Ab Initio Structure Determination of Medium-Sized Pharmaceuticals

Crystal structure determination from powder diffraction (SDPD) has attracted wide interest because of its huge potential to accelerate the design, synthesis, and characterization of materials. During the past decade, many SDPD studies have shown the methodology, software, and also the actual *ab initio* structural determinations. Presently, the structure of a small molecule with less than 30 atoms and approximately 10 degrees of freedom can be routinely solved from powder diffraction data using several software on a single personal computer. The SDPD for large systems such as medium-sized pharmaceuticals with more than 20 degrees of freedom and 100 atoms is still a very difficult task. High resolution powder diffraction data and additional analytical techniques have been normally required for SDPD in these cases. In the present study, we have performed SDPD for a medium-sized pharmaceutical, prednisolone succinate as shown in Fig. 1, using high-resolution synchrotron X-ray powder diffraction data at SPring-8.

The *d*-spacing range of the data collected at beamline **BL02B2** was $d > 1.0$ Å, which is much wider than that of normal laboratory data, $d > 2.0$-1.4 Å. The structure determination has been carried out using the original Genetic Algorithm (GA) system [1]. There were seven torsion angles in the succinate part of the molecule. The number of degrees of freedom in one molecule is thirteen, namely, three positional parameters, three orientation parameters, and seven torsion angles. The number of molecules in a crystallographic asymmetric unit was evaluated from the unit cell volume as two. Therefore, the total number of degrees of freedom became twenty-five, because one positional parameter must be fixed in the case of non-centro-symmetric space group. Rietveld refinement was carried out using the structure model determined using the GA. The reliability factors, R_{wp} and R_I, of the final structure analysis by the Rietveld refinement reach less than 3% and 5%, respectively. The crystal structure of prednisolone succinate is shown in Fig. 2. It clearly shows that the molecules are located parallel to the 101 direction. The reasonable structure including hydrogen atoms of medium-sized pharmaceutical with no checkCIF alert relating to the fundamental structure, such as interatomic distances and bond angles, has been determined from powder diffraction data in the present study.

In the final stage of the analysis, data covered with a wide *d*-spacing range, $d \geq 1.0$ Å, was required to reach a correct solution. It is normally very difficult to measure the powder diffraction peaks of medium-sized pharmaceuticals in the $d \approx 1.0$ Å resolution

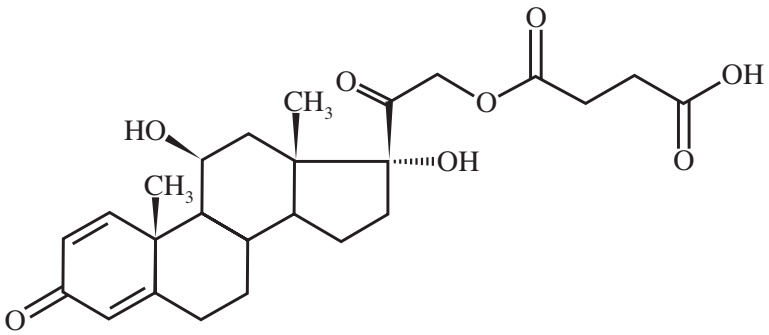

Fig. 1. Structural formula of prednisolone succinate.

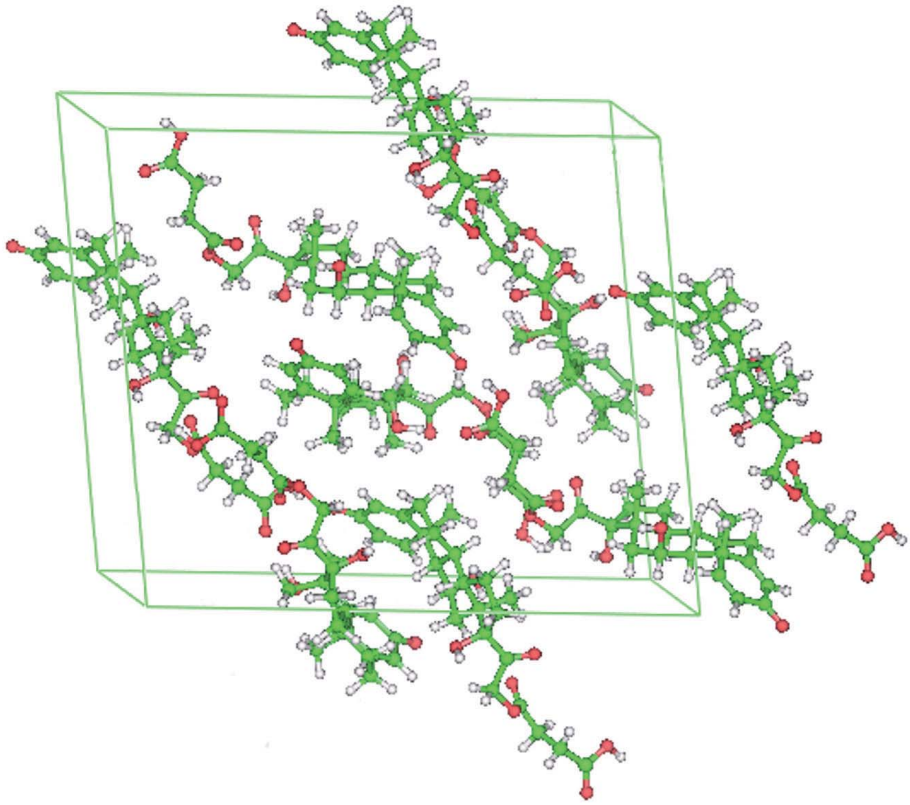

Fig. 2. Crystal structure of prednisolone succinate from powder diffraction data obtained at SPring-8.

range, because the peak intensity of Bragg reflection in this range is intrinsically weak with less than 1% of the maximum intensity. Furthermore, considerable peak overlaps and peak broadenings prevent the recognition of the higher angle peaks. In the powder diffraction experiment at SPring-8, an X-ray beam with the high-energy resolution, $\Delta E/E \approx 10^{-4}$, and sufficiently high intensity is available. Powder data at SPring-8 is the most appropriate for SDPD, which enables us to expand the limit of SDPD.

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References

[1] *E. Nishibori, T. Ogura, S. Aoyagi and M. Sakata: J. Appl. Cryst.* ***41*** *(2008) 292.*