Lactose as a Low Molecular Weight Carrier of Solid Dispersions for Carbamazepine and Ethenzamide

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Solid dispersions of carbamazepine or ethenzamide were prepared by melting and rapid cooling with liquid nitrogen using lactose as a carrier. The physical characteristics of these solid dispersions were investigated by powder X-ray diffraction, differential scanning calorimetry, and dissolution rate analysis. The degree of crystallinity of the drugs in solid dispersions decreased with decreases in the molar ratio of the drugs to lactose. Fourier-transform infrared (FT-IR) analysis demonstrated the presence of intermolecular hydrogen bonds between the primary amide group of carbamazepine and lactose. Dissolution studies indicated that the dissolution rate was markedly increased in solid dispersions compared with physical mixtures and pure drugs. These results indicated that lactose is useful as a carrier for the production of solid dispersions of drugs having a primary amide group in their structures.

Key words solid dispersion; lactose; carbamazepine; ethenzamide; dissolution; hydrogen bonding

Poorly water-soluble drugs often show low absorption and low bioavailability, and their uses are limited by their dissolution rates. Therefore, improvement of the dissolution rate and/or solubility is important for the development of drugs. The solid dispersion method for improving the dissolution rate of poorly water-soluble drugs was first proposed by Sekiguchi and Obi,[1] and the technique has been widely used to prepare both fast release and sustained release drugs by melting (fusion), solvent or melting-solvent methods.[2] It is occasionally difficult to apply these methods, however; thermal instability of the drug during melting is often a significant problem, as is selecting the solvent and residual solvent for use in the solvent method.[3,4] Several water-soluble polymer carrier systems, for example, polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), and hydroxypropylcellulose (HPC),[5—9] have been used for fast release preparations. The mechanisms of interaction between drug and carrier in solid dispersions have been studied.[10—12] However, there have been few studies of solid dispersions using low molecular weight substances as carriers.[13—15]

In the previous study, we examined lactose as a low molecular weight carrier for naproxen as a poorly water-soluble drug.[16] Naproxen formed solid dispersions with lactose when melted and solidified by the rapid quenching cooling method. The dissolution of naproxen was markedly improved using solid dispersions with drug and carrier at a molar ratio of 1/10. Fourier-transform infrared (FT-IR) analysis demonstrated that a carboxylic group in naproxen formed intermolecular hydrogen bonding with lactose in the solid dispersions. In this study, we further investigated the power of lactose as a carrier for poorly water-soluble drugs, carbamazepine and ethenzamide, which each have a primary amide group in their structures.

Experimental

Materials Lactose (De Melk-Industrie Veghel bv (DMV), Pharmatose, 80M) and carbamazepine (Wako Pure Chemical Industries, Ltd.) were purchased commercially. Ethenzamide was kindly supplied from Yoshitomi Pharmaceutical Industries, Ltd. Other materials and solvents were of analytical reagent grade.

Preparation of Solid Dispersion Solid dispersions of drug/lactose were prepared by the melting method. Lactose was heated at 220 °C to melt it completely. Carbamazepine or ethenzamide was added with constant stirring with a spatula. The homogeneous melt obtained was dropped into liquid nitrogen for solidification (rapid quench cooling method). The mixtures of drug and carrier were in molar ratios of 1/1, 1/5, and 1/10 for carbamazepine and 1/1, 1/3, and 1/5 for ethenzamide. The solid samples were ground with an agate mortar and pestle, passed through a 212 μm sieve and placed on a 106 μm sieve prior to use.

Preparation of Physical Mixture The physical mixtures were prepared by mixing drug and carrier with a test tube mixer (Scientific Industries, Vortex-Genie 2) for 5 min at a constant amplitude and rate. These samples were passed through a 212 μm sieve and placed on a 106 μm sieve prior to use.

Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (RAD-2VC) using Ni-filter, CuK_α radiation, a voltage of 40 kV, and a current of 20 mA. The scanning rate was 5°/min over a 2θ range of 2—60° and with a sampling interval of 0.02°.

Thermal Analysis Differential scanning calorimetry (DSC) was carried out with a type 3100 instrument (MAC Science Co., Ltd.). The operating conditions in the open pan system were: sample weight, 10 mg; heating rate, 10 °C/min.

Infrared Spectra FT-IR spectra were obtained with a type FT-200 instrument (Horiba) using the transformation of 100 scans by the KBr disk method.

Dissolution Test Dissolution tests were performed according to the JPXIII paddle method using sample powders (106—212 μm), including 50 mg of drug and 500 ml of dissolution medium JPXIII 1st fluid (pH 1.2) or 2nd fluid (pH 6.8) at 37±0.1 °C. The rotation speed of the paddle was 100 rpm. The quantity of carbamazepine and ethenzamide was assayed by HPLC at 285 nm and 292 nm, respectively. The mobile phase was methanol : water : phosphoric acid = 700 : 299 : 1, which flowed through an ODS column (Cosmosil 5C18-AR, 4.6×150 mm, Nacalai Tesque) at a rate of 1.0 ml/min.

Results and Discussion

Degree of Crystallinity of Carbamazepine and Ethenzamide in Solid Dispersions Powder X-ray diffraction patterns for lactose, carbamazepine, ethenzamide, their physical mixtures, and samples prepared by the melting method are shown in Fig. 1. The diffraction patterns of carbamazepine or ethenzamide in all physical mixtures were similar to those of the pure drug, indicating that the crystallinity of the drug did not change in the physical mixtures. In the diffraction patterns of the melted and cooled samples, on the other hand, the characteristic diffraction peak for the drug gradually decreased with increasing lactose content, and a change to a halo pattern was observed. This indicated that the crystallinity of the drug decreased as it dispersed in lactose.

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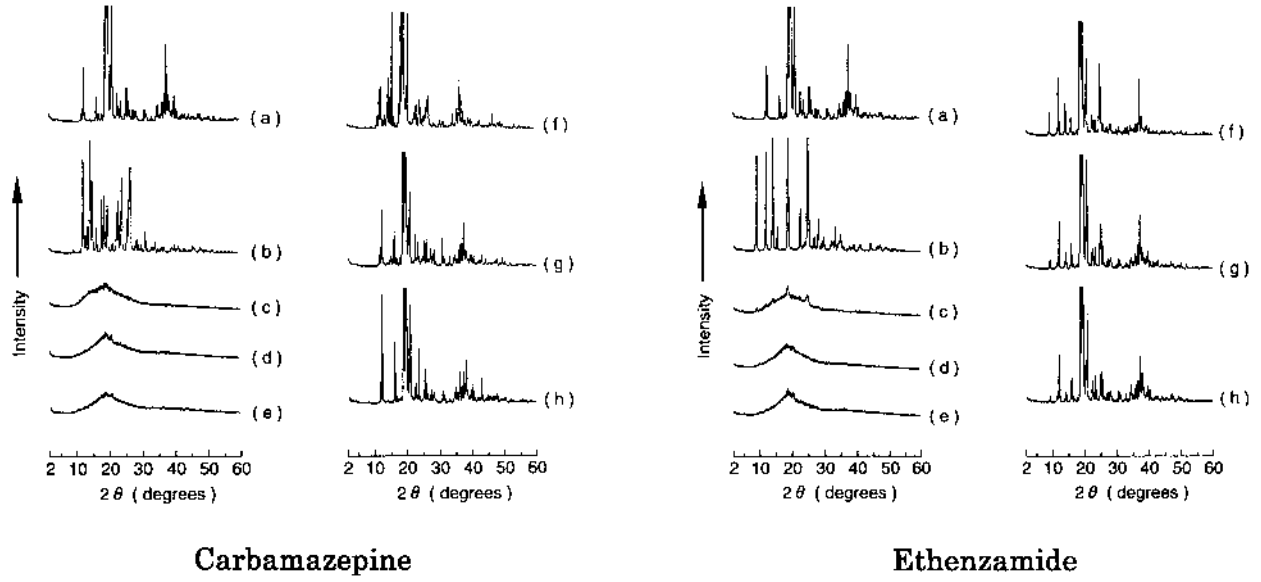

Fig. 1. Powder X-Ray Diffraction Patterns

Carbamazepine: (a), lactose; (b), pure drug; (c), drug/lactose=1/1 solid dispersion; (d), 1/5 solid dispersion; (e), 1/10 solid dispersion; (f), 1/1 physical mixture; (g), 1/5 physical mixture; (h), 1/10 physical mixture.

Ethenzamide: (a), lactose; (b), pure drug; (c), drug/lactose=1/1 solid dispersion; (d), 1/3 solid dispersion; (e), 1/5 solid dispersion; (f), 1/1 physical mixture; (g), 1/3 physical mixture; (h), 1/5 physical mixture.

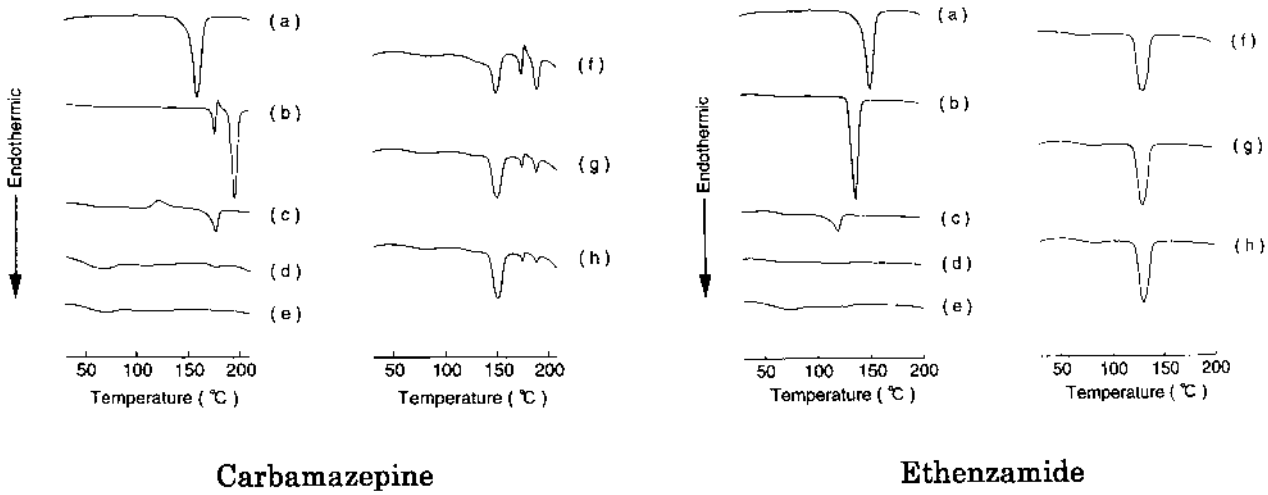

Fig. 2. DSC Thermograms

Carbamazepine: (a), lactose; (b), pure drug; (c), drug/lactose=1/1 solid dispersion; (d), 1/5 solid dispersion; (e), 1/10 solid dispersion; (f), 1/1 physical mixture; (g), 1/5 physical mixture; (h), 1/10 physical mixture.

Ethenzamide: (a), lactose; (b), pure drug; (c), drug/lactose=1/1 solid dispersion; (d), 1/3 solid dispersion; (e), 1/5 solid dispersion; (f), 1/1 physical mixture; (g), 1/3 physical mixture; (h), 1/5 physical mixture.

Therefore, it is believed that the drug could be dispersed homogeneously in an amorphous state or dissolved in the carrier.[5)]

DSC thermograms for lactose, carbamazepine, ethenzamide, their physical mixtures, and samples prepared by the melting method are shown in Fig. 2. Carbamazepine and ethenzamide showed an endothermic peak at about 195 °C and 140 °C, respectively, corresponding to the melting of the drugs. The heat of fusion of the drugs (ΔH), which is an index of crystallinity, is calculated and listed in Table 1.[17)] The physical mixtures at any ratios did not affect ΔH value. For samples prepared by the melting and cooling method, however, the ΔH values decreased as the ratio of drug to lactose decreased, suggesting a decrease in the crystallinity of

Table 1. Heat of Fusion (ΔH, kJ/mol) of Carbamazepine and Ethenzamide

Drug/lactose ratio	Carbamazepine		Ethenzamide	
	Physical mixture	Solid dispersion	Physical mixture	Solid dispersion
1/0 (Pure drug)	17.5		20.3	
1/1	17.0	13.2	21.1	11.3
1/3	—	—	21.2	No peak observed
1/5	16.4	4.27	19.1	No peak observed
1/10	15.6	No peak observed	—	—

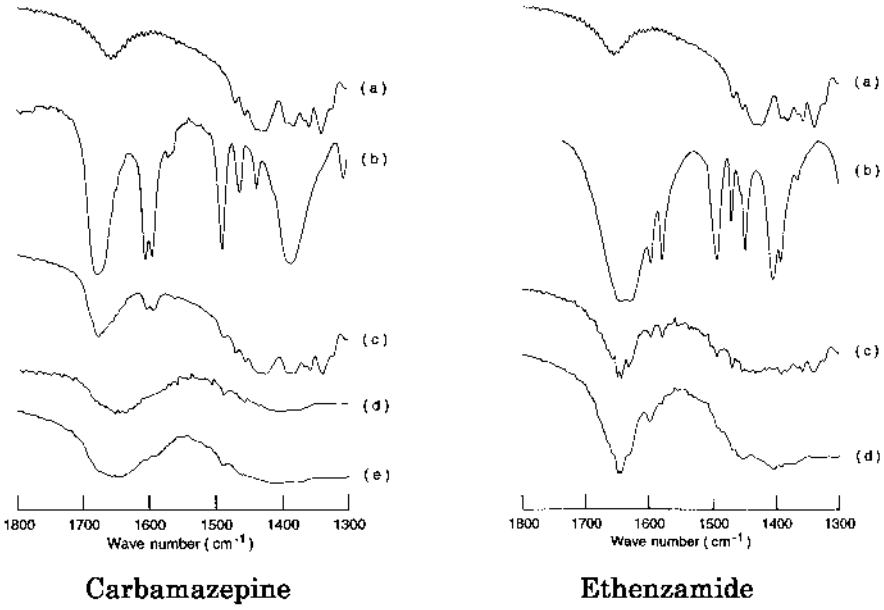

Fig. 3. FT-IR Spectra

Carbamazepine: (a), lactose; (b), pure drug; (c), drug/lactose=1/10 physical mixture; (d), 1/5 solid dispersion; (e), 1/10 solid dispersion.
Ethenzamide: (a), lactose; (b), pure drug; (c), drug/lactose=1/5 physical mixture; (d), 1/5 solid dispersion.

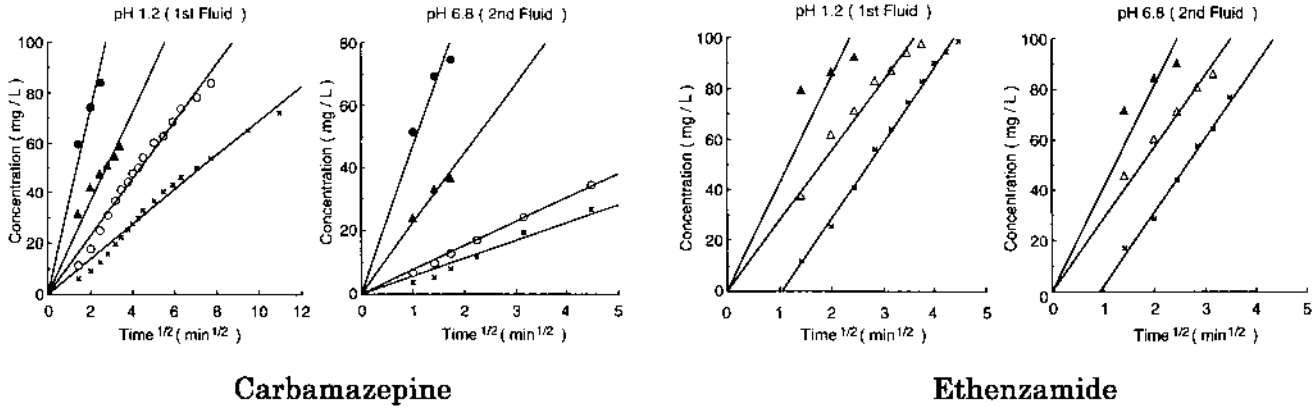

Fig. 4. Square Root Time Plots for Dissolution of Drug–Lactose System

Carbamazepine: ×, pure drug; ○, drug/lactose=1/10 physical mixture; ▲, 1/5 solid dispersion; ●, 1/10 solid dispersion.
Ethenzamide: ×, pure drug; △, drug/lactose=1/5 physical mixture; ▲, 1/5 solid dispersion.

the drugs.

These X-ray diffraction studies and DSC measurements suggested that although the drugs and lactose could not form solid dispersions by physical mixing, when the mixtures were melted and quenched, solid dispersions could then be obtained. The degree of crystallinity of the drugs in the solid dispersions was dependent on the molar ratio of the drugs to lactose.

Mechanism of Interaction between Drug and Carrier FT-IR spectra for lactose, carbamazepine, ethenzamide, their physical mixtures, and solid dispersions are shown in Fig. 3. Carbamazepine showed bands at 1680 cm^{-1} due to a carbonyl stretching vibration in the primary amide group and at 1489 cm^{-1} due to an NH_2 bending vibration. These bands were similarly observed for the physical mixtures of carbamazepine and lactose, suggesting that there was no interaction between carbamazepine and lactose in the physical mixtures. The band due to the carbonyl stretching vibration of carbamazepine in the 1/5 and 1/10 solid dispersions was broadened and shifted by 30 cm^{-1} down to 1650 cm^{-1}, while the band due to the NH_2 bending vibration was not affected. This indicated that lactose forms an intermolecular hydrogen bond with the C=O group in the primary amide group as well as in the carboxylic group.[16)]

As for ethenzamide, the band at 1638 cm^{-1} due to a carbonyl stretching vibration shifted to 1648 cm^{-1} and that at 1493 cm^{-1} due to an NH_2 bending vibration disappeared in the 1/5 solid dispersion, suggesting some interaction at the amide group in the solid dispersions.

Release Rate of Drug from Solid Dispersions The dissolution profiles of carbamazepine and ethenzamide from the solid dispersions were obtained at solution pHs 1.2 and 6.8. The dissolution of carbamazepine and ethenzamide from the solid dispersions was faster than that from the physical mixtures or from the pure drugs at both the pHs. Figure 4 shows the concentration of the drugs against the square root of time. The dissolution rate constants were calculated from the slope of the straight line indicated in Fig. 4 and are listed in Table

Table 2. Apparent Dissolution Constant (mg/l/min$^{1/2}$) of Carbamazepine and Ethenzamide

Drug/lactose ratio	Carbamazepine		Ethenzamide	
	pH 1.2	pH 6.8	pH 1.2	pH 6.8
1/0 (Pure drug)	6.90	5.63	29.9	29.5
1/5 PM	—	—	27.7	28.6
1/10 PM	11.4	7.62	—	—
1/5 SD	18.2	22.3	42.5	40.9
1/10 SD	36.5	46.4	—	—

PM=physical mixture; SD=solid dispersion.

2. The apparent dissolution rate of carbamazepine from the 1/10 solid dispersion was about 5 and 8 times faster than that of pure carbamazepine at pHs 1.2 and 6.8, respectively. The 1/5 solid dispersion of ethenzamide increased the apparent dissolution rate by 1.4 times compared to that of the pure drug at both the pHs. A lag time was observed for the dissolution of pure ethenzamide, which was diminished by using the physical mixture or solid dispersion. We speculated that ethenzamide is apt to aggregate by itself to delay the start of dissolution because of the low wettability of ethenzamide. Lactose would adhere to ethenzamide to decrease the lag time by improving drug wettability, even in the physical mixture.

Conclusion

Carbamazepine and ethenzamide formed solid dispersions with lactose when drug and carrier were melted completely and then solidified by the rapid quenching cooling method. The degree of crystallinity of the drugs in solid dispersions decreased according to the increase in the lactose ratio. Intermolecular hydrogen bonds between the carbonyl group in the carbamazepine primary amide group and lactose in the solid dispersions were suggested by FT-IR analysis. The dissolution rate of carbamazepine and ethenzamide was improved using the solid dispersions. The present study demonstrated that lactose is a potential carrier for the solid dispersion of drugs having a primary amide group as well as a carboxylic group in their structures.

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