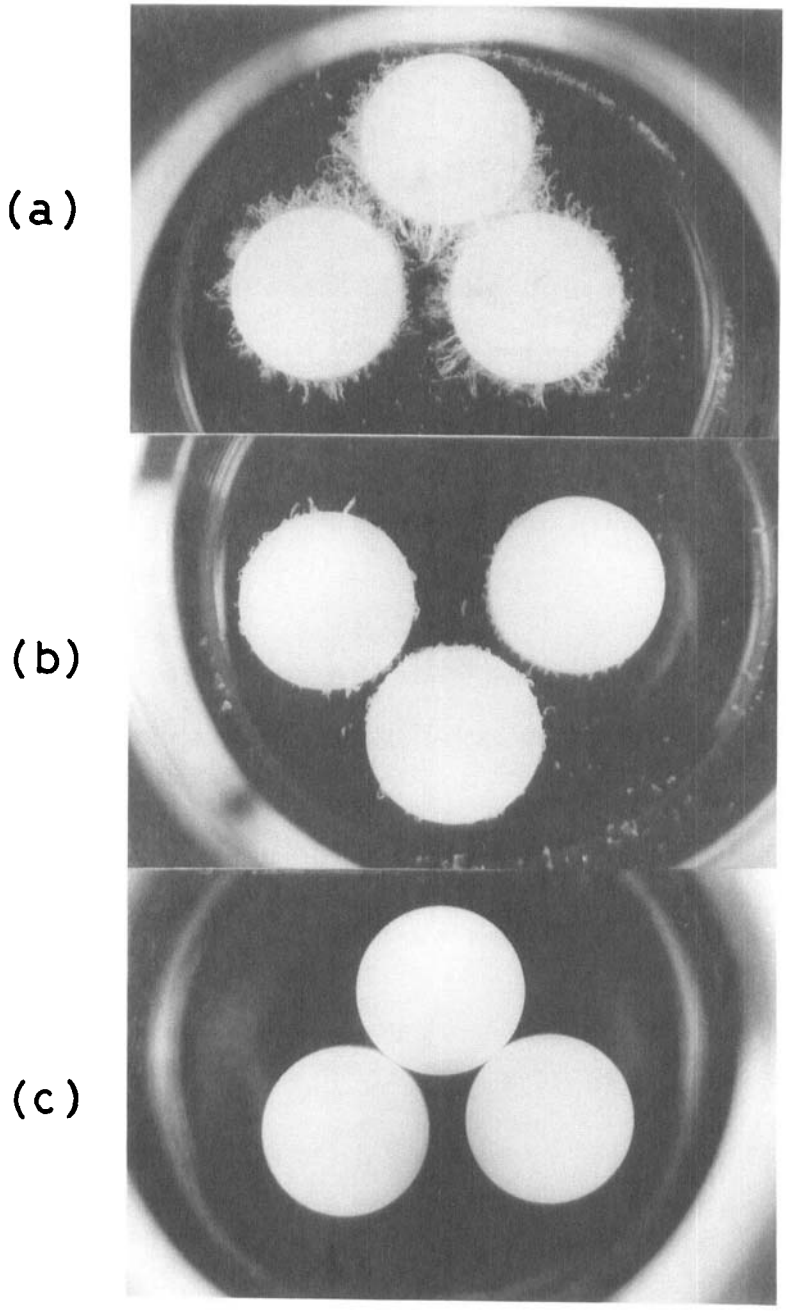

FIGURE 5

Photographs of Sample B Stored under 75, 90, and 95% Relative Humidity (RH) at 37°C for 4 Weeks. Key: (a)95% RH; (b)90% RH; (c)75% RH.

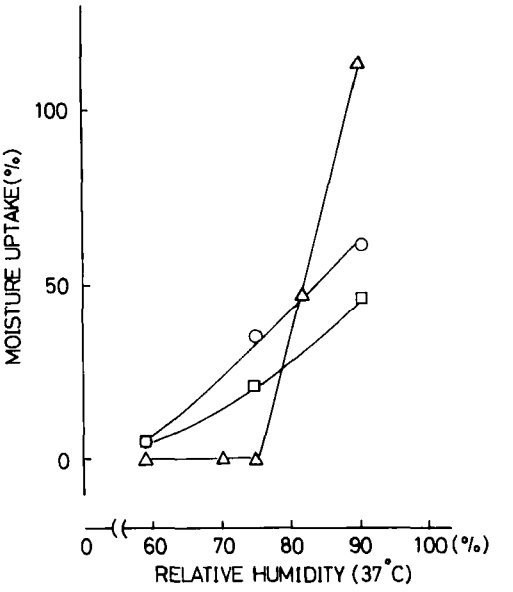

FIGURE 6

Percent Moisture Uptake at a Variety of Relative Humidities at 37 °C for 4 weeks. Key: (△)Sodium chloride; (□)Sample C; (○) Sample D.

assumption, the effect of moisture uptake on crystallization was investigated by using polyethylene glycol 6000 and sodium chloride as a hygroscopic agents. Fig.4 shows the moisture uptake of polyethylene glycol 6000 and sample B, stored for 4 weeks at 37°C, under a range of relative humidities. As shown in Fig. 5, moisture uptake and crystal growth of sample B, which contained polyethylene glycol 6000, increased with increasing relative humidities. Similarly, Fig.6 shows the moisture uptake of sodium chloride and samples C and D. The moisture uptake of sodium chloride increased under conditions exceeding 75% RH at 37 °C.

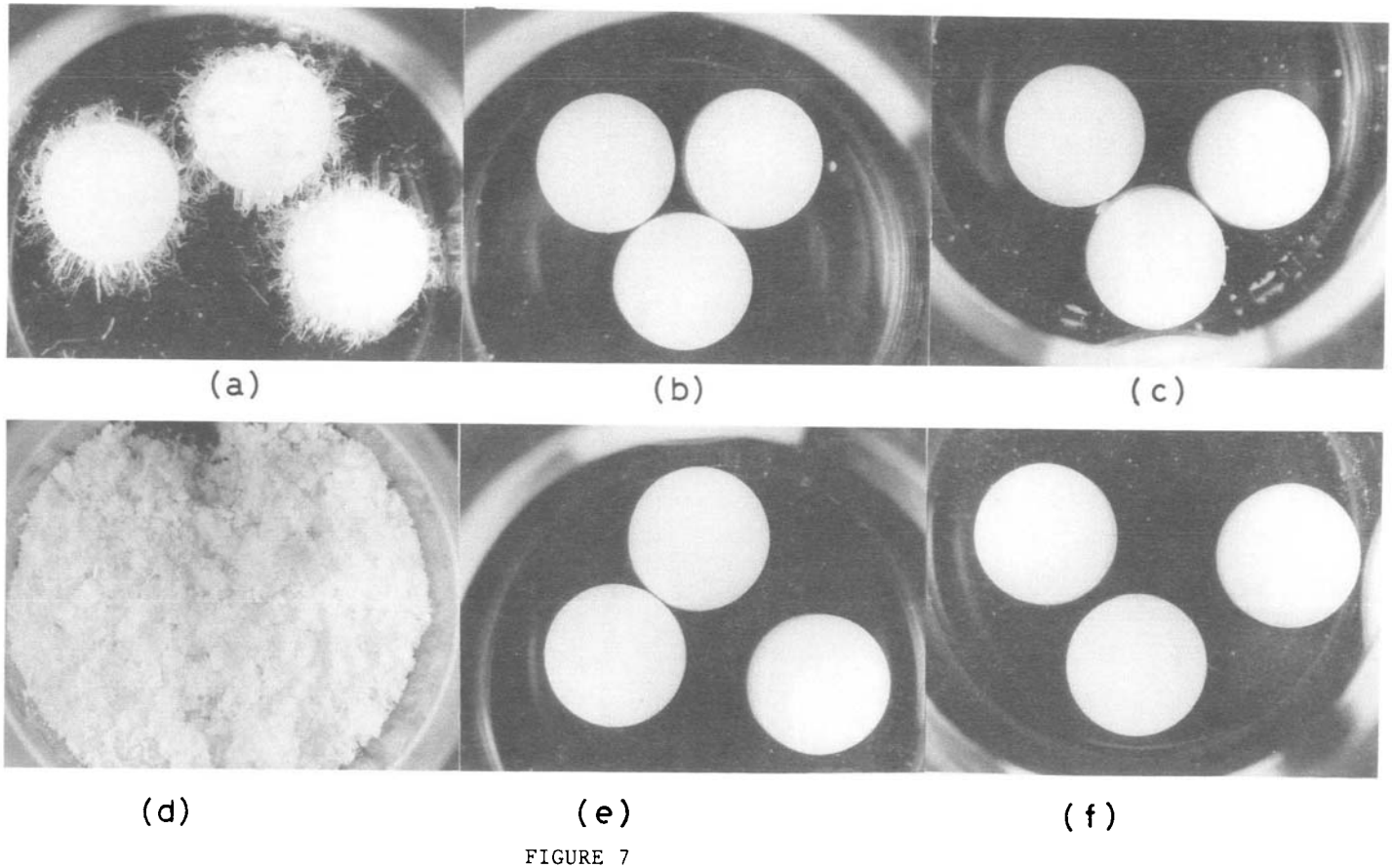

FIGURE 7

Photographs of Samples C and D Stored under 75 and 90% Relative Humidity (RH) at 37°C for 4 Weeks. Key; (a)Sample C, 90% RH; (b) Sample C, 75% RH; (c)Sample C, 59% RH; (d)Sample D, 90% RH; (e) Sample D, 75% RH; (f)Sample D, 59% RH.

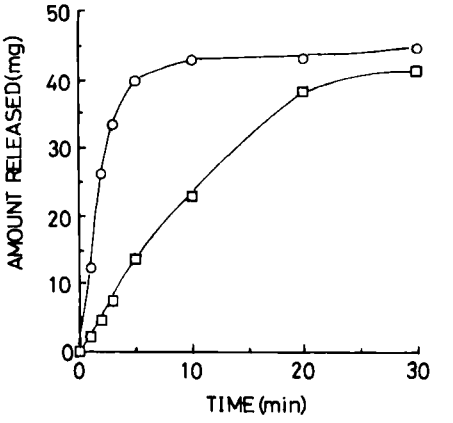

FIGURE 8

Dissolution Profiles of Sample E. Key; (○)Intial; (□)after Storage under 90% Relative Humidity at 37°C for 4 Weeks. (n=3)

Samples C and D, which contained 5 and 10 percent of sodium chloride respectively, were stored at 59, 75, and 90% RH at 37°C for 4 weeks. As shown in Fig.7, in samples C and D, crystal growth was not observed under storage conditions less than 75% RH. Comparatively in sample C, crystal growth was observed at 90% RH; in sample D, at 90% RH tablets disintegrated as a consequence of crystallization. These results confirm that moisture uptake by hygroscopic materials accelerated the crystal growth from tablets.

The release rate of theophylline from sample E, stored at 90% RH for 4 weeks, was prolonged (Fig.8). As shown in Fig. 9, in sample E crystal growth was observed on the surface of tablets, indicating that crystallization had an influence on this theophylline release rate.

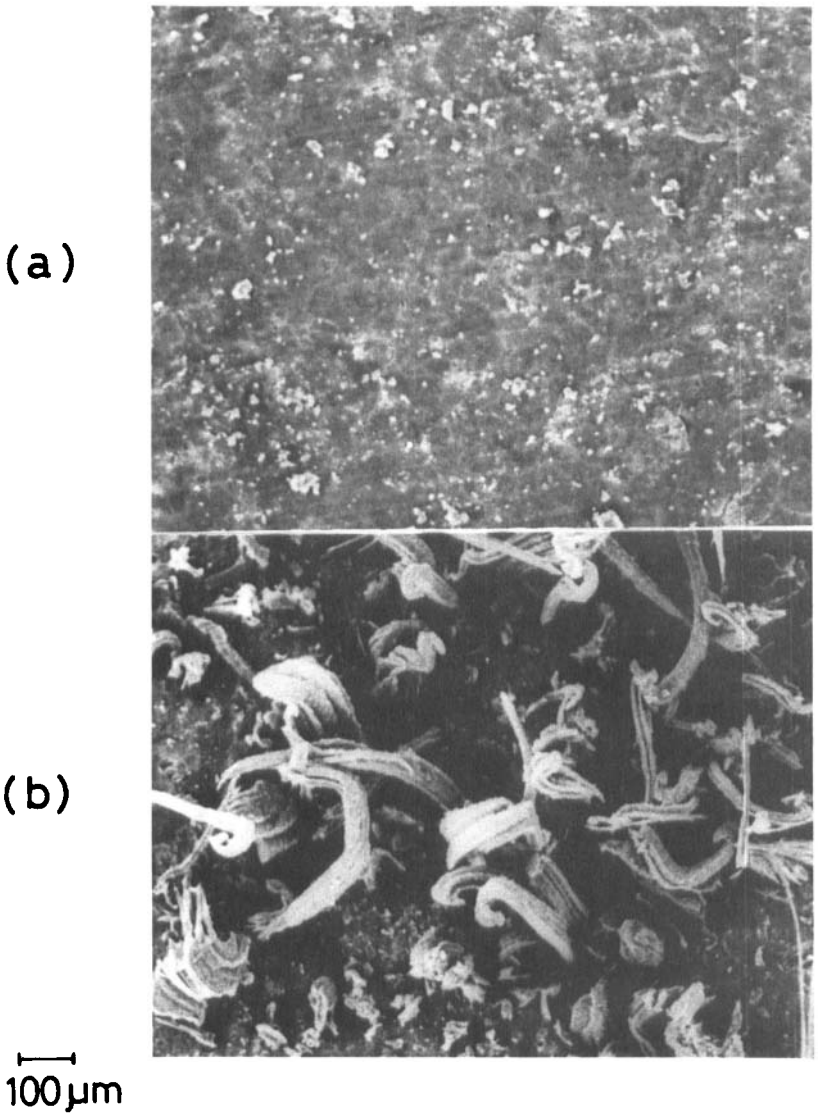

FIGURE 9

Scanning Electron Photomicrographs of Sample E. Key: (a)Intial; (b)after Storage under 90% Relative Humidity at 37°C for 4 Weeks.

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