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Inclusion Complex Formation of Acetaminophen by Heating and Cogrinding with Cyclodextrins

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Abstract. The effects of heating or grinding processes on the formation of the inclusion complex between acetaminophen and α- or β-cyclodextrin were investigated. The interaction of excess amounts of acetaminophen with acetaminophen–cyclodextrin systems was also examined. It was found that the process of grinding or freeze-drying did not cause any interaction between acetaminophen and α-cyclodextrin, but heating could result in its complex formation. However, all the processes (heating, freeze-drying and grinding), could improve the inclusion formation of acetaminophen and β-cyclodextrin. An excess of acetaminophen could easily interact with the inclusion complex of acetaminophen and β-cyclodextrin to result in an exothermic peak at 160°C in DSC thermograms. Consecutive endothermic and exothermic peaks around 150–160°C appeared in the DSC thermograms of acetaminophen–β-CD systems, but not in the DSC curves of acetaminophen–α-CD systems. This consecutive transition phenomenon might be due to the fusion of the amorphous state of excessive acetaminophen caused by grinding and the molecular interaction that occurred between an excess of fused acetaminophen and the inclusion complex

Key words. molecular interaction, inclusion complex, acetaminophen, cyclodextrins, heating, grinding.

1. Introduction

Cyclodextrins (CDs) can form inclusion complexes with many drugs, thus improving their physical, chemical and biopharmaceutical properties [1–3]. Solid inclusion complexes have been prepared by many methods, such as coprecipitation, kneading, freeze-drying and cogrinding [4–7]. In our laboratory we have used a one-step spray-drying technique to prepare amorphous state drug inclusion complexes within a short time [8]. The freeze-dried warfarin–β-CD inclusion complex not only improves the dissolution rate (> 1000-fold) but also controls the dissociation rate of warfarin from an inclusion complex to prolong the prothrombin time [9, 10]. Acetaminophen molecules can also be included into the cavity of β-CD by mechanical grinding, freeze-drying or humidity, resulting in an inclusion complex [11–13]. However, indomethacin, warfarin and hydrocortisone acetate did not form an inclusion complex by grinding [11].

Our previous study found that acetaminophen molecules can be included stepwise into the cavity of β-CD molecules by grinding to form an inclusion complex, but α-CD does not form an inclusion complex with acetaminophen, which only decreases the crystallinity of the ground mixtures [11, 12]. According to the DSC

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thermograms of acetaminophen–β-CD ground mixtures, a new, unknown exothermic peak at 160°C appeared before the melting point (168°C) of acetaminophen, but it did not appear in the DSC curves of acetaminophen–α-CD ground mixtures. This unknown exothermic peak is investigated in the present study. Moreover, the heating effect on the formation of the acetaminophen–CD inclusion complex was also studied.

2. Experimental

2.1. MATERIALS

Acetaminophen was purchased from Seven Star Pharmaceutical Co. Ltd., Taiwan, ROC. α- and β-Cyclodextrins (α- and β-CD) were obtained from Nihon Shokuhin Kako Co., Tokyo, Japan. All the other materials and reagents were of analytical reagent grade.

2.2. PREPARATION OF GROUND MIXTURES

(1) The first type of ground mixtures were prepared by grinding acetaminophen and α- or β-CD (1:1 molar ratio) in a ceramic ball mill for 24 h. During the grinding process, samples were withdrawn at prescribed intervals (0, 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0 and 24 h) for further examination.

(2) The second-type ground mixtures were prepared by grinding acetaminophen and the first-type ground mixture (total molar ratio of acetaminophen to each CD = 3:1) in a mortar (Labo-mill, Yamato, Tokyo, Japan). Samples were withdrawn at prescribed intervals during the grinding process for further use.

(3) The third type of ground mixtures were made by grinding acetaminophen and α- or β-CD (total molar ratio of acetaminophen to each CD = 3:1) in a mortar, as mentioned above.

2.3. PREPARATION OF FREEZE-DRIED SAMPLES

α- or β-CD and acetaminophen (molar ratio = 1:1) were dissolved in water and then freeze-dried to obtain the samples.

2.4. PREPARATION OF HEATED SAMPLES

Heated samples were prepared by heating the physical mixture of acetaminophen and α- or β-CD (molar ratio = 1:1) to the desired temperature (150, 160, 180, 265, 285 and 300°C), then cooling to room temperature for further examination.

2.5. EXAMINATION OF VARIOUS SAMPLES

The physical mixtures, ground mixtures, freeze-dried and heated samples were examined using differential scanning calorimetry (DSC-1090, DuPont, USA) and/or thermogravimetric analysis (TGA-951, DuPont, USA) at a scanning rate of

$10°C\,min^{-1}$ under a N_2 gas stream. An IR spectrophotometer (IR-700, Jasco, Tokyo, Japan) was used to record the spectra of the samples by the KBr disk method.

3. Results and Discussion

DSC thermograms of the physical and ground mixtures of acetaminophen and α- or β-CD (molar ratio = 1:1) as a function of grinding time are shown in Figure 1. Before grinding, a sharp endothermic peak at 168°C was observed in DSC curves of both mixtures due to the melting of acetaminophen. After melting, a small exothermic peak at 172°C also appeared in DSC thermograms of both mixtures, attributed to the complex formation by heating [14–15]. The endothermic peak for acetaminophen at 168°C decreased with grinding time, and the exothermic peak for inclusion complex formation at 172°C also decreased gradually and shifted to a higher temperature range with grinding time. The ground acetaminophen and inclusion complex embedded together by the grinding process might be responsible for this phenomenon. Another new exothermic peak at 160°C, which appeared before the melting peak (168°C) of acetaminophen, was also observed in DSC curves of acetaminophen–β-CD ground mixtures but it did not appear in DSC curves of acetaminophen–α-CD ground mixtures. This exothermic peak at 160°C will be discussed later.

The effect of grinding and heating on the IR spectra of acetaminophen and α-CD systems is indicated in Figure 2. It is apparent that the IR peaks of acetaminophen

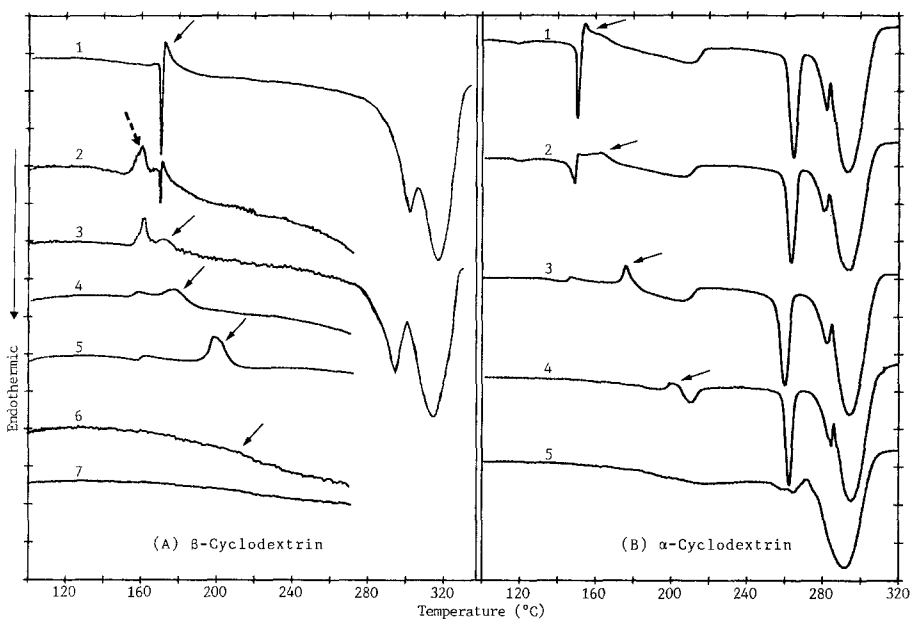

Fig. 1. DSC thermograms of acetaminophen–cyclodextrin ground mixtures (mole ratio = 1:1) with ball grinding. Key: grinding time: (A) β-Cyclodextrin: 1: 0 h; 2: 0.5 h; 3: 1.0 h; 4: 1.5 h; 5: 2.0 h; 6: 3.0 h; 7: 24 h. (B) α-Cyclodextrin: 1: 0 h; 2: 1.0 h; 3: 3.0 h; 4: 7.0 h; 5: 24 h.

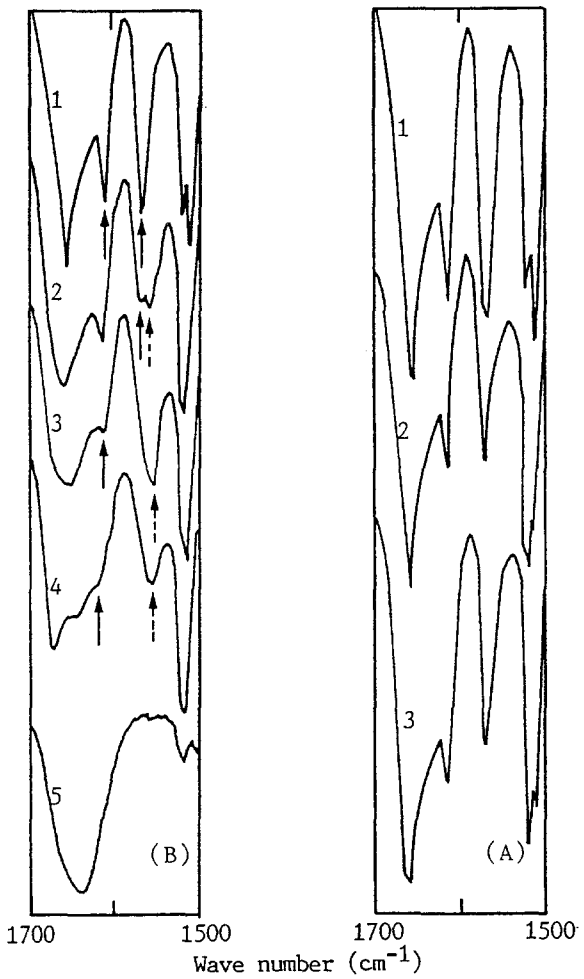

Fig. 2. IR spectra of acetaminophen–α-cyclodextrin systems. Key: (A) Grinding effect: 1: 0 h; 2: 24 h; 3: freeze-dried samples. (B) Heating effect: 1: 150°C; 2: 160°C; 3: 180°C; 4: 265°C; 5: 285°C.

in a 24-h ground mixture and freeze-dried sample are the same as in the physical mixture, suggesting the process of grinding or freeze drying did not cause any interaction between acetaminophen and α-CD (Figure 2) [11, 12]. However, the thermal effect may cause an interaction. The 1568 cm^{-1} band of the amido group in acetaminophen shifted gradually to 1555 cm^{-1} with the increase of the heating temperature, and the 1612 cm^{-1} band of the C=C of the benzene ring of acetaminophen also disappeared slowly with the rise of heating temperature. When the sample was heated to 285°C, the spectrum resembled that of the α-CD inclusion complex. This suggests that the heating process may cause the inclusion formation between acetaminophen and α-CD. The IR spectra of acetaminophen and β-CD systems affected by the process of grinding or heating are shown in Figure 3.

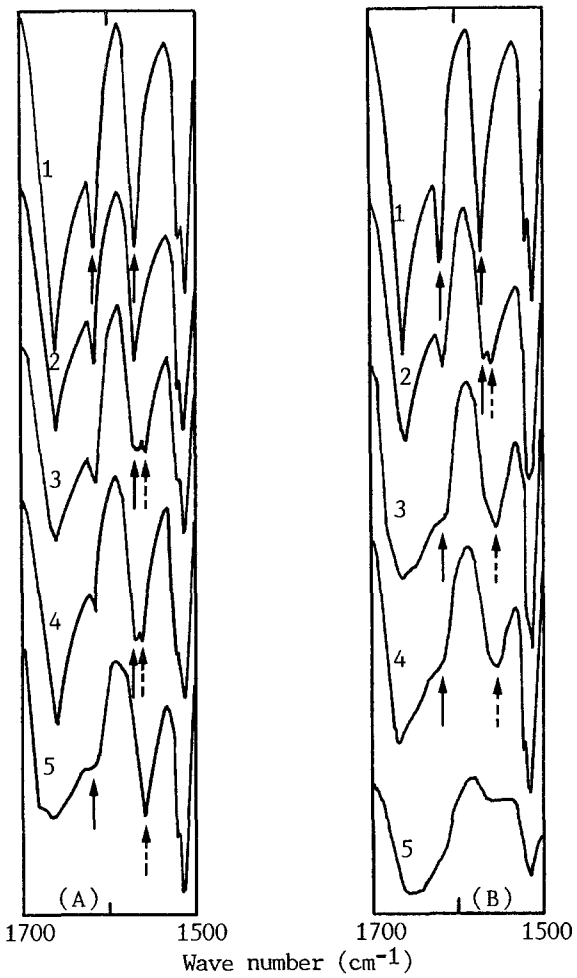

Fig. 3. IR spectra of acetaminophen–β-cyclodextrin systems. Key: (A) Grinding effect: 1: 0 h; 2: 0.5 h; 3: 1.0 h; 4: 1.5 h; 5: 24 h. (B) Heating effect: 1: 150°C; 2: 160°C; 3: 180°C; 4: 285°C; 5: 300°C.

Obviously, both grinding and heating processes can improve the inclusion formation between acetaminophen and β-CD by shifting the amido group of acetaminophen from 1568 cm^{-1} to 1555 cm^{-1} and eliminating the C=C of the benzene ring of acetaminophen from 1612 cm^{-1}.

The exothermic peak occurring at 160°C for the acetaminophen–β-CD system during the process of grinding (Figure 1), was examined as follows. Figure 4 shows the DSC thermograms of acetaminophen–CD systems (total molar ratio of acetaminophen to CD = 3:1) with mortar grinding. When 3 moles of acetaminophen was physically mixed with one mole of β-CD before grinding, its thermogram was similar to that of a 1:1 molar ratio of their physical mixture but another broad endothermic peak at 240°C was present due to the decomposition of

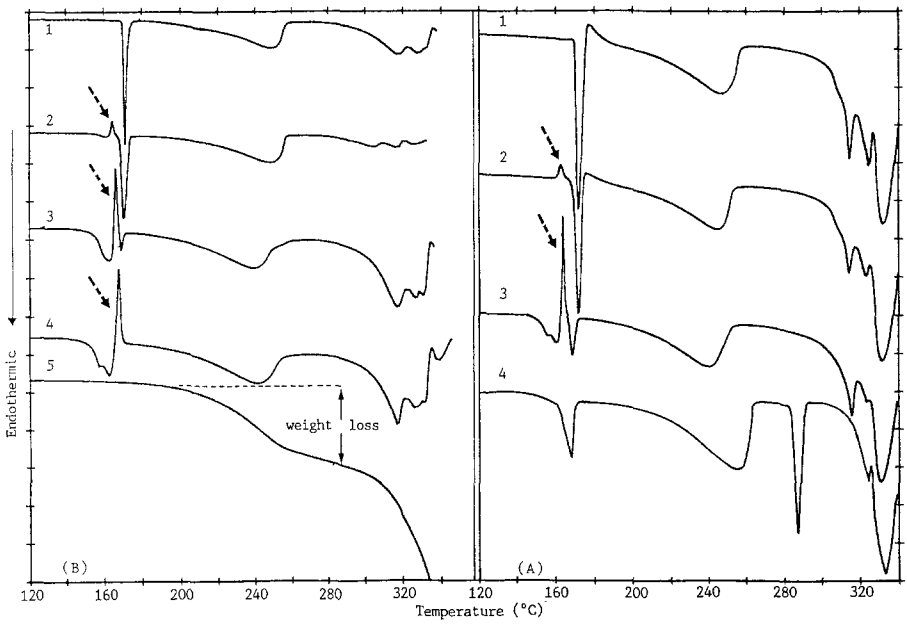

Fig. 4. DSC thermograms of acetaminophen–cyclodextrin ground mixtures (mole ratio = 3:1) with mortar grinding. Key: grinding time: (A) acetaminophen + α-CD or β-CD. β-CD 1: 0 min; 2: 15 min; 3: 60 min; α-CD 4: 60 min. (B) Freeze-dried (acetaminophen + β-CD) + acetaminophen. 1: 0 min; 2: 15 min; 3: 30 min; 4: 60 min; 5: TGA curve.

the excess acetaminophen. After mortar grinding, the consecutive endothermic and exothermic peaks around 150–160°C appeared with the increase of grinding time. The same result was also found in the mixture of the freeze-dried sample (intact inclusion complex) and acetaminophen (total molar ratio of acetaminophen to β-CD = 3:1). Before grinding, only one fusion peak at 168°C and one decomposition peak at 240°C were found since no excess of β-CD could be used to interact with acetaminophen, leading to no exothermic peak at 172°C. After grinding, the consecutive endothermic and exothermic peaks around 150–160°C appeared again. The TGA curve corresponded to the loss of acetaminophen. However, no other consecutive thermal peak was found with the molar ratio of 3:1 of acetaminophen and the α-CD system whether by grinding acetaminophen with the ground mixture or with α-CD. This consecutive transitional change of thermograms might be due to the fusion of the amorphous state of acetaminophen caused by grinding and the molecular interaction of the fused acetaminophen and the inclusion complex.

The above results can be postulated by a scheme, as shown in Figure 5. Before treatment, acetaminophen was previously mixed and distributed between α- or β-CD powders (Figure 5.a). After 24-h grinding, the amorphous state acetaminophen particles were still distributed in α-CD powders but interaction did not occur between each other (Figure 5.b) [12]. On heating, a trace of acetaminophen was fused and included into the cavity of α-CD to form an inclusion complex (Figures 1 and 2). However, acetaminophen was completely included into

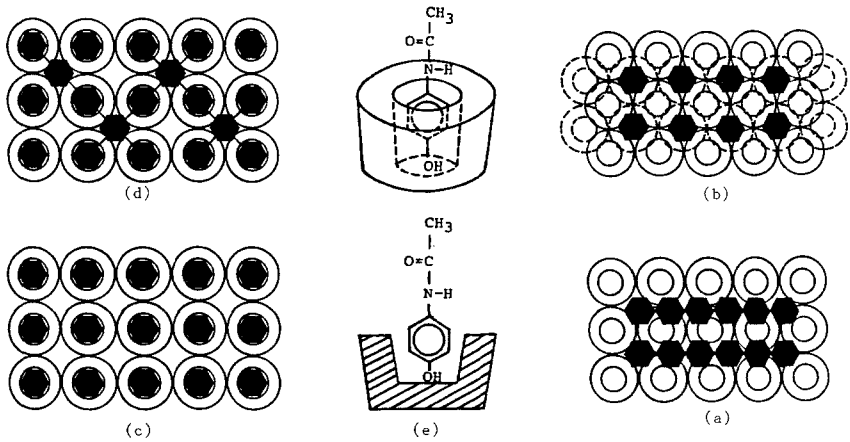

Fig. 5. Postulated scheme of the interaction between acetaminophen and cyclodextrin system by grinding and heating processes. Key: (a) Acetaminophen mixed with α- or β-CD; (b) The ground mixture of acetaminophen and α-CD; (c) Inclusion complex formation between acetaminophen and β-CD; (d) Interaction of excess acetaminophen with the acetaminophen–β-CD complex.

the cavity of β-CD after 24-h grinding of the physical mixture of acetaminophen and β-CD to form an inclusion complex (Figures 3 and 5.c). When the excess of acetaminophen was added to the inclusion complexes or the excluded acetaminophen in the initial grinding process in some of the inclusion complexes, acetaminophen might interact with the inclusion complexes to cause an exothermic peak (160°C) before the melting point of acetaminophen in DSC thermograms (Figure 5.d). The C—O stretch of the phenolic group of acetaminophen shifted from 1226 cm^{-1} to 1245 cm^{-1}, suggesting the dissociation of the intermolecular hydrogen bonds of acetaminophen through inclusion complexation. The C=C stretch of the benzene ring of acetaminophen at 1612 cm^{-1} disappeared when the acetaminophen–β-CD inclusion complex formed. This obviously indicates that the phenolic group was predominantly included into the cavity of β-CD, leading to the disappearance of the C=C band of the benzene ring of acetaminophen (Figure 5.e). The intermolecular hydrogen bonding occurred again between the amido group of acetaminophen and the hydroxyl group of cyclodextrin because the complex formation might result in the shifting of the amido group of acetaminophen from 1568 cm^{-1} to 1555 cm^{-1} [16, 17]. Thus the inclusion behavior might be postulated by the scheme of Figure 5.

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