International Journal of Pharmaceutics, 25 (1985) 339–346
Elsevier

IJP 00864

Stabilization of isosorbide 5-mononitrate in solid state by β-cyclodextrin complexation

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(Received February 14th, 1985)
(Modified version received and accepted April 16th, 1985)

Key words: isosorbide 5-mononitrate – β-cyclodextrin – inclusion complexation – volatility – whisker growth – stabilization

Summary

Inclusion complexation of isosorbide 5-mononitrate (5-ISMN) with β-cyclodextrin (β-CyD) was investigated by the solubility method, X-ray diffractometry and thermal analysis. An analysis of the phase solubility diagram indicates that the stoichiometry for the complex of 5-ISMN with β-CyD is 1 : 1 in the solid state. The volatility of 5-ISMN and the whisker-growth from tablet or powder were significantly retarded by the binding to β-CyD. In addition, the degradation of 5-ISMN stored at 60°C and 75% relative humidity was remarkably inhibited by the β-CyD complexation. The improvement of physicochemical properties of 5-ISMN by β-CyD complexation in the solid state may solve problems encountered by the storage.

Introduction

Although isosorbide dinitrate (ISDN), a long-acting organic nitrate vasodilator, has been used for many years to treat angina pectoris (Goldberg, 1948; Franciosa et al., 1974), it is readily biotransformed in animals and man by glutathione S-transferases to give the isosorbide 2-mononitrate (2-ISMN), isosorbide 5-mononitrate (5-ISMN) and isosorbide (Rosseel and Bogaert, 1973; Down et al., 1974). Since the main metabolite, 5-ISMN is known to be pharmacologically active in several animal

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species (Wendt, 1972) as well as in man (Michel, 1976), the 5-ISMN preparations have been introduced onto the Europian markets. When ISDN is administrated orally, it undergoes the first-pass metabolism, resulting in the high intra- and inter-dividual variances in ISDN blood levels (Taylar et al., 1980). In this respect, the variances of 5-ISMN blood levels after oral administration of 5-ISMN preparations would be very small. Although 5-ISMN appeared to be much more useful than ISDN, it contains some undesirable properties such as volatility and the growth of whiskers during the storage. Therefore, the improvement of the physical properties of 5-ISMN in the solid state is important in pharmaceutical formulation.

β-Cyclodextrin (β-CyD) has been extensively applied to improve the pharmaceutical characteristics of drug molecules through the inclusion complexations (Saenger, 1980; Uekama, 1981; Szejtli, 1982). We have recently reported (1983) that the thermal and photochemical stabilities of benzaldehyde were significantly improved by inclusion complexations. In the present study, therefore, an attempt was made to stabilize 5-ISMN in the solid state by β-CyD complexation.

Materials and Methods

Materials

5-ISMN was kindly supplied from Toa Eiyo (Fukushima, Japan). β-CyD was purchased from Nihon Shokuhin Kako (Tokyo, Japan) and recrystallized twice from water. All other materials and solvents were of analytical reagent grade. Deionized and double-distilled water was used throughout the study.

Solubility studies

Solubility measurements were carried out according to Higuchi and Lach (1954). Excess amounts of 5-ISMN (156 mg/ml) were added to aqueous solutions containing various concentrations of β-CyD and were shaken at 25 ± 0.5°C. After equilibration was attained (approximately 7 days), an aliquot was centrifuged and pippetted through a cotton plug. A portion of the sample (1 ml) was then diluted with water and analyzed spectrophotometrically.

Preparation of complex and tablet

The solid complex was derived by mixing appropriate amounts of the desired β-CyD and 5-ISMN in water. Amounts were calculated from the descending curvature of the phase solubility diagram (see Fig. 1). That is, 16.7 g of 5-ISMN and 22.7 g of β-CyD were added to 100 ml of water, sealed in a flask, and stirred at 25°C for 7 days. The complex, which precipitated as a microcrystalline powder, was filtered and dried under vacuum at room temperature for 2 days. Any sublimation of the solid complex was not observed under these conditions. From the result of chemical analysis, this powder corresponded to a 1 : 1 5-ISMN–β-CyD complex which had a molecular weight of 1326. The 5-ISMN and its β-CyD complex powders were passed through a screen (100 mesh) and used for the following studies. The sample powder (200 mg as 5-ISMN) was compressed into a cylindrical tablet

(diameter 8 mm, thinkness 0.3 mm) using a single punch tableting machine (Riken Seiki P-16, Tokyo, Japan) at a pressure of about 100 kg/cm^2.

X-Ray diffractometry

The powder X-ray diffraction patterns were obtained using a Rigaku Denki Geiger Flex 2012 (Tokyo, Japan) with Ni-filtered Cu-K_α radiation.

Thermal analysis

Differential thermal analysis (DTA) and thermal gravimetric analysis (TG) were carried out using a scanning rate of 10°C/min on a Shimadzu DT-20B thermal analyzer (Kyoto, Japan). The sample weight was 2–10 mg.

Stability tests

The tablets and powders for 5-ISMN and its β-CyD complex were put into the glass containers with or without stopper and stored in a controlled temperature-humidity oven (Tabai Platinus Rainbow PR-1G, Osaka, Japan). The powders stored at accelerated conditions were dried under reduced pressure at room temperature for 12 h before analysis, correcting the weight change caused by moisture sorption. The 5-ISMN concentrations were determined according to the specification of Japanese Pharmacopoeia X. For the examination of crystal growth of 5-ISMN during the storage, the photomicrographs of tablets and powders were obtained using a Nippon Kogaku stereoscopic microscope SM-5 (Tokyo, Japan) and a Olympus microscope EH (Tokyo, Japan), respectively.

Results and Discussion

Fig. 1 shows the phase solubility diagram obtained for 5-ISMN with β-CyD in water. The diagram showed a typical B_S-type (Higuchi and Connors, 1965) solubility curve with precipitation of microcrystalline complex at the higher β-CyD concentrations. The stoichiometry of the solid complex was determined by the analysis of plateau region of the solubility diagram and the chemical analysis of crystalline complex for 5-ISMN content, suggesting 1 : 1 complex formation in solid phase. However, it is possible that 5-ISMN forms higher order complexes with β-CyD in solution because the ascending portion of B_S curve had a slope greater than unity and the final concentration of the descending curve was not equal to the amount of increase of 5-ISMN in solution observed during the ascending portion of the B_S curve.

Fig. 2 shows the powder X-ray diffraction patterns of the 5-ISMN–β-CyD system. The diffraction pattern of the physical mixture was simply the superposition of each component. On the other hand, the pattern of β-CyD complex was significantly different from each constituent, indicating the constitution of a new solid phase. The β-CyD complex gave somewhat diffuse diffraction pattern, suggesting that it is much less crystalline compared with each component.

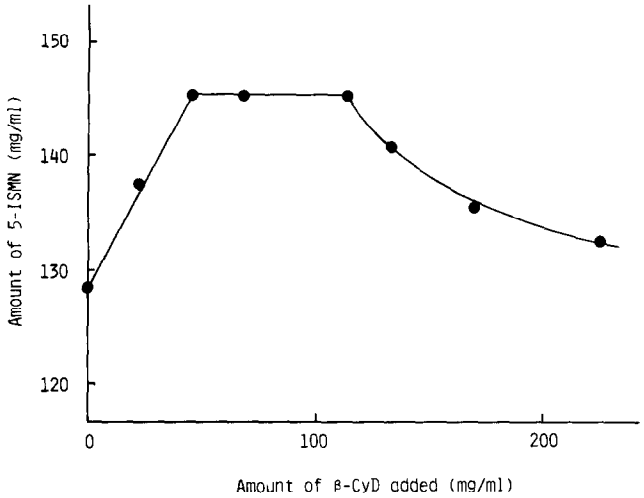

Fig. 1. Phase solubility diagram of 5-ISMN–β-CyD system in water at 25°C.

The effect of β-CyD complexation on the thermal behavior of 5-ISMN was examined by means of DTA and TG, and the results are shown in Fig. 3. In the DTA thermograms, 5-ISMN showed an endothermic peak around 90°C and an exothermic peak around 200°C, owing to the melting and the rapid decomposition of 5-ISMN, respectively. The physical mixture of 5-ISMN and β-CyD also gave the two distinct peaks. In the case of β-CyD complex, however, the endothermic peak of

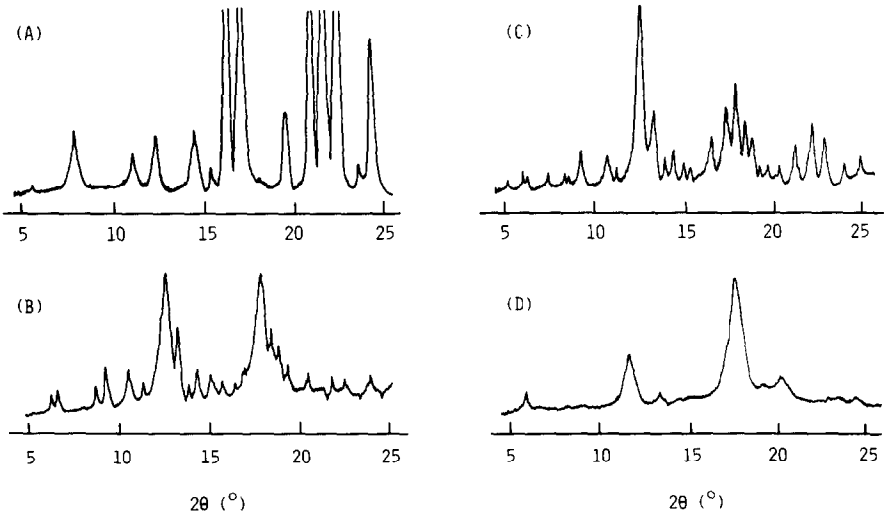

Fig. 2. Powder X-ray diffraction patterns of 5-ISMN–β-CyD system. A: 5-ISMN. B: β-CyD. C: physical mixture of 5-ISMN and β-CyD. D: 5-ISMN–β-CyD complex.

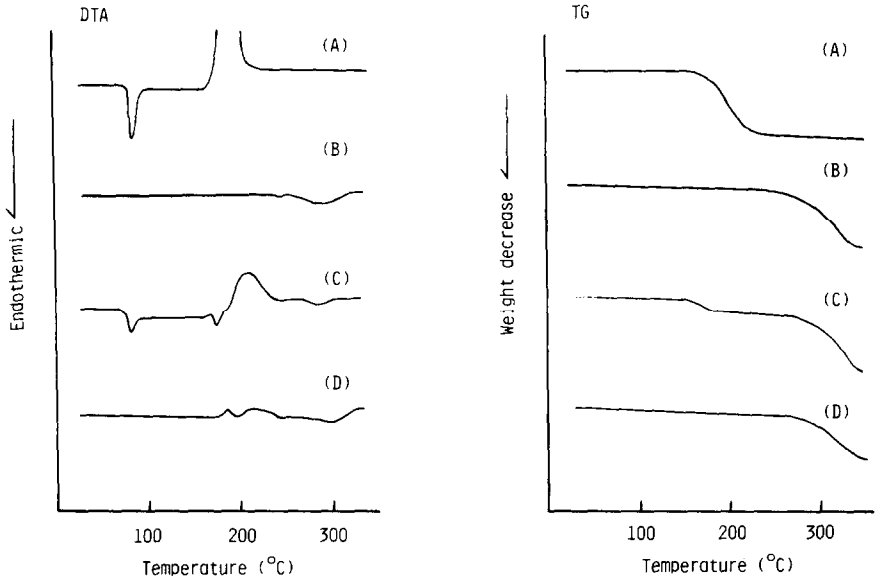

Fig. 3. DTA and TG thermograms of 5-ISMN–β-CyD system. A: 5-ISMN. B: β-CyD. C: physical mixture of 5-ISMN and β-CyD. D: 5-ISMN–β-CyD complex.

5-ISMN disappeared and the exothermic peak decreased remarkably. Furthermore, the volatility of 5-ISMN was greatly depressed by the complexation as shown in TG curves.

Fig. 4 shows the stereoscopic micrographs of tablet surfaces containing 5-ISMN and β-CyD complex before and after storage at 60°C. In the case of 5-ISMN tablet, needle-like crystals, the so-called whiskers, were found to grow on the surface of the tablets after storage for 30 days. Moreover, the crystal growth proceeded with the passage of time. In contrast to 5-ISMN itself, β-CyD complex showed no crystal growth on the surface of the tablet even after storage of 60 days. Similar findings were also obtained for the powder of 5-ISMN or β-CyD complex, as can be seen in Fig. 5. That is, the whiskers appeared on the surface of 5-ISMN powder and the crystal grew with the lapse of time. However, no appreciable generation of whisker was observed for the powder of β-CyD complex. It is generally accepted that temperature and humidity are important factors for the generation and growth of whiskers (Jacson, 1965; Yamada et al., 1976). Therefore, the depression of whisker growth by β-CyD may be due to the inhibition of the volatility of 5-ISMN by inclusion complexation.

Fig. 6 shows the time courses of the stability of 5-ISMN and its β-CyD complex in the solid state at 60°C and 75% relative humidity. It is evident that the degradation of 5-ISMN was remarkably inhibited by the inclusion complexation. For example, the 5-ISMN powder stored at 60°C and 75% relative humidity for 30 days had only 8% remaining of intact 5-ISMN. In addition, the 5-ISMN powder after storage at 45°C and 75% relative humidity for 30 days was found to exhibit

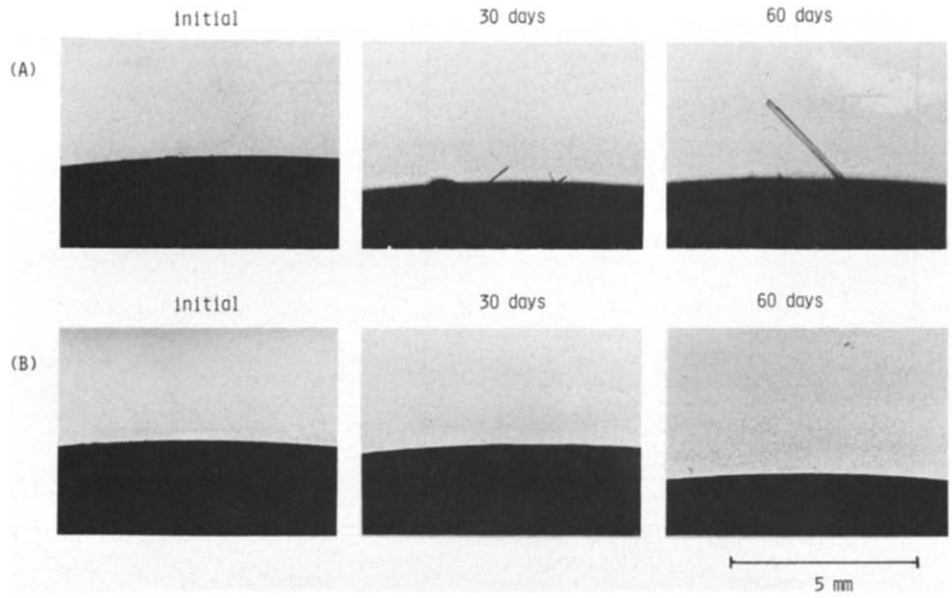

Fig. 4. Effect of β-CyD on the growth of whisker from 5-ISMN tablets. A: 5-ISMN tablet. B: 5-ISMN–β-CyD complex tablet.

63% remaining of intact 5-ISMN (not shown here). In contrast to 5-ISMN alone, the β-CyD complex was extremely stable, in which the complexed 5-ISMN had 99% remaining after 30 days, indicating no appreciable decomposition. The stabilization

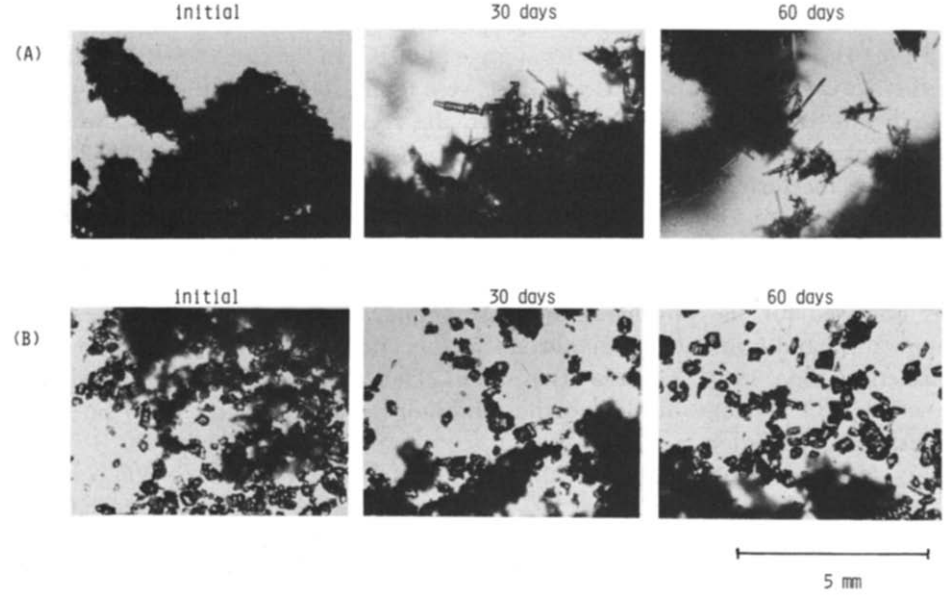

Fig. 5. Effect of β-CyD on the growth of whisker from 5-ISMN powders. A: 5-ISMN powder. B: 5-ISMN–β-CyD complex powder.

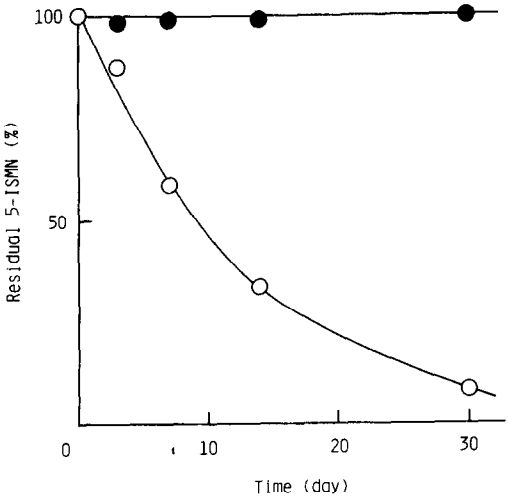

Fig. 6. Degradation curves of 5-ISMN powder and its β-CyD complex powder at 60°C and 75% relative humidity. ○, 5-ISMN; ●, 5-ISMN–β-CyD complex.

of 5-ISMN by β-CyD can be ascribed to the inhibition of volatility of 5-ISMN, as expected from the results of Figs. 3, 4 and 5.

The present data indicate that some pharmaceutical properties of 5-ISMN such as volatility, whisker-generation and thermal stability are improved by the β-CyD complexation. Thus, the formulation of 5-ISMN with β-CyD may solve the problems encountered by the storage.

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