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Polymorphic Cyclodextrin-Based Polypseudorotaxanes as Supramolecular Hosts for Rational Modulation of Encapsulated Drug Properties

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1. Introduction

While working as an Assistant Manager in the Research and Development division at Cipla Ltd., India, Dr. Sudeshna Kundu was exposed to interdisciplinary and international research environments. This experience motivated her to pursue advanced research training abroad, leading her to secure the prestigious Japanese Government (MEXT) Scholarship for doctoral studies in Japan. Her time in Japan as a doctoral and postdoctoral researcher proved academically enriching and professionally transformative.

In 2020, Dr. Kundu joined the Laboratory of Pharmaceutical Technology at the Graduate School of Pharmaceutical Sciences, Chiba University, and commenced her doctoral studies under the supervision of Prof. Kunikazu Moribe, an internationally recognized researcher in the field of molecular pharmaceutics, formulation engineering, and advanced physicochemical characterization of complex formulations. During her doctoral research at Chiba University, her work focused on cyclodextrin-based supramolecular complexes, particularly polypseudorotaxane systems and correlating physicochemical properties of encapsulated drugs with molecular dynamics, as probed using advanced solid-state nuclear magnetic resonance (NMR) spectroscopy. Following the completion of her doctoral studies, she continued her research at Chiba University as a postdoctoral researcher, where she further extended the application of solid-state NMR techniques to investigate the molecular state of amorphous pharmaceutical formulations and cocrystals and to elucidate the chemical structures of novel biopolymers.

Her research at Chiba University resulted in multiple peer-reviewed publications in high-impact journals and presentations at national and international scientific conferences. These research contributions were further recognized with the Post-Doctoral Presentation Award from the Academy of Pharmaceutical Sciences and Technology, Japan, in 2024. In the next section, an overview of her doctoral research and significant scientific contributions is presented.

2. Polymorphic Cyclodextrin-Based Polypseudorotaxane Structures as Hosts for Drug Encapsulation

A significant proportion of marketed active pharmaceutical ingredients (APIs) suffer from poor physicochemical properties, including solubility, dissolution, and stability, which limit their therapeutic efficacy. Encapsulation of APIs in macrocyclic host compounds or ordered porous structures, such as cyclodextrins, cucurbit[*n*]urils, metal-organic frameworks, mesoporous silica, or carbon nanotubes, has been proven to be a promising technique for overcoming these limitations.

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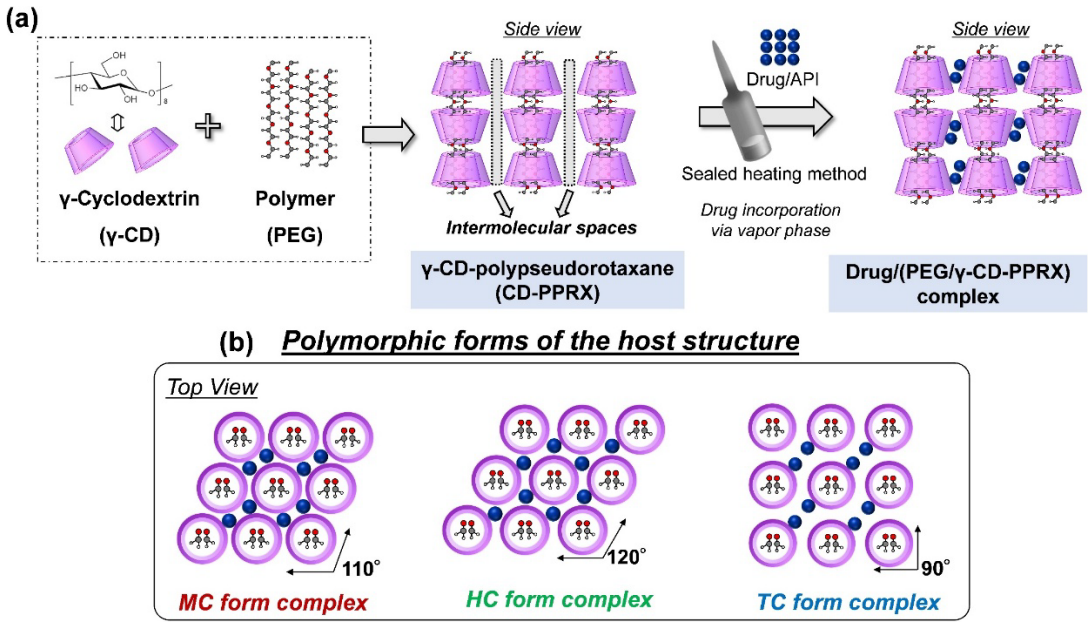


Fig. 1. (a) Schematic representation of the γ-CD-polypseudorotaxane structure and the development of a new drug/(PEG/γ-CD-PPRX) complex, and (b) different polymorphic forms of the drug/(PEG/γ-CD-PPRX) complex.

The encapsulation of APIs within such host structures in molecularly confined spaces directly impacts their physical properties due to changes in their molecular state and mobility.

Among various host structures, cyclodextrins (CDs) are the most widely used supramolecular hosts in pharmaceutical applications. CDs are cyclic oligosaccharides composed of six or more D-glucopyranose units linked by α-1,4-glycosidic bonds and possess a truncated conical structure with a hydrophilic exterior and a hollow hydrophobic cavity. Natural CDs (α-, β-, and γ-CDs) are commonly used to enhance drug solubility and stability by encapsulating guest molecules within their cavities. In addition to the CD cavity, the crystal structure of CDs contains intermolecular spaces with dimensions comparable to the cavity, which can serve as potential sites for drug encapsulation and the development of new CD-based complexes. CDs are capable of forming supramolecular assemblies with linear polymers, such as polyethylene glycol (PEG), known as CD-polypseudorotaxanes (CD-PPRXs). In this supramolecular structure, CD-polymer inclusion complexes stack on top of one another, forming parallel columnar structures with intermolecular spaces between adjacent columns (Fig. 1a). Previous research by our laboratory has established that drug molecules can be incorporated into the intermolecular spaces of PEG/γ-CD-PPRX by a sealed-heating technique, yielding a unique multicomponent supramolecular complex, drug/(PEG/γ-CD-PPRX)(Fig. 1a). Such complexes have improved the dissolution and stability of the encapsulated drug.

Furthermore, the host structure of PEG/γ-CD-PPRX can exist in three polymorphic forms, namely, monoclinic columnar (MC), hexagonal columnar (HC), and tetragonal columnar (TC) forms, which arise due to varying hydration states (Fig. 1b). These polymorphic forms differ in lateral packing structure and the dimensions of the intermolecular spaces. The effect of polymorphism in APIs is extensively investigated, as variations in crystal packing and molecular conformation can significantly impact physicochemical properties, such as solubility and bioavailability. In contrast, polymorphism in supramolecular complexes, such as rotaxanes and pseudorotaxanes, has received limited attention. The influence of polymorphic supramolecular structures in drug/(PEG/γ-CD-PPRX) complexes on physical properties remains largely unexplored. Addressing this gap, the overall objective of the study was to prepare three polymorphic forms of drug/(PEG/γ-CD-PPRX) complexes and to elucidate how polymorphism of the host structure governs the physical stability of encapsulated drugs by studying the molecular-level differences using solid-state NMR.

3. Vapor Pressure and Size-Dependent Drug Encapsulation in the Hexagonal Columnar Form of the Host Structure[1)]

Prior research has successfully prepared the drug/(PEG/γ-CD-PPRX) complexes with 17 different guest drugs by a sealed-heating technique, in which a physical mixture of the guest drug and the host polypseudorotaxane is heated in a closed space (e.g., glass am-

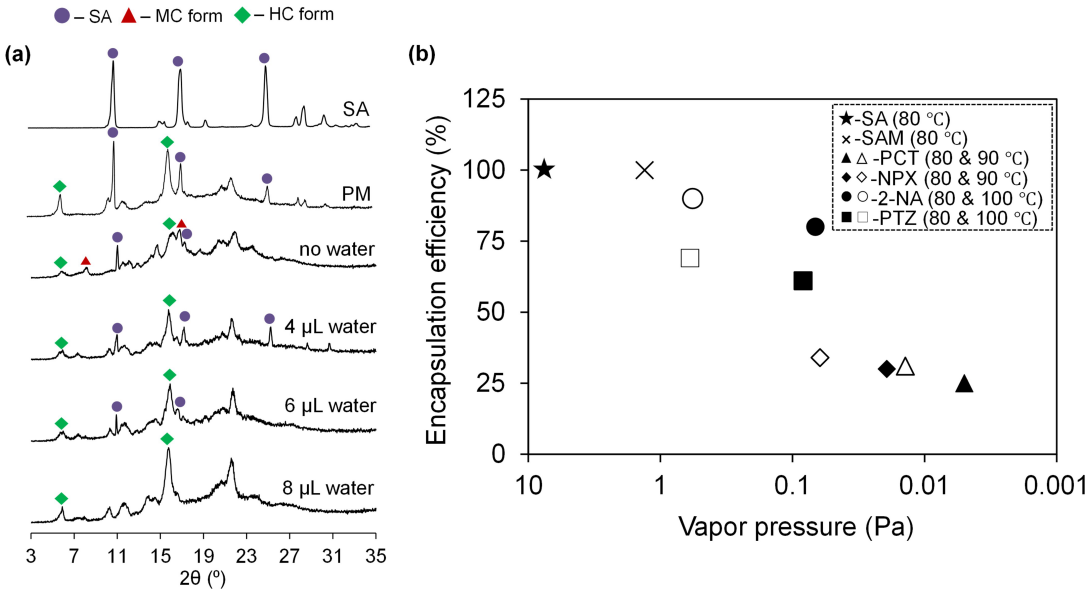


Fig. 2. (a) PXRD patterns of SH samples with salicylic acid (SA) prepared at 80°C for three hours with different water content, and (b) Correlation plot between guest drug and its encapsulation efficiency in HC form complex at respective sealed-heating temperatures.

pule) and the encapsulation occurs via the vapor phase. The high sealed heating temperature above 110°C has predominantly yielded the monoclinic columnar (MC) polymorphic form of the complex, irrespective of the guest compound. The high sealed-heating temperature promoted structural rearrangement of the host structure during guest incorporation. Consequently, most investigations have focused on the MC form of the complex. In contrast, the hexagonal columnar (HC) form complex has been deemed difficult to obtain and retain during encapsulation due to its sensitivity to temperature and hydration.

In line with this, a systematic investigation of sealed-heating parameters was carried out to enable guest encapsulation while preserving the HC form structure of PEG/γ-CD-PPRX. Six different guest drugs, namely, salicylic acid (SA), salicylamide (SAM), paracetamol (PCM), 2-naphthoic acid (2-NA), phenothiazine (PTZ), and naproxen (NPX), were selected to evaluate the formation of the HC-form complex and understand the encapsulation behavior. Physical mixtures (PM) of the HC form of PEG/γ-CD-PPRX and each guest drug were sealed in glass ampules and heated under various sealed-heating conditions. The powder X-ray diffraction patterns (PXRD) of the sealed-heated (SH) samples revealed that at elevated sealed-heating temperatures, transformation to the MC form occurred, consistent with earlier reports. In contrast, lowering the sealed-heating temperature (80°C) effectively suppressed this transformation but was insufficient to achieve complete guest encapsulation. However, the addition of a small amount of water (8–10 μL) with low sealed-heating temperatures resulted in successful guest encapsulation while retaining the HC form structure (Fig. 2a). Water acted as a structural stabilizer, maintaining the columnar stacking order of γ-CDs and preserving their crystallinity, thereby facilitating the encapsulation of guest molecules. However, a higher amount of water (20–25 μL) promoted transformation to the tetragonal columnar (TC) form. This sealed-heating condition, i.e., a low sealed-heating temperature with a small amount of water, was applicable to all guest drugs examined in this study for the successful preparation of the HC-form complexes. Stability studies showed that the HC-form complexes retained their structure even after drying to low water content, indicating the formation of a stable anhydrous polymorphic form of the HC form complex.

The quantitative determination of the encapsulated guest molecules was performed using solution-state ^{1}H NMR spectroscopy after removal of the non-encapsulated drug. The stoichiometric ratio of drug/γ-CD in each HC form complex was found to be related to their cross-sectional area. The vapor pressure of the guest drug showed a good correlation with the encapsulation efficiency (Fig. 2b). The increased vapor pressure with temperature led to the enhancement of encapsulation efficiency. However, the encapsulation efficiency could not be explained only by the vapor pressure in some cases of 2-NA, PTZ, and NPX. The increased molecular size of these guest drugs would have decreased the encapsulation efficiency despite a comparable vapor

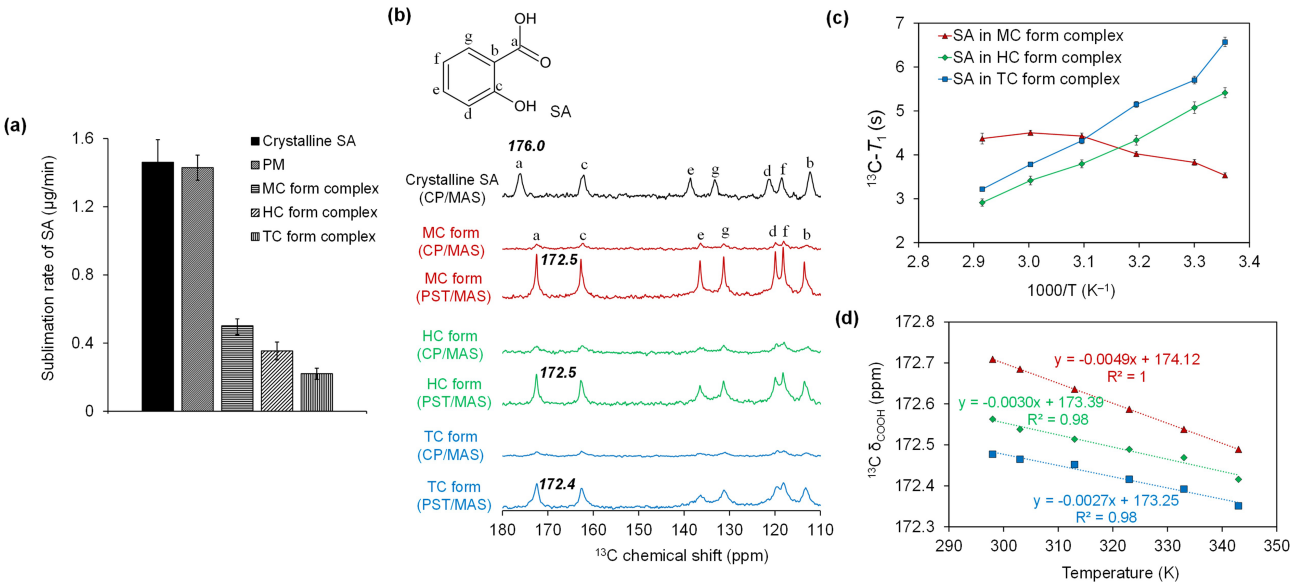


Fig. 3. (a) Sublimation rate of SA from its crystalline state, PM, and the complexes (b) ^{13}C CP/MAS and PST/MAS spectra of SA in the complexes, (c) ^{13}C-T_1, and (d) ^{13}C chemical shift of the carbonyl carbon of SA in the temperature range of 25–70˚C.

pressure. Guest drugs with smaller cross-sectional areas and high vapor pressure were more easily encapsulated within the intermolecular spaces of the HC structure, in contrast to bulkier guest molecules with lower vapor pressure. The findings from this study demonstrated that HC-form of the drug/(PEG/γ-CD-PPRX) complexes can be rationally prepared through precise control of sealed-heating conditions. The study established vapor pressure and molecular size as key determinants of encapsulation efficiency in the HC form and expanded the accessible polymorphic landscape of CD-based polypseudorotaxane complexes.

4. Effect of Polymorphic Host Structure on the Physical Stability of the Encapsulated Drug and its correlation with Molecular Dynamics[2)]

To investigate the effect of the different host structures on the physical properties of the encapsulated drug, SA was selected as a model drug to prepare the three polymorphic forms of the complex were prepared. SA is widely used in topical formulations for the treatment of chronic skin disorders owing to its keratolytic, anti-inflammatory, and bacteriostatic properties. However, SA exhibits a high vapor pressure and undergoes significant sublimation at skin temperature (32˚C), leading to significant weight loss from the crystalline state and formulations.

The three polymorphic forms of the SA/(PEG/γ-CD-PPRX) complex were prepared using controlled sealed-heating and humidification processes. Successful preparation of each polymorphic form was confirmed by PXRD, which showed the characteristic diffraction peaks of the host structures and the absence of crystalline SA peaks. Isothermal thermogravimetric analysis was employed to evaluate the sublimation behavior of SA under identical experimental conditions, with similar particle size and monolayer surface area. The sublimation rate of SA was significantly reduced by complexation. Moreover, the sublimation rate decreased in the order of MC form > HC form > TC form (Fig. 3a). This result clearly demonstrated that the polymorphic structure of the host framework affects the physical stability of the encapsulated drug.

To elucidate the cause of the different sublimation rates, the molecular state of the complexes was then evaluated using magic-angle spinning (MAS)-based solid-state NMR techniques. In the solid-state NMR spectra, the carbonyl carbon peak of SA was observed at 176.0 ppm in crystalline SA, while the carbonyl carbon peak of SA was shifted to 172.5 ppm in the complexes (Fig. 3b). This shift suggests a disruption of the SA dimeric structure in the crystalline state and the formation of new interactions between monomeric SA and γ-CD in the complexes. Furthermore, the SA peak intensity in the complexes was significantly enhanced in the ^{13}C pulse saturation transfer (PST) spectra compared to its ^{13}C cross-polarization (CP) spectra (Figure 3b), suggesting that SA and PEG in the complexes were highly mobile.

By comparing the NMR peak shapes, the molecular mobility of SA, PEG, and γ-CD in the complexes decreased in the order of MC form > HC form > TC form. Furthermore, the SA peak exhibited an asymmetrical shape, indicating a superimposition of narrow

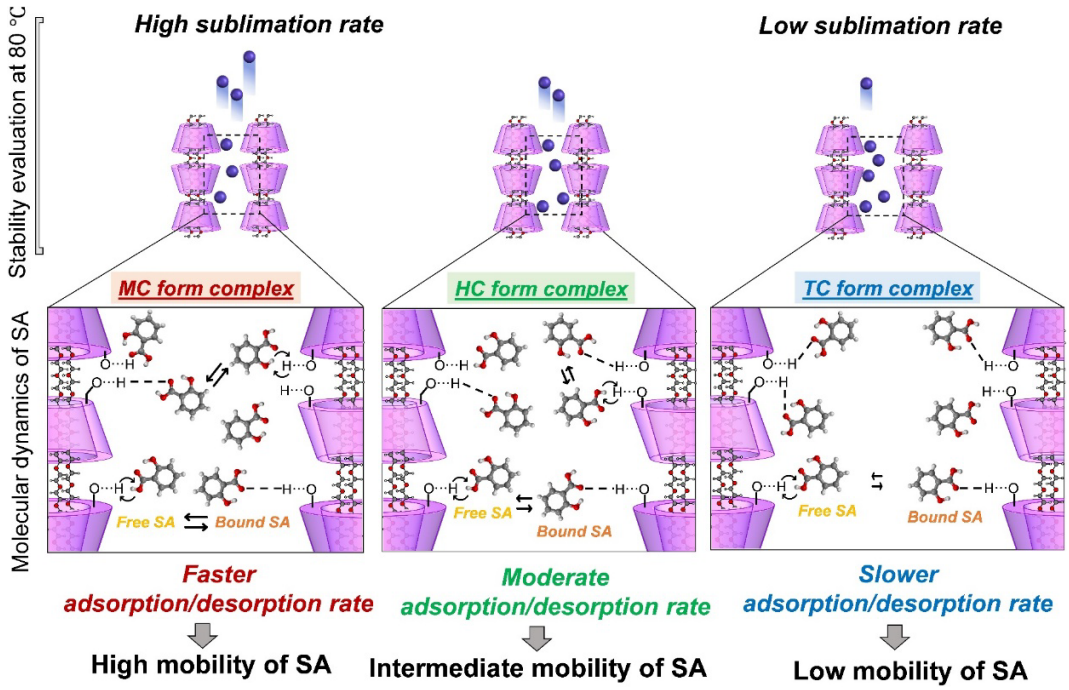


Fig. 4. Correlation of molecular mobility and sublimation rate of SA in the complexes.

and broad peaks, possibly due to the two dynamic states of SA corresponding to free and bound SA, respectively. However, it is noteworthy that the individual peaks for each dynamic state were not clearly separated, indicating a rapid chemical exchange between the free and bound SA that occurs faster than the NMR timescale. This reflects the adsorption/desorption process of SA on the millisecond timescale in the complexes. The temperature-dependent ^{13}C PST spectra exhibited that the temperature-dependent increase of the free SA peaks was relatively higher in the MC form than in the HC and TC form complexes. This implies that the adsorption/desorption rate of SA was faster in the MC form, followed by the HC and TC form complexes. From the ^{13}C-T_1 measurements, it was also quantitatively confirmed that the molecular mobility of SA decreased in the order of MC form > HC form > TC form (Fig. 3c). With increasing temperature, the carbonyl carbon of SA in the complexes shifted upfield and showed linear dependency, indicating a weakening of the interaction between SA and γ-CD in the complexes. From the magnitude of the temperature coefficient of this chemical shift, it was implied that the interaction strength of SA in the complexes was in the order of TC form > HC form > MC form (Fig. 3d). Furthermore, from the NMR results, it was inferred that the mobility order of γ-CD and PEG in the complexes coincided with the mobility of SA.

From the solid-state NMR characterization, it was deduced that the different SA mobility in the complexes can be attributed to the different adsorption/desorption rates influenced by the interaction strength. The faster adsorption/desorption rate of SA in the MC form complex compared to the HC and TC form complex could result in a higher population of free SA and, hence, a higher sublimation rate (Fig. 4).

This study established the relationship between the molecular dynamics of the encapsulated drug in polymorphic supramolecular hosts and the macroscopic physical stability of an encapsulated API. The findings demonstrate that polymorphic host structures can be strategically selected to tune drug stability. The molecular-level understanding of the multicomponent CD-based polypseudorotaxane complex obtained in this study provides valuable insights for the rational design and broader application of supramolecular nanomaterials and biomaterials.

5. Summary and Acknowledgement

In summary, a new sealed-heating technique for the preparation of the HC form of drug/(PEG/γ-CD-PPRX) complex was developed through systematic investigation. Furthermore, the relationship between the different host-structure-dependent sublimation behavior of the encapsulated drug and its molecular mobility was elucidated through solid-state NMR characterization. The pharmaceutical relevance of these polymorphic complexes was demonstrated using salicylic acid as a model drug. Supramolecular encapsulation markedly suppressed sublimation compared with the crystalline

drug, with the extent of suppression depending on the polymorphic host structure. This work represents the first report demonstrating rational control of physical properties, such as the sublimation rate of an active pharmaceutical ingredient, through complexation within polymorphic supramolecular host structures. The insights from this study provide a foundation for the rational design of supramolecular drug delivery systems, aiming to improve the physicochemical properties of pharmaceutical compounds.

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