Effects of Compression on the Interaction between 1,4-Dihydropyridine Compounds and Lactose Monohydrate (II): Differences in Powder Properties of 1,4-Dihydropyridine Compounds

Shouichi Hosaka,* Takeshi Sadoshima, Mika Sato, Chikayuki Hamada, Yoshiteru Takahashi, and Nobuyuki Kitamori

Research and Development Division, Sawai Pharmaceutical Co., Ltd.; 5–2–30 Miyahara, Yodogawa-ku, Osaka 532–0003, Japan. Received June 15, 2006; accepted March 4, 2007

The solid-state interaction between manidipine dihydrochloride (Man) or benidipine hydrochloride (Ben) and lactose monohydrate (Lac) was investigated. An endothermic peak area at 170 °C was observed when their mixtures were subjected to differential scanning calorimetry (DSC) measurement, and this interaction was accelerated by compression. In the present study, dependency on the particle size of Lac was examined in this solid-state interaction. The DSC peak area at 170 °C as a function of the compression force profile was influenced by different particle sizes of Lac in combination with the two medicinal compounds in a different manner. The profile of the onset temperature of Lac dehydration, which indicates the degree of crystalline structure disruption, changed with differing Lac particle size. Moreover, when the particle size of Lac was large, the dehydration onset temperature of Lac with Man decreased from the lower compression force than that of Lac with Ben. The reason for this is thought to be the difference in the powder properties between Man and Ben, although the physicochemical properties of Man and Ben are similar.

Key words solid-state interaction; particle size; compression; powder property; thermal analysis

1,4-Dihydropyridine-type compounds such as nifedipine and nicardipine hydrochloride are frequently prescribed calcium channel antagonists with antihypertensive activity. Manidipine dihydrochloride (Man) and benidipine hydrochloride (Ben) have been shown to be more potent and longer-acting than previous generations of 1,4-dihydropyridines.[1,2]

We described the dissolution behaviors of the anhydrate and monohydrate forms of Ben.[3,4] We also found that an interaction occurred during differential scanning calorimetry (DSC) measurements of physical mixtures of Man or Ben with lactose monohydrate (Lac), but no interaction was observed with lactose anhydrate.[5] The water of crystallization in Lac was clearly participated in this interaction. Moreover, we investigated the effects of compression on this interaction and found that it was accelerated by compression and related to disruption of the Lac crystal structure.[6]

In the solid-state reaction, it is important to consider the particle size of compounds because the extent of the reaction may depend on the contact area of the particles. In the present study, the effects of the particle size of Lac on the interaction between Man or Ben and Lac relative to compression force were investigated and discuss the difference in the powder properties between Man and Ben.

Experimental

Materials Man (Sanyo Kagaku, Japan); Ben (Daito, Japan); three types of Lac, Pharmatose® 200M (DMV, The Netherlands), Dilactose® S (Freund Sangyo, Japan), and Dilactose® R (Freund Sangyo, Japan); and magnesium stearate (Taihei Kagaku, Japan) were used for the preparation of tablets. The volume mean diameter of Man and Ben used in this study were almost identical at 3—4 μm, and those of the three different types of Lac were 25 μm (Lac25; Pharmatose® 200M), 75 μm (Lac75; Dilactose® S), and 125 μm (Lac125; Dilactose® R), as determined by laser diffraction method (HEROS SYSTEM, Particle size analyzer, JEOL, Japan). Man was obtained as the β-form.

Preparation of Man and Ben Tablets The mixtures of Man or Ben with Lac in an equimolar ratio were mixed with 1% magnesium stearate. Flat-faced tablets, 8 mm in diameter, each weighing 100 mg, were prepared using a physical testing machine (Compaction analyzer, Kikusui, Japan) at different compression forces.

Thermal Analysis DSC analysis was performed with a DSC-50 (Shimadzu, Japan) in open pans under following conditions: sample weight, 8.0±0.5 mg; and heating rate, 5.0 °C/min. All of the samples were measured one time. Samples of physical mixtures or tablets for DSC measurements were prepared by gently mixing the two drugs with Lac or by gentle crushing. It was confirmed in DSC that the crystal structure of Lac was not disrupted during these operations. A dry nitrogen purge was used throughout the measurement, and indium was used for calibration.

Results and Discussion

Effects of Particle Size on Interactions with Man In the physical mixture of Man and Lac25, endothermic peaks at 147 °C and 201 °C in DSC profiles, corresponding to the dehydration of Lac and melting point of the eutectic mixture of Man and Lac were observed and a new endothermic peak appeared at 170 °C as a result of the interaction between Man and Lac.[5] The endothermic peaks at 170 °C were observed for all particle sizes of Lac and their area increased with the increase in compression force not only for Lac25[6] but also for Lac75 and Lac125. These results show that the interaction between Man and Lac during thermal treatment was accelerated by the mechanical energy of compression. At the same time, the profile of the endothermic peak due to the dehydration of Lac became broader with the increase in compression force. In the solid-state interaction with Lac, its water of crystallization should have an important role.[7] The interaction accelerated by compression event is essentially the same as the case of the solid-state reaction, for example, transformation of the crystal form or chemical reaction, which could be due to or enhanced by mechanical stress during pharmaceutical processing such as grinding or compression.[7—11]

The DSC peak area at 170 °C is plotted against the compression force in Fig. 1, which shows the results for the three

* To whom correspondence should be addressed. e-mail: s.hosaka@sawai.co.jp

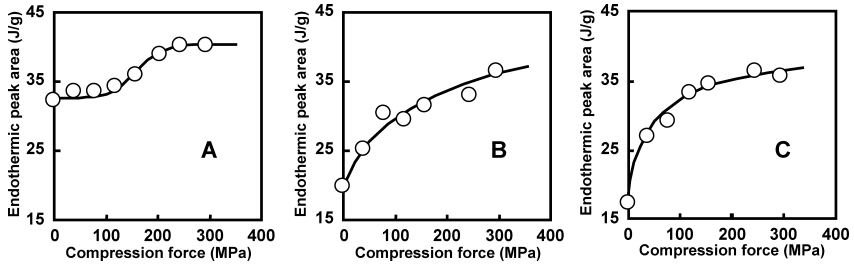

Fig. 1. Effects of Compression Force on the Interaction between Man and Various Lac Particle Sizes at the Molar Ratio of Man : Lac = 1 : 1
A, Man/Lac25; B, Man/Lac75; C, Man/Lac125.

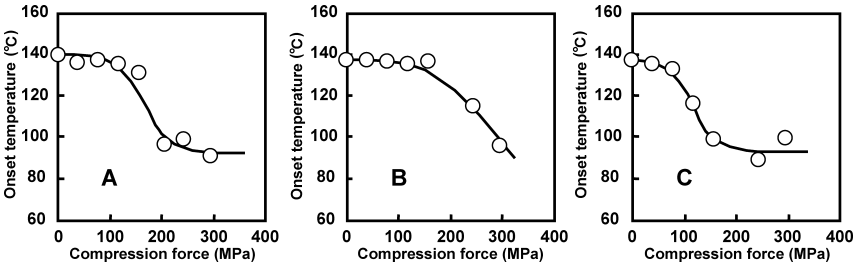

Fig. 2. Changes in the Onset Temperature of Dehydration of Various Lac Particle Sizes Relative to Compression Force at the Molar Ratio of Man : Lac = 1 : 1
A, Man/Lac25; B, Man/Lac75; C, Man/Lac125.

different particle sizes of Lac. The endothermic peak area of the physical mixture (0 MPa) of Man and Lac25 was larger than that of other particle sizes of Lac. The reason of this is thought that the contact area between Man and Lac25 was larger and the interaction increased.

For Lac25, after a lag compression force region, the DSC peak area increased rapidly and then reached a plateau. For Lac75 and Lac125, the lag compression force region disappeared, and the DSC peak area increased rapidly as compression force increased. The acceleration of this interaction with increasing compression force may be due to: 1) the increase in the contact area among particles of drug substances and Lac; and 2) the disruption of the crystal structure of Lac. In the previous paper, the endothermic peak areas at 170 °C for the physical mixtures of drug substances and untreated Lac25, tablets compressed at 245 MPa, and physical mixtures of drugs and Lac25 compressed at 245 MPa (pre-compressed Lac) were compared.[6] The endothermic peak area at 170 °C for the tablets was almost the same as that of the physical mixture of drugs and pre-compressed Lac, which were both greater than that of the physical mixture of drugs and untreated Lac. It was concluded that the interaction was accelerated mainly by the disruption of the crystal lattice of Lac25.

Our examination of the detailed mechanism of the increased interaction for the three types of Lac focused on changes in the temperature at which the onset of Lac dehydration occurs because it decreases when the crystal lattice is disordered by compression. To clarify the relationship between the disruption of the crystal lattice and the increased interaction, the temperature of onset of Lac dehydration is plotted against the compression force in Fig. 2, which shows the results for the three different particle sizes of Lac. Here, we should consider that Lac75 and Lac125 are granulated lactose monohydrate, which are different type from Lac25.

For Lac25, after the lag compression force region (up to 100 MPa) the onset temperature of Lac25 dehydration decreased rapidly and then reached a plateau. This profile corresponds well with the profile of changes in the DSC peak area against compression force, as shown in Fig. 1A. This shows that the interaction mainly increased due to the disruption of the crystal lattice of Lac25 as we mentioned above. For Lac75 or Lac125, after the lag compression force region, the onset temperature of Lac dehydration decreased rapidly. At lower compression forces, the onset temperature of dehydration did not change though the interaction increased, as shown in Figs. 1B and C. These results suggest that the interaction increased not only due to the disruption of the crystal lattice but also due to the increased contact area of Man and Lac75 or Lac125. In the plateau region in Figs. 2B and C, the interaction is suggested to be accelerated due to the increase in contact area, because only a slight difference in the dehydration onset temperature was observed. In this region, it is suggested that the disruption of the granulated particles of Lac75 or Lac125 is promoted by compression (which is not the disruption of the crystal lattice), so that the contact area of Man and Lac increases. In the region of compression force greater than plateau region, the interaction appeared to be accelerated by the disruption of the crystal lattice of Lac, because a rapid decrease in the onset temperature was observed. For Lac125, a shorter lag region was observed than for Lac75. Therefore, Lac125 is thought to be more sensitive to disruption than Lac75.

Effects of Particle Size on Interactions with Ben Similar to the case of Man, a new endothermic peak at 170 °C as a result of the interaction between Ben and Lac were observed for all particle sizes of Lac, and their area increased with the increase in compression force. The DSC peak area at 170 °C is plotted against the compression force in Fig. 3, which shows the results for the three different particle sizes

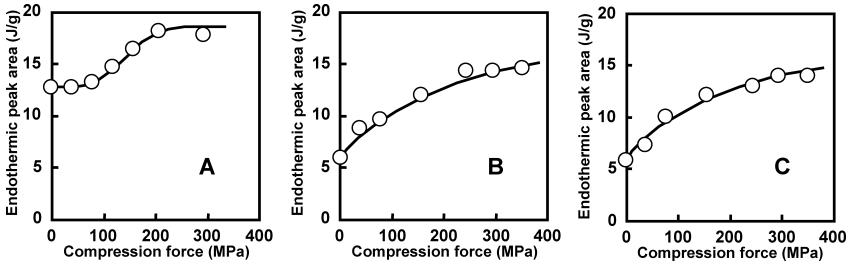

Fig. 3. Effects of Compression Force on the Interaction between Ben and Various Lac Particle Sizes at the Molar Ratio of Ben : Lac = 1 : 1
A, Ben/Lac25; B, Ben/Lac75; C, Ben/Lac125.

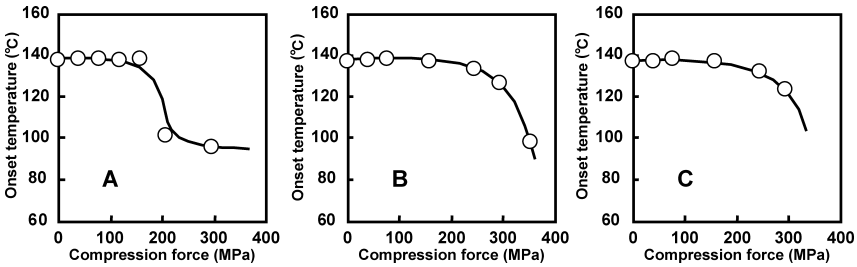

Fig. 4. Changes in the Onset Temperature of Dehydration of Various Lac Particle Sizes Relative to Compression Force at the Molar Ratio of Ben : Lac = 1 : 1
A, Ben/Lac25; B, Ben/Lac75; C, Ben/Lac125.

of Lac.

It is clear from Figs. 1 and 3 that almost the same profile was obtained for each Lac particle size. The onset temperature of Lac dehydration is also plotted against the compression force in Fig. 4, which shows the results for the three different particle sizes of Lac.

It is clear from Figs. 2 and 4 that the similar profile was observed for each Lac particle size. Here, we should note that in the case of Lac125, the lag compression force region was at least up to 200 MPa for Ben (Fig. 4C), whereas it was up to 100 MPa for Man (Fig. 2C). This is not a large but an important difference.

Why did the onset temperature of dehydration decrease from a lower compression force for Man than for Ben? We focused on the differences in powder properties between Man and Ben. In a previous paper, the DSC peak area ratio-*versus*-compression force profile showed different behavior at higher ratios of medicinal compounds. Moreover, upon adding more lubricant to the mixture of Man/Lac25 to reduce internal friction, the profile changed to resemble that of Ben/Lac25. Based on these results, it was concluded that Man is more adherent than Ben.[6] It is strongly suggested that the disruption of the Lac crystalline structure is accelerated more by Man than by Ben. In the present study, the reason for the rapid decrease in the onset temperature from the lower compression force observed in the case of Man/Lac125 is suggested to be due to greater internal friction during compression than in the case of Ben/Lac125. The result obtained in this experiment, agrees well that obtained in the previous paper which focused on the differences in internal friction of two compounds during compression.

It is interesting that Man and Ben, which have similar physicochemical properties, exhibit differences in powder properties when they interact with different types of Lac. The investigations reported here represent a new approach to evaluate the powder properties through thermal analysis.

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