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EFFECT OF CRYSTALLIZATION OF THEOPHYLLINE ON PHYSICAL PROPERTIES OF TABLETS

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ABSTRACT

Tablets containing anhydrous theophylline, a hygroscopic material such as magnesium chloride or potassium acetate, and other constituents were stored for 4 and 12 weeks under 90% relative humidity at 37°C. During storage, whisker-like crystals appeared on the surface of the tablets. The crystals were observed under a scanning electron microscope. Changes were found in the physical properties of these tablets: crushing strength, friability, disintegration time and dissolution rate.

INTRODUCTION

We have previously reported the formation of needle-like crystals, identified as theophylline hydrate, on the surface of tablets containing anhydrous theophylline, a hygroscopic material such as magnesium chloride or potassium acetate, and other constituents, when stored in an atmosphere of high relative humidity (1). Crystal growth was accelerated by increased moisture uptake in tablets containing hygroscopic materials (2,3). In addition, it has been reported that the tablets disintegrated as a consequence of crystallization. It is known that crystallization of the active ingredient in tablets can result in slowed disintegration, cracks, altered appearance, and may possibly influence bioavailability (4-9). In the present study, the effect of crystal growth on the physical properties of tablets was examined by determining the crushing strength, thickness, friability, disintegration time and dissolution rate after storage at various high relative humidities.

EXPERIMENTAL

Materials

JP-grade crystalline cellulose (Asahi Kasei Kogyo Co., Japan), hydroxypropylcellulose (Nihon Soda, Japan), calcium stearate (Nikko Chemicals, Japan) and NF-grade croscarmellose sodium (Asahi Kasei Kogyo Co., Japan) were used. Anhydrous theophylline was supplied by Shiratori Pharmaceutical Co., Ltd.,

TABLE 1
SAMPLE FORMULATION

Ingredient	Sample A	Sample B
Theophylline	20	20
Magnesium chloride	10	-
Potassium acetate	-	10
Silicic acid	40	40
Crystalline cellulose	21.5	21.5
Hydroxypropylcellulose	3	3
Croscarmellose sodium	5	5
Calcium stearate	0.5	0.5
Total	100	100

The table shows the ratio of ingredients in each sample formulation.

Japan and silicic acid (Syloid 244) was from Fuji-Davison Chemicals, Japan. Magnesium chloride (Katayama Kagaku Kogyo, Japan), and potassium acetate (Wako Pure Chemical Industries, Japan) were of reagent grade.

Preparation of Samples

Table 1 shows the various formulations. The batch size was 2 kg scale. Magnesium chloride and potassium acetate (200 g of each) were dissolved separately in 400 ml of distilled water, and 60 g of hydroxypropylcellulose was dissolved in 1000 ml of distilled water. Using a 20-L Henshel-type mixer, silicic acid and crystalline cellulose were blended for 3 minutes, and then all samples were granulated for approximately 10 minutes with an aqueous solution of magnesium chloride or potassium acetate, hydroxypropyl-cellulose solution and 800 ml of distilled water. After drying at 60°C for 24 hours, samples were passed through a no. 16 JP mesh screen using a mill machine, and then blended with anhydrous theophylline, croscarmellose sodium and calcium stearate according to the ratios shown in the formulations in Table 1, for 10 minutes in a 20-L ribbon blender.

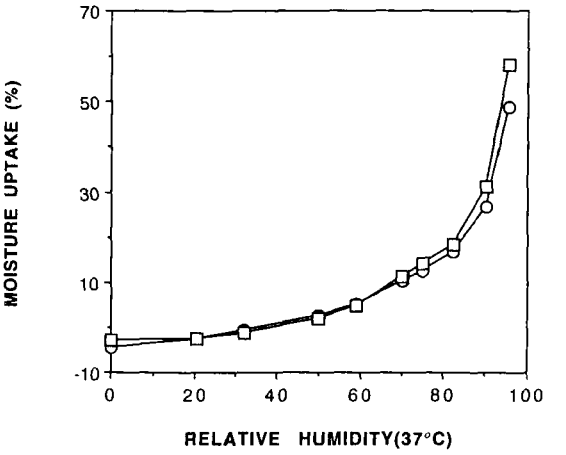


FIGURE 1
Percent Moisture Uptake of Samples A and B at Various Relative Humidities (RH) at 37°C for 4 Weeks. Key: (○) Sample A; (□) Sample B.

Tablet Compression Procedure

The 200 mg samples A and B were compressed into round face tablets, 8 mm in diameter, at a pressure of ca. 1000 kg, using a rotary punch machine (HATA P-13, Japan) at a rotation speed of 30 rpm.

Storage Conditions

The tablets were stored in a chamber maintained at a relative humidity (RH) of 90% and a temperature of 37°C. This relative humidity was maintained using a saturated solution of potassium nitrate (Wako Pure Chemical Industries, Japan).

Crystal Observation

The crystals found forming on the surface of the tablets were observed with a scanning electron microscope (Hitachi Seisakusho S-2400 type, Japan).

Dissolution Test

The dissolution test was performed in 500 ml of distilled water at 37°C using the paddle method at a rotation speed of 50 rpm. Samples were taken frequently and analyzed by HPLC. Separation was achieved with a column (4.6x150 mm packed with Nucleosil $5C_{18}$). The mobile phase consisted of methanol and distilled water (200:800). A flow rate of 1.2 ml/min was used. The absorbance at 271 nm for theophylline was determined. The mean of six determinations was reported.

Tablet Characteristics

The crushing strength of tablets was determined in a hardness tester (Kiya Seisakusho, Japan). The mean values of ten measurements were reported. The tablet thickness was measured with a digimatic indicator (Mitsutoyo Corporation, Japan). The disintegration time was tested in distilled water using an apparatus

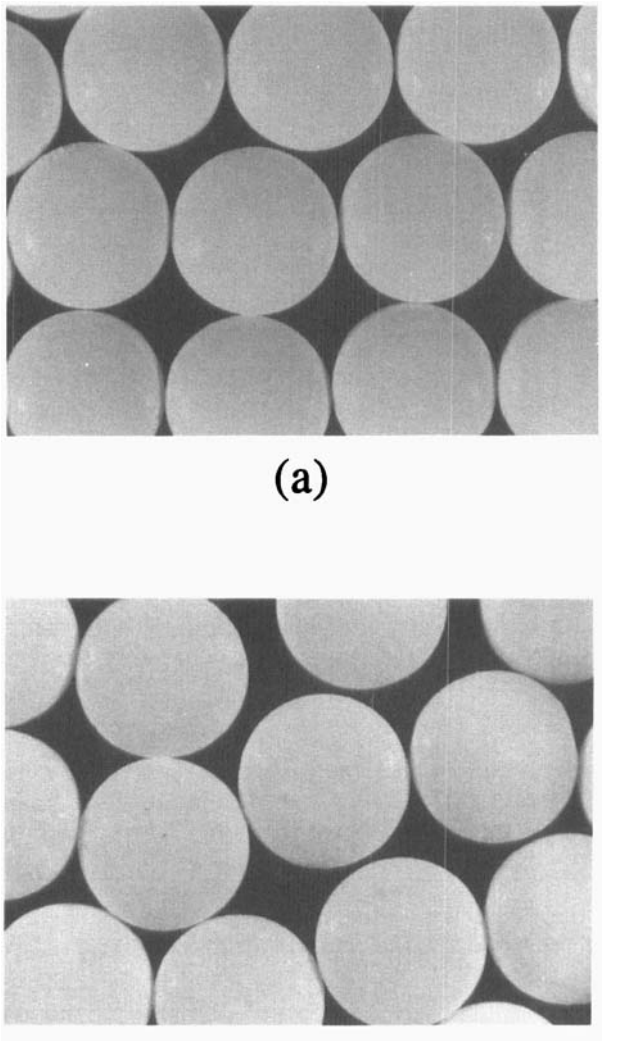
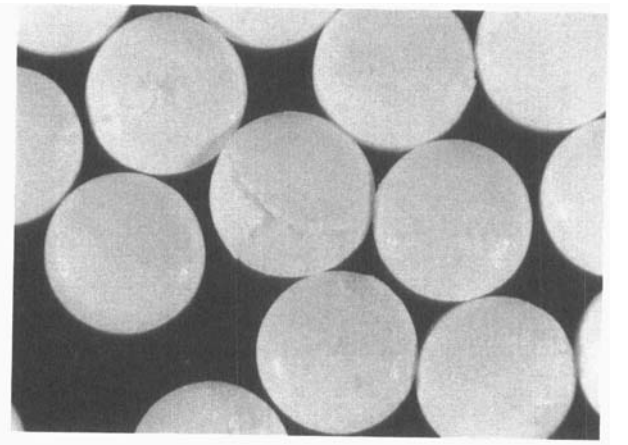


FIGURE 2
Photographs of Samples A and B Stored under 90% Relative Humidity at 37°C for 4 and 12 Weeks. Key : (a) Sample A for 4 Weeks ; (b) Sample A for 12Weeks ; (c) Sample B for 4 Weeks ; (d) Sample B for 12Weeks.



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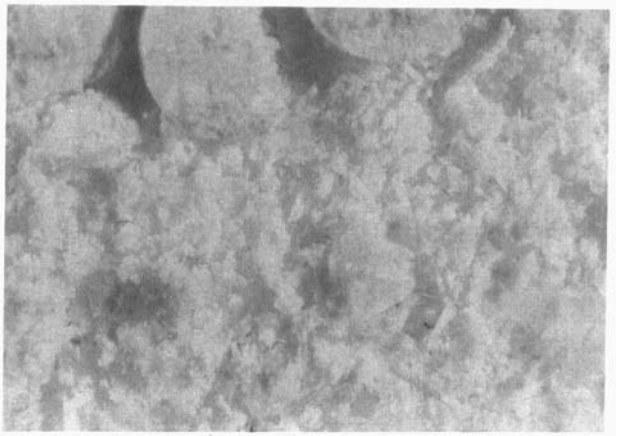

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FIGURE 2. Continued

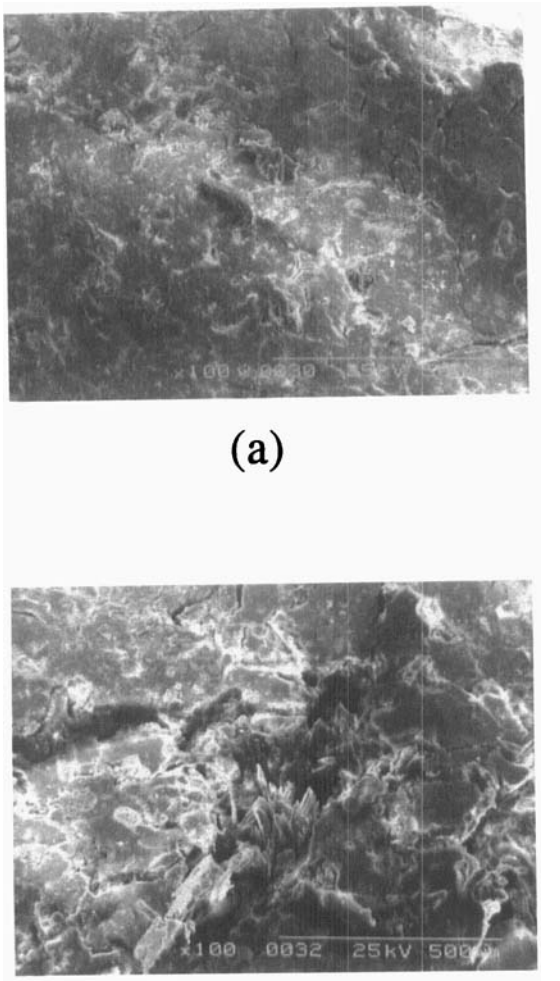
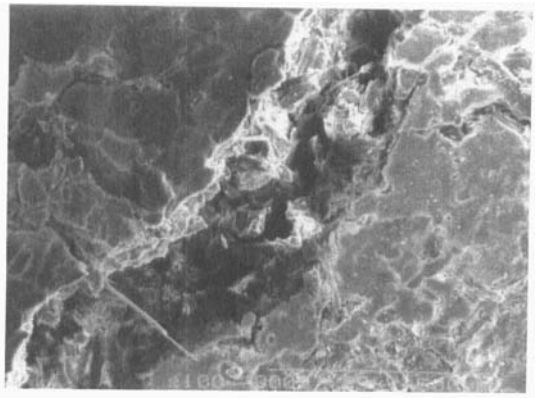


FIGURE 3
Scanning Electron Photomicrographs of Samples A and B after Storage under 90% Relative Humididy at 37°C for 4 and 12 Weeks.
Key: (a) Sample A for 4 Weeks; (b) Sample A for 12 Weeks; (c) Sample B for 4 Weeks; (d) Sample B for 12 Weeks.



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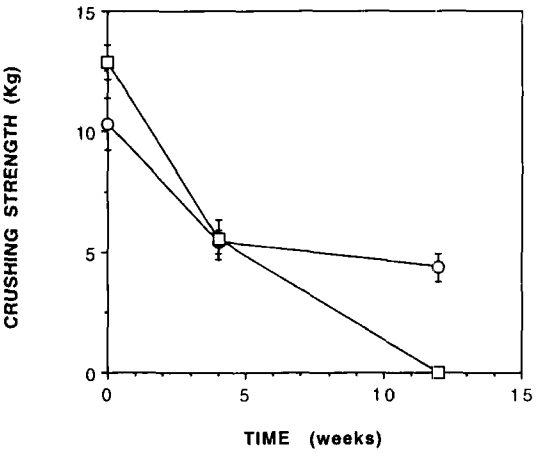

FIGURE 4
Crushing Strength of Tablets of Samples A and B after Storage under 90% Relative Humidity at 37°C for 4 and 12 Weeks. Key: (○) Sample A; (□) Sample B. (Vertical lines represent S.D. of the mean for ten tablets.)

according to JP. The friability was measured with a friabilator (Kayagaki Irika Kogyo, Japan). After rotation at 25 rpm for 4 minutes, the loss in weight of 20 tablets was measured.

RESULTS AND DISCUSSION

Figure 1 shows the moisture uptake of samples A and B, stored for 4 weeks under a range of relative humidities at 37°C. The moisture uptake of samples A and B increased with increasing relative humidity. This water sorption property was secondary to hygroscopic materials such as magnesium chloride and potassium acetate contained in the tablets. The tablets of samples A and B were stored at 90% relative humidity (RH) at 37°C for 4 and 12 weeks. The moisture gain following the addition of hygroscopic material might induce crystallization. As shown in Fig. 2, the appearance of sample A did not change during storage for 4 weeks; however, after storage for 12 weeks cracks appeared on the surface of tablets. As shown in Fig. 3, the growth of crystals in cracks in the tablets was observed by scanning electron microscopy. On the other hand, concerning sample B, cracks were observed on the surface of tablets after storage for 4 weeks, and after 12 weeks the tablets disintegrated as a consequence of crystallization. As shown in Fig. 3, needle-like crystals were observed in the cracks of tablets and on the pieces of broken tablets. The phenomenon of crystallization of theophylline in tablets was consistent with the results of previous reports (1,3).

In order to study the effect of crystal growth on tablet properties, the crystallized tablets of samples A and B were investigated for physical tablet properties such as crushing strength, disintegration time and friability. Figure 4 shows the change in crushing strength of samples A and B as a function of storage time. The crushing

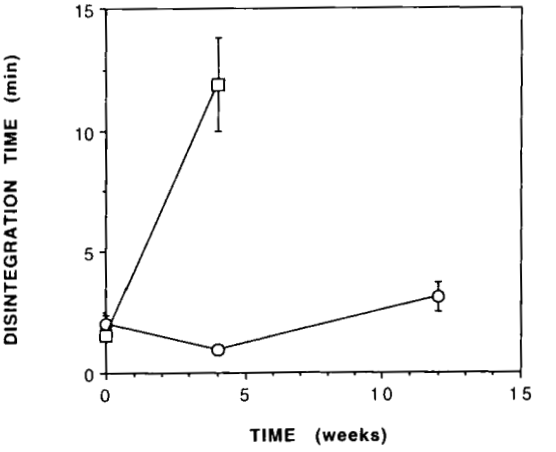

FIGURE 5
Disintegration Time of Tablets of Samples A and B after Storage under 90% Relative Humidity at 37°C for 4 and 12 Weeks. Key: (○) Sample A; (□) Sample B.

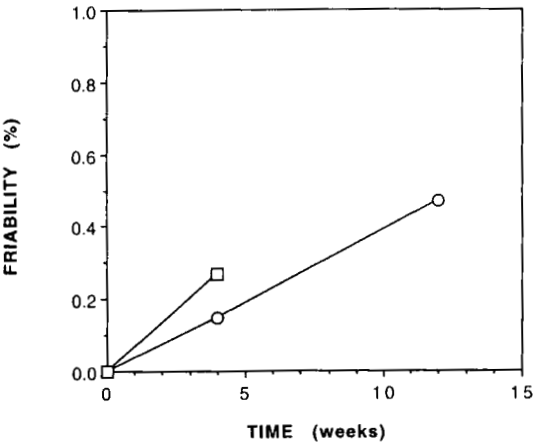

FIGURE 6
Friability of Tablets of Samples A and B after Storage under 90% Relative Humidity at 37°C for 4 and 12 Weeks. Key: (○) Sample A; (□) Sample B.

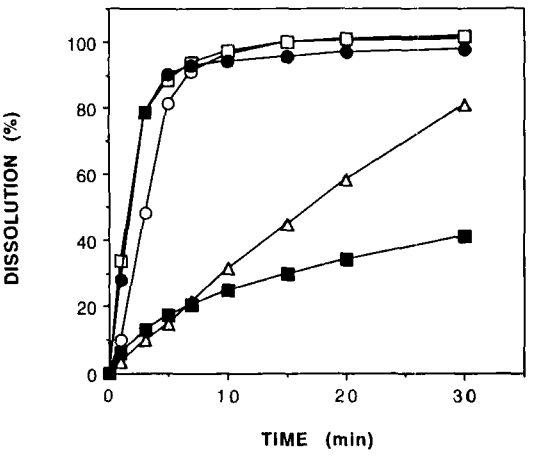

FIGURE 7
Dissolution Profiles of Samples A and B after Storage under 90% Relative Humidity at 37°C for 4 and 12 Weeks. Key: (○) Sample A, Initial;(□) Sample A, 4 Weeks; (△)Sample A, 12 Weeks; (●) Sample B, Initial; (■) Sample B, 4Weeks.

strength of samples A and B decreased as a function of time. The tablets of sample B were broken after storage for 12 weeks, and so their crushing strength was not determined. Figure 5 shows the change in disintegration time of samples A and B as a function of storage time. The disintegration time of samples A and B increased as a function of time. Figure 6 shows the change in friability of samples A and B. Their friability increased as a function of time. The changes in crushing strength, disintegration time and friability were dependent on the crystallization of tablets. Figure 7 shows the results of dissolution studies of samples A and B. The release rate of theophylline from sample A was not changed after storage at 90% RH at 37°C for 4 weeks, but was decreased in sample A stored for 12 weeks. Similarly, the release rate of theophylline from sample B stored at 90% RH at 37°C for 4 weeks was decreased. These results indicate that the crystallization of theophylline in tablets might cause the changes in the various physical properties of tablets.

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