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EFFECT OF ENVIRONMENT ON CRYSTALLINITY AND CHEMICAL STABILITY IN SOLID-STATE OF GROUND CEPHALOTIN SODIUM DURING STORAGE

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ABSTRACT

Effects of environmental conditions on the crystallinity and the decomposition point (Dp) of ground cephalotin sodium during storage were investigated by X-ray diffraction and differential thermal analysis (DTA). The X-ray diffraction peaks of ground products increased after storage at 0% and 75% relative humidity (R.H.), at 35°C. The crystallinity of ground product increased at 75% R.H. and 0% R.H.,35°C, but that of ground product at 0% R.H., -30°C was not changed. The Dp measured by DTA of the ground product increased from 189.5°C to 197°C after 4 days at 75% R.H., but the Dp of the ground product at 0% R.H., -30°C for 4 days was 190.1°C. Relation between the Dp and the crystallinity of ground cefalotin sodium was a

straight suggesting that the thermal stability of cefalotin sodium in the solid-state depends on the degree of crystallinity.

INTRODUCTION

Changes of physicochemical properties of pharmaceutical preparations during storage are very important to preformulation scientists, because the properties of drug powders affect their bioavailability through effects on the dissolution rate (F.D.A. paper; Guide line)[1]. Grinding is often carried out to reduce the particle size of powders, and to mix drugs, but the ground products of some pharmaceuticals (i.e. lactose, indomethacin, cefixime and cephalexin) were very unstable under normal condition[2-5]. Pikal et al.[6] reported relations between the crystallinity of various kinds of cephalotin sodium obtained by freeze-drying or recrystallization and decomposition rate in the solid-state. They concluded that the chemical stability and crystallinity of cephalotin sodium in the solid-state change depending on the preparation method. Suzuki et al.,[7] reported the crystallinity determination method for freeze-dried cephalotin sodium by differential scanning calorimetry. We reported changes of physicochemical properties due to freeze-drying and grinding of cephalexin[5,8,9], indomethacin (1989)[10], and phenylbutazone[11] during storage under various conditions. In a previous study, we investigated the effect of mechanochemical stress on the crystallinity and chemical stability of cephalotin sodium in the solid-state during grinding. In the present study, we investigated the chemical stability of ground cefalotin sodium during storage and relations between decomposition point and crystallinity of ground cephalotin sodium.

MATERIALS AND METHODS

Materials

Bulk powder of crystalline cephalotin sodium (Lot. No. ERON-1300; Meiji Seika Ltd.) was used. A sample of cephalotin sodium powder (10 g) was ground in an agate centrifugal ball mill (Fritsch Co. Ltd.) for 10 h with a capacity of 350 ml, as described previously[12].

Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature with a type JDX 7E diffractometer (Nihon Denshi Co., Ltd.). The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; time constant, 2 sec; measured from $2\theta=3^{\circ}$ to $2\theta=40^{\circ}$.

Determination of crystallinity

Crystallinity was estimated by Hermans' method[13]. The degree of crystallinity of an intact sample was regarded as 100% and estimated from the X-ray diffraction profiles as reported previously[12].

Thermal analysis

Differential thermal analysis (DTA) curves were measured with a type DT-20 DTA instrument (Shimadzu Seisakusho Co. Ltd.). The measurement conditions were: sample weight, 3 mg for DTA; heating rate, 10°C/min; N_2 gas flow, 30 ml/min; sample cell, aluminium crimp cell.

Storage conditions

The ground products were stored in desiccator containing P_2O_5 (0% relative humidity (R.H.)) at 0°C and 35°C, and NaCl saturated solution (75% R.H.) at 35°C.

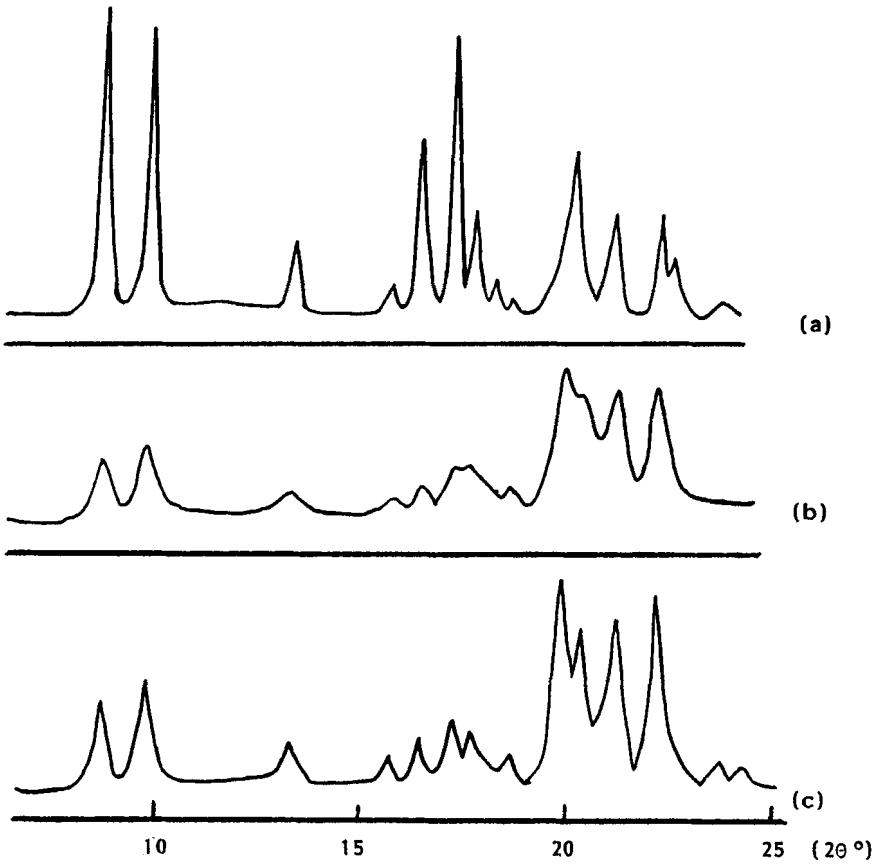

Fig. 1 Change of X-ray diffraction profiles of ground cephalotin sodium during storage
(a), Intact powder; (b), the fresh product ground for 10 h; (c), after storage the ground product at 75% R.H. 35°C for 4 days.

RESULTS

Change in crystallinity of cephalotin sodium during storage period

Figure 1 shows the change of X-ray diffraction profiles of ground cephalotin sodium during storage. The X-ray diffraction peaks of ground cephalotin sodium increased with increasing storage time, suggesting that crystal growth in the solid-state occurred in the ground cephalotin sodium bulk.

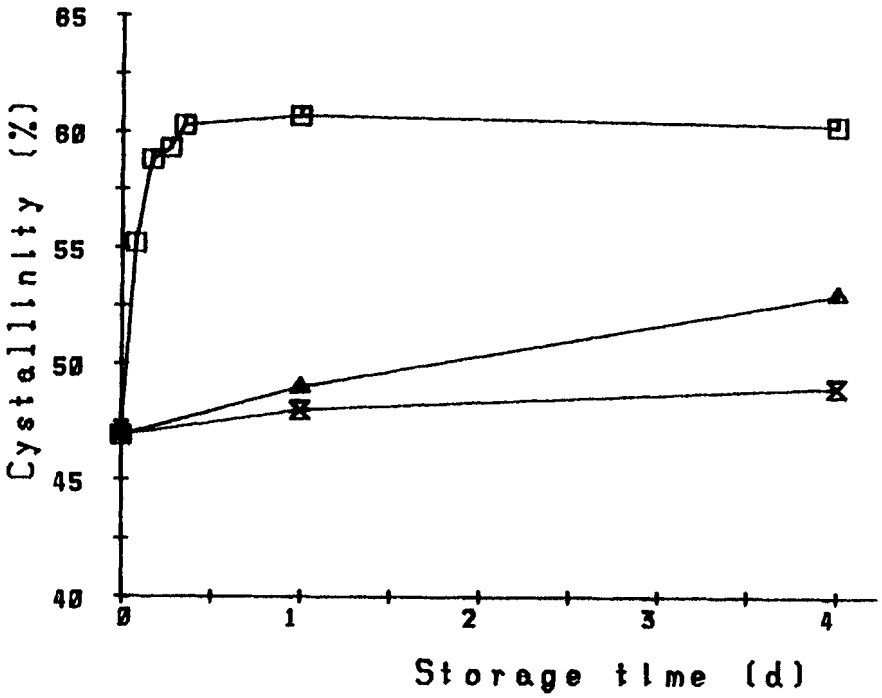

Fig. 2 Effects of storage conditions on the crystallinity of ground cephalotin sodium
△, 0% R.H. at 35°C; ⋈, 0% R.H. at -30°C;
□, 75% R.H. at 35°C.

Figure 2 shows the change in crystallinity of ground cephalotin sodium during storage at 0% and 75% R.H., 35°C and -30°C. When stored at 75% R.H., 35°C the crystallinity of ground product increased very rapidly, initially, to plateau at about 60%. However, the crystallinity of ground product at 0% R.H., 35°C was almost linear, and increased very slow than that at 75% R.H., 35°C, and that of ground product at 0% R.H., -30°C was not changed.

Figure 3 shows changes of the decomposition point (Dp) of ground cephalotin sodium during storage. The Dp was estimated from DTA curves by extrapolation of the exothermic peak. The Dp

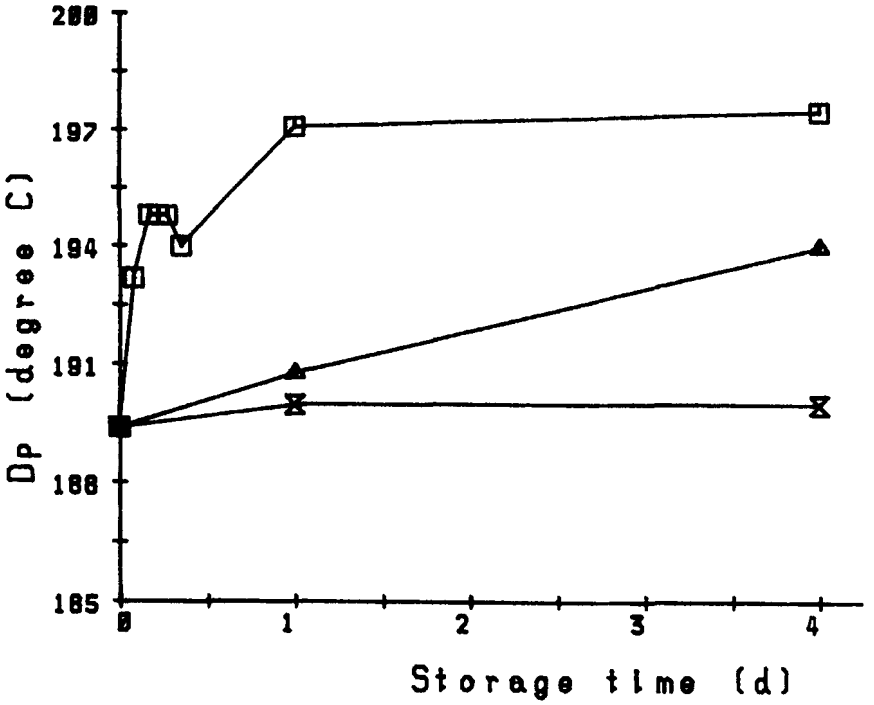

Fig. 3 Effects of storage conditions on the decomposition point (Dp) of ground cephalotin sodium
△, 0% R.H. at 35° C; ⋈, 0% R.H. at -30° C;
□, 75% R.H. at 35° C.

of the intact cephalotin sodium did not changed after storage at 75% R.H., 35° C for 2 weeks. The Dp of the ground product increased to about 8° C, after storage for 1 day at 75% R.H., 35° C. However, the Dp of the ground sample increased only 2° C after storage at 0% R.H., 35° C for 4 days, and the Dp did not changed after storage at 0% R.H., -30° C for 4 days. The adsorbed water amount of the intact and ground samples were less than 0.1%, respectively, after storage at 75% R.H., 35° C for 4 days, as shown in previously[12].

Relations between decomposition point and crystallinity of ground cephalotin sodium

Figure 4 shows the relation between the Dp and crystallinity of the freshly ground samples reported in the previous study[12], and of samples ground and stored at 0% and 75% R.H., 35° C. The relations fall on a straight line, which suggests that the thermal stability of cephalotin sodium in the solid-state depended on the degree of crystallinity.

DISCUSSION

Effect of R.H. on the of crystallinity and the Dp of ground cephalotin sodium during storage

We reported that the Dp of ground cephalotin sodium[12] fell with increase of grinding time, because the thermal stability of cephalotin sodium in the solid-state depended on the crystallinity of the bulk solid. Pikal et al.[6] reported the relation between the chemical stability of freeze-dried cephalotin sodium and the crystallinity in an isothermal environment. Suzuki et al.,[7] reported that three kinds of solid-state for freeze-dried cephalotin sodium were amorphus, quasi-crystalline and crystalline by differential scanning calorimetry. The amorphus, quasi-crystalline and crystalline freeze-dried cephalotin sodium had the decomposition points at 140° C, 175° C and 195° C, respectively, and they concluded that the crystallinity of freeze-dried cephalotin sodium affected on the decomposition point. The thermal stability of freeze-dried and ground cephalexin, an antibiotic with a B-lactam ring structure, decreased with decrease in crystallinity[5,9]. In the present study, the Dp of intact cephalotin sodium was not changed after storage at 75% R.H., 35° C for 2 weeks, but the Dp of ground cephalotin sodium after storage at 0% and 75% R.H., 35° C for 4

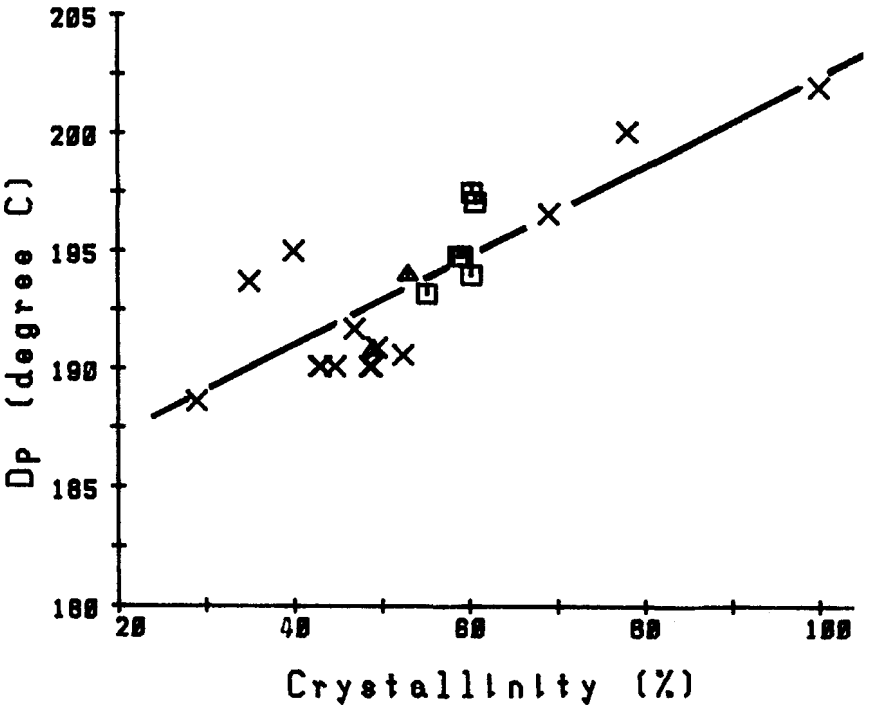

Fig. 4 Relation between the decomposition point (Dp) and the crystallinity of ground cephalotin sodium
△, after storage at 0% R.H., 35°C; □, at 75% R.H., 35°C;
×, Fresh ground cephalotin sodium.

days increased with increased storage (Fig. 3), because the crystallinity of ground sample increased during storage. This suggests that part of the noncrystalline solid of ground cephalotin sodium recrystallized in the solid-state. The recrystallization of ground cephalotin sodium at 75%, 35°C was faster than that at 0% R.H., 35°C, since the recrystallization process was affected by the environment (Fig. 2). At the high 75% R.H., the noncrystalline solid of cephalotin sodium adsorbed water, as reported about freeze-dried cephalexin in a previous study[9], so the recrystallization accelerated by the presence of water.

On the other hand, at 0% R.H. (P_2O_5), -30° C the recrystallization of ground cephalotin sodium was more slow than that at 0% R.H., 35° C, and the Dp of the ground product did not change during storage for 2 weeks. This suggests that the recrystallization of the noncrystalline solid of cephalotin sodium was accelerated by the temperature and the adsorbed water. The linear relation (Fig. 4) between the Dp of all ground samples and the crystallinity suggests that the thermal stability of ground cephalotin sodium is controlled by the degree of crystallinity.

In the present study, we used different instruments, measurement conditions and sample preparation method from Pikal et al.[6] and Suzuki et al.[7] for estimating of solid stability of cephalotin sodium, but the stability of ground cephalotin sodium was controlled by the crystallinity as almost the same as freeze-dried cephalotin sodium[6,7].

CONCLUSION

The recrystallization of ground cephalotin sodium was affected by the environmental (R.H. and temperature). Since the noncrystalline solid of cephalotin sodium has higher hygroscopicity, adsorbed water accelerated the recrystallization of ground cephalotin sodium. The chemical stability of cephalotin sodium in the solid-state depended on its crystallinity because the noncrystalline solid was very unstable at high R.H. and temperature.

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