Preparation and Dissolution Behavior of Ethenzamide Solid Dispersions Using Various Sugars as Dispersion Carriers

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Received April 30, 1997; accepted August 4, 1997

Ethenzamide (ETZ) solid dispersions were prepared using the sugars sucrose, maltose, galactose and mannitol as carriers by melting and rapid cooling with liquid nitrogen. The physical chararcteristics of these solid dispersions were investigated by powder X-ray diffraction, differential scanning calorimetry and dissolution rate analyses. The dissolution rate of ETZ can be significantly increased by decreasing the crystallinity of ETZ in solid dispersions. The maximum dissolution rate was observed with solid dispersions containing sucrose, and X-ray diffraction analysis suggested that ETZ was present in a totally amorphous state.

The physical stability of amorphous sugars in dispersions prepared by rapid cooling was also investigated. Solid dispersions made with amorphous sucrose were more stable than those with other sugars. These results indicated that amorphous sucrose is useful as a carrier for production of solid dispersions.

Key words ethenzamide; sucrose; solid dispersion; dissolution; rapid cooling

The use of solid dispersions containing water-soluble carriers to enhance the dissolution rate and bioavailability of poorly water-soluble drugs has been reported by a number of investigators.[1-6] For example, polyvinypirrolidone (PVP), hydroxypropylmethylcellulose (HPMC) and polyethylene glycol (PEG) have been used to enhance the dissolution rates of a number of drugs such as ibuprofen,[7] gruseofulvin,[8] sulfathiazole,[9] reserpine[10] and indomethacin.[11] However, there have been few studies of solid dispersions using low molecular substances as carriers.

In this study, we characterized the release of ethenzamide (ETZ) from sugar–ETZ solid dispersion systems. This was done by determining the dissolution rate constants of solid dispersions prepared with different sugars and by studying the nature of the interaction in the solid state using powder X-ray diffraction, differential scanning calorimetry and IR spectroscopy.

Experimental

Materials 2-Ethoxybenzamide (ETZ) was a gift from Yoshitomi Pharmaceutical Co., Ltd. Sucrose (Kanto Chemical Co., Ltd.), galactose, maltose (Yoneyama Chemical Ind., Ltd.) and mannintol (Wako Pure Chemical Ind., Ltd.) were used as carriers.

Preparation of Solid Dispersions ETZ and carriers (weight ratios of 1:2, 1:3, 1:4) were melted with a mantle heater at the melting point of each sugar, and the mixtures were solidified by dropping into liquid nitrogen or onto aluminum foil cooled with ice. These solid mixtures were ground with an agate mortar and pestle, and passed through a 100—200 μm sieve prior to use.

Preparation of Physical Mixtures ETZ and carriers were mixed in various proportions with a test tube mixer (Vortex-Genie-2, Scientific Ind. Inc.) for 5 min at constant amplitude and rate (500 rpm).

Powder X-Ray Diffractometry Powder X-ray diffraction analysis was performed with a Rigaku Geiger–Flex diffractometer (Type RAD-IIVC) using Ni-filtered, Cu$K\alpha$ radiation at 40 kV, and a current of 20 mA. The scanning rate was 2°/min over a 2θ range at 2—60°. A diffractogram of pure ethenzamide was used as a reference for quantitative analyses. In the qualitative studies, a standard plot of the peak height ratio (I/I_0) of pure ethenzamide to the internal standard lithium fluoride was constructed by the procedure reported by Kislalioglu *et al.*[12]

Thermal Analysis Differential scanning calorimetry (DSC, Type DSC-3100, Mac Science Co., Ltd., Tokyo, Japan) was used to measure glass transition, melting point and heat of fusion. The measurements were performed at a heating rate of 10 °C/min, using a low temperature cell with liquid nitrogen.

IR Spectra IR spectra were obtained on a Fourier-transform IR spectrophotometer (FT-IR, Type FT200, Horiba Co., Ltd.) using the KBr method.

Sugar Stability Test Stability of sugars was examined using amorphous sugars prepared by rapid cooling, followed by leaving them in the desiccator with a saturated solution of sodium chloride (relative humidity (R.H.) = 76%) at 40 °C; changes in X-ray diffraction patterns of sugars were then examined.

Release Experiment ETZ release was determined using a JP XIII dissolution apparatus-2 by a paddle method in which 100 mg of drug was released for each sample at 37±0.1 °C. The release medium was distilled water, and the drug concentration was determined by high-performance liquid chromatography (HPLC, Shimadzu C-R4A).

Results and Discussion

Effects of Cooling Rate on Crystallinity Powder X-ray diffraction patterns of ETZ, sucrose, maltose, galactose and mannitol are shown in Figs. 1 and 2. When cooled rapidly with liquid nitrogen, the diffraction peaks of ETZ and sucrose at ratios of 1:3 and 1:4 disappeared almost completely, and ETZ became amorphous. At an ETZ to sucrose ratio of 1:2, ETZ did not become perfectly amorphous, but a decrease in crystallinity was observed.

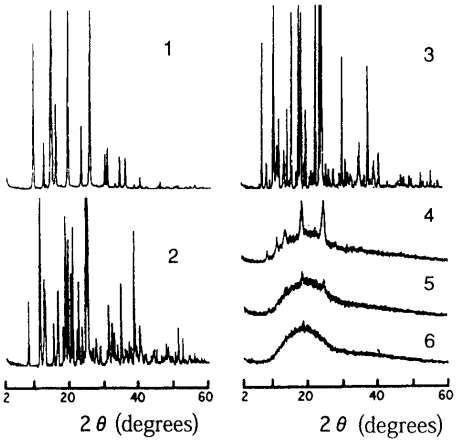

Fig. 1. X-Ray Powder Diffraction Patterns of ETZ–Sucrose Systems

1, ETZ; 2, sucrose; 3, ETZ : sucrose = 1 : 4 physical mixture; 4, ETZ : sucrose = 1 : 2 rapid cooling; 5, ETZ : sucrose = 1 : 3 rapid cooling; 6, ETZ : sucrose = 1 : 4 rapid cooling.

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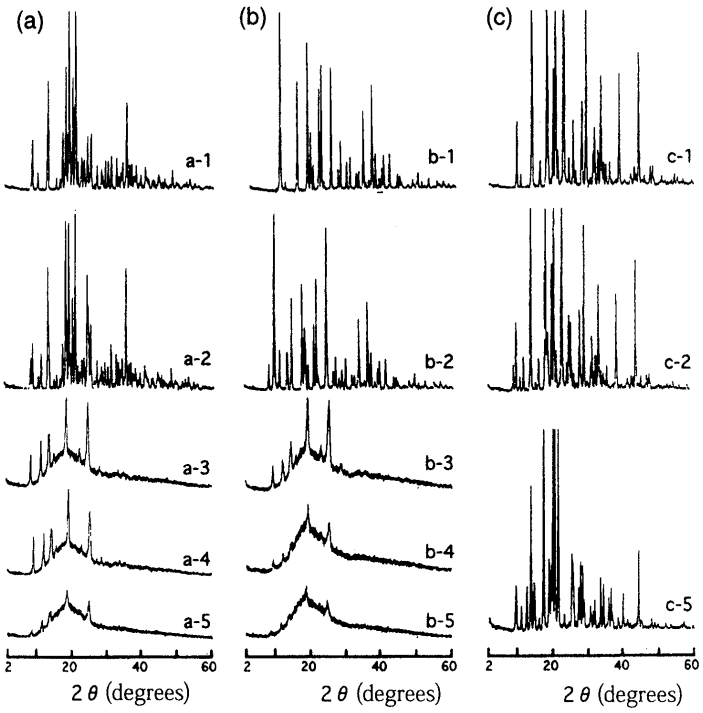

Fig. 2. X-Ray Powder Diffraction Patterns of ETZ–Sugar Systems

(a), ETZ–maltose; (b), ETZ–galactose; (c), ETZ–mannitol; 1, sugar; 2, ETZ : sucrose = 1 : 4 physical mixture; 3, ETZ : sugar = 1 : 2 rapid cooling; 4, ETZ : sugar = 1 : 3 rapid cooling; 5, ETZ : sugar = 1 : 4 rapid cooling.

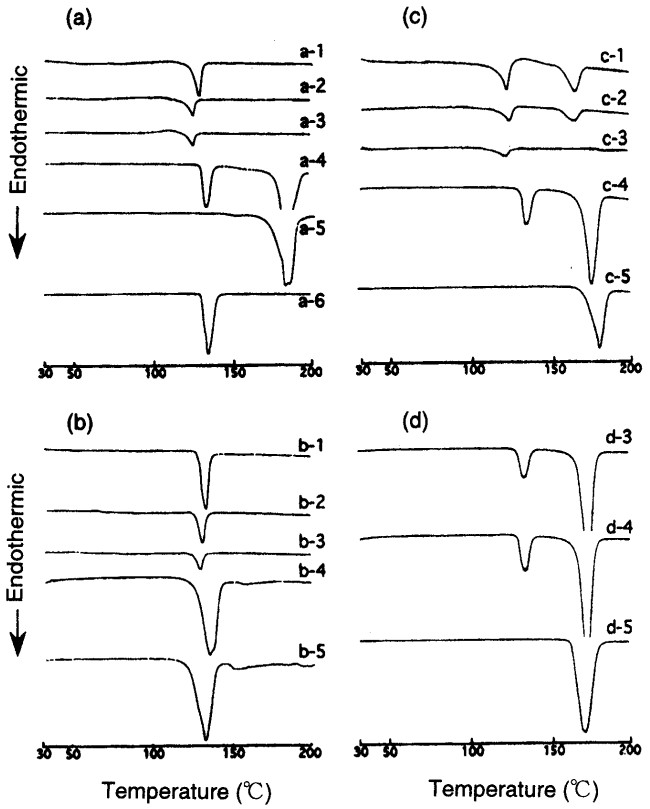

Fig. 3. DSC Thermograms of ETZ–Sugar Systems

(a), ETZ–sucrose; (b), ETZ–maltose; (c), ETZ–galactose; (d), ETZ–mannitol; 1, ETZ : sugar = 1 : 2 rapid cooling; 2, ETZ : sugar = 1 : 3 rapid cooling; 3, ETZ : sugar = 1 : 4 rapid cooling; 4, ETZ : sugar = 1 : 4 physical mixture; 5, sugar; 6, ETZ.

As shown in Fig. 2(a) and (b), ETZ diffraction peaks decreased with increases in amount of carrier, while, with mannitol as the carrier, X-ray diffraction peaks of ETZ showed little change (Fig. 2(c)). In this case, ETZ and mannitol remained in the crystalline state. These results suggested that sucrose, maltose and galactose are useful as carriers for solid dispersions, while mannitol is not suitable.

Thermal Analysis Figure 3 shows the results of thermal analysis. The endothermic peaks of ETZ–sucrose and ETZ–galactose systems showed marked decreases with increases in the amount of sugar used to make solid dispersions. Moreover, the endothermic peaks of sucrose, galactose and maltose disappeared completely due to the change from the crystalline to the amorphous state at an ETZ–sugar mix ratio of 1 : 5. In the ETZ–mannitol system, however, endothermic peaks showed only slight decrease with increase in the amount of mannitol.

Stability of Amorphous Sugars We hypothesized that the crystallinity of sugars used as carriers would influence the formation of solid dispersions, and thus we examined the stability of sugars in dispersions prepared by the rapid cooling method. Figure 4 shows the results of stability tests. Sucrose and galactose remained amorphous after 12 h in a desiccator with 75% R.H. at 40 °C as shown. However, for maltose the degree of crystallinity increased continuously with time, and the stability of the amorphous sugar became poor. Maltose showed a tendency to return to the crystalline from the amorphous state more easily than sucrose or galactose. As mannitol itself was not changed to the amorphous state by the rapid cooling method, its crystallinity did not change even after a standing time of 12 h. Sucrose and galactose were stable in the amorphous state and readily formed solid dispersions, while, maltose was unstable in the amorphous state, and thus it was difficult to make solid dispersions using this sugar. Sucrose and galactose interact readily with ETZ to form solid

dispersions due to the stability of the disordered state. Maltose formed a solid dispersion immediately after preparation of the sample by the rapid cooling method similarly to sucrose and galactose, but we predicted that ETZ would become crystallized with time because the amorphous state is unstable. As mannitol did not change to the amorphous state on rapid cooling, it did not interact readily with ETZ and thus it was difficult to form soild dispersions with this sugar.

Dissolution Rate of ETZ from ETZ–Sugar Solid Dispersions Figure 5 shows the dissolution profiles of ETZ of both physical mixtures and solid dispersions of ETZ–sugars. Samples of solid dispersions dissolved faster than the original and physical mixtures. With sucrose and galactose as carriers, the dissolution rate showed especially sharp increases; with maltose and mannitol as carriers, the dissolution rates were slower than those with sucrose and galactose. Next, we examined the effects of crystallinity of ETZ on the dissolution rate for 60% ETZ (T_{60}). Figure 6 shows the relationship between X-ray diffraction intensity of ETZ ($2\theta = 9.66°$) and T_{60}. T_{60} increased with increasing X-ray diffraction intensity of ETZ ($2\theta = 9.66°$) and then the dissolution rate increased with decreasing crystallinity of ETZ. If a crystalline substance changes to the amorphous form, the dissolution rate increases due to lattice energy decrease.

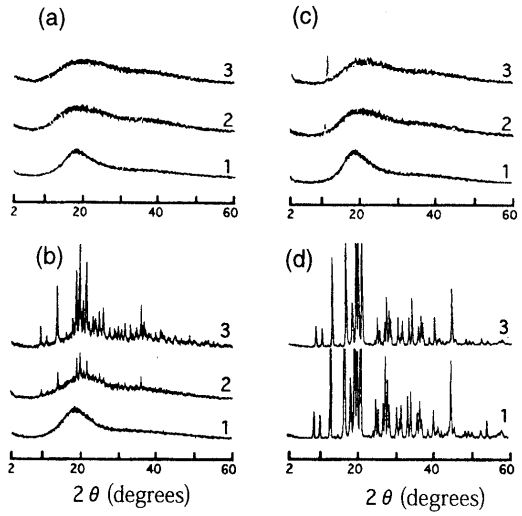

Fig. 4. X-Ray Powder Diffraction Patterns of Rapidly Cooled Sugars During Storage at 40 °C, 75% R.H.

a, sucrose; b, maltose; c, galactose; d, mannitol; 1, initial; 2, after 6 h; 3, after 12 h.

Confirmation of Interaction between ETZ and Carriers The IR spectra of solid dispersions at a weight ratio of 1 : 4 were compared with those of ETZ, sugars and physical mixtures as shown in Fig. 7. The spectrum of the drug showed two peaks due to NH stretching for ETZ at 3393 and 3316 cm^{-1} and showed a narrow strong band at 1750 cm^{-1} due to C=O stretching. Sugars showed strong bands at 3400—3500 cm^{-1} and 1200—1500 cm^{-1} due to OH stretching. In solid dispersions of ETZ and sucrose, on the other hand, maltose and galactose OH stretching were seen as broad bands at 3200—3500 cm^{-1} and 1200—1500 cm^{-1}, indicating the presence of marked hydrogen bonding between ETZ and sugars in solution. For physical mixtures in which there was no hydrogen bonding, the amide band of ETZ appeared as a shoulder in the broad OH stretch band of the sugar at 3500 cm^{-1}, and remained as a sharp OH stretching band of the sugar at 1200—1500 cm^{-1}. In the solid dispersion, however,

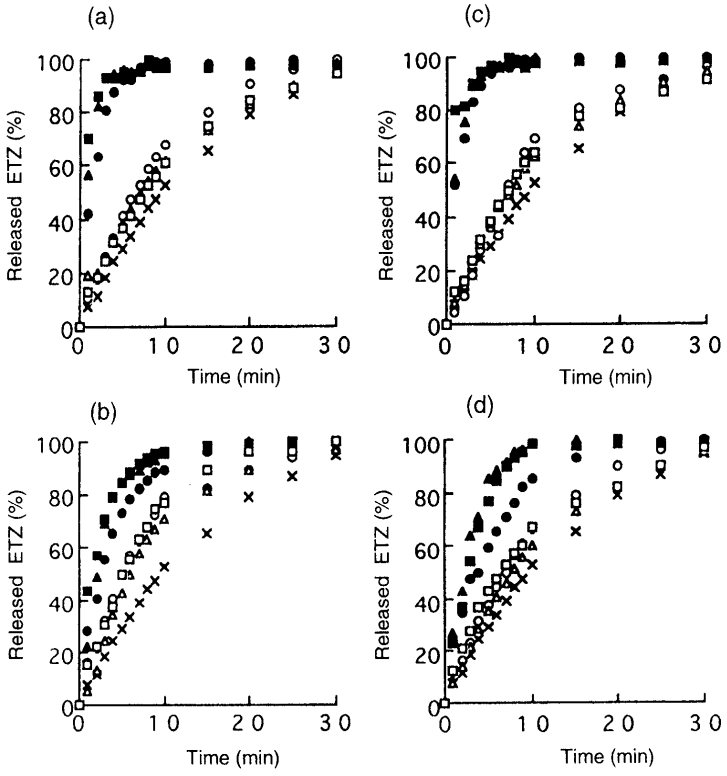

Fig. 5. Dissolution Profiles of ETZ from ETZ–Sugar Solid Dispersions

(a), ETZ–sucrose; (b), ETZ–maltose; (c), ETZ–galactose; (d), ETZ–mannitol; X, ETZ only; ○, ETZ : sugar = 1 : 2 physical mixture; △, ETZ : sugar = 1 : 3 physical mixture; □, ETZ : sugar = 1 : 4 physical mixture; ●, ETZ : sugar = 1 : 2 solid dispersion; ▲, ETZ : sugar = 1 : 3 solid dispersion; ■, ETZ : sugar = 1 : 4 solid dispersion.

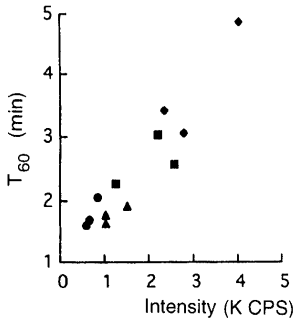

Fig. 6. Relationship between X-Ray Powder Diffraction Intensities of ETZ and T_{60}

●, ETZ–sucrose solid dispersion; ■, ETZ–maltose solid dispersion; ▲, ETZ–galactose solid dispersion; ◆, ETZ–mannitol solid dispersion.

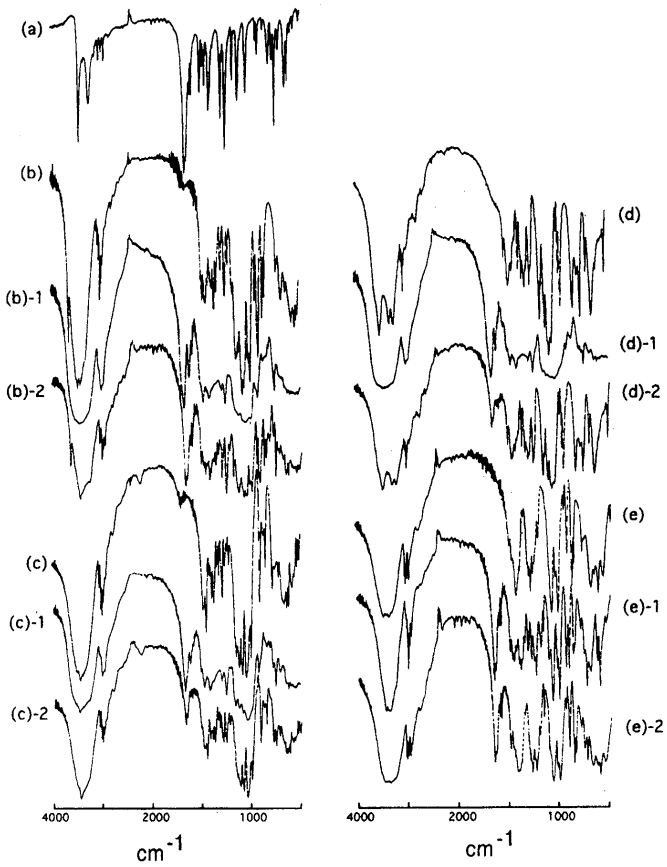

Fig. 7. IR Spectra of ETZ–Sugar Systems

(a), ETZ; (b), sucrose; (c), maltose; (d), galactose; (e), mannitol; 1, ETZ–sugar solid dispersions; 2, ETZ–sugar physical mixtures (1 : 4).

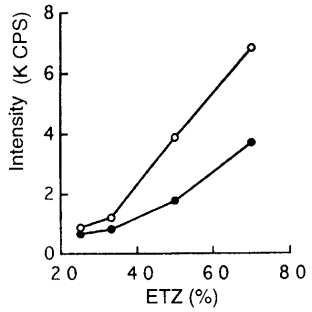

Fig. 8. Influence of Cooling Rate on the Crystallinity of ETZ in Solid Dispersions

○, cooling with ice; ●, cooling with liquid nitrogen.

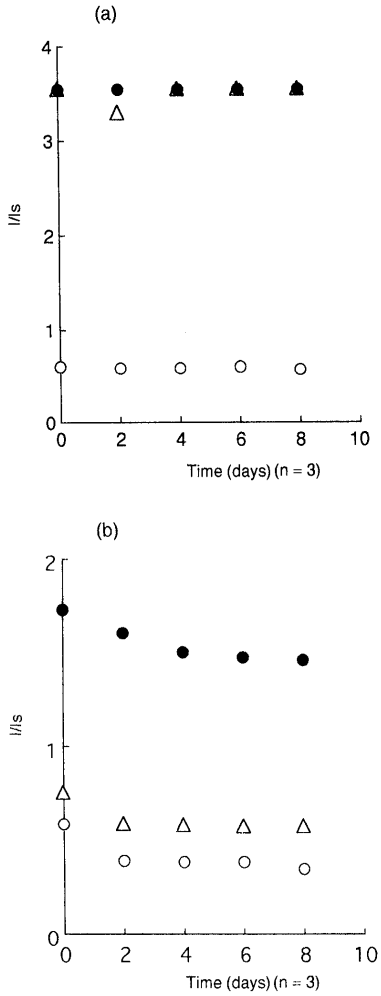

Fig. 9. Influence of Crystallinity on the Solid-State Reaction

(a), crystal sucrose; (b), amorphous sucrose. ○, $2\theta=9.66°$; △, $2\theta=12.5°$; ●, $2\theta=25.4°$.

both appeared as broad bands at 3200—3500 cm^{-1} and 1200—1500 cm^{-1}, presumably due to complex formation, most likely through hydrogen bonding. As mannitol itself was not changed to the amorphous state by the rapid cooling method, the drug did not interact with mannitol. From the results described above, it is supposed that crystallinity with freezing of the carrier after fusion participates in the formation of solid dispersions when low molecular weight substances are used as carriers.

Influence of Cooling Speed on the Formation of Solid Dispersions As the above results indicated that sucrose formed solid dispersions most readily, we next examined the influence of cooling speed on the formation of solid dispersions using this sugar. Figure 8 shows the X-ray diffraction intensity ($2\theta=9.66°$) of ETZ with changes in cooling speed. As the X-ray diffraction intensity of the samples cooled with liquid nitrogen showed a greater decrease than those cooled by ice, cooling speed was suggested to affect ease of formation of solid dispersions. Thus, ETZ and sucrose easily interacted due to the hydrogen bonds between OH groups of the sugar and the NH_2 group of ETZ.

Influence of Crystallinity of Carrier on Formation of Solid Dispersions We reported previously[13] that the solid-state interaction of ibuprofen and polyvinylpyrrolidone oc-

curred at $T/T_m = 0.85$—0.93 (where T/T_m is the homologous temperature and denotes the ratio of experimental temperature to melting point in terms of absolute temperature). In this study, physical mixtures of crystalline and amorphous sucrose and ETZ were prepared at a weight ratio of 1:4 for solid-solid reaction at 100 °C ($T/T_m = 0.921$) to examine the influence of crystallinity of carrier on the formation of solid dispersions. Figure 9 shows the changing crystallinity of ETZ with reaction time at 100 °C. Here, crystallinity is shown by the ratio of I/I_s, where I_s is the intensity of X-ray diffraction of an internal standard material (LiF, $2\theta = 44.98°$) and I is the intensity of X-ray diffraction of ETZ ($2\theta = 9.66°$, $= 12.5°$, $= 25.4°$). I/I_s values showed little change with crystalline sucrose as the carrier (Fig. 9(a)), while the crystallinity of ETZ decreased with increasing reaction time with amorphous sucrose as the carrier in this solid-state reaction (Fig. 9(b)). The molecular state was disordered by decreasing crystallinity of the carrier, and this suggests that formation of solid dispersions was facilitated due to ease of interaction between carrier and drug.

Conclusion

Sugars with low molecular weight formed solid dispersions with ETZ and dissolution of ETZ was markedly increased. Thus, such sugars are useful as carriers. The amorphous state of the sugar markedly affects its usefulness as a carrier for formation of solid dispersions; an amorphous sugar in which the molecular arrangement is disordered forms solid dispersions more easily than the same sugar in the crystalline state.

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