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**Original Article**

# Properties of tropolone/γ-cyclodextrin complexes prepared using different methods

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## ABSTRACT

The aim of the present study is to evaluate the properties of the inclusion complex of tropolone (TPN)/γ-cyclodextrin (γCD) prepared by cogrinding method and coprecipitation method. The physical properties of the preparation were evaluated by differential scanning calorimetry, powder X-ray diffraction, infrared absorption spectra, and $^{1}$H-$^{1}$H NOESY NMR spectrum. Intermolecular interactions in the solid state were confirmed to be in the molar ratios TPN/γCD = 2/1 and TPN/γCD = 4/1 in the cogrinding method and molar ratio TPN/γCD = 2/1 in the coprecipitation method. In addition, in GM (TPN/γCD = 4/1), two molecules of TPN were encapsulated in the molecular space formed between γCD. Therefore, it was suggested that different inclusion structures of TPN/γCD complexes were formed using different preparation methods.

Keywords: Tropolone, Cyclodextrin, Ground mixture, Copreciptate, Molecular interaction

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## INTRODUCTION

Tropolone (TPN, 2-hydroxy-2,4,6-cycloheptatriene-1-one) is a non-benzenoid aromatic compound with a planar seven-member ring structure, and it is an isomer of benzoic acid. Notably, TPN has been reported to form intra- and intermolecular hydrogen bonds and exhibit specific properties. It possesses pharmacological and biochemical effects such as antibacterial [1], anti-inflammatory [2], antioxidant [3], and antitumor [4] activities. Owing to these properties, TPN derivatives colchicine and hinokitiol (HT) have been applied and studied in various fields as pharmaceuticals and quasi-drugs [5, 6]. In addition, the TPN skeleton can be induced to various compounds, and it would be possible to develop a wide range of structures as a new pharmacophore in the pharmaceutical field in the future.

Cyclodextrin (CD) is a cyclic polysaccharide in which D-glucopyranose is cyclically bound by a α-1, 4 bond. It is classified as α-cyclodextrin (αCD), β-cyclodextrin (βCD), and γ-cyclodextrin (γCD) according to the number of glucopyranose units, and these CDs are widely used as host molecules in the formation of inclusion complex. CDs are hydrophilic near the edge and on the outside of the ring, while the interior cavity shows hydrophobic properties. It is known that a host is capable of including a guest to form an inclusion complex by hydrophobic interactions in aqueous solution [7]. The methods for preparing inclusion complexes include cogrinding [8], coprecipitation [9], freeze drying [10], spray drying [11], and sealed heating [12] methods. There are reports that different inclusion structures are formed depending on the preparation method, even when the same CD is used. For example, in the case of actarit, an antirheumatic drug, it has been reported that inclusion complexes of different molar ratios are obtained using cogrinding and freeze-drying methods, and the inclusion structures formed by both the methods are different [13]. Higashi et al. reported that salicylic acid is encapsulated in the outer molecular space formed not only within the cavity of γCD, but also between γCD [14]. This specific inclusion mode can be applied for the development of new medicines in the future. Thus, elucidating the mechanism of formation of a new inclusion complex via encapsulation of guest molecules in the molecular space formed between CDs is useful in the development of future products. Authors previously reported that the TPN derivative HT forms inclusion complexes with α-, β-, and γCDs [15, 16].

The purpose of this study is to evaluate the mechanism of TPN/γCD inclusion complex formation using the space where TPN is formed between γCDs, using different preparation methods.

## MATERIALS AND METHODS

**Materials:** TPN used as a bulk powder was purchased from Sigma-ALDRICH Ltd. (Fig.1). γCD was donated by Cyclo Chem Co. Ltd (Tokyo, Japan) and used after storage at 40°C at a relative humidity of 82% for 7 days [17]. The moisture content of CDs was confirmed by coulometric titration using Karl Fischer moisture meter (CA-06, Mitsubishi Chemical Co., Ltd). All other reagents were special grade reagents manufactured by Wako Pure Chemical Industries, Ltd.

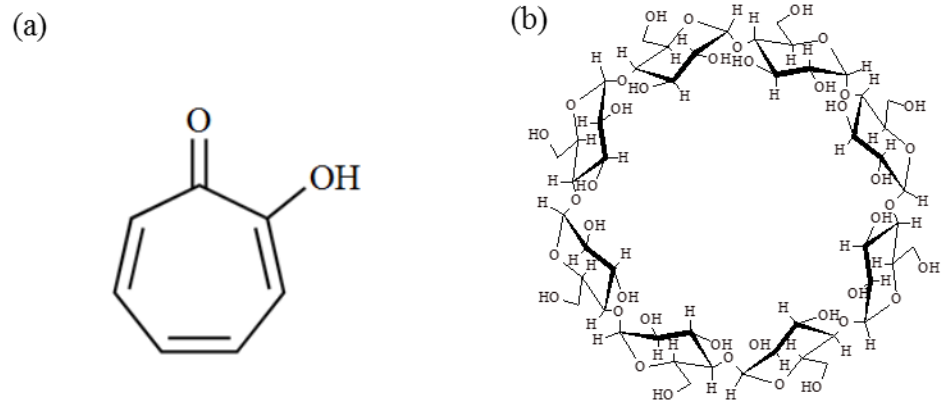


Fig. 1 Chemical Structures of (a) Tropolone (TPN) and (b) γ -cyclodextrin (γCD)

**Preparation of physical mixture (PM) and ground mixture (GM):** HT/γCD was weighed at molar ratios of 5/1, 4/1, 3/1, 2/1, and 1/1, respectively, and mixed for 1 min using a vortex mixer to prepare a physical mixture (PM). The ground mixture (GM) was prepared from the PM. For each PM, 1 g of material was charged in an alumina cell and cogrinding was conducted for 30

min using a vibration rod mill (TI-500ET, CMT Co., Ltd) to obtain GM.

**Preparation of humidification:** GM was conditioned and recrystallized by storing in a desiccator at 40°C and 82% relative humidity in the presence of a saturated aqueous solution of potassium chloride.

**Preparation of coprecipitate (CP):** To 5 mL of TPN aqueous solution (0.10 mol/L), 5 mL of γCD aqueous solution (0.13 mol/L) was added in portions, stirred for 6 h at room temperature, and allowed to stand at room temperature for 24 hours. Then, the precipitate was separated by filtration and dried in a desiccator, under vacuum for 24 h at room temperature.

**Physicochemical characterization**

**Differential scanning calorimetry (DSC):** The thermal behavior of samples was recorded using a differential scanning calorimeter (Thermo plus Evo, Rigaku). Approximately 2 mg of a sample was filled in a sealed aluminum pan, and the measurement was conducted under $N_2$ gas flow rate of 60 mL/min and heating rate of 5°C /min.

**Thermogravimetry (TG):** The thermal behavior of the samples was recorded using a differential scanning calorimeter (Thermo plus Evo, Rigaku). Approximately 10 mg of a sample was placed in an aluminum pan, and the measurement was conducted under $N_2$ gas flow rate of 200 mL/min and heating rate of 5°C /min.

**Powder X-ray diffraction (PXRD):** PXRD was performed on an X-ray diffractometer (MiniFlex II, Rigaku), and the diffraction intensity was measured with a NaI scintillation counter. Cu line (30 kV, 15 mA) with a scan speed of 4°/min over the 2θ ranges of 3-35° were used to carry out X-ray diffraction measurement. The powder sample was filled in a glass plate so that the sample plane became flat and measured.

**Fourier transform infrared (FT-IR) spectroscopy:** FT-IR absorption spectroscopy of the samples was performed using the KBr tablet method and recorded using a spectrometer (FT/IR-410, JASCO). The number of integration steps was 32, resolution was 4 $cm^{-1}$, and measurements were recorded in the wavenumber range of 4000-400 $cm^{-1}$. For preparing tablets, potassium bromide (KBr) was added to the sample at a weight ratio of 1/10 (sample/KBr), mixed, and compressed by a manual press. Background correction was performed using KBr only tablet.

**$^1$H- nuclear magnetic resonance (NMR) measurement:** NMR spectra were obtained using a Varian NMR System 400 MHz (manufactured by Agilent Technologies). Dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) was used as a solvent, and the measurement was carried out with a pulse-width of 90°, delay time of 6.4 μs, scan time of 3.723 s, and 128 integration steps at 26°C.

**$^1$H-$^1$H nuclear overhauser effect difference spectroscopy (NOESY) NMR measurement:** $^1$H-$^1$H NOESY spectra were recorded using the Varian NMR System 400 MHz (manufactured by Agilent Technologies). Using $D_2O$ as a solvent, the measurement was carried out with a pulse-width of 90°, relaxation time 500 ms, scan time 0.500 s, and cumulative frequency of 256 integration steps at 25°C.

## RESULTS AND DISCUSSION

**DSC analysis:** It has been reported that inclusion complexes are formed by intermolecular interactions, resulting in changes in their thermal behavior [19]. Therefore, thermal behavior of TPN/γCD complexes was examined by DSC measurement (Fig. 2). The endothermic peak derived from the melting point of TPN was confirmed to be around 57°C in TPN crystals and ground TPN alone (Fig. 2a, 2b). For PM (TPN/γCD=2/1), PM (TPN/γCD=4/1), and GM (TPN/γCD=5/1), an endothermic peak derived from the melting of TPN crystal was observed at around 57°C (Fig. 2e-f, 2k). However, for GM (TPN/γCD=1/1), GM (TPN/γCD=2/1), GM (TPN/γCD=3/1), GM (TPN/γCD=4/1), and CP (TPN/γCD), no endothermic peak derived from the melting of TPN crystal was observed (Fig. 2g-j, 2l). In a previous study, it has been reported that changes in thermal behavior indicate the inclusion complexes of guest drug and CD in solid dispersion or the formation of inclusion complexes with different properties [20]. From the results of DSC measurement, it was inferred that intermolecular interaction is formed between TPN and γCD. The low temperature shift of the endothermic peak derived from the melting of TPN in GM and the decrease in caloric value were attributed to the mechanochemical effect caused by the mechanical energy developed in the grinding method.

**PXRD analysis:** PXRD measurement was carried out to investigate the crystalline state of TPN/γCD in the cogrinding method and coprecipitation method.

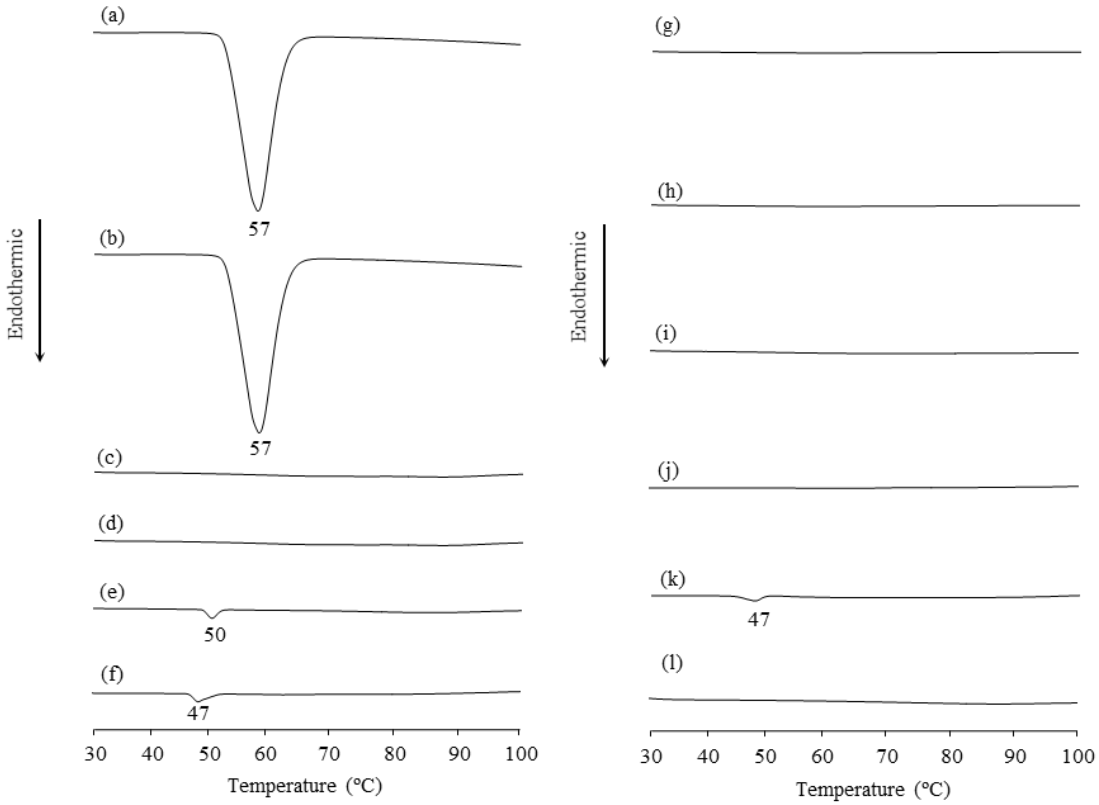


Fig. 2 DSC curves of TPN/γCD systems
(a) TPN, (b) TPN ground, (c) γCD, (d) γCD ground, (e) PM (TPN/γCD=2/1), (f) PM (TPN/γCD=4/1), (g) GM (TPN/γCD=1/1), (h) GM (TPN/γCD=2/1), (i) GM (TPN/γCD=3/1), (j) GM (TPN/γCD=4/1), (k) GM (TPN/γCD=5/1), (l) CP (TPN/γCD)

Characteristic peaks of TPN were observed at 2θ = 14.4°, 25.3° in TPN crystal and ground TPN alone (Fig. 3a, 3b). The peak of γCD alone was observed at 2θ = 14.4°, 18.3° (Fig. 3c). In PM (TPN/γCD = 2/1) and PM (TPN/γCD = 4/1), diffraction peaks derived from TPN crystals were observed around 2θ = 14.5°, 24.7°, and diffraction peaks derived from γCD were observed near 2θ = 12.2°, 18.8° (Fig. 3e, 3f). However, in the case of GM (TPN/γCD = 1/1), GM (TPN/γCD = 2/1), and GM (TPN/γCD = 3/1), diffraction peaks derived from the TPN crystal and γCD showed a halo pattern (Fig. 3g-i).

It is known that inclusion complexes formed by cogrinding method become amorphous [21]. During cogrinding with γCD, the regularity of the crystal lattice in the TPN crystal structure is disturbed and crystallinity declines; thus, there is a possibility of the complex becoming amorphous or the mechanochemical reaction progresses to form inclusion complexes. It was presumed that the complex might become amorphous in the process of changing to a different crystalline structure from the TPN crystal [22, 23].

A previous study reported that crystallization occurs when an amorphous sample is stored in a humidity-controlled environment [24]. Therefore, PXRD measurement was performed after GM (TPN/γCD = 2/1) and GM (TPN/γCD = 4/1), which showed a halo pattern in cogrinding, were stored under humidity-controlled conditions. Diffraction peaks derived from TPN and CD were not found in the diffraction pattern even after crystallization. The diffraction peaks of humidity-conditioned GM (TPN/γCD = 2/1) and humidity-conditioned GM (TPN/γCD = 4/1) were approximately 2θ = 7.5°, 12.0°, and 16.7° (Fig. 3l, 3m). When inclusion complexes are formed by tetragonal columnar type CD, characteristic diffraction peaks are known to be observed around 2θ = 7.4°, 12.1°, and 16.5° [24]. In the diffraction pattern of humidity-conditioned GM (TPN/γCD = 2/1), humidity-conditioned GM (TPN/γCD = 4/1), and CP, diffraction peaks similar to the tetragonal columnar type structure of γCD (2θ = 7.3°, 12.0° and 16.5°) were observed. From the results, it was speculated that a complex of TPN and γCD with a tetragonal columnar type structure was formed.

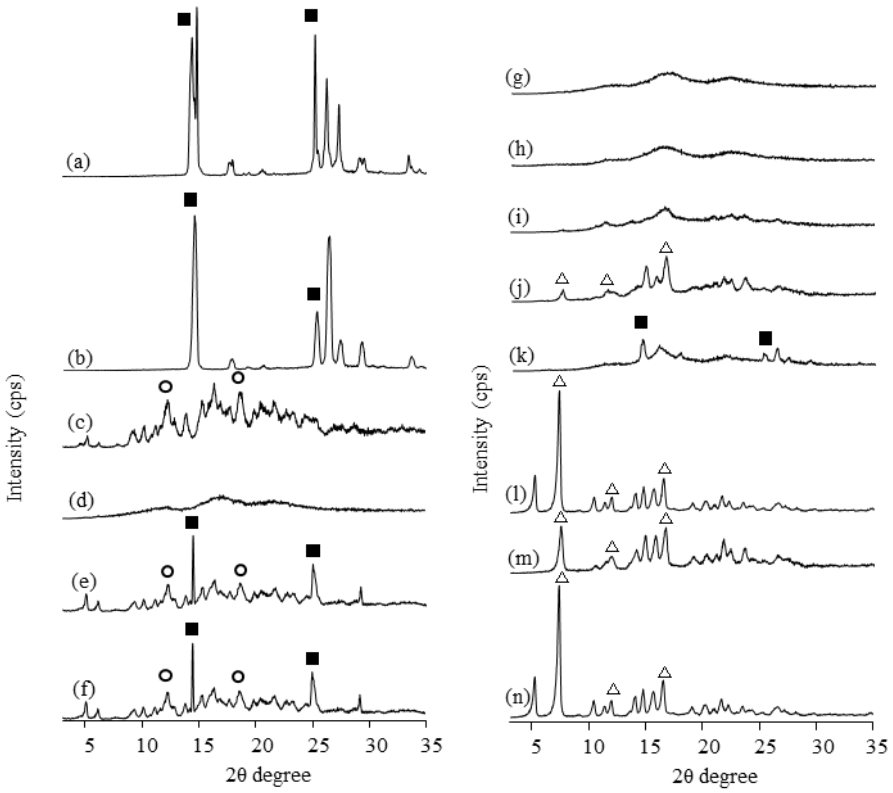


Fig. 3 PXRD patterns of TPN/γCD systems

(a) TPN, (b) TPN ground, (c) γCD, (d) γCD ground, (e) PM (TPN/γCD=2/1), (f) PM (TPN/γCD=4/1), (g) GM (TPN/γCD=1/1), (h) GM (TPN/γCD=2/1), (i) GM (TPN/γCD=3/1), (j) GM (TPN/γCD=4/1), (k) GM (TPN/γCD=5/1), (l) GM (TPN/γCD=2/1) after storage at 40ºC and 82% for 7days, (m) GM (TPN/γCD=4/1) after storage at 40ºC and 82% for 7days, (n) CP (TPN/γCD)

■:TPN, ○:γCD, ∆: tetragonal columnar form

**TG analysis:** TG measurement was carried out to examine the weight change of TPN molecules involved in complex formation (Fig. 4). In TPN alone, around 99% weight loss from the TPN crystal was confirmed from around 60ºC. In addition, weight loss of 11.5% in GM (TPN/γCD = 2/1), 6.0% in GM (TPN/γCD = 4/1), and 5.4% in CP (TPN/γCD) was observed between 30-100ºC. These weight losses were presumed to be from the degree of decrease in the TG curve, which was suggested to be due to the evaporation of crystal water or absorbed water of CD. For GM (TPN/γCD = 2/1), a weight loss of approximately 11.2% was confirmed from around 157-260ºC. This weight reduction corresponded to 91.3% of TPN contained in the sample. For GM (TPN/γCD = 4/1), a weight loss of approximately 8.0% from around 100-178ºC and approximately 9.7% from around 178-260ºC was confirmed. This weight reduction corresponded to 98.3% of TPN contained in the sample. In CP, a weight loss of about 14.7% was confirmed from around 153-260ºC.

According to the report by Daniel, the weight loss of drugs observed above 110ºC is considered to be due to the formation of complexes [25]. It is considered that the respective weight losses observed from around 157 ºC in GM and CP were due to TPN/γCD complex formation. Similar weight loss was observed in GM (TPN/γCD = 2/1) and CP (TPN/γCD), which suggested the presence of TPN with the same molecular state. However, in GM (TPN/γCD = 4/1), two-stage weight loss was confirmed at 100-178ºC and 178-260°C, indicating that GM (TPN/γCD = 2/1) and TPN had different molecular states.

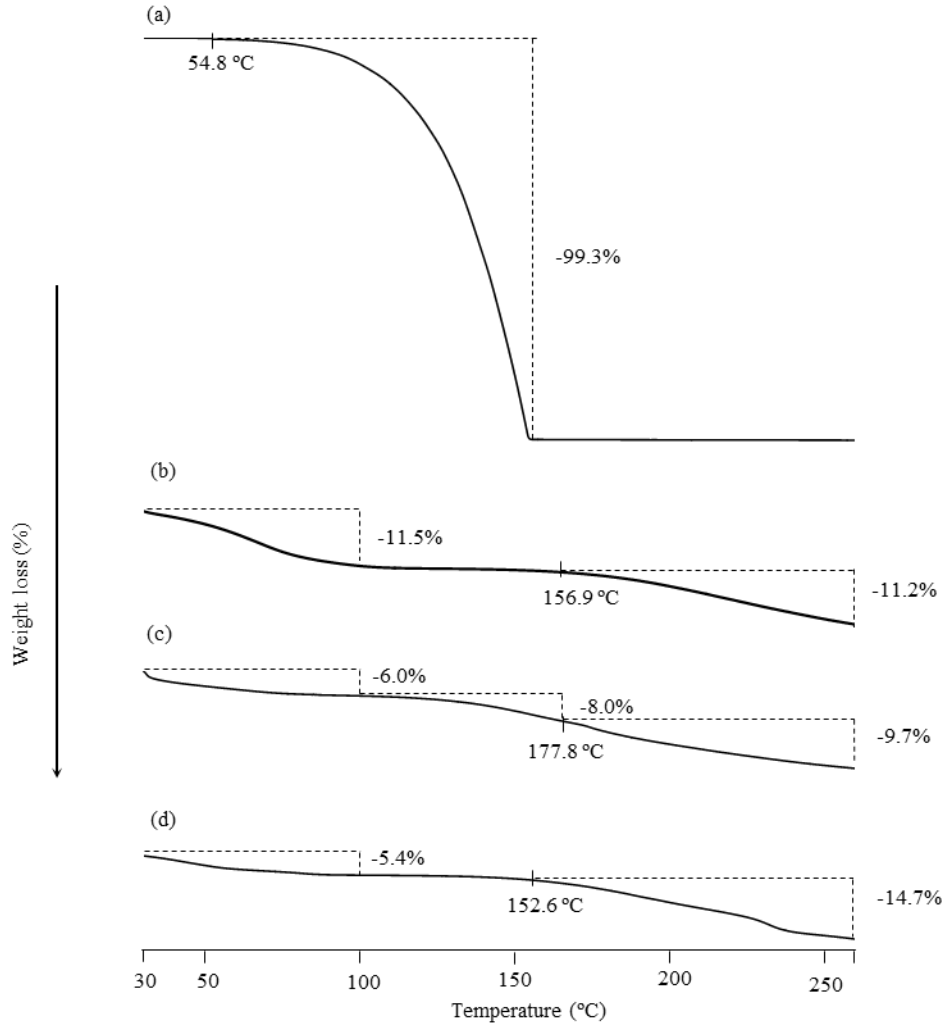


Fig. 4 TG curves of TPN/γCD systems
(a) TPN, (b) GM (TPN/γCD=2/1), (c) GM (TPN/γCD=4/1), (d) CP (TPN/γCD)

**$^1$H-NMR analysis:** From the results of DSC, PXRD, and TG measurements, intermolecular interactions in both GM and CP can be inferred. $^1$H-NMR spectrum measurement was carried out to investigate the inclusion molar ratio of CP [26]. The results of the $^1$H-NMR spectrum measurement of TPN, γCD, GM (TPN/γCD = 4/1), and CP are shown in Fig. 5. In TPN, a signal derived from the seven-membered ring hydrogen was observed around 7.0-7.5 ppm. In γCD, signals derived from hydrogen and hydroxyl groups of the glucose unit were observed. In CP, signals from TPN and γCD were confirmed respectively. Since the number of protons of the signal derived from the seven-membered ring hydrogen of TPN observed around 7.0-7.41 ppm was 1.32, it was shown that the number of protons per hydrogen atom of TPN in CP was 0.264. In addition, since the number of protons of the signal derived from hydrogen number 1 in the glucose unit of γCD was 1, it was shown that the number of protons per hydrogen atom of γCD was 0.125. From this result, it's can suggest that when the inclusion molar ratio of CP was calculated using the formula, the molar ratio of inclusion complex formation between γCD and TPN was TPN/γCD = 2/1 when TPN/γCD = 2.15/1 [27].

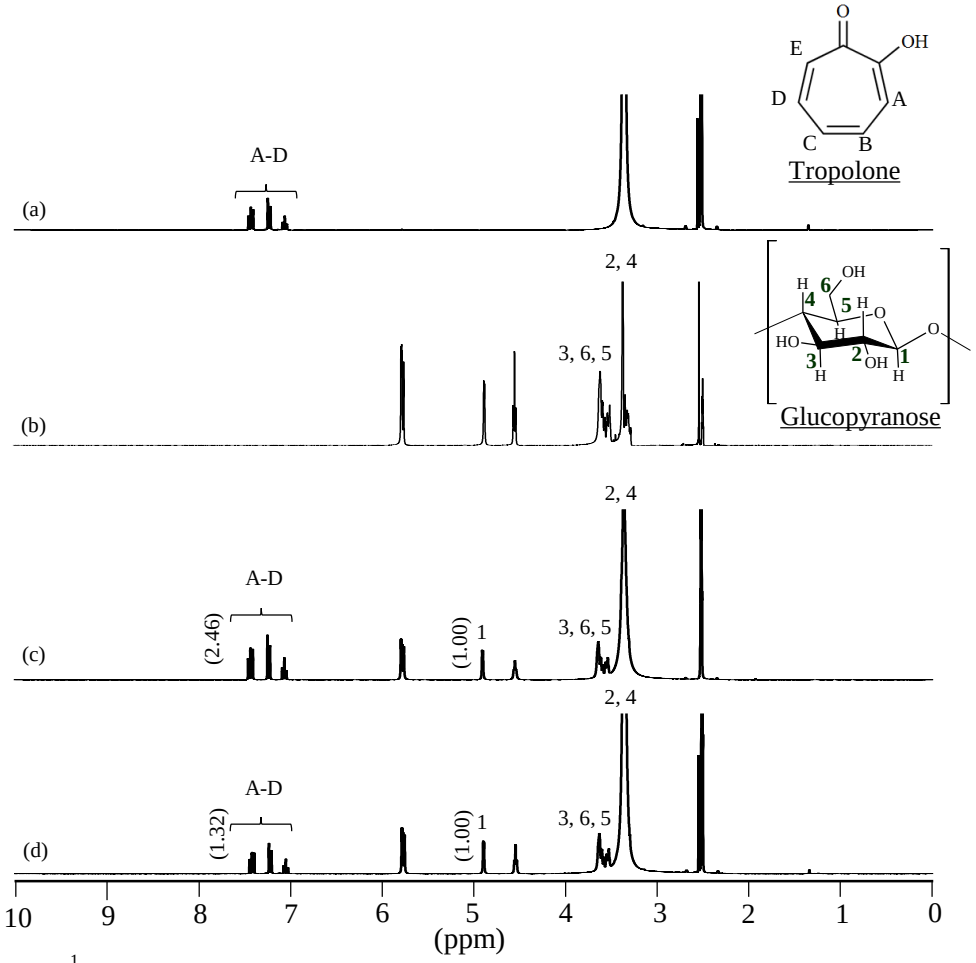


Fig.5 $^{1}$H-NMR (DMSO-$d_6$) spectra of TPN/γCD systems

(a) TPN, (b) γCD, (c) GM (TPN/γCD=4/1), (d) CP (TPN/γCD)

**FT-IR analysis:** From the results of DSC, TG, and PXRD measurements, intermolecular interaction between TPN and γCD was inferred. FT-IR spectroscopy is a useful analytical method to confirm the formation of inclusion complexes in solid state [28]. Therefore, FT-IR spectrum measurement was performed to examine the molecular state of the inclusion complex (Fig. 6).

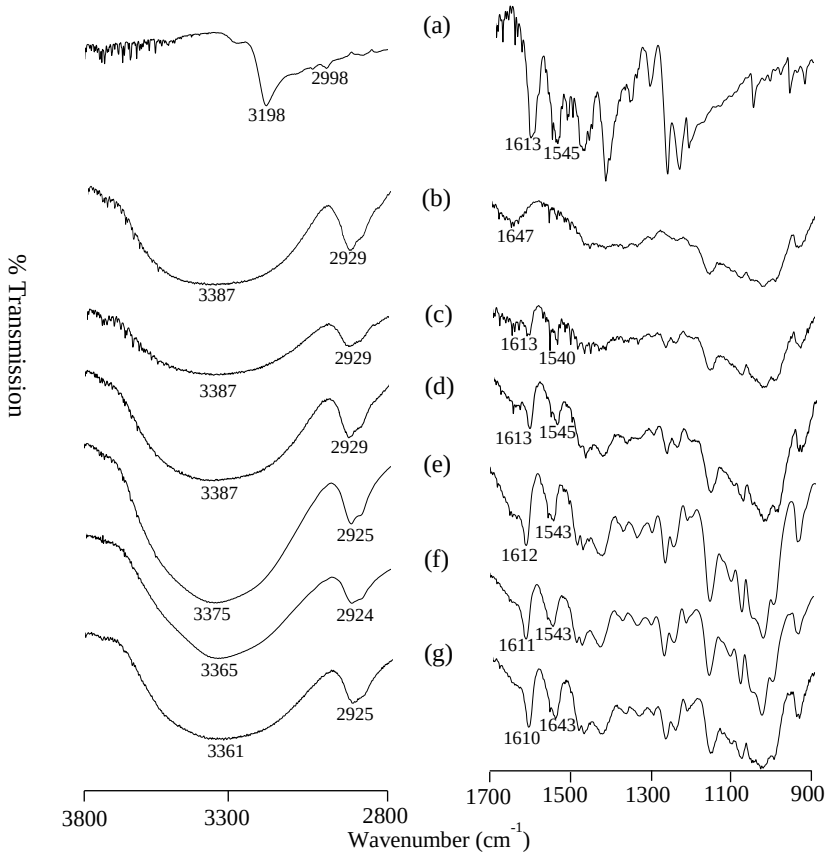


Fig. 6 FT-IR spectra of TPN/γCD systems

(a) TPN, (b) γCD, (c) PM (TPN/γCD=2/1), (d) PM (TPN/γCD=4/1), (e) GM (TPN/γCD=2/1), (f) GM (TPN/γCD=4/1), (g) CP (TPN/γCD)

In the TPN crystal, an absorption peak in the vicinity of 1613 $cm^{-1}$ derived from the carbonyl group (C=O stretching vibration) in the TPN molecular structure and an absorption peak near 3198 $cm^{-1}$ derived from the hydroxyl group (O-H stretching vibration) were observed using FT-IR (Fig. 6a). In γCD alone, a broad absorption peak derived from hydroxyl group (O-H stretching vibration) was confirmed between 3800-3100 $cm^{-1}$ centered on 3387 $cm^{-1}$ (Fig. 6b). In PM (TPN/γCD = 2/1) and PM (TPN/γCD = 4/1), the absorption peaks that were derived from carbonyl and hydroxyl groups in the TPN molecular structure were similar to that in TPN crystal (Fig. 6c, 6d). However, the absorption peak in the vicinity of 1613 $cm^{-1}$ derived from the TPN carbonyl group (C=O stretching vibration) is 1612 $cm^{-1}$ in GM (TPN/γCD = 2/1). It was observed that for the absorption peak in GM (TPN/γCD = 4/1), the wave number shifted to 1611 $cm^{-1}$, and the absorption peak in CP was 1610 $cm^{-1}$ (Fig. 6e-g). In addition, in GM (TPN/γCD = 2/1), GM (TPN/γCD = 4/1), and CP, the absorption peak near 3198 $cm^{-1}$ derived from the hydroxyl group (OH stretching vibration) disappeared. It has been reported that TPN forms a dimer through intermolecular hydrogen bonding in its crystal structure [29]. The peak shift observed in this study was presumed to be due to the cleavage of intermolecular hydrogen bond forming the TPN dimer and formation of new intermolecular interactions between TPN and γCD. In general, CDs incorporate water molecules when guest molecules are not clathrated. Moreover, the water molecules and guest molecules in the CD cavity exchange with each other leading to a stable energy state during the formation of inclusion complexes [30]. The peaks derived from crystal water present inside the γCD ring that were confirmed around 1647 $cm^{-1}$ were lost in GM (TPN/γCD = 2/1), GM (TPN/γCD = 4/1), and CP. Thus, it was inferred that intermolecular interaction with the guest molecules was due to the dehydration of water of crystallization in CD [31].

**$^{1}$H-$^{1}$H NOESY NMR measurement:** $^{1}$H - $^{1}$H NOESY NMR measurement was performed to evaluate the molecular state in aqueous solution [32].

In GM (TPN/γCD = 2/1), a cross peak was observed between H-A, H-B, H-D, and H-E peaks derived from the seven-membered ring of TPN and H-3, H-5, and H-6 peaks of γCD (Fig. 7-a). In GM (TPN/γCD = 4/1), a cross peak was observed between the H-A, H-B, H-D, and H-E peaks derived from the seven-membered ring of TPN and the H-3, H-5, and H-6 peaks located inside γCD. In addition, a cross peak was observed between H-2 and H-4 located outside γCD (Fig. 7-b). In CP, a cross peak was observed between H-A, H-B, H-D and H-E peaks derived from the seven-membered ring of TPN and H-5 and H-6 peaks located inside γCD (Fig. 7-c).

From the results of $^{1}$H-$^{1}$H NOESY NMR measurement, GM (TPN/γCD = 2/1) was inferred to be located near the wide edge of the seven-membered ring of TPN is a γCD. Furthermore, from the cross peaks between H-6 of γCD and H-A and H-E of TPN, it was suggested that the carbonyl and hydroxyl groups of TPN were located in the narrower edge of γCD. However, in GM (TPN/γCD = 4/1), it was inferred that the seven-membered ring of two molecules of TPN is in the cavity and located near the narrower edge of γCD. Furthermore, since a cross peak between H-2 and H-4 located outside γCD was confirmed, it is speculated that the remaining two molecules of TPN were present in the molecular space formed by γCDs. In CP, it was inferred that the seven-membered ring of TPN is located near the narrow edges of γCD. Since cross peaks were confirmed between H-A, H-B, H-D, and H-E of TPN and H-5 and H-6 of γCD as well as between H-C of TPN and H-6 of γCD, it is assumed that the carbonyl and hydroxyl groups are located on the narrower edge side of γCD. Higashi et al. reported similar results using the sealed heating method for salicylic acid and γCD [24]. In other words, TPN has a planar structure similar to salicylic acid, and it is not only included into γCD, but also interacts with γCD in the void space between γCD molecules. This may be because of the strong interaction between the void space and TPN structure. From these results, can suggest that TPN and γCD form inclusion complexes of different structures due to differences in preparation methods.

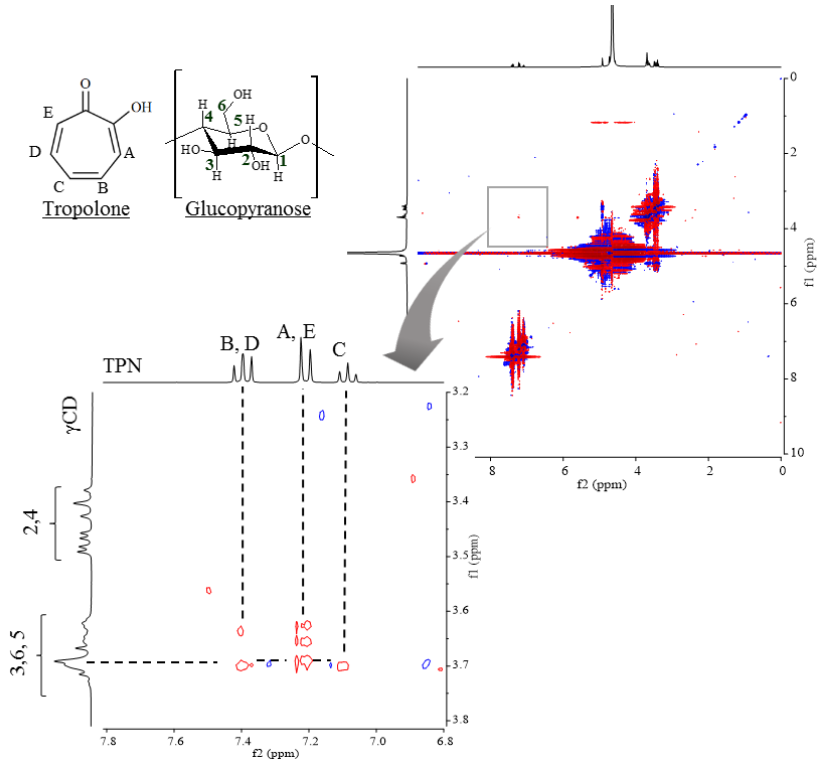


Fig. 7-a $^{1}$H-$^{1}$H NOESY NMR spectrum of GM (TPN/γCD=2/1) in $D_2O$

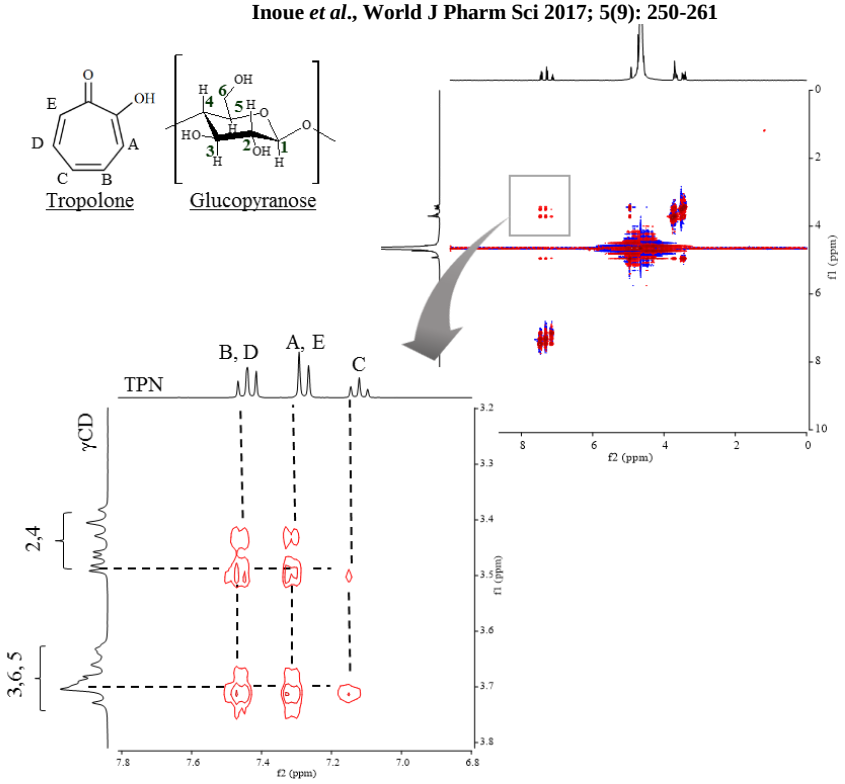


Fig. 7-b $^{1}$H-$^{1}$H NOESY NMR spectrum of GM (TPN/γCD=4/1) in $D_2O$

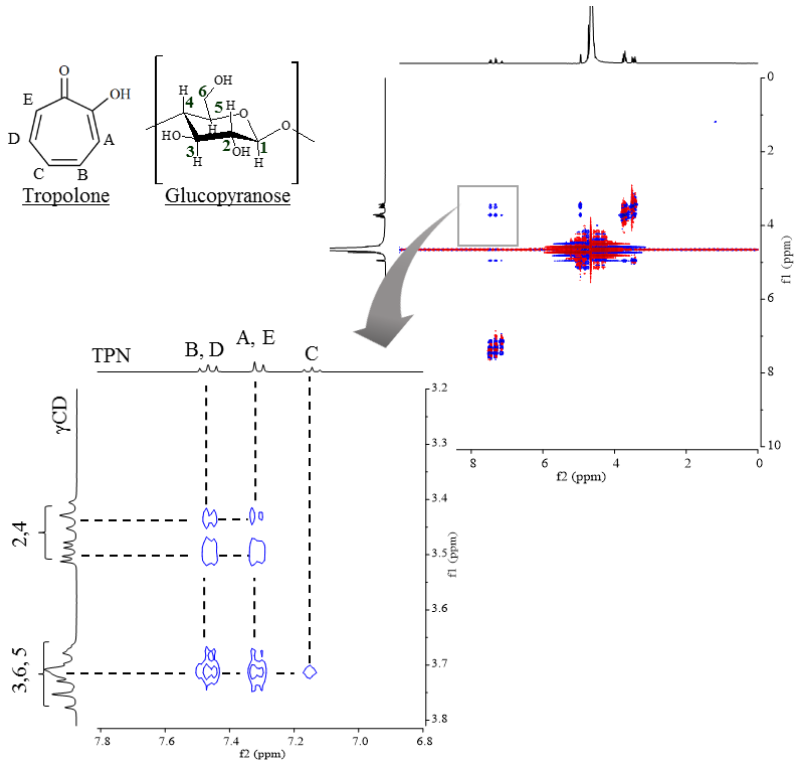


Fig. 7-c $^{1}$H-$^{1}$H NOESY NMR spectrum of CP (TPN/γCD) in $D_2O$

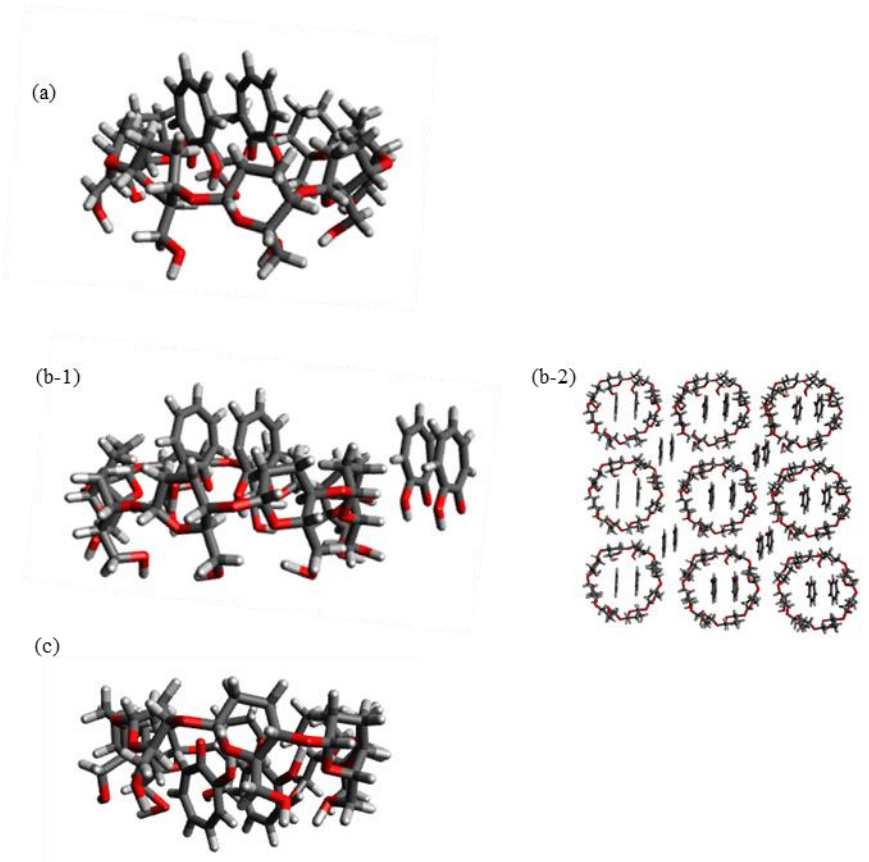


Diagram1 Structural view of TPN/γCD complex
(a) GM (TPN/γCD=2/1), (b-1) GM (TPN/γCD=4/1) side view, (b-2) GM (TPN/γCD=4/1) top view, (c) CP (TPN/γCD=2/1)

## CONCLUSIONS

In this study, revealed the formation of TPN/γCD inclusion complex using cogrinding and coprecipitation methods. Owing to the differences in preparation methods, inclusion complex with different structures were formed. The molar ratio of the inclusion complex formed by the cogrinding method was TPN/γCD = 2/1 and TPN/γCD = 4/1 and that by coprecipitation method was TPN/γCD = 2/1. In addition, in GM (TPN/γCD = 4/1), two molecules of TPN were encapsulated in the molecular space formed between γCD. Encapsulation of drugs in the molecular space between CDs in the cogrinding method has become an interesting new discovery. As with the salicylic acid system, it became possible to form a novel ternary complex. In the future, further elucidation of the encapsulation mechanism of the drug in the molecular space formed by these specific CDs would broaden the use of CD as drug carriers in pharmaceutical development.

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**Conflict of Interests:** The authors declare no conflict of interests regarding the publication of this paper.

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