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ORIGINAL ARTICLE

Characterization of multicomponent crystal formed between indomethacin and lidocaine

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Abstract

Purpose: Crystalline complex was formed between indomethacin (IDM) and lidocaine (LDC) at molar ratio 2:1 from ethanol solution. The purpose of this study was elucidation of an interactive manner between IDM and LDC in ethanol solution and mechanism of the complex formation through solid state as well as liquid state. *Methods*: The chemical and physical nature of the complex was clearly elucidated by the alliance of powder X-ray diffractometry, differential scanning calorimetry, and infrared spectroscopy. The complex was also formed via solid-state reaction by cogrinding and heating treatment without any solvent. *Results*: The complexation process was estimated to be as follows: (i) mixing and contact of two components, (ii) disorder of crystalline LDC by grinding or fusion, and then (iii) crystal growth by heating. In addition, 1H-NMR coupled with microchanneled cell for synthesis monitoring revealed that a primary interactive force between IDM and LDC molecule was coulomb energy.

Key words: *Crystal; indomethacin; lidocaine; multicomponent; pharmaceutical salts*

Introduction

Multicomponent systems, which mean molecular assemblies consisting of a drug substance and complementary molecules such as solvent, additives, and other substances, are one of the most attractive pharmaceutical techniques in recent years[1]. Although there is currently some controversy in the literature regarding the naming conventions for crystals that contain more than one component, these systems are typically classified into salts, solvates (including hydrates), and cocrystals[2,3]. Crystallizing active pharmaceutical ingredients (APIs) as a multicomponent system has become an accepted approach to generating solid forms and physical property diversity, such as solubility, chemical stability, and hygroscopicity.[4,5].

Multicomponent crystals containing pharmaceutically active molecules were reported as early as 1944 with regard to theophylline/phenobarbital[6]. However, a rapid increase in the number of multicomponent systems reported started from 1990, a period that coincided with the emergence of the paradigm of crystal engineering[7]. Thus, it would be reasonable to consider this system as being long-known but little-studied.

Indomethacin (IDM) is a common nonsteroidal anti-inflammatory drug commonly used to heat muscle pain, sprain, and rheumatism. Lidocaine (LDC) is a local anesthetic ester used to relieve pain and discomfort in the form of liquids, creams, and gels. Both of them have been widely used as typical external applications. We reported a 1:1 molecular complex formed between IDM and LDC in aqueous solution, when studying external combination drugs[8]. In addition, a crystalline complex consisting of IDM and LDC at molar ratio 2:1 was obtained from ethanol solution, and then the molecular arrangement was solved by single-crystal X-ray structure analysis[9].

From our previous results, the molecular complex (1:1) showed enhanced solubility of IDM in water, and

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the crystalline complex (2:1) seemed to be chemically stable in solid state. Both the complexes have possible features for developing a new pharmaceutical dosage form. In any case, we have some questions that should be considered for better understanding about the formation of IDM–LDC complex: (i) how is the solid properties of crystalline complex (2:1) compared with intact components, (ii) which complex or new one is formed in solid state without water, and (iii) what is the difference in molecular states of components in aqueous or alcoholic solution? In this study, the crystalline complex (2:1) formed between IDM and LDC was characterized by some techniques including powder X-ray diffractometry (XRD), differential scanning calorimetry (DSC), and IR spectroscopy. Additionally, preparation of the complex via solid-state reaction was attempted by cogrinding and heating treatment to understand its formation process. ^{1}H-NMR spectroscopy was employed to investigate the primary interactive force between IDM and LDC molecules in alcoholic solution.

Materials and methods

Materials

IDM and LDC were of reagent grade and purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). All other chemicals and solvents were of reagent grade and used without further purification.

Preparation of the complex consists of IDM and LDC

Equimolar IDM and LDC were lightly mixed with agate pestle and mortar as a physical mixture. This physical mixture dissolved in ethanol solution yielded transparent crystals showing a 2:1 complex at room temperature[9]. To study the effects of mechanical and/or heating treatment on complex formation in solid state, the physical mixture was ground with a vibrating rod mill (HI-200; CMT, Fukushima, Japan) at room temperature for 10 minutes. The ground mixture was then heated at 100°C for 1 hour. All samples, IDM, LDC, physical mixture, and ground mixture, were stored in desiccators equilibrated at 0% relative humidity using phosphorous pentoxide at room temperature (23–25°C).

Powder X-ray diffractometry

Powder XRD was carried out with a Miniflex with a Cu-Kα radiation source (Rigaku Co., Tokyo, Japan). Data were collected at a scan rate of 4°/min over a 2θ range of 5–35°. The accelerating voltage was 35 kV and the current was 25 mA.

Differential scanning calorimetry

DSC was carried out with a DSC 8230 (Rigaku Co., Tokyo, Japan). IDM, LDC, or their mixture (3–5 mg) was put into an aluminum-crimped pan and measured at a scanning speed of 5°C/min under a nitrogen gas flow (50 mL/min).

Infrared spectroscopy

A model FT/IR-230 spectrometer (Jasco Co., Tokyo, Japan) was used. The measurements were carried out using the KBr method. Disks were obtained by mixing 100 mg of dry KBr with 1 mg of studied samples. Spectra (64 scans at 4 cm^{-1} resolution) were collected in the 4000–400 cm^{-1} range.

MICCS-^{1}H-NMR

MICCS (MIcroChanneled Cell for Synthesis monitoring) is a microfluidic device that simultaneously works as a microreaction device and as an interface to a conventional NMR instrument as shown in Figure 1[10,11]. The ^{1}H-NMR spectra were obtained on a JNM-ECA 600 (JEOL Ltd., Tokyo, Japan) with a standard 5-mm φ-probe into which the glass part of MICCS was inserted. Ethanol solutions of IDM (20 mmol/L) and LDC (15 mmol/L) were delivered into the two inlet ports of microchannels using syringe pumps (MD1001 with the BS-MD1200; Bioanalytical Systems Inc., West Lafayette, IN, USA). The flow-rate ratio of IDM/LDC was consecutively changed from 5.0/0.0 to 0.0/5.0 μL/min during measurement. Deuterated solvent was introduced into a gap between the microchip and the NMR sample tube, used as an NMR lock. NMR measurement was performed without spinning of MICCS and the rotor set.

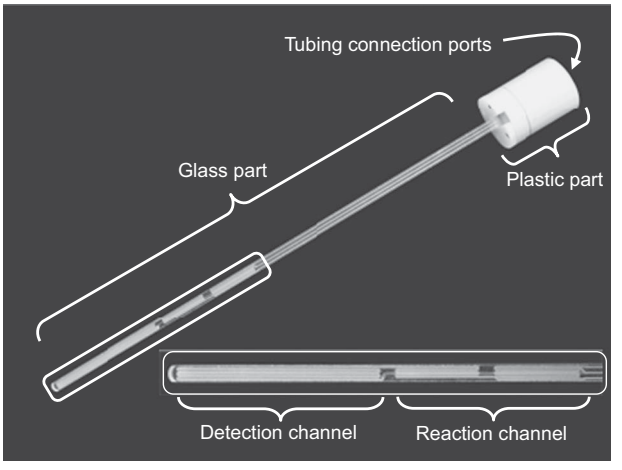

Figure 1. Photographs of sample tube in the MICCS-NMR system: sample tube and the magnified tip-part of the sample tube.

Results and discussion

Characterization of crystalline complex

Powder XRD

Figure 2 shows the changes in diffraction patterns of the IDM–LDC system measured by powder XRD. Characteristic diffraction peaks were observed at 11.7°, 21.9°, and 26.7° (Figure 2A), and 10.1 and 12.6° (Figure 2B) corresponding to the crystalline IDM and LDC, respectively. The diffraction pattern of the physical mixture was a superposition of those of the raw materials (Figure 2C). After coprecipitation from ethanol, the characteristic peaks derived from crystalline IDM and LDC disappeared and new diffraction peaks, not found in the XRD patterns of IDM and LDC crystals, appeared at 2θ = 13.2°, 13.7°, and 18.2° (as indicated by closed circles in Figure 2D). These new peaks agreed well with those calculated from crystallographic data for IDM–LDC crystalline complex[9]. This implied that intact crystal structures of IDM and LDC completely altered, and the new molecular arrangement was identical to that of the crystalline complex resolved by single-crystal X-ray analysis. The powder XRD pattern of the IDM–LDC complex will be used to confirm the formation of the complex via solid state in the following section.

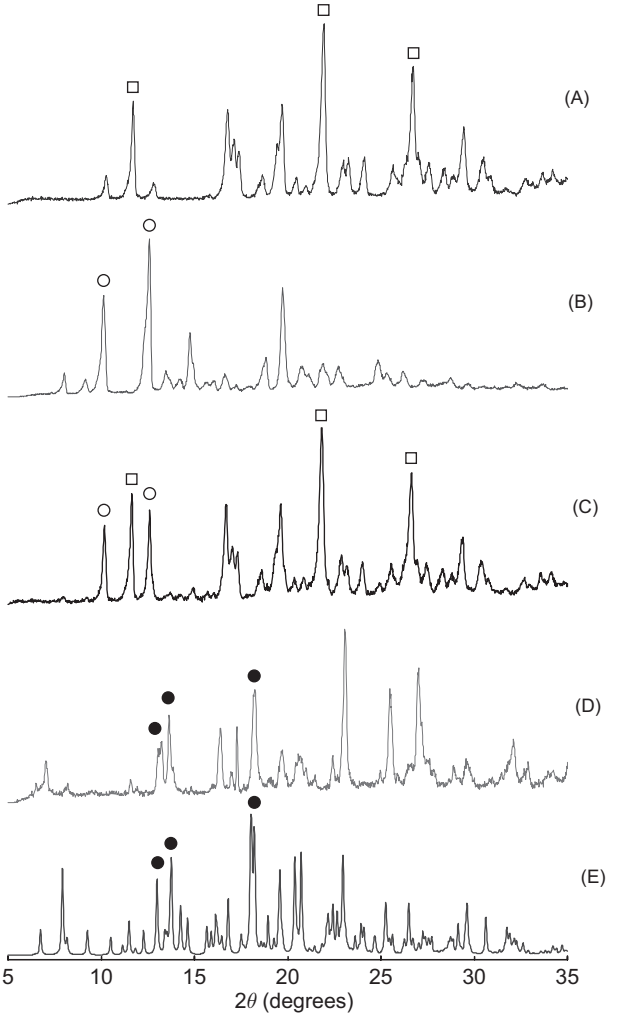

Figure 2. Powder XRD showing crystalline complex formation and simulated pattern of IDM–LDC systems, (A) IDM, (B) LDC, (C) physical mixture, (D) precipitated complex, and (E) calculated complex (symbols □, ○, and ● indicate IDM, LDC, and complex, respectively).

DSC study

DSC measurements were carried out to clarify the thermal behaviors of IDM, LDC, and their mixture (Figure 3). Two sharp endothermic peaks were observed around 68°C and 160°C, which were attributed to the fusion of crystalline LDC and IDM, respectively. The physical mixture showed a broad endothermic peak corresponding to the fusion of LDC crystals around 52°C even though a temperature depression of the endothermic peak possibly because of the existence of IDM as an impurity was observed. In contrast, the coprecipitated complex showed no clear endothermic peak because of the fusion of LDC crystals and showed a new endothermic peak at 123°C. The thermodynamic parameters are summarized in Table 1.

DSC is frequently used to predict the compatibility between drug and excipients in preliminary stability tests. Marini et al.[15] reported that IDM interacted with polyvinylpyrrolidone, and the melting enthalpy of IDM fell into the 8.2–9.8 J/g range, that is, about half its expected value of 19 J/g in binary blends. The heat of fusion of the IDM–LDC binary mixture (2:1) was estimated at 28.1 kJ/mol by calculation from values in the literature[12–14]. This drastic decrease of endothermic peak area in the physical mixture suggested that most IDM molecules should be molecularly dispersed with melted LDC (Figure 3C and Table 1). In contrast, the crystalline complex showed a heat of fusion similar to the estimated value, which was equal to the total enthalpy of the individual components. This implies the formation of a new crystalline lattice with an intermolecular network composed of IDM and LDC.

Infrared spectroscopy

For structural characterization of the complex, infrared (IR) spectroscopy was employed. In the IR spectra for both IDM alone and the physical mixture, characteristic bands were observed at 1717 and 1692 cm^{-1} (Figure 4A–C), corresponding to the carbonic stretching band of the carboxylic acid dimer and the nonprotonated amide in the γ-form of IDM, respectively[16]. A broad peak was also observed at 1664 cm^{-1}, being assigned to the carbonyl stretching vibration of LDC (Figure 4B).

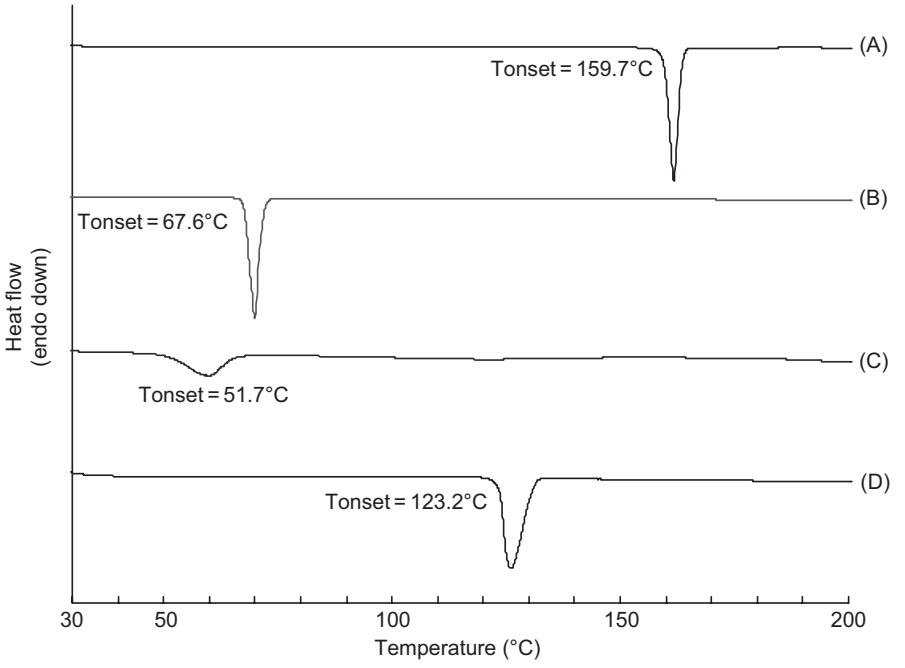

Figure 3. Changes in the DSC curves of IDM–LDC systems: (A) IDM, (B) LDC, (C) physical mixture, and (D) precipitated complex.

Table 1. Thermometric parameters of IDM–LDC system.

		ΔH_f		
	Temperature (°C)	J/g	kJ/mol	kJ/mol
IDM	159.7 ± 0.4	92.6 ± 2.0	33.2 ± 0.7	33.8[a]
LDC	67.6 ± 0.5	57.6 ± 0.7	13.5 ± 0.2	16.6[b]
Physical mixture	51.7 ± 0.6	16.1 ± 0.7	5.1 ± 0.2	28.1[c]
Complex (2:1)	123.2 ± 0.4	77.0 ± 3.8	24.4 ± 1.2	—

Each value represents the mean ± SD (n = 3). [a]Otsuka et al., 1986[12]; Legendre et al., 2004[13]. [b]Approximate value estimated from the literature[14]. [c]Calculated from the data of raw compounds.

Coprecipitated complex showed the carbonyl stretching bands uniting into a broad peak at around 1685 cm^{-1} in the C=O stretching region. We previously reported that spectral change similar to the complex was observed when IDM and LDC were kneaded with small amount of water. In that paper, it was concluded that each intact hydrogen bond network collapsed and strong interactions between IDM and LDC were formed[8] (Figure 4E). Accordingly, the molecular states of IDM and LDC in the coprecipitated complex would be similar to those in the kneaded mixture. In summary, the chemical and physical nature of the crystalline complex formed between IDM and LDC was clearly elucidated by the alliance of powder XRD, DSC, and IR spectroscopy. Current studies in our laboratories are addressing the pharmaceutical behavior of this complex. The pharmacological features and relating properties of this complex are the subjects of a manuscript in preparation.

Elucidation of formation process in the complex

Effects of mechanical force, heating, and storage on complexation

Preparation of the complex in the solid state was attempted to investigate the complexation process of IDM and LDC. The physical mixture of IDM and LDC was ground and heated, then evaluated by using powder XRD and DSC measurement. As mentioned above, the physical mixture showed diffraction peaks corresponding to both crystalline IDM and LDC. When IDM and LDC were, however, coground for 10 minutes at room temperature, the diffraction peaks of crystalline LDC disappeared, thus LDC crystal was amorphized as shown in Figure 5IC. In the DSC curve of this ground mixture, an exothermic peak was observed around 100°C followed by an endothermic peak which was similar to the IDM–LDC complex. Accordingly, the coground mixture was heated in a thermostatic oven at 100°C for 1 hour, and the characteristic diffraction peak and endothermic peak corresponding to the complex were observed on powder XRD and DSC (Figure 5ID and IID). In addition, the physical mixture was stored in dried condition (0% relative humidity) at room temperature for 1 week without any physical treatment. As a result, no obvious change was realized in the XRD (Figure 5IB), whereas endothermic peaks were

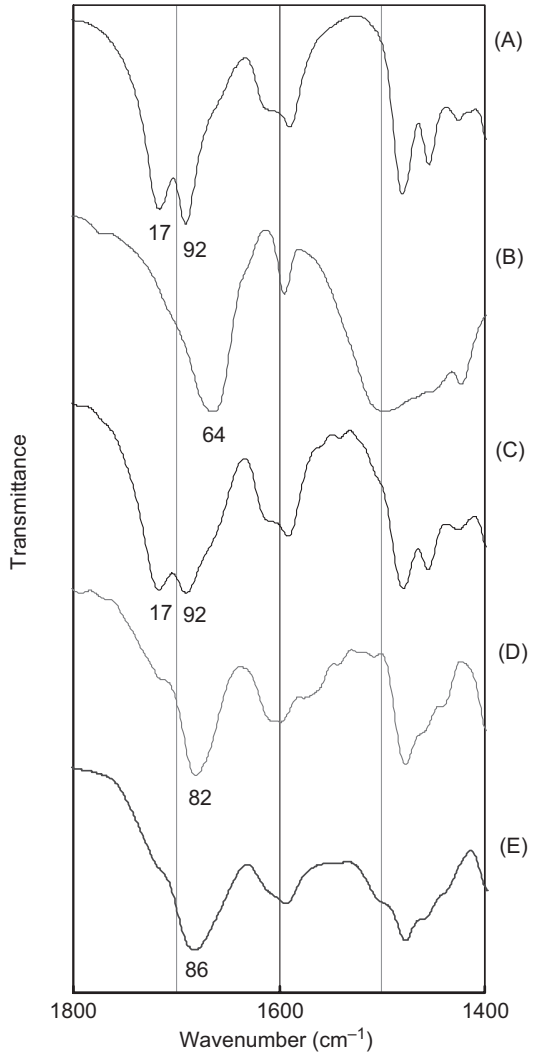

Figure 4. FT-IR spectra of IDM–LDC systems: (A) IDM, (B) LDC, (C) physical mixture, (D) precipitated complex, and (E) kneaded mixture[8].

observed around 122°C as well as 62°C, which were similar to the crystalline complex and LDC, respectively (Figure 5IIB). Although the mechanisms of cocrystal formation from the melt are not completely understood and warrant further investigation, similar endothermic peaks around 120°C suggests formation of the complex in solid state.

These results are presented schematically in Figure 6. Mechanical force and generated frictional heat could play an important role during mechanochemical synthesis of crystalline complex[17]. Thus, the complex might be formed in association with the following factors: (i) mixing and contact of two components, (ii) disorder of crystalline LDC (amorphization by grinding or fusion by heating), and then (iii) crystal growth by heating. As IDM–LDC complex was formed via the preparation in solid state, the driving force regarding complexation is discussed in the next section.

Reviewing the crystal structure of IDM–LDC complex

As stated above, the multicomponent system is composed of two or more components associated through intermolecular interactions where a component is an atom, ion, or molecule[18]. Although the definition of multicomponent systems is still a matter of controversy, distinctions between salts and cocrystals can be based on whether a proton transfer has occurred from an acid to a base[19]. The crystal structure of IDM–LDC complex, which was reported previously[9], was thus reviewed in detail to clarify the fashion of intermolecular interaction. Figure 7A shows the interaction site between carboxyl group of IDM and amide group of LDC, which also indicates the C—O bond lengths. There was also a free carboxylic group in another IDM molecule. The ratio of the C—O (long) to C—O (short) bond lengths was 1.020 in the carboxylic group interacting with LDC amide group but 1.071 in the free carboxylic group. Aakeröy et al. reported a distinction of salts from cocrystals by analyzing the 85 crystal structures. Each compound was the product of a reaction between a carboxylic acid and *N*-heterocyclic rings and was classified as a salt or cocrystal by the degree of proton transfer as shown in Figure 7B. They concluded that the average ratio of the C—O bond length was 1.027(15) for salts and 1.081(12) for cocrystals[20]. These components, therefore, would associate with charge-assisted hydrogen bonds, and thus the IDM–LDC crystalline complex would be regarded as a salt.

MICCS-^{1}H-NMR

The primary interacting force would be ionic coulomb energy from the study in the crystal structure of the IDM–LDC complex. Hence, NMR spectroscopy was employed to reveal the molecular states of the components in ethanol solution. Figure 8 shows MICCS-^{1}H-NMR spectra of the IDM–LDC system. The peaks of the methylene protons belonging to the diethyl amino group of LDC shifted downfield with a decrease in the ratio of LDC to IDM. This suggests an increment of nuclear shielding effect around the tertiary amine of LDC, which was caused by acidic IDM molecules acting as hydrogen donors. ^{1}H-NMR spectroscopy has frequently been applied to the investigation of ionic association, such as ion pair formation between polyethylene oxide and barium salts[21] and in the imidazolium halide salts as ionic liquid[22]. Downfield shift of ^{1}H signal was induced by the shift of the ion pair equilibrium toward tight ion pairs from free ions. Thus, the induction of the chemical shift was because of the ionic pairing between acidic proton of IDM and nucleophilic diethyl amino group of LDC. We reported the ^{1}H-NMR spectra of IDM–LDC system

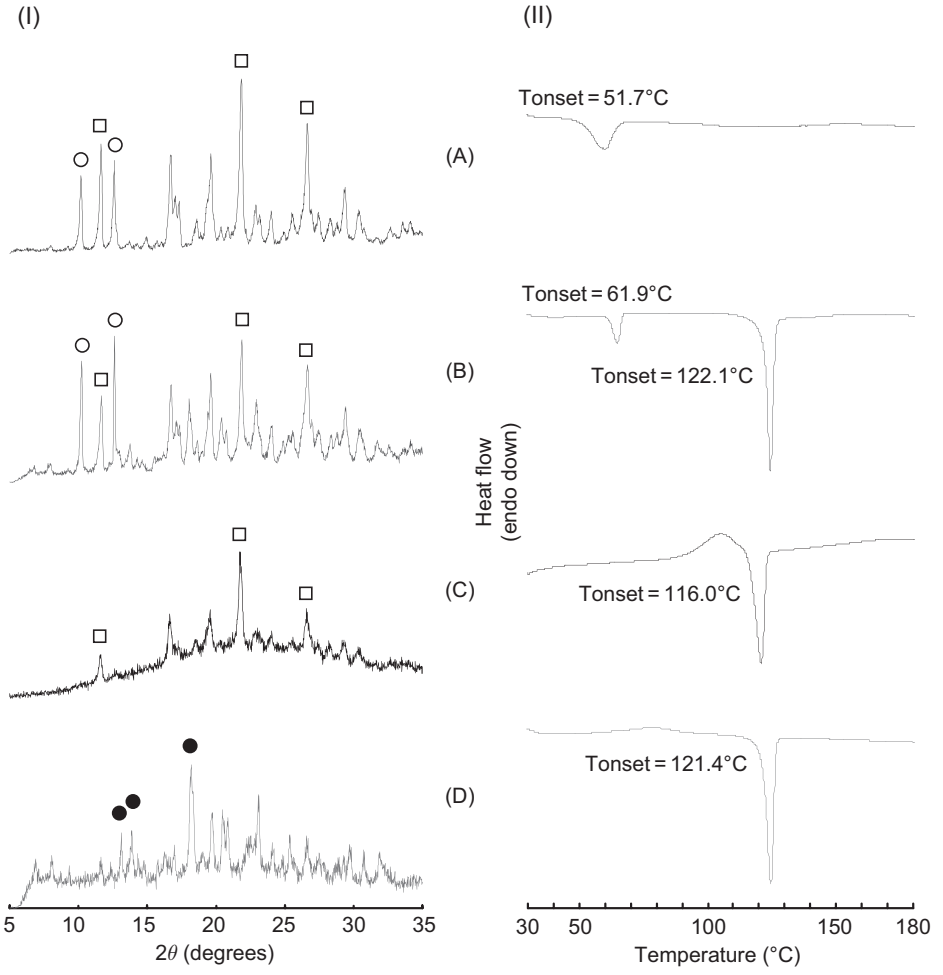

Figure 5. Comparison of powder X-ray diffractograms (I) and DSC curves (II) varying through the storage or mechanical treatment in the IDM–LDC system: (A) physical mixture, (B) specimen A stored at room temperature for 1 week, (C) specimen A coground at room temperature for 10 minutes, and (D) specimen C heated at 100°C for 1 hour after cogrinding (symbols □, ○, and ● indicate IDM, LDC, and complex, respectively).

measured in D_2O and observed ionic interaction between IDM and LDC[8]. In this study, the formation of ion pair was suggested even though the ^{1}H-NMR measurement was performed in ethanol solution. Although ethanol is freely miscible with water, its polarity is lower than that of water. In fact, hydrophobic IDM is more soluble in ethanol than water. As concentration of components in solvent affects stoichiometry of complex formed[23], higher solubility of IDM in ethanol might be responsible for the formation of 2:1 complex. In addition, some reaction conditions such as sample amount, mixing ratio and rate, solvent, and even temperature could be modified during spectroscopic measurement in the MICCS-NMR system. The reaction occurred in microchannel was captured spontaneously. The MICCS-NMR provides useful information about the optimization of reaction conditions as well as qualitative structural information, as compared with conventional NMR techniques.

Conclusion

In this study, we concluded that IDM and LDC formed proton-transferred crystalline complex via solid-state as well as liquid-state routes. In general, a wide range of chemically varied acids and bases, with a range of pK_a values, molecular weights, and solubilities, can be employed for designing pharmaceutical salts[24,25]. Salt screening can be performed in a completely empirical manner, conducting experiments using comprehensive matching between API and ingredients demonstrated by automated equipment[26,27]. However, this is not the most efficient approach[3]. The complex consisting of IDM and LDC is chemically stable and more soluble in water than each drug alone; therefore it is expected to have a synergistic pharmacological effect on the transdermal therapeutic system, which is currently being examined in our laboratory. Accordingly, this medicinal-oriented approach can offer new possibilities for the

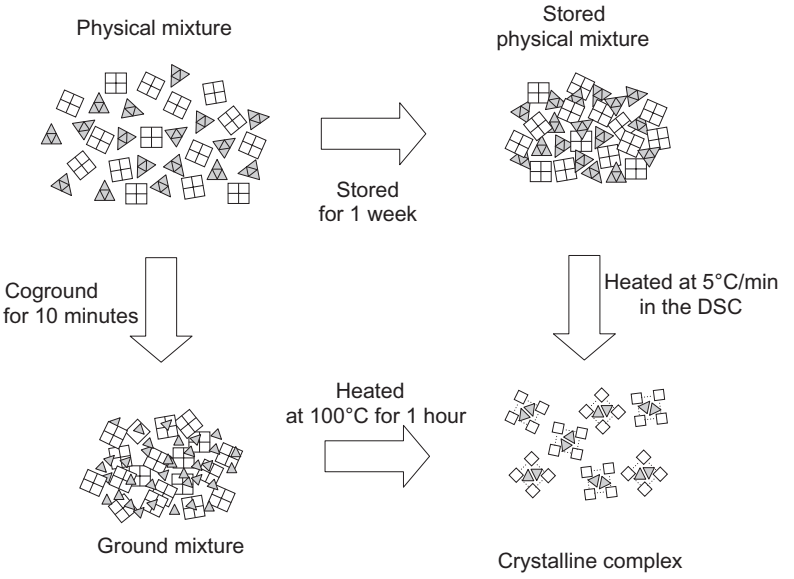

Figure 6. Schematic representation for the process of crystalline complex formation in the IDM and LDC system (symbols □ and ▲ indicate IDM and LDC, respectively).

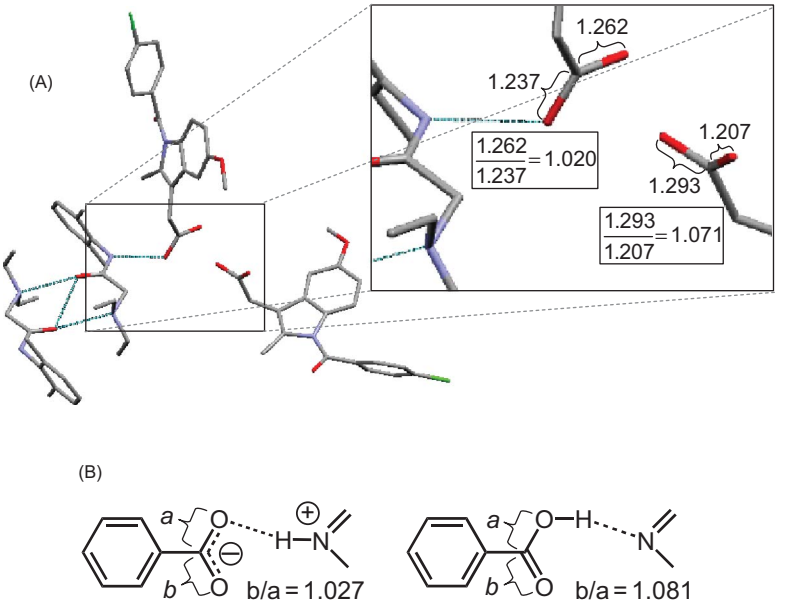

Figure 7. Environment around the carboxyl group of IDM, indicating C–O bond length as structural parameter in the IDM–LDC complex, (A) IDM–LDC crystalline complex, (B) classification as a salt (left) or cocrystal (right) determined by proton transfer[19].

development and life-cycle management of pharmaceutical products as well.

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Declaration of interest: The authors report no conflicts of interest.

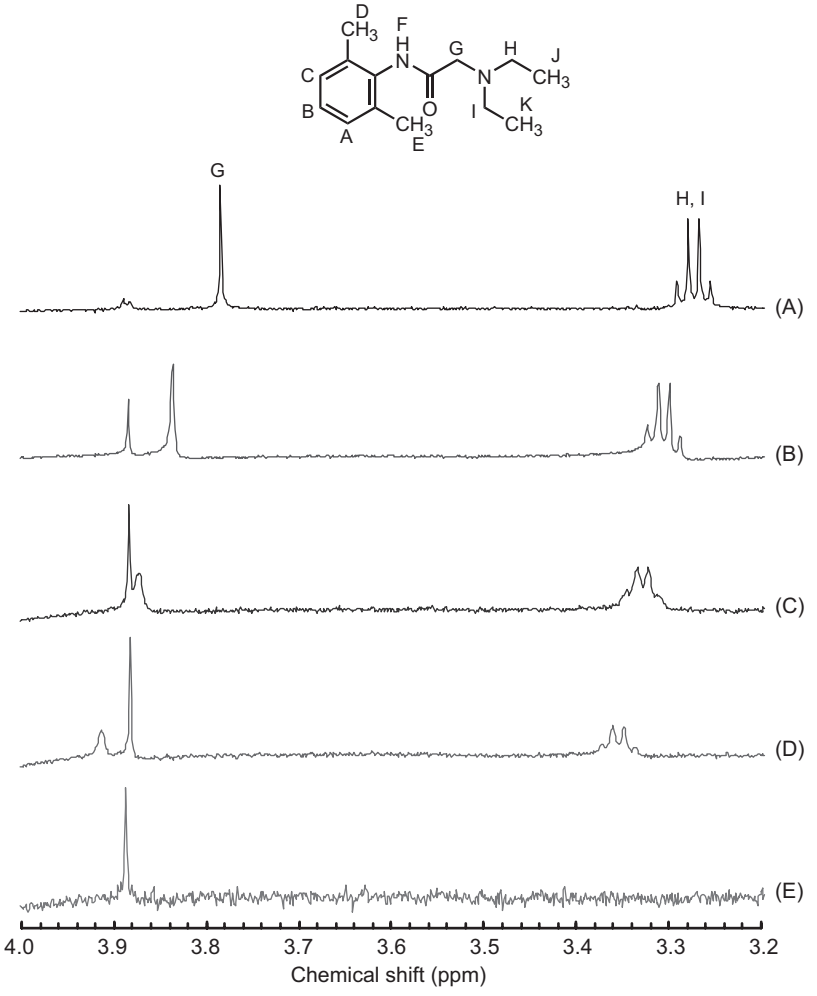

Figure 8. ^{1}H-NMR spectra for IDM–LDC systems measured by using MICCS-NMR, (A) LDC, (B) LDC–IDM (3:2), (C) LDC–IDM (1:2), (D) LDC-IDM (1:5), and (E) IDM.

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