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Dehydration Processes of Lisinopril investigated by *Ab Initio* Crystal Structure Analysis from Powder X-ray Diffraction Data

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Introduction

A widely used anti-hypertension drug, lisinopril is available as a dihydrate form by recrystallization. Interestingly, the dihydrate form undergoes two step dehydrations via monohydrate form. The dehydration processes are very important in the pharmaceutical field because solid-state transformation may occur during manufacturing and storage step, and it affects to the pharmaceutical properties (e.g. solubility, dissolution rate and bioavailability). Although crystal structures of these hydrates or anhydrous form are necessary for understanding the transformation mechanisms, and properties of each forms, there is no report on their crystal structures because of difficulty to obtain a single crystal for these forms mainly caused by disintegration of single crystal form due to the dehydration. In the present work, crystal structures of lisinopril dihydrate, monohydrate and anhydrous forms are determined from powder X-ray diffraction data and the mechanistic aspects of two step dehydration processes has been established from the crystal structural changes.

Results and Discussions

High resolution synchrotron X-ray powder diffraction data were recorded for lisinopril dihydrate form at ambient condition on beamline 4B2 (Multiple Detector System) at Photon Factory with wavelength 1.20853(2)Å. The sample was mounted on flat sample holder and diffraction measurement was carried out using reflection mode with rotation of sample holder. Data collection time was ca. 12 hours. From high resolution diffraction data, the crystal structures of lisinopril dihydrate, monohydrate and anhydrous forms were successfully determined using the programs DICVOL, DASH and GSAS.

Figure 1(a) shows the crystal structure of dihydrate form viewed along *b* axis. The two independent water molecules are arranged along *b* axis and they form two types of water channel as shown in dashed circle(central channel) and solid circle(side channel) in Figure 1(a). In monohydrate structure (Figure 1(b)), it is revealed that the structural change in the first dehydrateion from dihydrate is the loss of this central channel water only. And the central channel remains open. On the other hand, in the second dehydration, the side channel water is also removed from monohydrate structure with closing motion of the side channel. The interesting point is twist motion of ethylphenyl group about 170° accompanying with the closing motion of the side channel. Because of the steric repulsion between lisinopril molecules which placed across the side channel, the side channel cannot close with retaining their molecular conformation. However twisting motion of ethylphenyl group enable the molecules approach each other and, as a result, the side channel can be close. The difference of two water channels can be explained from hydrogen bond condition of the two independent waters in dihydrate form. Although both the central and side channel waters have three hydrogen bonds, the central channel water has longer hydrogen bonds than the side channel water and it clearly suggests that the central channel water is weaker hydrogen bonded than the side channel water. Thus, it is natural that weaker hydrogen bonded water is dehydrated in first step.

In this study, the mechanistic aspects of the two step dehydration processes of lisinopril dihydrate form have been clearly revealed. The technique to solve the crystal structure from powder diffraction data is essential technique to reveal such dynamic behaviour in crystalline materials and the high resolution X-ray powder diffraction data is important for the analysis.

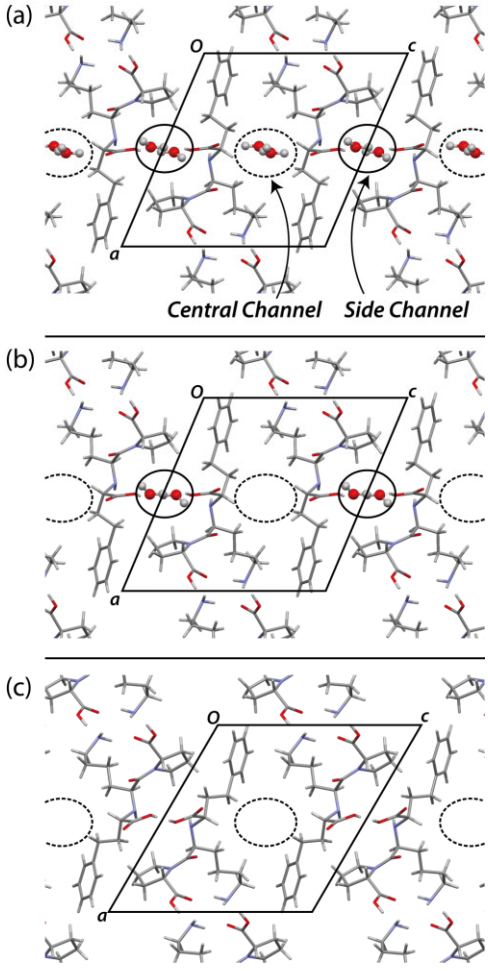

Figure 1 : Crystal structures of Lisinopril (a) dihydrate, (b) monohydrate and (c) anhydrous form, view along the *b* axis.

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