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著者(和文)	溝口亮
Author(English)	Ryo Mizoguchi
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論 文 要 旨

THESIS SUMMARY

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学生氏名： Student's Name	溝口亮		指導教員（主）： Academic Supervisor(main)	植草秀裕	
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要旨（英文 800 語程度）
Thesis Summary (approx.800 English Words)

The importance of physicochemical properties for drug discovery is well known, and a lot of studies have been conducted in early drug discovery stage. Since the solid state of API represents the physicochemical properties, the changing of the solid state should be carefully handled despite the changing is expected or unexpected. In case of hydrates, the unexpected form change in the manufacture process and under the storage condition was sometimes observed, so the elucidation of dehydration mechanism using the crystal structure is carried out for understanding the solid state of hydrates. In this research, precise elucidation the dehydration mechanism was conducted. The purpose is to prove that the combination of crystal structure analysis and kinetic analysis is effective for understanding the dehydration mechanism by using ondansetron and ozagrel as model compounds.

In chapter 2, ondansetron hydrochloride dihydrate was selected as one of the model compounds for elucidating the dehydration mechanism and evaluating the relationship of between the crystal structure and physicochemical properties. Ondansetron hydcochloride dihydrate transformed into an anhydrate under heating condition. Interestingly, that dihydrate transformed into a hemihydrate under heating conditions as an intermediate before the transformation into an anhydrate. Both the hemihydrate and the anhydrate were unstable at room environment and these forms immediately went back to the initial dihydrate. Crystal structure analysis for two unstable forms succeeded with powder X-ray patterns. Changing of the hydrogen bonds network was observed through these transformations although the overall structures were similar. The void structure was observed in an anhydrate, so this void structure was considered to be accountable for the root cause of the instability of an anhydrate at room conditions.

In chapter 3, kinetic analysis was carried out about the dehydration reactions of ondansetron HCl dihydrate and consideration of mechanism was discussed. Two kinds of analyses which were the isothermal method and the isoreaction ratio method (Ozawa method) were conducted for the dehydration reaction. Both methods estimated the activation energy and these values for the first dehydration reaction (Ea^{1st}) were almost equivalent. Ea values of first dehydration and second dehydration reaction were almost the same, and Ea^{1st} was slightly larger than Ea^{2nd}, 114 ± 7 and 104 ± 6 kJ/mol, respectively. The Ea^{rev} was calculated as 61 ± 7 kJ/mol and was approximately half of the value of forward reaction. This result supported that a dihydrate is more stable than a hemihydrate at a normal environment.

In chapter 4, the mechanism of dehydration of ozagrel hydrochloride monohydrate was elucidated. Crystal structure analysis of that monohydrate using powder X-ray diffraction was succeeded. The monohydrate transformed into an anhydrate A, and an anhydrate A transformed into an anhydrate B. Transformation reaction into an anhydrate A was evaluated with kinetic analysis, the mechanism of dehydration reaction depended on the temperature. At the lower temperature, the dehydration was dominant. On the other hands, at the higher temperature, the crystal form changing was dominant. These mechanism has not been supported by the crystal structure because crystal structure of an anhydrate A has not been obtained, yet. Further evaluation will be needed.

Salt exchange is useful and powerful method for controlling the physicochemical properties of APIs. In chapter 5, it was examined that salt exchange affected the forming the hydrate form and physicochemical properties such as hygroscopicity, dehydration mechanism, the activation energy. Ondansetron HCl was used as a model compound. Ondansetron HCl, HBr and HI salts could be synthesized and formed the dihydrates. The relationship between ondansetron HCl and HBr dihydrate was isomorphous, but ondansetron HI dihydrate showed the different structure. Ondansetron HBr did not show the two-stage dehydration despite the crystal structure of the dihydrate was isomorphic. Ondansetron HI salt

showed the stability against humidity, therefore, the dihydrate was considered to be more stable than those of HCl and HBr salt. Halogen anions would be involved in forming hydrogen bonds with water molecules because of their hydrophilic properties. Exchange of halogen anion contributed to and was effective for the improvement of hygroscopicity. The anhydrates which were stable at room environment were observed on both ondansetron HBr and HI salt although an anhydrate of HCl salt was unstable. Crystal structures of both anhydrates were quite different from that of an anhydrate of HCl salt which was unstable at room environment and was difficult to isolate. These results also indicated that exchange of halogen anion contributed to the changing of the crystal structure.

In summary, I proved that the combined usage of kinetic analysis and crystal structure is powerful tool for the mechanistic consideration of dehydration using ondansetron and ozagrel as model compounds. Deep understanding for the dehydration mechanism is expected to adapt the rational design of salt optimization and accelerate drug discovery. I believe that deep understanding for the solid state and transition mechanism will help us increasing the probability of drug discovery.