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Structural Investigations of Physicochemical Properties Alteration in Multicomponent Pharmaceutical Crystals

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(Introduction)

One of the manifolds of solid active pharmaceutical ingredients (APIs) is multicomponent crystals in which API crystalline molecules incorporates other(s) molecule, such as solvents and coformer molecules into the crystal lattice. Multicomponent crystals have gained an increasing amount of the attention over the last few decades due to its high propensity to be utilized as functional materials which has better physicochemical properties than that of parent drugs. Multicomponent crystals in pharmaceutical field are generally utilized to alter solubility, dissolution rate, stability, hygroscopicity, tabletability, etc. Therefore, many APIs which have unfavorable physicochemical properties are designed and converted into multicomponent crystals.

However, no matter that some drugs have been ideally marketed in the specific multicomponent crystal form and possess a requirement as a drugs, there is no guarantee that these crystal forms do not transform into another form which have different and/or unfavorable physicochemical properties during the manufacturing processes, *e.g.* heating, grinding and solubilization. As these drugs have been widely marketed, we consider these multicomponent crystals to have unsolved pre-formulation problem. Up to this points, there are two main concepts related to multicomponent crystals: multicomponent crystal as solution to overcome unfavorable physicochemical properties, and unsolved pre-formulation problem in multicomponent crystal.

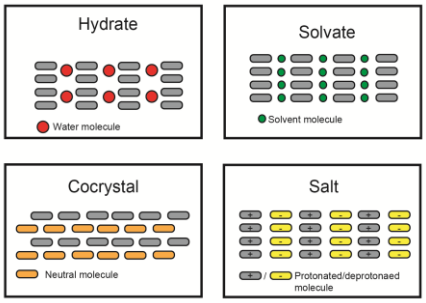

Figure 1. The representative illustrations of multicomponent crystals.

Certainly, the most important aspect to understand the nature of multicomponent crystals and its physicochemical properties is the range of analytical method used to perform structural investigations, namely the structural science. The importance of this area has been recognized from both scientific and regulatory approaches. Crystallography, as a part to determine the arrangement of the atoms in the crystalline solids and the frontiers in structural investigations, is important in understanding the nature of materials, especially multicomponent crystals of APIs. Such a significance was led by the information of how the molecules fit together in the tiniest level of detail and show different manner.

Taking a correlation to two main above mentioned concepts, the structural sciences can be utilized to explain the changes of physicochemical properties both in designing and transformation in multicomponent crystals. However, it is very conceivable that the structural investigations of the physicochemical alterations in multicomponent crystals are rarely investigated and provide a promiscuous area to explore. Genuinely, there are a lot of a high demand to conduct a structural investigation in multicomponent crystal in pharmaceutical field. Therefore, we aimed to take a part in the structural investigation involving multicomponent crystal. In this dissertation, the structural investigations in multicomponent crystal cases such as drug-drug multicomponent crystal, isostructural multicomponent crystal and transformation in hydrate multicomponent crystal were carried out and a brief detail are described as follows.

(1) Drug-Drug Multicomponent Crystals as an Effective Technique to Overcome Weaknesses in Parent Drug

The preparation of multicomponent crystals is a well-established technique for forming new phase(s) and altering the physicochemical properties of drug materials. Interestingly, recent studies have investigated the potential of multicomponent crystals containing combinations of drugs. This family of crystals, in addition to providing technological advantages, also offers improved pharmacological benefits and patient compliance. Screening of marketed combination drug formulations yielded the combination of the non-insulin-dependent diabetes mellitus (NIDDM) drugs metformin (MET) and gliclazide (GLI). MET and GLI are effective in the treatment of NIDDM in both single and combined therapies. However, the combination of MET and GLI provides better results regarding glycemic control and the lipid index, which are often major problems during the treatment of diabetes. Unfortunately, both MET and GLI exhibit unfavorable physicochemical properties. The base form of MET is a hygroscopic powder and GLI has poor solubility.

In this part, we prepared novel multidrug crystals consisting antidiabetic drugs of MET and GLI. We also performed structural analyses of these crystals. Additionally, we describe molecular insights derived from crystal

structure into changes in the physicochemical properties of MET and GLI.

Single crystal X-ray structure analysis revealed that this multicomponent crystal is salt-type multicomponent crystal. Multicomponent crystals of MET-GLI were present as a non-hygroscopic and more soluble which is related with the existence of hydrophilic channel structure (Figure 2). The reduced hygroscopicity of the multicomponent crystals as compared with MET alone could be explained by the crystal structure. MET was located in the channel formed by GLI molecules; thus, the GLI molecules, which were less hydrophilic, protected MET and formed hydrogen bonds to close potential hydrogen bonding sites. Thus, it is reasonable to conclude that the multicomponent crystals of MET-GLI showed lower hygroscopicity than MET. Interestingly, the multicomponent crystals showed an improvement in solubility and dissolution rate compared to GLI. These improvements were related with the existence of channel structures that could play an important role in improving solubility owing to the molecular characteristics of the surface. In this case, we were also able to establish the first method to observe directly the existence of the channel structure in the crystal during solubilization.

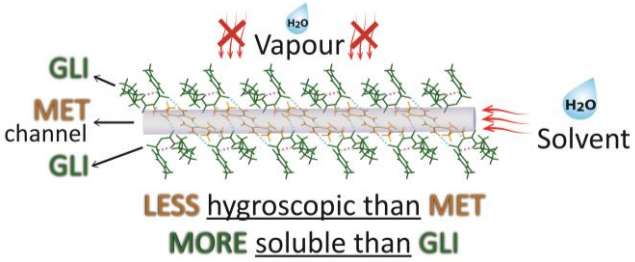

Figure 2. The illustration of physicochemical alterations in MET-GLI drug-drug multicomponent crystals.

(2) Isostructural Multicomponent Gliclazide Crystals with Improved Solubility

An isostructural multicomponent crystal is a rarely explored class of materials in pharmaceutical solids, possibly because they are rare. In the pharmaceutical field, isostructurality means producing more than one molecular complex using a common structural blueprint. In this case, although molecular arrangements are similar, the physicochemical properties can be modified owing to the differences among coformer molecules and the small packing difference. A pharmaceutical multicomponent crystal, especially a salt, can be synthesized by systematic crystallization screening, in which a common API component is combined with various coformer components having similar molecular structures. In this part, we aimed to prepare isostructural of antidiabetic gliclazide (GLI) with the aminopyridine derivatives (4-aminopyridine (4AP), and 3,4-diaminopyridine (34AP)) and compare the physicochemical properties of an isostructural salt.

Crystal structure analysis reveals that these crystals were categorized as salts because they showed proton transfer. The crystal structures revealed a robust one-dimensional hydrogen bond chain of GLI by the crystallographic 2_1 screw axis along the *b*-axis and the interaction between these two chains, which includes the coformer, to construct a dimeric structure were crucial to the isostructurality. In this study, we found that isostructural salts show enhanced dissolution rate relative to their raw material, although the dissolution profile between the salts is slightly different. In this case, the dissolution rate of GLI-4AP is faster than that of GLI-34AP. Packing efficiency and energetical aspects were used to rationalize the differences in the dissolution profiles. The lower packing efficiency and lower lattice energy which was represented by melting point difference in GLI-4AP turn leads to faster dissolution.

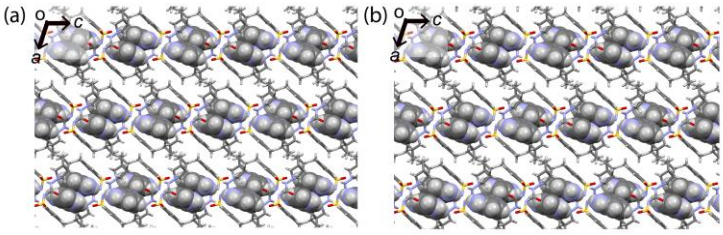

Figure 3. Packing view of (a) GLI-4AP, and (b) GLI-34AP along *b*-axis shows the isostructurality between these two crystals.

(3) Understanding Physicochemical Properties Differences Induced by Solid-state Dehydration and Polymorphic Transformation of Ciprofloxacin Hydrochloride

Understanding the diversity of multicomponent crystal which incorporate solvent molecules into the crystal structure as well as its structural aspects is becoming intriguing phenomena. This class of solids is further classified into hydrates and solvates. Hydrates are crystalline solid adducts containing water molecule and known as the largest class in this group. By exposing the hydrate crystals to sufficient energetical barrier, phase transformation is predicted to exist resulting dehydrated crystal. In some cases, further energetical exposure to dehydrated crystal giving rise to a new polymorphic form. Knowing the crystal structure of hydrate and corresponding water-free form(s) are essential to understand solid-state dehydration mechanism which is often predicted from the structural correlation among the phases. In addition, the understanding of physicochemical properties can also be derived from structural differences among the phases.

In this part, our goal is achieving a clear picture from molecular insight to get better understanding between physicochemical properties and solid-state phenomena such as dehydration and polymorphic transformation in hydrated multicomponent crystal. Therefore, we selected ciprofloxacin hydrochloride (CIP) which is known as an important antibiotic for medical treatment to achieve previously mentioned goal.

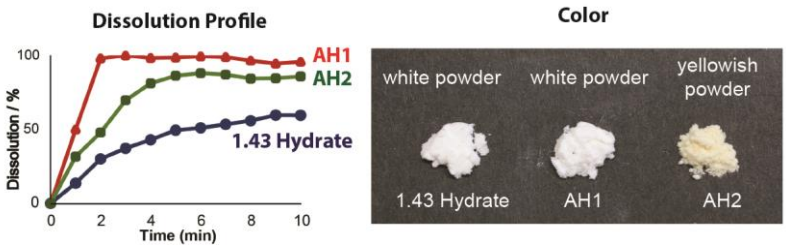

Figure 4. The Illustration of physicochemical property differences among CIP phases.

From thermal analysis, CIP can exist as sesqui-hydrate form which transform to anhydrous form I at 140 °C and anhydrous form II at 172 °C. The structure of sesqui-hydrate and anhydrous form II were obtained from single crystal X-ray structure analysis. However, anhydrous form I could not be obtained as single crystal, so the structure was solved by ab initio powder structure analysis using synchrotron technique. The structure of anhydrous I partly related to hydrate in the packing, *i.e.*, both show one-dimensional (1-D) chain and two-dimensional sheet structure. However, only 1-D chain was retained in anhydrous II. All of the anhydrous forms showed faster and higher dissolution in aqueous medium compared to hydrate. In addition, anhydrous I showed the highest and fastest dissolution rate which indicate anhydrous I as metastable crystal. These anhydrous crystals exhibit different stability during storage in which anhydrous I again showed its less stability. Interestingly, the color of powder of hydrate and anhydrous I was white, meanwhile, anhydrous II appeared as yellowish powder. The color changes may be explained from their molecular conformation which the total nitrogen pyramidal angle of piperazine of hydrate, anhydrous I, and II was 343.00°, 343.05° and 348.83°, respectively. Thus, the significant change in anhydrous II might affect the conjugation in aromatic group and result the color change.

(List of Publications)

1. O. D. Putra, T. Yoshida, D. Umeda, M. Gunji, H. Uekusa, E. Yonemochi. Crystallographic Analysis of Phase Dissociation Related to Anomalous Solubility of Irsogladine Maleate. *Cryst. Growth Des.* 2016, 16, 12, 6714-6718.
2. O. D. Putra, E. Yonemochi, H. Uekusa. Isostructural Multicomponent Gliclazide Crystals with Improved Solubility. *Cryst. Growth Des.* 2016, 16, 11, 6568-6573.
3. O. D. Putra, T. Yoshida, D. Umeda, K. Higashi, H. Uekusa, E. Yonemochi. Crystal Structure Determination of Dimenhydrinate after more than Sixty Years: Solving Salt–Co-crystal Ambiguity via Solid-state Characterizations and Solubility Study. *Cryst. Growth Des.* 2016, 16, 9, 5223-5229.
4. O. D. Putra, T. Furuishi, E. Yonemochi, K. Terada, H. Uekusa. Drug–Drug Multicomponent Crystals as an Effective Technique to Overcome Weaknesses in Parent Drugs. *Cryst. Growth Des.* 2016, 16, 7, 3577-3581.
5. O. D. Putra, D. Umeda, Y. P. Nugraha, T. Furuishi, H. Nagase, K. Fukuzawa, H. Uekusa, E. Yonemochi. Solubility Improvement of Epalerstat by Layered Structure Formation via Cocrystallization. Submitted to *Cryst. Eng. Comm.*
6. O. D. Putra, P. A. Williams, E. Yonemochi, H. Uekusa, K. D. M. Harris. Understanding Physicochemical Differences Induced by Solid-state Dehydratyion and Polymorphic Transformation of Ciprofloxacin Hydrochloride. In preparation to be submitted to *Cryst. Growth Des.*