1. Introduction

Differences in drug crystals in pre-formulation study including polymorphism, crystal morphology, or habit significantly affect not only manufacturing processes but also pharmaceutical properties of final products, such as dissolution, physical and chemical stabilities, powder flow, bulk handling, ease of compression, and wettability. For the development of drugs with superior pharmaceutical properties, it is important to select an appropriate drug polymorph and to control their transformation and morphology. In addition, recent efforts in solid pharmaceutics have refocused on the development of drugs with superior pharmaceutical properties, including polymorphism, crystal morphology, or habit selection based on the host–guest interaction. For solid formulation, stable amorphous drug/CDs complex under humid conditions was prepared using two different CDs. An overview of some recent progress in the use of CDs in crystal engineering and in amorphous formulation is described in this review.

Key words cyclodextrin (CD); polymorph; crystal habit; amorphous; solution-mediated transition; solid state

2. Modification of Solution-Mediated Polymorphic Transition by CDs

Solution-mediated polymorphic transition is controlled by differences in solubility of metastable and stable crystals, according to “Ostwald's Rule of Stages.” The crystal nuclei of a metastable form initially appear in solution; thus a metastable form with higher solubility precipitates at first from solution. However, once the nuclei of stable crystals are formed in solution, the transformation into a stable form with a lower solubility proceeds involving the dissolution of the metastable crystals. Therefore we usually obtain the most stable polymorph at experimental conditions and it is difficult to isolate the intermediate metastable crystals appearing in earlier steps of crystallization. Recently, advanced approaches that selectively modify the crystallization behavior of drugs by adding tailor-made additives such as compounds having similar structure, surfactants, and polymers have been reported. However, such tailor-made additives are likely to incorporate into the crystal lattice of drugs due to their structural similarities, which is particularly caused when...
using low-molecular weight additives. Surfactants and polymers have been studied to modify drug crystallization; however, they are sometimes used in higher concentrations, which cause an undesirable increase in the viscosity of the crystallization media leading to difficulties in the filtration step.

Complexation with CDs generally enhances the solubility of drugs in water, slows down the diffusion rate of drug molecules due to an increase in molecular mass, and inhibits association of drugs due to a masking of the site that is associated with intermolecular interaction. Below, we describe the use of CDs as tailor-made additives that can modify solution-mediated polymorphic transition of drugs during crystallization.

2.1. Selective Crystallization of Metastable Polymorph of Drugs in CDs Solution

The effects of CDs on the crystallization and polymorphic transition of the oral hypoglycemic agents tolbutamide\(^{29,30}\) and chlorpropamide\(^{31}\) were studied in aqueous solution. Crystallization of the drug was conducted in pH 8.0 sodium phosphate buffer solution in the absence and presence of various CDs, then the solution was titrated with aqueous 0.5M HCl solution and placed at 4°C to slowly obtain crystals. Interestingly, metastable Form IV crystals were obtained exclusively from solution containing 2,6-di-O-methyl-\(\beta\)-CD (DM-\(\beta\)-CD) in 60–70% yield of the initially added amounts, whereas tolbutamide crystallized into stable Form I in the absence of CDs as well as in solution containing other hydrophilic CD derivatives (Fig. 1). Monitoring the crystallization behavior in solution (from 1 h to 1 week), Form IV was exclusively crystallized and presented showing no transformation to stable form in DM-\(\beta\)-CD solution for more than 1 week. In the absence of CD, tolbutamide crystallized into metastable Form IV at early stages of crystallization; however, rapid transformation to stable Form I occurred within 20 h. The interaction between tolbutamide and DM-\(\beta\)-CD was stronger than that of other CDs. DM-\(\beta\)-CD had not co-crystallized within the drug, which was confirmed by elementary analysis; thus it was concluded that DM-\(\beta\)-CD suppressed polymorphic transition of the drug to the stable form during crystallization by the host–guest interaction. As a result, metastable form selectively appeared in solution. A possible mechanism for the selective crystallization of tolbutamide metastable crystals in DM-\(\beta\)-CD solutions is shown in Fig. 2. In the absence of CDs, rapid nucleation of metastable Form IV crystals occurred at first from the solution and the metastable Form IV then precipitated according to Ostwald’s Rule of Stages. However, once the stable crystal nuclei are formed in solution, the solution becomes supersaturated with respect to stable Form I crystals, and therefore Form I nuclei rapidly grow involving the dissolution of Form IV crystals. In the case of DM-\(\beta\)-CD solution, the host–guest interaction occurred between the drug and CD in solution, and this equilibrium may compete with the nucleation and the following crystal growth to the stable Form I crystals. The inclusion equilibrium that was newly introduced in the system functioned as a buffer, and as a result, the metastable form might have selectively precipitated in the solution.\(^{29,30}\)

Fig. 1. Photographs and Powder X-Ray Diffraction Patterns of Form I and Form IV Crystals of Tolbutamide Precipitated in the Absence and Presence of DM-\(\beta\)-CD

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Fig. 2. Mechanism for Inhibition of Solution-Mediated Polymorphic Transition of Tolbutamide Form IV to Form I by DM-\(\beta\)-CD

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In the case of chlorpropamide, selective crystallization of metastable polymorphs occurred depending on 2-hydroxybutyl-β-CD (HB-β-CD) concentrations, as shown in Fig. 3. Chlorpropamide crystallized into stable Form A crystal in aqueous solution without CDs. On the other hand, Form II crystals precipitated in the solution with 5 mM HB-β-CD (with high CD concentration), whereas Form III crystals were obtained in 0.5 mM HB-β-CD solution (with low CD concentration). Form II crystals were also obtained at an intermediate CD concentration (2 mM), but the crystal transformed to Form III crystal over time. In other words, HB-β-CD suppressed each step of solution-mediated polymorphic transition, which proceeded according to “Ostwald’s Rule of Stages” by simply changing the CD concentration. DM-β-CD and HB-β-CD, which generally show high stability constant with drugs, may be useful for stabilization and isolation of metastable forms that appeared at an early stage of crystallization.

2.2. Precipitation of Amorphous Indomethacin in DM-β-CD Solution Surprisingly, we succeeded to obtain amorphous form of indomethacin from solutions. The experiments were conducted according to the same procedure described above, i.e., indomethacin (2.0 mM) was dissolved in pH 8.0 sodium phosphate buffer containing DM-β-CD at room temperature, then the solution was slowly titrated with aqueous 0.5 M HCl solution to approximately pH 5.0 where the drug did not yet precipitate. The solution was paper-filtered and the filtrate placed at 4°C. Indomethacin precipitated in an amorphous form in the presence of DM-β-CD and the amorphous was stable in DM-β-CD solution for approximately 5 d; subsequently, metastable Form V crystals appeared in the solution. The mechanism responsible for the precipitation of amorphous form was proposed that DM-β-CD inhibited solution-mediated crystallization occurring at the initial step of “Ostwald’s Rule of Stages.” The physical properties of the amorphous form obtained from DM-β-CD solution were different from the amorphous prepared by other preparation methods such as melt-quenching and grinding method; especially, the amorphous form obtained from DM-β-CD solution showed a higher dissolution rate. We believe that the study represents the first example of preparation of amorphous drug by recrystallization procedure. The procedure for the control of polymorphic transition based on the host-guest interaction of CDs would provide an opportunity to isolate labile interme-

diate metastable form including amorphous form and may be useful for understanding the drug polymorphism occurring in pre-formulation study.

3. Crystallization of a New Polymorph of Acetohexamide in HB-β-CD Solution

In previous sections, we described that HB-β-CD and DM-β-CD inhibited solution-mediated polymorphic transitions of tolbutamide, chlorpropamide, and indomethacin; i.e., these CDs inhibited the polymorphic transition from the metastable crystal to the stable form during crystallization from aqueous solution, and as a result, the metastable polymorphs selectively precipitated in the CDs solution. In this section we describe the changing of the crystallization pathway of a compound by HB-β-CD. Acetohexamide was used as a model drug and recrystallized in the presence or absence of HB-β-CD in the same manner described above. Form III polymorph of acetohexamide obtained in the absence of HB-β-CD. On the other hand, acetohexamide crystallized exclusively to Form VI, a new polymorph, in 5.0 mM HB-β-CD solution. In the presence of intermediate HB-β-CD concentrations (0.5–3.0 mM), a mixture of Forms III and VI crystals was precipitated in the
solution. In the case of acetohexamide, we did not elucidate the consecutive transition process (acetohexamide solution → Form VI → Form III) throughout the study. Forms III and VI crystals were simultaneously obtained in the presence of low concentrations (0.5 mM) of HB-β-CD. Polymorphic transition from Form VI to Form III was not observed even in the presence of nuclei of Form III in the solution; thus we expected that crystallization in the presence of CDs proceeded with a different mechanism from solution-mediated transition in the case of acetohexamide. HB-β-CD probably altered the route of crystallization of acetohexamide (Fig. 4). The crystallization pathway to Form III is dominant over the pathway to other forms in the absence of HB-β-CD. Nucleation of crystals was probably affected by adding HB-β-CD in the solution, leading to a crystallization pathway to other polymorph, resulting in a new polymorph was obtained. Form VI, a new polymorph, rapidly dissolved in aqueous media including the JP first and second fluids, and showed a high solubility compared with...
other polymorphs (Forms I, III, IV, and V). The high solubility of Form VI was maintained in dissolution media for 7 d because the polymorphic transition of Form VI was not observed at these conditions. Such superior dissolution property was reflected in the higher plasma concentration of the drug after oral administration to rats. The use of HB-β-CD in crystal engineering may provide an opportunity for the detection of new polymorphs with superior pharmaceutical properties that are undiscovered so far.

4. Cyclodextrin-Induced Change in Crystal Habit of Acetylsalicylic Acid in Aqueous Solution

This section refers to a modification of crystal growth of a drug by CDs. HB-β-CD and DM-β-CD were used as a growth inhibitor on the crystallization of acetylsalicylic acid (ASA). ASA appeared in hexagonal plate crystals in solution in the absence of CDs as shown in Fig. 5. In contrast, the morphology of crystals changed to needle by the addition of HB- or DM-β-CD to the solution. Powder X-ray diffraction studies confirmed that all crystals precipitated in these solutions were stable Form I crystals. However, the peak intensity at 2θ = 15.6° of ASA crystals that was precipitated in the HB- or DM-β-CD solution significantly increased. These collective results suggest that HB- and DM-β-CD modified the crystal habit of ASA. We revealed that HB- and DM-β-CD markedly suppressed the crystal growth toward the c-axis direction. In the c-axis direction, the phenyl and methyl groups of ASA face each other and interact weakly through van der Waals force. HB- and DM-β-CD preferably included the phenyl group of ASA in its cavity in aqueous solution and in solid state. We thus concluded that these CDs inhibit the approach of ASA molecules to the c-axis direction by the inclusion complex formation with ASA molecules that is presented in solution and/or adsorption on the surface of c-axis direction, as shown in Fig. 6. As a result of the growth inhibition toward the c-axis direction, the ASA crystals preferably elongated along the b-axis because the intermolecular hydrogen-bonding networks run roughly along the b-axis, whereby the needle crystals precipitated in these CDs solutions. The needle crystals showed good dissolution property compared with hexagonal plate crystals because of differences in the wettability of the largest facets appearing on the crystals. CDs suppress the approach of drug molecules onto specific crystal surfaces by stereospecifically containing some parts of molecules within the cavity; thus they can function as tailor-made additives that are useful in modifying the crystal habit of drugs.

5. Formation of Stable Amorphous Limaprost/α-/β-CD Ternary Inclusion Complex in Solid State

Complexation with amorphous CDs such as 2-hydroxypropyl-β-CD (HP-β-CD) which is widely used in cosmetics and medicines converts crystalline drugs into the amorphous state. Crystallization behavior of drugs from HP-β-CD complexes under accelerated storage conditions was different from those in solid dispersion prepared with polyvinylpyrrolidone. For example, these drugs crystallized to metastable form in CD matrix, whereas crystallized to stable form in the formulation of polyvinylpyrrolidone solid dispersion. Recently, we found that the combination of two different CDs dramatically stabilized amorphous state of drug under humid conditions. Amorphous CD complex was prepared by freeze-drying the solution containing limaprost (a prostaglandin E1 derivative), α-CD, and β-CD. The resulting amorphous complex was stable under 30°C/75% relative humidity (RH) over 4 weeks and no crystallization to the parent drug occurred from the complex. The high physical stability was reflected in the chemical stability of limaprost; thus the degradation level was only 2.2% after storage under humid conditions for 4 weeks. The mechanism responsible for the high physical and chemical stabilities was concluded due to the formation of stable ternary inclusion complex with the drug and both α- and β-CDs, in which α-CD and β-CD predominantly included the alkyl ω-chain and the five-membered ring of limaprost, respectively (Fig. 7). Furthermore, crystallization of β-CD during storage was suppressed in the presence of α-CD, which also contributed to prevent dissociation of the drug from the ternary complex. Currently, the ternary inclusion complex is used in the formulation of Opalmon® tablet (ONO Pharmaceutical Co., Ltd.). The tablet shows high stability under humid conditions. The combination of two different CDs is useful for the preparation and formulation design of amorphous drugs, and detailed molecular states of drugs in amorphous complexes in the presence of two different CDs will be reported elsewhere.

6. Conclusion

This review describes the use of hydrophilic CDs in crystal modifications. By simply adding CDs in the recrystallization process, it may be possible to obtain metastable polymorph, undiscovered polymorph, and to change crystal morphology. The combination of two different CDs in solid formulation produces stable amorphous complexes that confer high stability and solubility to drugs. Modification of crystallization based on the host–guest interaction between drug and CD will be a useful strategy for not only the development of high-quality drugs but also our understanding of drug polymorphism occurring in pre-formulation study.

Conflict of Interest The authors declare no conflict of interest.

References

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