Review

Analysis of Molecular Interactions in Solid Dosage Forms; Challenge to Molecular Pharmaceutics

Keiji Yamamoto,* Waree Limwikrant, and Kunikazu Moribe

Graduate School of Pharmaceutical Sciences, Chiba University; 1–8–1 Inohana, Chuo-ku, Chiba 260–8675, Japan.

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The molecular states of active pharmaceutical ingredients (APIs) in pharmaceutical dosage forms strongly affect the properties and quality of a drug. Various important fundamental physicochemical studies were reviewed from the standpoint of molecular pharmaceutics. Mechanochemical effects were evaluated in mixtures of APIs and pharmaceutical additives. Amorphization, complex formation and nanoparticle formation are observed after grinding process depending on the combination of APIs and pharmaceutical additives. Sealed-heating method and mesoporous materials have been used to investigate drug molecular interactions in dosage forms. Molecular states have been investigated using powder X-ray diffraction, thermal analysis, IR, solid state fluorometry, and NMR.

Key words molecular pharmaceutics; interaction; mechanochemistry; porous material; amorphous; complex formation

1. Introduction

Chemistry is the science of the composition, structure, properties, and reactions of matter, especially of atomic and molecular systems. As the interface of active pharmaceutical ingredients (APIs) and living bodies, there is a discipline of pharmaceutics. Pharmaceutics can be defined as the overall science and technology based on chemistry, physics and biology. It involves from the discovery of new formulation, manufacturing the dosage form, administering the appropriate amount of drug into the body, and up to the pharmacokinetic analysis of those APIs.

Biology is developed and become the molecular biology, whereas thermodynamics was progressed to the molecular thermodynamics as well. These developments have enabled us to study the laws of the nature world. Furthermore, various disciplines such as molecular genetics, molecular diagnosis, molecular imaging, and molecular targeting that focus on molecules are also advancing rapidly.

Molecular Pharmaceutics, an international scientific journal, has been published since 2004 by the American Chemical Society and is now highly regarded among researchers. The editor of *Molecular Pharmaceutics*, Dr. G. L. Amidon, has stated that this journal will focus on the rapidly developing molecular and mechanistic fields impacting drug delivery and drug development.[1)]

In the field of formulation study and physical pharmacy, pioneering research that focused on molecules were performed by R. Hüttenrauch, Y. Nakai, and P. York. In the 1970s, Hüttenrauch performed a series of studies entitled "molecular galenic" that examined the importance of hydrogen bonding in the pharmaceutical formulation and mechanism of inactivation of pepsin by pressure.[2,3)] Nakai wrote a review of the molecular behavior of medicinals in pharmaceutical preparations in 1985,[4)] while York investigated polymorphism using inverse gas chromatography and *in situ* Fourier transform (FT)-Raman spectroscopy.[5,6)]

Recently, Aso and Yoshioka studied the molecular mobility of APIs in amorphous solid dispersions by using solid state NMR, FT-IR spectroscopy, and dielectric spectroscopy.[7—9)] Their results suggested that the physicochemical stability of a drug can be predicted by its the molecular mobility. Rodríguez-Hornedo and colleagues investigated pharmaceutical solids in terms of supramolecular chemistry and crystal engineering concepts. Her research focused on the understanding of molecular crystals, *e.g.* polymorphism,[10)] transformation pathways of hydrate cocrystals,[11)] crystallization pathways, and kinetics of cocrystals from an amorphous state.[12)]

During the process of manufacturing pharmaceutical dosage forms such as tablets, suspensions, and ointments, each processing unit can affect the properties of APIs and/or excipients, resulting in changes in crystalline form, crystallinity, hydration state and interactions between substances at the molecular level. All these changes strongly influence the stability, solubility, and finally performance of the dosage form. Therefore, we are continuing our research that focuses on the state of molecules in the formulation in order to obtain a better understanding of phenomena that have not yet been elucidated. Our research also aims to control the nature of a drug in the dosage forms. The following are examples of our research that explain the phenomena of molecular states of APIs found in solid dosage forms.

2. Improvement of Physicochemical Properties of Active Pharmaceutical Ingredients by Mechanochemical Processing

Mechanochemistry involves to the conversion of chemical energy into kinetic energy. It is also applied to the reverse process, *i.e.*, using mechanical energy from equipment to alter the structure and physicochemical properties of a phar-

* To whom correspondence should be addressed. e-mail: k-yamamoto@faculty.chiba-u.jp

maceutical solid form. We have studied mechanochemical reactions through a project on cogrinding crystalline cellulose with various APIs. Recent studies have examined inclusion complex formation of drugs with cyclodextrin and cholic acid and the mechanisms, as well as the formation of a novel cocrystal of erythritol and benzylbenzoate. Several characterization methods such as powder X-ray diffractometry (PXRD), thermal analysis and FT-IR spectroscopy have been used as conventional methods to characterize solid forms.[13)]

We have found that time-resolved fluorometry and solid-state ^{13}C-NMR are alternative techniques for clarifying the complexation phenomenon. Figure 1 shows the PXRD pattern of a γ-cyclodextrin (γ-CD) and 2,5-diphenyloxazole (PPO) system.[14)] When γ-CD was coground with PPO at a molar ratio of 1 : 2 using a vibration mill, crystalline diffraction peaks of PPO, indicated by an arrow, disappeared, suggesting the amorphization of PPO was induced by cogrinding. Changes in the solid-state fluorescence spectrum of a γ-CD/PPO system are shown in Fig. 2. In the fluorescence spectra of ground mixtures, the intensity of a peak derived from crystalline PPO reduced as a function of grinding time and a new

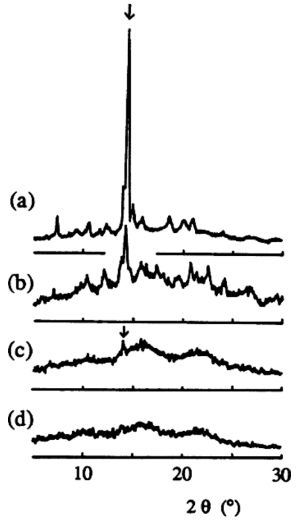

Fig. 1. Changes Observed in the Powder X-Ray Diffraction Pattern of the γ-CD/PPO (1 : 2) System by Grinding

(a) Intact, (b) 1 min of grinding, (c) 5 min of grinding, (d) 10 min of grinding.

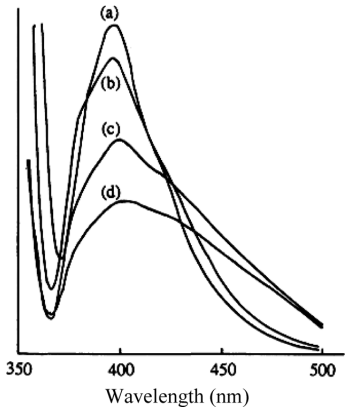

Fig. 2. Changes Observed in the Solid-State Fluorescence Spectrum of the γ-CD/PPO (1 : 2) System by Grinding (λ_{ex}=352 nm)

(a) Intact, (b) 1 min of grinding, (c) 5 min of grinding, (d) 10 min of grinding.

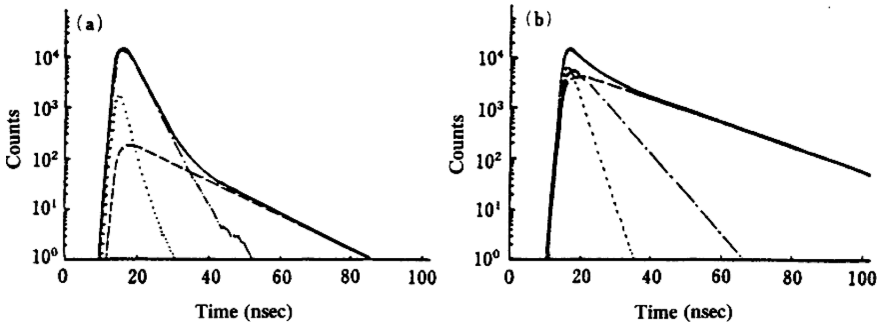

Fig. 3. Fluorescence Decay Curves of γ-CD/PPO (1 : 2) System (λ_{ex}=352 nm, λ_{obs}=420 nm)

(a) Physical mixture, (b) ground mixture (15 min of grinding). (——) Fluorescence decay curve, (····) component 1, (–·–) component 2, (– – –) component 3.

Keiji Yamamoto

Keiji Yamamoto (b.1948.12.17) is currently a vice-president of Chiba University and Professor in the Division of Pharmaceutical Technology at the Graduate School of Pharmaceutical Sciences, Chiba University, Japan. He graduated in 1971 from Chiba University with a Bachelor of Pharmacy and in 1973 with a Master of Pharmacy degree. In 1976, he obtained his Ph. D. from Hokkaido University and started his academic career as an assistant professor at Chiba University. In 1983, he spent a year as a research fellow at the College of Pharmacy, University of Utah, under the supervision of Prof. W. I. Higuchi. He was promoted to professor in 1991. He has received the APSTJ Takeru & Aya Higuchi Memorial Prize (1994), Senji Miyata Foundation Award (1995), Particulate Preparations and Designs Award from the Society of Powder Technology (1996), and the Pharmaceutical Society of Japan Award for divisional scientific contributions (2010). He has served as president of the Japan Society of Pharmaceutical Machinery and Engineering, and as the dean of the Graduate School of Pharmaceutical Sciences, Chiba University from 2002 to 2006. His research interest involves the analysis of solid state molecular interactions.

Table 1. Changes of Fluorescence Lifetime (τ) and Relative Quantum Yield (Q) of PPO by Cogrinding with γ-CD (Molar Ratio of γ-CD : PPO = 1 : 2, λ_{ex} = 352 nm, λ_{obs} = 420 nm)

	τ_1 (ns)	Q_1 (%)	τ_2 (ns)	Q_2 (%)	τ_3 (ns)	Q_3 (%)	$\chi^{2a)}$
Ground mixture							
0 min[b)]	0.856	1.8	2.79	90.3	16.1	7.9	1.52
1 min	1.11	8.4	4.16	71.2	13.5	20.4	1.18
2 min	0.913	7.8	4.08	64.7	15.7	27.5	0.940
5 min	0.873	9.0	4.16	41.3	17.5	49.7	1.46
10 min	0.909	9.6	4.29	33.3	17.8	57.1	1.06
15 min	0.849	10.0	4.08	33.2	17.7	56.8	1.10
PPO crystals	0.291	5.4	2.97	94.6			1.23
Aggregate	0.408	2.5	5.59	18.5	19.4	79.0	1.25

a) A parameter for judging the goodness of fit; an ideal fit will yield a χ^2 value of unity. *b*) Grinding time.

fluorescene peak that contributed to the formation of PPO excimer was observed. Figure 3 and Table 1 present the fluorescence decay curves and kinetic values of the γ-CD/PPO system. These results suggested that cogrinding with γ-CD caused drastic conversion of the molecular state of PPO monomer to excimer being included in γ-CD cavity.

3. Amorphization

Amorphization is one of the methods used to enhance the solubility of a poorly soluble drug. We have reported that the grinding of crystalline cefalexin, an antibiotic drug, can lead to an amorphous state.[15] The crystallinity of cefalexin decreases with an increase in grinding time, resulting in differences in solubility parameters and dissolution behavior. Not only grinding but also spray drying can be used for the preparation of an amorphous state of 4″-*O*-(4-methoxyphenyl) acetyltylosin. The glassy state could be altered by the spray drying conditions.[16] Variation in the dissolution of various amorphous samples prepared by changing the inlet temperature of the spray dryer was observed even though the PXRD patterns displayed almost identical halo pattern.

Mura *et al.* revealed that the dissolution property of glisentide, a poorly water soluble antidiabetic drug, was improved by grinding in a high energy micromill.[17] The grinding conditions, including vibrational frequency and grinding time, were the factors affecting the complete amorphization of drug. In addition, it was found that cogrinding with polyvinylpyrrolidone (PVP) at an appropriate drug : PVP ratio resulted in a higher degree of dissolution, indicating that the presence of polymer facilitated drug amorphization. Bates *et al.* analyzed the PXRD patterns of amorphous indomethacin and piroxicam using the pair distribution functions, Rietveld, total scattering, and an amorphous packing model to assign structural differences in pharmaceutical amorphous forms.[18] It was proposed that even materials exhibiting PXRD halo patterns can be present in different solid-state forms, such as disordered nanocrystalline, glassy, and amorphous.

We studied the crystallization behavior of amorphous chenodeoxycholic acid (CDCA) by using differential scanning calorimetry.[19] CDCA form I and form III that were individually ground using a vibrational rod mill for 45 min resulted in amorphized polymorphs. As shown in Figs. 4a and g, the differential scanning calorimetry (DSC) curve for ground CDCA form I was different from that of form III, indicating a difference in crystallization behavior. The temperatures at which the crystallization to form I derived from

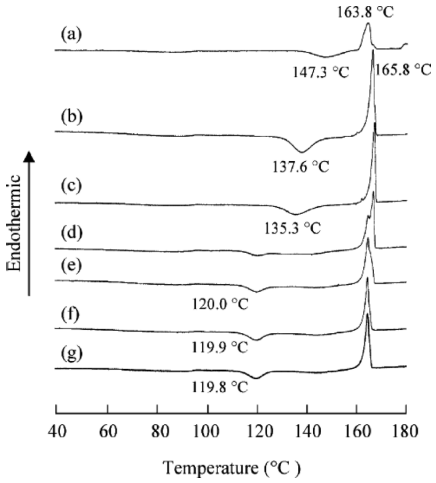

Fig. 4. DSC Curves of Physical Mixture of Ground Form I and Ground Form III of CDCA

Mixing weight ratio of form III/form I: (a) 100/0, (b) 99/1, (c) 95/5, (d) 50/50, (e) 20/80, (f) 1/99, (g) 0/100.

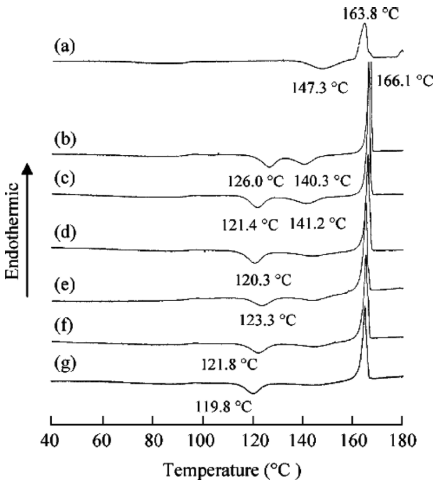

Fig. 5. DSC Curves of Coground Sample of the Form I and Form III

Mixing weight ratio of form III/form I: (a) 100/0, (b) 99/1, (c) 95/5, (d) 50/50, (e) 5/95, (f) 1/99, (g) 0/100.

amorphous form I and form III were 120 and 147 °C, respectively. In the amorphous mixture, the crystallization temperature to form I shifted to a lower temperature with an increase in the form I portion. Figure 5 shows the DSC curves of coground samples of form I and form III at various mixing

ratios of form III to form I. The results suggested the crystallization to form I can be explained by two processes; 1) a crystal growth process in which form I crystallites act as the crystal nuclei and 2) a nucleation process of form I that occurred in the absence of form I crystallites.

4. Preparation of Pharmaceutical Nanoparticles by Cogrinding

Pharmaceutical particle engineering has gained more attention as means of producing particles having a defined morphology, particle size distribution, and composition with desirable physicochemical properties. Fine particles of a drug can be prepared by spray drying, rapid expansion of the supercritical solutions method and grinding. Compared to other methods, the grinding method is easy to perform and organic solvent-free. However, the size reduction is limited to approximately 3 μm due to drug particle aggregation.[20] Size reduction to the nanometer range should be carried out using other techniques.

Cogrinding with some additives is known to be a simple and effective method to prepare drug nanoparticles. Cyclodextrins (CDs) and a combination of PVP and sodium dodecyl sufate (SDS) are examples of cogrinding additives. We investigated the formation of fine drug particles of pranlukast by cogrinding with CDs.[21,22] Pranlukast fine particles at a submicron level were found to be dispersed as small crystals observed by scanning electron microscopy (SEM). The relationship between percent of pranlukast recovered as fine particles and water content in the mixtures is shown in Fig. 6. Cogrinding with α-CD and γ-CD gave similar profiles to that of β-CD. The moisture content at the optimum range in the cogrinding process significantly influenced the fine particle formation. It is speculated that CD molecules and a suitable amount of water stabilized the submicron particles by formation of CD network covering pranlukast particles; this prevented the aggregation of particles.

We also investigated the formation and stability of poorly water-soluble drug nanoparticles obtained from a drug/PVP/SDS ternary ground mixture.[23,24] For example, after cogrinding a ternary system consisting of probucol, PVP, and SDS at a weight ratio of 1 : 3 : 1, probucol nanoparticles were formed when the ternary coground mixture was dispersed in distilled water (mean particle size 90 nm). Even after keeping the suspension at 25 °C for 28 d, mean particle size was less than 200 nm, indicating the drug nanoparticles had long-term stability (Fig. 7). The zeta potential measurement revealed that the obtained nanoparticles were stable in aqueous solution because the particle agglomeration was effectively inhibited by the adsorption of both PVP and SDS onto the particle surface. Further studies on the effects of PVP molecular weight on the solid-state intermolecular interactions among probucol/PVP/SDS ternary ground mixtures and nanoparticle formation were investigated by solid-state NMR spectroscopy.[25] The results revealed that both probucol–PVP and PVP–SDS interactions induced by simultaneous grinding of ternary components contributed to size reduction and the formation of nanoparticles. The formation mechanism of colloidal nanoparticles after dispersion of probucol/PVP/SDS ternary ground mixture into water was evaluated by SEM, environmental SEM, atomic force microscopy, particle size analysis, zeta potential measurement, and ^{13}C-NMR.[26,27] Key factors related to nanoparticle formation, *e.g.* species of polymer, type of surfactants, chain length, and composition of ternary ground system were thoroughly investigated as well.[28,29]

For *in vivo* study,[30] when orally administered to rats, formulation of probucol/PVP K12/SDS at weight ratio of 1 : 3 : 0.5 showed markedly higher plasma concentration of probucol than that of the others, as shown in Fig. 8. Mean particle size of the suspension was about 28 nm, which is the smallest among that of probucol/PVP K17/SDS and probucol/PVP K30/SDS at the same weight ratio. These results suggested that the particle size reduction and the difference in particle surface condition covered with PVP and SDS facilitated higher dissolution and absorption in the ternary system with PVP K12. Therefore, preparation of probucol nanoparticles by cogrinding ternary system of probucol/PVP K12/SDS could be a promising method for increasing its bioavailability. Wu and Ho stated that the bioavailability of realgar (As_2S_2), which is an inorganic anticancer compound, was substantially increased by nanoparticle formation with PVP and/or SDS induced by cryo-grinding.[31] Fukami *et al.* reported that the nanoparticles of probucol were formed by cogrinding with SDS and methacrylic copolymer increased

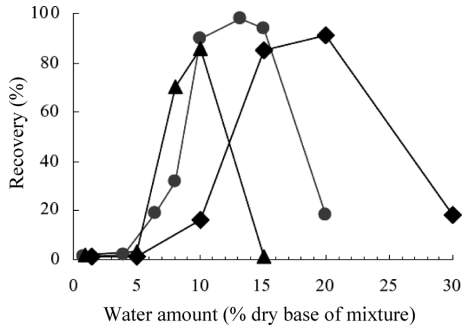

Fig. 6. Fine Particle Fraction in the Suspensions of CD/Pranlukast Ground Mixtures as a Function of Water Amount in Ground Mixtures (Molar Ratio; CD : Pranlukast = 2 : 1, Ground for 10 min) (▲) α-CD, (●) β-CD, (◆) γ-CD

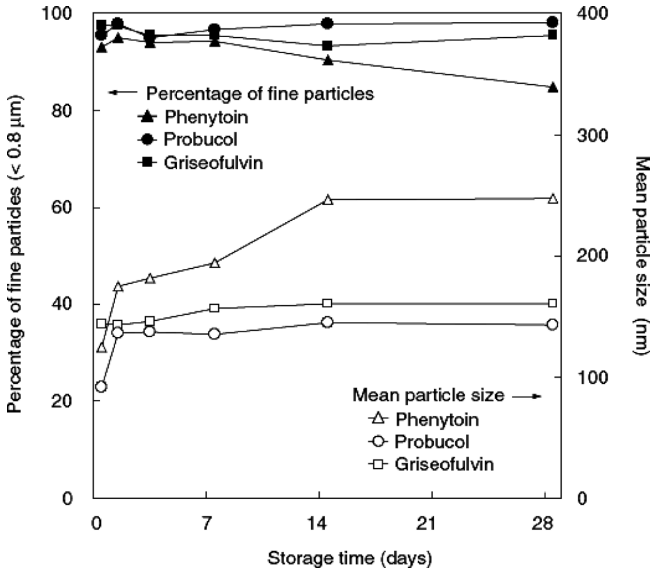

Fig. 7. Long-Term Stability of the Suspensions Obtained from Ternary Ground Mixtures

Changes in the mean particle size (solid symbols) and changes in the amount of fine drug particles (<0.8 μm) (open symbols) with storage time.

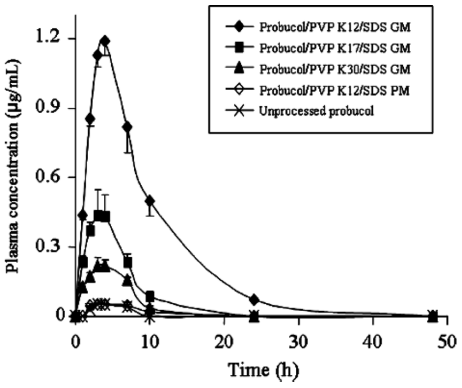

Fig. 8. Plasma Concentration of Probucol Following Oral Administration of Probucol/PVP/SDS Ternary Mixture Suspension

Results are expressed as mean±S.E. (n=3).

the solubility of probucol in water and its permeability through the cell membrane.[32)]

5. Specific Properties of Drug Molecules Located in Porous Powder Materials

Since drug fine particles smaller than 1 μm can be prepared, it became important to analyze the properties of such fine particles which have never been investigated. Determination of the nature of a limited number of aggregated molecules in detail can lead to the understanding of the macroscopic properties of pharmaceutical powder; this notion is consistent with molecular pharmaceutics.

Many APIs and excipients have a porous structure. When drug exists in the porous material, especially in those with a pore size less than 300 Å, the behavior of the drug molecule is affected dramatically. For example, after heating mixtures of benzocaine (ethyl *p*-aminobenzoate) at the content below 30% and controlled pore glass (CPG) with 75 Å pore size, their DSC thermograms showed a fusion peak at a temperature that was 20—30 °C lower than that of benzocaine, indicating that benzocaine molecules penetrated into the pore space of the CPG during the heating process. It was speculated that drug molecules in the crystal phase changed to the gas phase by sublimation, and then condensed molecules adsorbed onto the pore surface.

Pyrene was physically mixed with porous crystalline cellulose (PCC), having a pore diameter of 40 Å and specific surface area of 87.2 m^2/g, to explore the interaction between pyrene and PCC by fluorescence spectroscopy and lifetime analysis.[33)] When pyrene crystals are excited at 300 nm, excimer emission occurs at 475 nm because of its crystal structure where two molecules are overlapped in a parallel conformation. As shown in Fig. 9, the monomer emission of pyrene molecules was observed at 398 nm immediately after mixing with PCC and the intensity increased as a function of time indicating that at equilibrium pyrene was adsorbed on the surface of PCC as a monolayer. Furthermore, changes in the fluorescence emission spectra of the mixture containing 1.0% pyrene during storage are shown in Fig. 10. The intensity of monomer emission increased and that of excimer emission subsequently increased. This indicated that pyrene molecules were maintained in a parallel arrangement when they entered into the pore, although the PXRD pattern did not show any peak of pyrene. Taking into account the pore

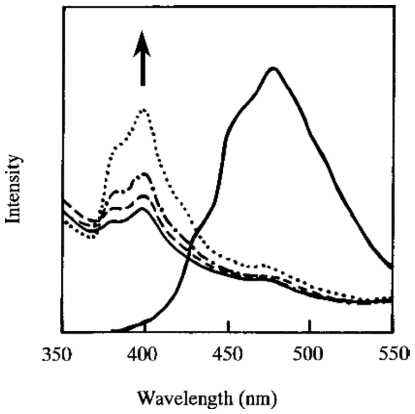

Fig. 9. Solid-State Fluorescence Emission Spectra of 0.1% Pyrene–PCC Mixture after Storage at 25 °C, λ_{ex}=300.0 nm

Pyrene crystals (——); simple mixture (——); stored for 6 h (– – –); stored for 1 d (—●—); stored for 7 d (· · · ·).

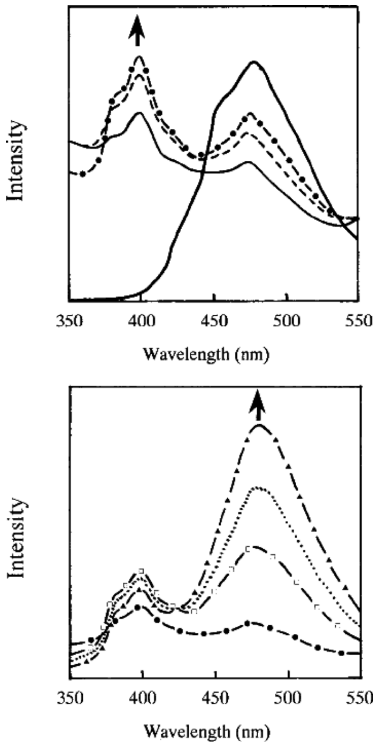

Fig. 10. Solid-State Fluorescence Emission Spectra of 1.0% Pyrene–PCC Mixture after Storage at 25 °C, λ_{ex}=300.0 nm

Pyrene crystals (——); simple mixture (——); stored for 6 h (– – –); stored for 1 d (—●—); stored for 3 d (—□—); stored for 7 d (· · · ·); stored for 14 d (—▲—).

size of pyrene, it can be concluded that repeating units of pyrene molecules less than 10 were aggregated in the pore. Moreover, when 2-naphthoic acid was used as a guest molecule, the fluorescence spectral data indicated that the molecular state of the drug was modified by heating with PCC. Results similar to those of the time-resolved fluorescence analysis in heated sample with PCC and in coground sample of 2-naphthoic acid with γ-CD were obtained, suggesting that the interaction between the drug and the surface of PCC pore was similar to the interaction between drug and CD.[34)]

Recently, coloration phenomenon of mefenamic acid (MFA) in mesoporous silica FSM-16 with different pore

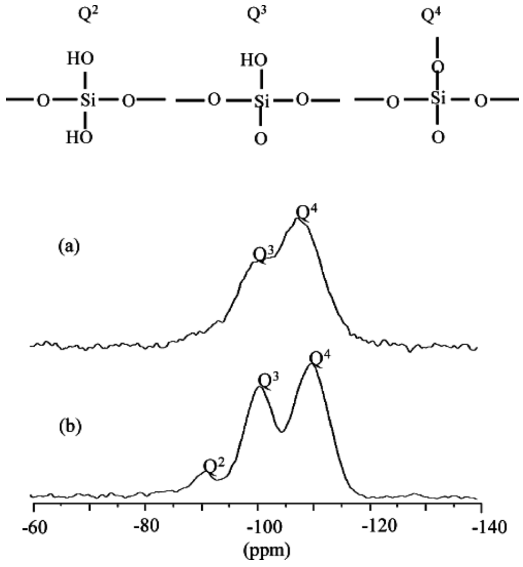

Fig. 11. Changes in ^{29}Si-DD/MAS NMR Spectra of FSM-16 (Doc)
(a) Before and (b) after humidifying at 40 °C and 82% RH for 3 months.

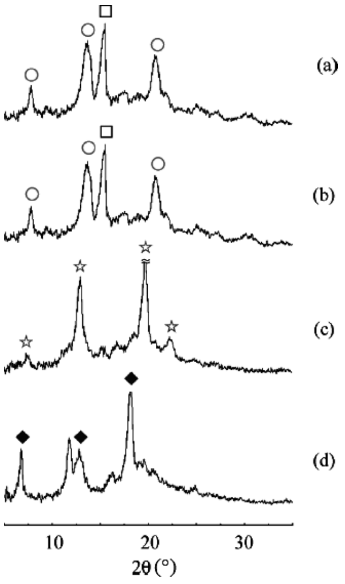

Fig. 12. Changes in PXRD Patterns of AS100-PA Systems by Sealed-Heating at Various Temperatures (6 Glucose Units : PA = 1 : 1)
(a) Physical mixture, sample sealed-heated at (b) 50 °C for 6 h, (c) 100 °C for 6 h, (d) 150 °C for 1 h. □: PA, ○: 6_1-helix V_a-type, ☆: 6_1-helix V_h-type, ◆: 7_1-helix amylose.

sizes was evaluated.[35] A change in color of the MFA/FSM-16 mixture was observed in sealed-heated samples and humidified sealed-heated samples. The results from solid-state ^{13}C-NMR spectroscopy showed the mobility of MFA molecules dispersed in FSM-16 mesopores increased compared with the crystalline state. The solid-state ^{29}Si NMR spectra of FSM-16 before and after humidification indicated that the humidification induced structural changes in silanol groups in FSM-16 (Fig. 11). Adsorption of MFA in FSM-16 mesopores by a sealed-heating method and changes in the surface of FSM-16 by humidification affected the coloration of MFA. It can be concluded that dispersed drug molecules in the pore interacted with water molecules adsorbed to the surface of FSM-16.

It is expected that dispersed drug from porous material will improve drug dissolution and lead to practical pharmaceutical applications. Moreover, recent study about the 3-dimensional porous structure of zeolite has been achieved.

6. Complex Formation by Sealed-Heating Method

Pharmaceutical products, composed of APIs and additives, are formulated to maintain efficacy and stability. For the most frequently used solid dosage form, the portion of additive is usually more than 90%, or at least 10% of total weight. The quality of the product must be preserved throughout the unit processing operation, transportation and storage, however, heating and adsorption/desorption of water commonly found in manufacturing processes can easily affect the quality of a pharmaceutical product.

We have developed a sealed heating method to prepare solid complexes between guest compounds and various kinds of CD. A physical mixture of guest compound and CD was sealed in a glass ampoule and heated under various conditions. The method has the great advantage of allowing preparation of inclusion compounds without using water as a solvent. The formation mechanism was concluded that the guest molecules were sublimed and then adsorbed to the surface of CD particles, followed by inclusion within the cavity.

Since linear amylose with a molecular weight of 100000 was recently synthesized, complex formation of pharmaceutical drugs with linear amylose using a sealed-heating method was investigated. Amylose is a linear polysaccharide composed of D-glucopyranose units linked by $\alpha 1 \rightarrow 4$ glucoside bonds. It is classified according to its crystal structure as A-, B-, and V-amylose. This V-structure defined as 6 glucose units per helical turn (6_1-helix) is usually formed in the inclusion complex, though it has been reported that its structure could change to a 7_1-helix or 8_1-helix upon the size of the guest molecules. We investigated the inclusion complex formation between amylose with a molecular weight of 102500 (AS100) and *p*-aminobenzoic acid (PA). It was found that sealed-heating of AS100 with PA resulted in the formation of two inclusion complexes, a 7_1-helix complex and a 6_1-helix complex.[36] The difference in the helical structures of these complexes depended on the sealed-heating temperature; that is 6_1-helix and 7_1-helix structures were obtained by heating at 100 °C for 6 h and 150 °C for 1 h, respectively (Fig. 12). Solid-state NMR spectroscopy results revealed that the magnetic environment around the benzene ring of PA in the 7_1-helix inclusion complex was in a different state compared to that in the 6_1-helix inclusion complex (Fig. 13). It is suggested that PA molecules become entrapped in the amylose helix cores in the 7_1-helix inclusion complex, whereas PA molecules existed in the interstitial space between amylose helices in the 6_1-helix inclusion complex. In addition, the size of the guest molecules on the inclusion complex formation was investigated as well by using PA analogues (methyl *p*-aminobenzoate, ethyl *p*-aminobenzoate, *n*-propyl *p*-aminobenzoate, and *n*-butyl *p*-aminobenzoate) as guest molecules. The binding ratios of AS100 and PA analogues changed according to the size of the guest molecules. Furthermore, the molecular state of salicylic acid (SA) in amylose complex prepared by sealed-heating treatment was evaluated.[37] When excess amounts of SA (two SA molecules to one helical unit of amylose) were sealed-heated with amylose at 150 °C for 3 h, the structure of 6_1-helix amylose changed

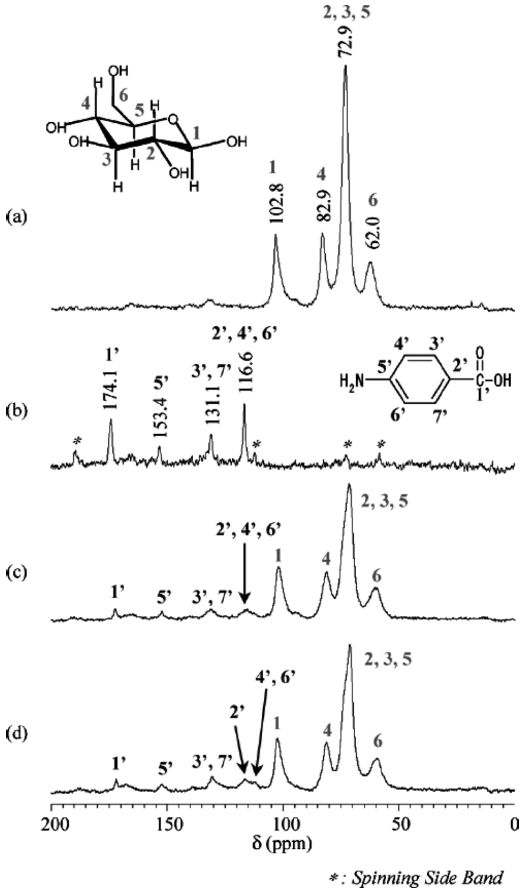

Fig. 13. Solid State ^{13}C CP/MAS NMR Spectra of AS100: PA (6 Glucose Units : PA = 1 : 1) System

(a) AS100, (b) PA, (c) $6_1(V_h)$-helix inclusion compound, (d) 7_1-helix inclusion compound.

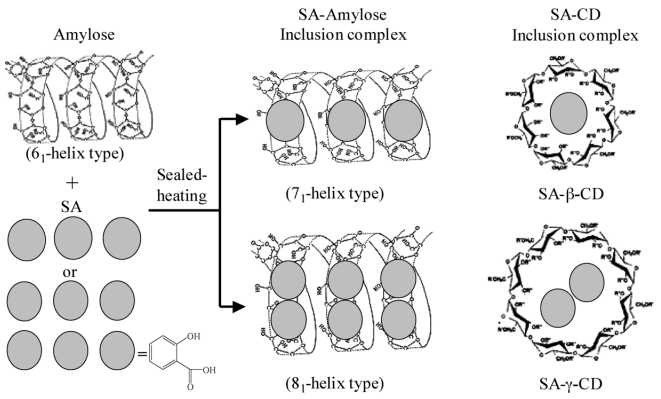

Fig. 14. Proposed Structure of SA-Amylose Inclusion Complexes in Comparison with SA-CD Inclusion Complexes

to the 8_1-helix form in SA-amylose inclusion complex, indicating the helical structure of the inclusion complex depended on the concentration of guest molecules (Fig. 14). Compared to drug–CD complex, the solid-state NMR results revealed that the molecular states of SA in 7_1-helix and 8_1-helix amylose complexes were similar to those in the β-CD and γ-CD inclusion complexes, respectively.

7. Conclusion

The bioavailability of API is greatly dependent on its molecular state. Typical examples are polymorphs of chloramphenicol palmitate, pseudo-polymorphs of ampicillin, and many kinds of solid dispersion of water-insoluble APIs. The specific molecular state has its intrinsic chemical potential, *i.e.*, each polymorphic form shows characteristic differences in solubility and melting point. There is a wide variety of molecular states in solid form: amorphous, partial amorphous, molecular dispersion, disordered state, and crystalline. Modes of intermolecular interaction between APIs, and between API and pharmaceutical additives are key factors governing the quality of pharmaceutical products. It is important to control intra- and inter-molecular interactions which are generated during the production process and storage period. This concept will make possible comprehensive understanding of the formulation, stability, effectiveness and adverse effects. Molecular thermodynamics is developed from considering the behavior of each particle assembling to the system. Hence molecular pharmaceutics should be extended for the total understanding of properties of pharmaceutical dosage forms.

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