# Effect of Compression on Interaction between 1,4-Dihydropyridine Compounds and Lactose Monohydrate[1)]

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**Manidipine dihydrochloride or benidipine hydrochloride will change to hydrate form in part, when differential scanning calorimetric (DSC) measurement is carried out together with lactose monohydrate. This interaction was accelerated by compressing their mixture. It can be suggested that the interaction may cause by the disruption of crystal structure of lactose monohydrate due to compression to set free of water molecules. A new DSC peak at 170 °C, which was not observed in each component, appeared in DSC measurement of a mixture. This will be based on hydrate formed by the interaction, *i.e.*, movement of water molecules. The profile of the plotting of the DSC peak area ratio before and after compression against the compression force changed by the molar ratio of lactose monohydrate in a mixture. In the case of low molar ratio of lactose monohydrate, profiles for manidipine dihydrochloride and benidipine hydrochloride differed from each other. This will be because manidipine dihydrochloride is stickier than benidipine hydrochloride. The profile for manidipine dihydrochloride became more gradual and showed lag compression force region when the amount of addition of the lubricant, magnesium stearate in a mixture increased. The endothermic peak area at 170 °C for manidipine dihydrochloride was larger than that for benidipine hydrochloride. It should be suggested that benidipine hydrochloride is easier to be transformed to its hydrate than manidipine dihydrochloride.**

**Key words** solid–solid interaction; compression; crystal water; crystal structure; thermal analysis

1,4-Dihydropyridine type compounds such as Nifedipine and Nicardipine hydrochloride have antihypertensive activity, which are frequently used as a calcium channel antagonist. Especially, manidipine dihydrochloride and benidipine hydrochloride have the characteristics of more potent and longer acting than the other 1,4-dihydropyridines, which have been developed in the earlier time.[2,3)]

The drug molecules commonly have polymorphs and/or solvate forms whose solubility, stability and also bioavailability are well known to be different from their mother compounds.[4)] In the series of 1,4-dihydropyridines, the existences of polymorph and/or hydrate form have been reported in nicardipine hydrochloride,[5)] nilvadipine[6)] and manidipine dihydrochloride.[2)]

We have reported in the previous paper[7)] that the dissolution behaviors of anhydrate and monohydrate forms of benidipine hydrochloride, which is one of the 1,4-dihydropyridines and has a similar structure of manidipine dihydrochloride. We also have reported[8)] that during thermal treatment of physical mixtures of manidipine dihydrochloride or benidipine hydrochloride with lactose monohydrate, the interaction was observed between them but not with lactose anhydrate. The water of crystallization in lactose monohydrate was clearly participated in this interaction and it was suggested that a portion of water molecule in lactose monohydrate migrated to these compounds during thermal treatment.

Pharmaceutical preparation process consists of several processes such as manipulation, granulation, drying, compression and so on. Some medicinal compounds were reported that transformation of crystal form could occur by mechanical manipulation during these processes.[9—11)] The pharmaceutical formulations usually contain medicinal compounds and excipients. Therefore, the approach to discuss the interaction between drug molecules and excipient molecules induced by mechanical and also thermal energy during pharmaceutical process must be important in the formulation studies. In the present paper, the effect of compression process on the interaction between manidipine dihydrochloride or benidipine hydrochloride and lactose monohydrate during thermal treatment is described.

## Experimental

**Materials** Manidipine dihydrochloride (Sanyo Kagaku), benidipine hydrochloride (Daito), lactose monohydrate (DMV 200#), and magnesium stearate (Taiheikagaku) were used for preparation of tablets. Manidipine dihydrochloride was obtained as $\beta$-form and was used.

**Measurement of Particle Size** Particle size of manidipine dihydrochloride (Man), benidipine hydrochloride (Ben) and lactose monohydrate (Lac) was measured by laser diffraction method (HEROS SYSTEM, Particle size analyzer, JEOL). Particle size was expressed as volume mean diameter ($D_{50}$).

**Preparation for Man and Ben Tablets** The mixtures of Man or Ben with Lac in three different molar ratios were mixed with 1% or more amount of magnesium stearate (Mgst). Tablets each weighing 100 mg, flat-shaped, 8 mm in diameter, were prepared using a physical testing machine (Compaction analyzer, Kikusui) in different levels of compression forces with the constant rate of compression in this study. The flat-shaped tablet punch was used to compress more homogenously.

**Thermal Analysis** Differential scanning calorimetric (DSC) analysis was performed by DSC-50 (Shimadzu) in open pans under following conditions: sample weight, 8.0±0.5 mg; heating rate, 5.0 °C/min. Samples of physical mixtures or tablets for the DSC measurements were prepared by mixing drugs with lactose monohydrate gently or by crashing tablets gently. It was confirmed by DSC that crystal structure of lactose monohydrate was not disrupted during these operations. A dry nitrogen purge was used throughout the measurement and indium was used for the calibration.

**Increase Ratio of Interaction by Compression** Ratio of endothermic peak area at 170 °C in DSC for tablets against that of physical mixture (DSC peak area ratio) was calculated. The ratios were plotted against compression force. Compression force: 0 MPa means physical mixture.

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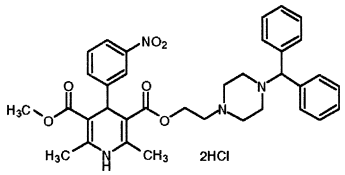
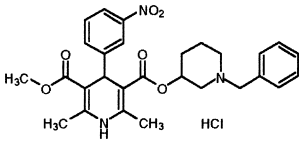
Table 1. Structures and Physicochemical Properties of Manidipine Dihydrochloride and Benidipine Hydrochloride

| Compound | MW | mp | Particle size ($D_{50}$) |
|---|---|---|---|
| Manidipine dihydrochloride (Man)  | 683.61 | 174—180 °C ($\beta$-form) | 3.88 $\mu$m |
| Benidipine hydrochloride (Ben)  | 542.02 | 199—200 °C | 4.42 $\mu$m |

## Results and Discussion

**Physical Properties of Man and Ben** Physical properties and chemical structures of Man and Ben are shown in Table 1. Particle sizes of Man and Ben used in this study were almost identical, 3—4 $\mu$m and that of Lac was about 25 $\mu$m. According to the measurements of X-ray diffraction, both Man and Ben have crystal forms. DSC profiles of Man, Ben and Lac are shown in Fig. 1.

In DSC profile for Man, two endothermic peaks were observed at 196 °C and 216 °C corresponding to decomposition and melting, respectively. The decomposition of the compound at 196 °C was confirmed by HPLC analysis of the heated Man at 205 °C in DSC chamber. On the other hand, in DSC profile for Ben, only one endothermic peak was observed at 206 °C corresponding to melting. In DSC profile for Lac, two endothermic peaks were observed at 148 °C and 218 °C corresponding to dehydration and melting of dehydrated lactose, respectively. There was no endothermic peak around 170 °C in these materials.

**Effect of Compression on the Interactions between Drug Substances and Lac** (a) In the Case of Man: DSC profiles of the physical mixture and their tablets compressed at different compression forces are shown in Fig. 2.

In physical mixture of Man and Lac, endothermic peaks at 147 °C and 201 °C corresponding to dehydration of Lac and melting point of the eutectic mixture of Man and Lac were observed, and additionally a new endothermic peak appeared at 170 °C as a result of interaction between them.[7] This interaction occurred just during the thermal treatment. The endothermic peak area at 170 °C increased with an increase in compression force. The result represents that the interaction between Man and Lac during thermal analysis was accelerated by mechanical energy of compression. In the same time, the pattern of endothermic peak by dehydration of Lac became broad with an increase in compression force. It has been reported[11] that the disruption of the hydrate structure by mechanical manipulation such as grinding or compression so that water of crystallization of Lac became easy to remove from the crystal lattice. Therefore, the induced interaction by the increasing compression force would be accelerated by the following mechanism. (1) Dehydration of Lac easily occurs by disruption of crystal lattice, and (2) contact area between

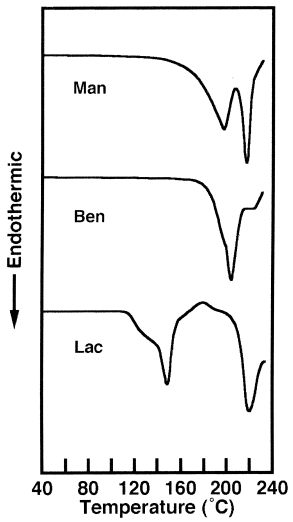



Fig. 1. DSC Profiles of Manidipine Dihydrochloride (Man), Benidipine Hydrochloride (Ben), and Lactose Monohydrate (Lac)

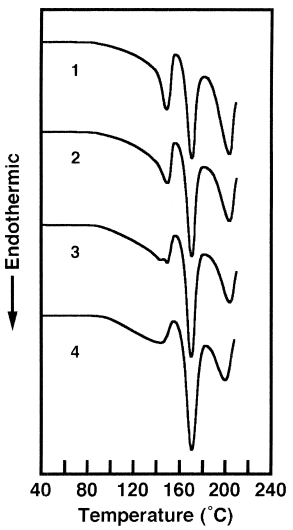



Fig. 2. DSC Profiles of Physical Mixture and Tablets of Manidipine Dihydrochloride and Lactose Monohydrate (Molar Ratio, 1 : 1)

1: Physical mixture, 2: tablet compressed at 118 MPa, 3: tablet compressed at 206 MPa, 4: tablet compressed at 245 MPa.

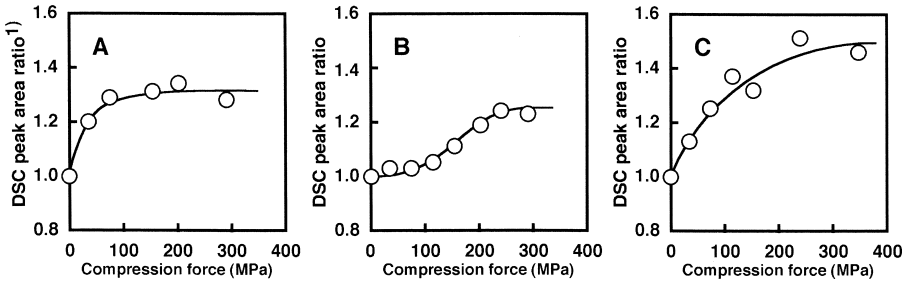



Fig. 3. Effect of Compression Force on Interaction between Manidipine Dihydrochloride (Man) and Lactose Monohydrate (Lac) in Different Mixing Ratios

Compression force: 0 MPa means physical mixture. A: Man/Lac=2/1, B: Man/Lac=1/1, C: Man/Lac=1/2. 1) Ratio of DSC peak areas at 170 °C before and after compression.

drug substance and Lac increases.

The ratios of the DSC peak area at 170 °C were plotted against the compression force in Fig. 3, where the results for three different ratios of Man and Lac, Man/Lac=2/1, Man/Lac=1/1 and Man/Lac=1/2 are shown. The sigmoidal pattern was observed in the case of Man/Lac=1/1.

(b) In the Case of Ben: DSC profiles of physical mixture and tablets compressed at different compression forces for the Ben are shown in Fig. 4.

Similar to the case of Man, in physical mixture of Ben and Lac, endothermic peaks at 146 °C and 201 °C corresponding to dehydration of Lac and melting point of the eutectic mixture of Ben and Lac were observed. Also a new endothermic peak appeared at 170 °C as a result of interaction between them.[8] The ratios of the DSC peak area at 170 °C are plotted against the compression force in Fig. 5. In this figure, as the same as the case of Man the results for three different ratios of Ben and Lac are shown.

It is clear from Figs. 3 and 5 that both are almost the same pattern for each mixing molar ratio of drug substance and Lac, except the case of low Lac ratio. In the molar ratio of 1/1, after some lag compression force region the DSC peak area ratios increased rapidly and then reached a plateau of about 1.3 for Man and about 1.4 for Ben. In the molar ratio of 1/2, a lag region disappeared and the DSC peak area ratios increased rapidly and reached a plateau level of about 1.5 for Man and about 1.6 for Ben.

In the molar ratio of 2/1, however, the somewhat different behaviors were seen for Man and Ben. In the Ben case, there was the longer lag compression force region than in the molar ratio of 1/1 were seen and then the DSC peak area ratio increased gradually as compression force increased. In the Man case, the DSC peak area ratio increased rapidly even from low compression force and then reached a plateau level.

From these results obtained, in the case of Ben the more Lac ratio, the more influenced of compression force for this interaction. At the lower compression force region, the interaction did not occur and with an increase in compression force, the interaction increased and then reached a plateau level. In the case of Man, even in the lower compression force region, the interaction did occur.

This interaction during thermal analysis occurred by water of crystallization of Lac has already reported.[8] In the solid-state interaction with Lac, its water of crystallization should have an important role. 4-Methoxyphenylaminoacetate hydrochloride decomposed during storage at 37 °C and 80% RH when it was mixed with Lac. The water of crystallization

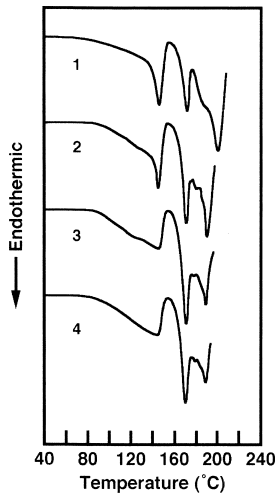



Fig. 4. DSC Profiles of Physical Mixture and Tablets of Benidipine Hydrochloride and Lactose Monohydrate (Molar Ratio, 1 : 1)

1: Physical mixture, 2: tablet compressed at 118 MPa, 3: tablet compressed at 206 MPa, 4: tablet compressed at 245 MPa.

of Lac caused the decomposition of 4-methoxyphenylaminoacetate hydrochloride during storage. Moreover, the decomposition was accelerated when crystal lattice of Lac was disordered by mechanical manipulation, for example, by grinding.[12] The interaction accelerated by compression event is thought to be essentially the same as the case of the decomposition of 4-methoxyphenylaminoacetate hydrochloride. Therefore, it is suggested that this interaction promoted in accordance with an increase in the available amount of water of crystallization of Lac.

Why the interaction occurred at even lower compression force region in the case of the Man and Lac? Man is stickier than Ben. It can be assumed in the case of Man that the disruption of crystal lattice of Lac should occur at even lower compression force region by the higher inner friction of the mixture. Adding the more lubricant in the mixture to reduce the inner friction would change that DSC peak ratio *versus* compression force profile. Figure 6 shows the DSC peak area ratio *versus* compression force profiles for different lubricant content and a certain mixing molar ratio of Man and Lac, Man/Lac=2/1. Although the plateau level was similar, the profiles changed in accordance with the amount of Mgst. Since the profile for 10% of Mgst had lag compression force region, the profiles depend not only on the compression force but also on the powder characteristics, such as an inner fric-

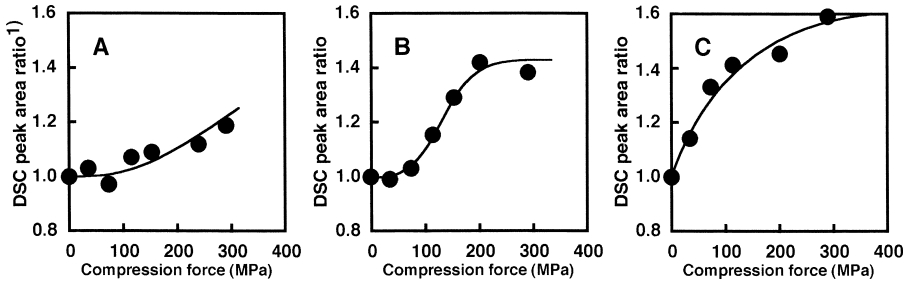



Fig. 5. Effect of Compression Force on Interaction between Benidipine Hydrochloride (Ben) and Lactose Monohydrate (Lac) in Different Mixing Ratios

Compression force: 0 MPa means physical mixture. A: Ben/Lac=2/1, B: Ben/Lac=1/1, C: Ben/Lac=1/2. 1) Ratio of DSC peak areas at 170 °C before and after compression.

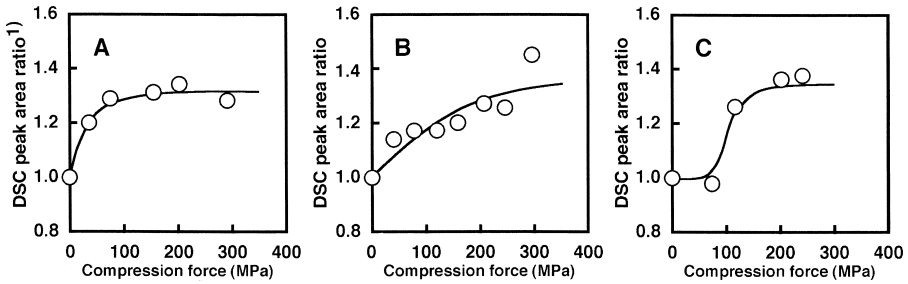



Fig. 6. Effect of the Amount of Magnesium Stearate (Mgst) on the Interaction Profiles at the Ratio of Man/Lac=2/1

Compression force: 0 MPa means physical mixture. A: Mgst 1%, B: Mgst 5%, C: Mgst 10%. 1) Ratio of DSC peak areas at 170 °C before and after compression.

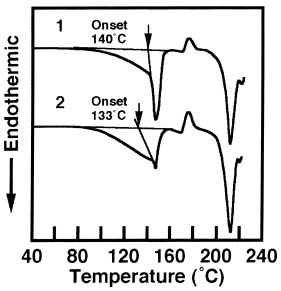



Fig. 7. DSC Profiles of Lactose Monohydrate before and after Compression

1: Before compression, 2: after compression at 245 MPa.

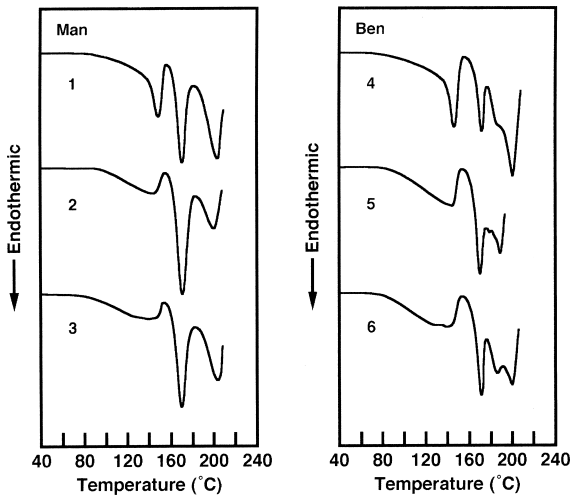



Fig. 8. DSC Profiles of Physical Mixtures and Tablets (Molar Ratio, 1 : 1)

1: Physical mixture of Man and Lac, 2: tablets of Man and Lac compressed at 245 MPa, 3: tablets of Man and pre-compressed Lac at 245 MPa, 4: physical mixture of Ben and Lac, 5: tablets of Ben and Lac compressed at 245 MPa, 6: tablets of Ben and pre-compressed Lac at 245 MPa.

tion property.

**The Importance of Crystal Structure of Lac** As mentioned above, the acceleration of this interaction by increasing compression force may be due to the disruption of crystal structure of Lac and the increase in contact area of Man or Ben and Lac. In fact, peak profile of dehydration of Lac broadened as the compression force increased. It can be seen that the bonding strength of water of crystallization decreased in the lattice.

Change of DSC profiles of Lac before and after compression at 245 MPa is shown in Fig. 7.

The peak profile of dehydration of Lac alone compressed at 245 MPa broadened and the onset temperature became lower from 140 °C to 133 °C. This phenomenon indicated that the disruption of crystal structure occurred by compression. The equimolar physical mixture of Man or Ben and Lac compressed at 245 MPa (pre-compressed Lac) were prepared. The endothermic peak areas derived from interaction on physical mixture of both compounds and Lac were compared with or without pre-compression of Lac at 245 MPa. The results are shown in Fig. 8 and Table 2.

Table 2. Endothermic Peak Area in DSC Profiles Derived from Interaction at the Molar Ratio of Compound/Lactose=1/1

| Sample | Endothermic peak area |
|---|---|
| Physical mixture of Man and Lac | 32.32 J/g |
| Tablets of Man and Lac compressed at 245 MPa | 40.43 J/g |
| Physical mixture of Man and pre-compressed Lac at 245 MPa | 38.14 J/g |
| Physical mixture of Ben and Lac | 12.79 J/g |
| Tablets of Ben and Lac compressed at 245 MPa | 17.80 J/g |
| Physical mixture of Ben and pre-compressed Lac at 245 MPa | 17.08 J/g |

The endothermic peak area at 170 °C of physical mixture of both compounds and pre-compressed Lac was larger than that for both compounds and non-treated Lac and also was almost the same as that for tablets of Man and Lac compressed at 245 MPa. These results show that the interaction is accelerated mainly by the disruption of the crystal structure of Lac during compression.

The endothermic peak area for Man was larger than that for Ben. It may suggest that Ben is easier to be transformed to its hydrate than Man.

**References and Notes**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