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Crystallization of theophylline in tablets

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Summary

Whisker-like crystals appeared on the surface of tablets that contained anhydrous theophylline, a hygroscopic material such as magnesium chloride or potassium acetate, and ingredients stored in an atmosphere of high relative humidity. The crystals were determined using differential scanning calorimetry and TLC. The crystals contained theophylline and were hydrated.

Introduction

The crystallization of the active ingredient in tablets can result in prolonged disintegration (Utsumi et al., 1961), cracks (Utsumi et al., 1962), altered appearance (Yamada et al., 1976), and may possibly influence bioavailability. In addition, it has been reported that the excipients lactose and mannitol can crystallize from tablets as whisker-like crystals (Ando et al., 1985).

In suspension, anhydrous theophylline shows crystal growth, which occurs as a result of hydration following solvent-mediated transformation (Pearson et al., 1969). If this environment can appear in anhydrous theophylline tablets, crystal growth may occur. To investigate this possibility, tablets containing anhydrous theophylline and a hygroscopic material were stored in an atmosphere of high relative humidity.

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Materials and Methods

Materials

JP-grade crystalline cellulose (Asahi Kasei Kogyo, Japan) was used as supplied. Anhydrous theophylline, magnesium chloride ($MgCl_2 \cdot 6H_2O$) and potassium acetate were supplied by Wako Pure Chemical Industries, Japan and silicic acid (Syloid 244) was from Fuji-Davison Chemicals, Japan.

Preparation of samples

Table 1 shows various formulations. The load size was 50 g. Magnesium chloride and potassium acetate (0.5 g of each) were dissolved separately in 50 ml of distilled water.

After blending of the silicic acid and the crystalline cellulose for 3 min, samples A and B were granulated in about 5 min by the addition of an aqueous solution of magnesium chloride or potassium acetate and 10 ml of distilled water in a 1-L Henschel-type mixer. These samples, which were passed through a no. 32JP mesh screen after dry-

TABLE 1

SAMPLE FORMULATION

Ingredient	Sample		
	A	B	C
Magnesium chloride	10	–	–
Potassium acetate	–	10	–
Silicic acid	50	50	50
Crystalline cellulose	20	20	30
Theophylline	20	20	20
Total	100	100	100

ing at 60°C for 24 h, were blended with anhydrous theophylline in a 1-L Henschel-type mixer for 3 min according to the ratios of the formulations shown in Table 1.

Tablet compression procedure

The 200 mg samples A–C were compressed into 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% at 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 (Diffractometer JDX-7E, Nihon Denshi, Tokyo) with nickel-filter Cukα radiation.

Identification of crystals

The crystals that grew on the surface of the tablets were identified using a Rigaku Denki Differential scanning calorimeter (DSC, Model 8085 E1) and TLC (precoated silica gel plates). These plates were developed in chloroform which was separated from the mixed solution (chloroform/MtOH/H_2O = 10 : 5 : 3), and visualized under UV light.

Results and Discussion

When anhydrous theophylline was stored at a variety of humidities at 37°C for 4 weeks, at more than 90% RH, it absorbed an amount of water corresponding approximately to that required to form the monohydrate, as shown Fig. 1.

The differential scanning calorimetric thermograms and X-ray powder diffraction patterns (Shefter et al., 1963, 1973; Kawashima et al., 1985) of the sample at 90% RH also showed that anhydrous theophylline was converted to the hydrate at very high humidities. This conversion at very high humidities may possibly be influenced by addition of hygroscopic excipients.

Samples A, B, and C were stored at 59%, 75%, and 90% RH at 37°C for 4 weeks. During storage at 90% RH, crystals started growing on the surfaces of samples A and B which contained, respectively, magnesium chloride and potassium acetate (Fig. 2). However, no such crystals were observed on sample C which contained neither hygroscopic materials, or on any samples stored at 59% and 75% RH.

The results of differential scanning calorimetry of these crystals showed that they were theophyl-

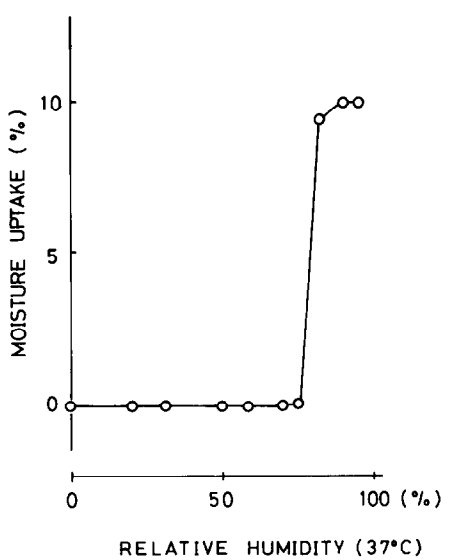

Fig. 1. Percent moisture uptake of anhydrous theophylline at a variety of relative humidities (RH) at 37°C for 4 weeks.

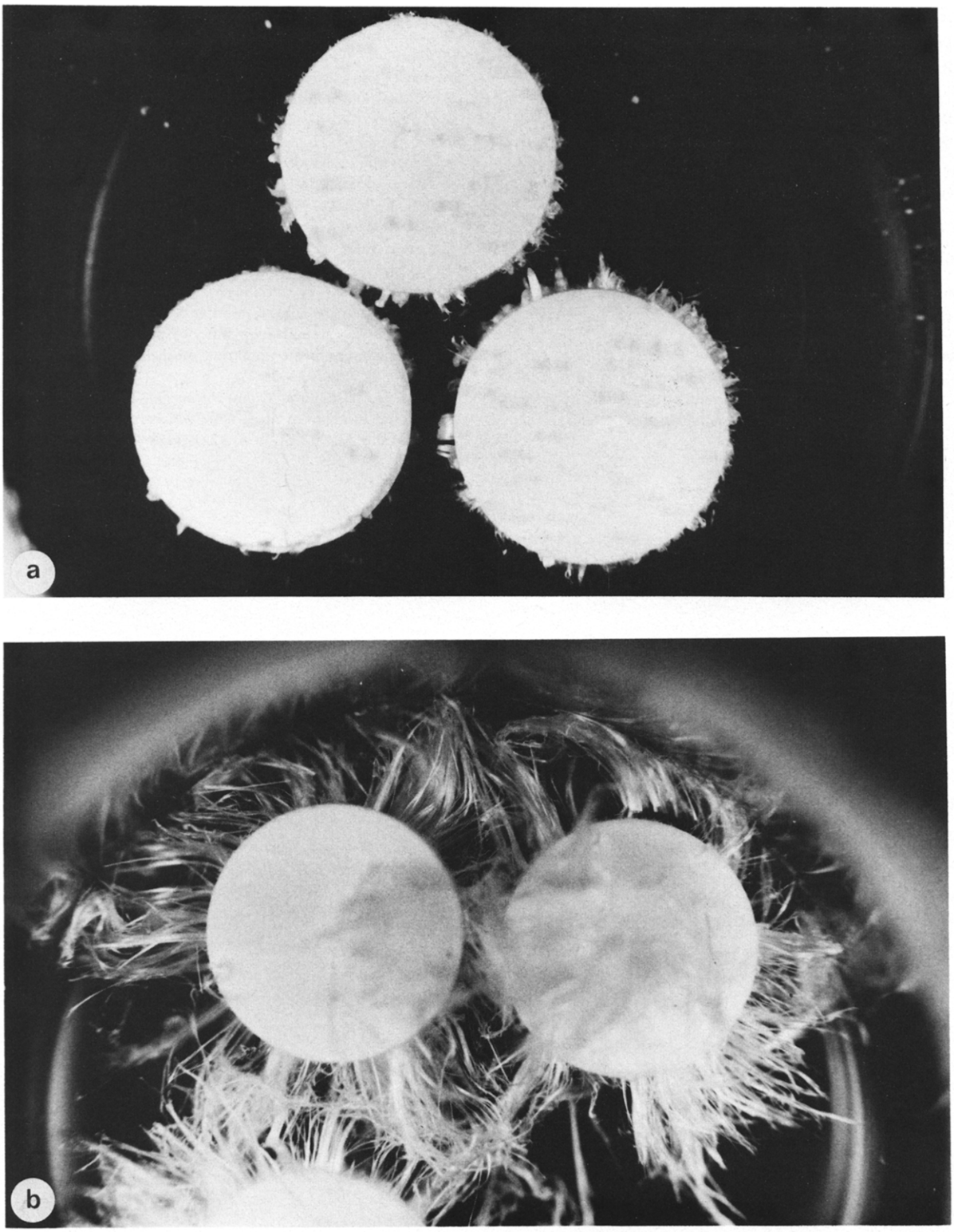

Fig. 2. Photographs of samples A and B stored at 90% relative himidity (RH) at 37°C for 4 weeks.

line hydrate. Furthermore, the TLC R_f value of these crystals was identical with that of theophylline (~ 0.6). These results indicated that the crystals of samples A and B at 90% RH were theophylline hydrate. It was suggested that the presence of hygroscopic materials might lead to the crystal growth of theophylline hydrate from tablets by solvent-mediated transformation.

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