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11

Thermodynamic Study of Grinding-Induced Loratadine Inclusion Complex Formation Using Thermal Analysis and Curve-Fitted FTIR Determination

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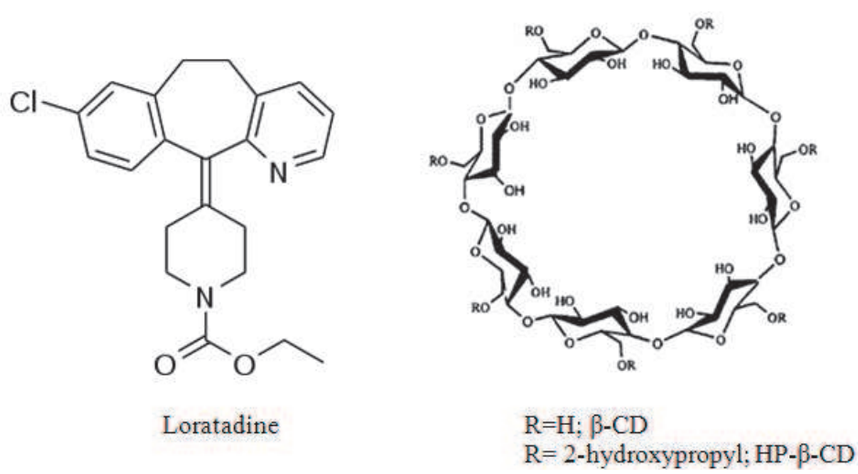
1. Introduction

Cyclodextrins (CDs) have been considerably raised interest and attention in the pharmaceutical sciences due to their specific ability to form inclusion complexes with many drugs, leading to significant enhancements of the solubility, stability and bioavailability, as well as decrease in the bitterness and tissue irritation of the drugs (Carrier et al., 2007; Challa et al., 2005; Miller et al., 2007). Thus, CDs have been extensively applied to the pharmaceutical dosage form development for various drugs. Up-to-date, over 30 CD-containing drug products have been commercialized on the global pharmaceutical market for clinical use (Davis & Brewster, 2004; Loftsson & Brewster, 2010).



Chemical structures of loratadine, β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD)

Loratadine (LOR) is the most commonly used second-generation antihistamine drug for the symptomatic relief of allergic disorders without significant side effects on the central and autonomic nervous systems (Kaiser et al., 2008; Kay & Harris, 1999). One major limited use

of LOR is its water insoluble property. It has been reported that LOR belongs to a BSC (Biopharmaceutical Classification System) class II low solubility and high permeation drug (Khan et al., 2004). Due to the poor water-soluble property and low dissolution rate of LOR, the oral bioavailability of LOR exhibited high intra and inter subject variabilities (Khan et al., 2004; Ramirez et al., 2010). Therefore, how to improve the solubility of LOR in an aqueous solution plays an important role in the pharmaceutical formulation design.

A lot of methods such as grinding, kneading, freeze drying, spray drying and slow evaporation have been widely reported to prepare the inclusion complexes for numerous drugs (Carrier et al., 2007; Challa et al., 2005; Miller et al., 2007; Singh et al., 2010). Grinding is one of the most effective processes not only to alter the molecular behavior of the ground drugs with or without additives but also to improve the molecular interaction between drugs and additives in the ground mixture (Morris et al., 2001; Zhang et al., 2004). The inclusion complex of LOR with β-cyclodextrin (β-CD), hydroxypropyl-β-CD (HP-β-CD) or dimethyl-β-CD had been studied by kneading, spray-drying, freeze-drying and microwave irradiation (Nacsa et al., 2008; Omar et al., 2007; Nacsa et al., 2009), but the conventional solid-state grinding usually used in the pharmaceutical industry for preparing inclusion complex of LOR is scanty investigated (Lin et al., 2010).

Although the grinding has been used to prepare the inclusion complex of the drug, the grinding-induced inclusion mechanism of the drug into the cavity of β-CD or HP-β-CD to form an inclusion complex is less studied. In the present study, the progressive steps of inclusion complex formation caused by grinding the LOR with β-CD were quantitatively investigated by differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) microspectroscopy with curve-fitting analysis, as compared with the ground mixture of LOR/HP-β-CD (Lin et al., 2010). The thermodynamic kinetics and inclusion efficiency of LOR entering the cavity of β-CD or HP-β-CD to form an inclusion complex were explored.

2. Materials and methods

2.1 Materials

A pharmaceutical grade of loratadine (LOR, Jai Radhe Sales, Gujarat, India) was used without further purification. Beta-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) were obtained from Chinoin Pharm. & Chem. Works Ltd, Budapest, Hungary and Roquette Freres, Lestrem, France, respectively. All the other materials were of analytical reagent grade.

2.2 Preparation of ground mixtures of LOR with β-CD or HP-β-CD

Each ground mixture of LOR and β-CD (LOR/β-CD) or LOR and HP-β-CD (LOR/HP-β-CD) with a 1:1 molar ratio was respectively prepared in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) with 15 Hz oscillation frequency. About 0.2 g of powder sample was placed in a 25 ml volume stainless steel milling jar containing two 15 mm diameter stainless steel balls, and then oscillated. In the grinding process, the sample was withdrawn at the prescribed intervals for further examination (Lin et al., 2010).

2.3 Thermal analysis

Each sample was determined by using a differential scanning calorimetry (DSC, Q20, TA Instruments, Inc., New Castle, DE, USA) at a heating rate of 3°C/min with an open pan

system in a stream of N_2 gas. The enthalpy of endothermic peak in the DSC curve was calculated. There was no oxidation or decomposition phenomenon observed in these determining conditions before the melting of LOR (Gao & Lin, 2010; Lin et al., 2006, 2010).

2.4 Curve-fitted FTIR determination

The infrared spectrum of each sample was analyzed with a Fourier transform infrared (FTIR) microspectroscopy (IRT-5000-16/FTIR-6200, Jasco Co., Tokyo, Japan) equipped with a mercury cadmium telluride (MCT) detector via a transmission technique (Gao & Lin, 2010; Lin et al., 2006, 2010). All the FTIR spectra were obtained at a 4 cm^{-1} resolution and at 100 scans. The components and relative compositions of each sample were estimated quantitatively within the 1740-1600 cm^{-1} region of FTIR spectra by a curve-fitting algorithm with a Gaussian-Lorenzian function (Cheng et al., 2008; Hu et al., 2002). The best curve-fitting procedure was performed by iterative fits toward a minimum standard error. The relative composition of the component was computed to be the fractional area of the corresponding peak, divided by the sum of the area for all the peaks.

3. Results and discussion

Mechanical grinding is well known to be one of the important manufacturing procedures in the pharmaceutical industry (Morris et al., 2001; Zhang et al., 2004). The energetic input of solid-state grinding has been reported not only to alter the particle size, crystallinity, and solid-state polymorphic conversion of the drug but also to produce the drug-excipient interaction, resulting in the modification of physical and chemical properties of drug to finally influence the drug bioavailability (Carrier et al., 2007; Challa et al., 2005; Davis & Brewster, 2004; Loftsson & Brewster, 2010; Miller et al., 2007; Morris et al., 2001; Zhang et al., 2004).

3.1 Grinding-induced changes in LOR crystallinity in the presence of β-CD or HP-β-CD

The grinding-induced enthalpy changes in the DSC curves of the physical and ground mixtures of LOR/β-CD or LOR/HP-β-CD with a 1:1 molar ratio after different grinding times are shown in Figs. 1 and 2, respectively. It clearly indicates that a sharp endothermic peak at 135.1 or 134.6°C was observed in the DSC curve of the physical mixture of LOR/β-CD or LOR/HP-β-CD, which was close to the endothermic peak at 136.1°C for intact LOR (Lin et al., 2010; Ramos & Cavalheiro, 2007). This endothermic peak at 135.1 or 134.6°C was due to the melting point of LOR in the presence of β-CD or HP-β-CD, because the temperature range within 30-160oC lacked an endothermic peak for intact β-CD or HP-β-CD. A sharp endothermic peak at 135.1°C for LOR in the physical mixture of LOR/β-CD became smaller with the increase of the grinding time, and this endothermic peak disappeared after grinding for 15 min. The disappearance of this endothermic peak might be due to the amorphization and/or inclusion complex formation after grinding (Chowdary & Srinivas, 2006; Giordano et al., 2001; Willart & Descamps, 2008). By grinding the physical mixture of LOR/HP-β-CD, on the other hand, the DSC endothermic peak disappeared after a 7 min-grinding course. The disappearance of this endothermic peak was also similar to that of LOR/β-CD, due to the grinding-induced amorphization and/or inclusion complex formation. It is evident that HP-β-CD was more efficient than that of the β-CD to reduce the peak intensity of LOR in the DSC curve.

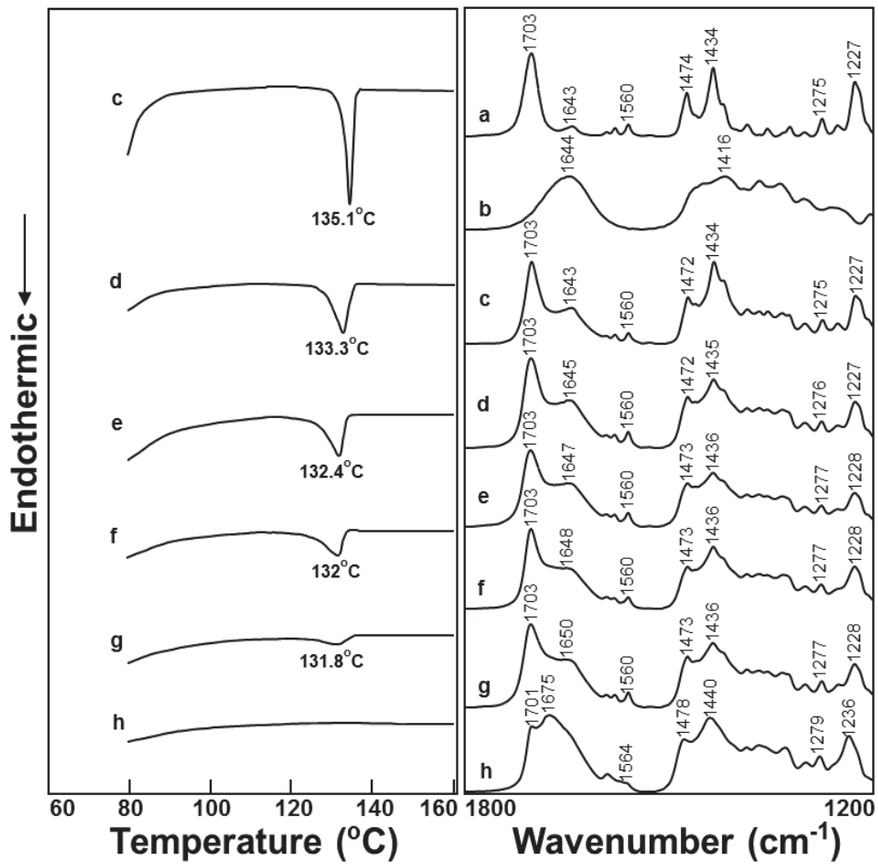


Fig. 1. The grinding-induced enthalpy changes and FTIR spectral shifts of the physical and ground mixtures of LOR/β-CD with a 1:1 molar ratio. Key, a, LOR; b, β-CD; Grinding time: c, o min; d, 3 min; e, 5 min, f, 7 min; g, 10 min, h, 15 min.

Once the physical mixture of drug and CDs was ground, two possible mechanisms can occur. One is the reduction in drug crystallinity due to the cogrinding effect with additive; another is the intact formation of inclusion complex. It is well-known that when the drug was amorphized or formed an inclusion complex, its endothermic peak in the DSC curve commonly disappeared (Chowdary & Srinivas, 2006; Giordano et al., 2001; Willart & Descamps, 2008). From the explanation of DSC results alone, the decrease in the value of DSC enthalpy was difficult to attribute whether the actual CD inclusion complex formation or the amorphization of drug after grinding process. However, the total changes in DSC enthalpy induced by grinding process could be easily evaluated. The relative degree of LOR crystallinity (RDC_{LOR}, %) in the physical or ground mixture might be estimated from the DSC curve by the ratio between the melting enthalpy of the LOR calculated in each sample and that of the melting enthalpy of starting physical mixture or pure LOR (Mura et al., 2003; Sauceau et al., 2008), according to the Eq. (1)

$$\mathrm{RDC}_{\mathrm{LOR}}(\%) = \frac{\Delta H_{MIX}}{\Delta H_{LOR}} \times 100 \tag{1}$$

where ΔH_{MIX} is the melting enthalpy of LOR calculated in the physical or ground mixture, and ΔH_{LOR} is the melting enthalpy of starting physical mixture or pure LOR.

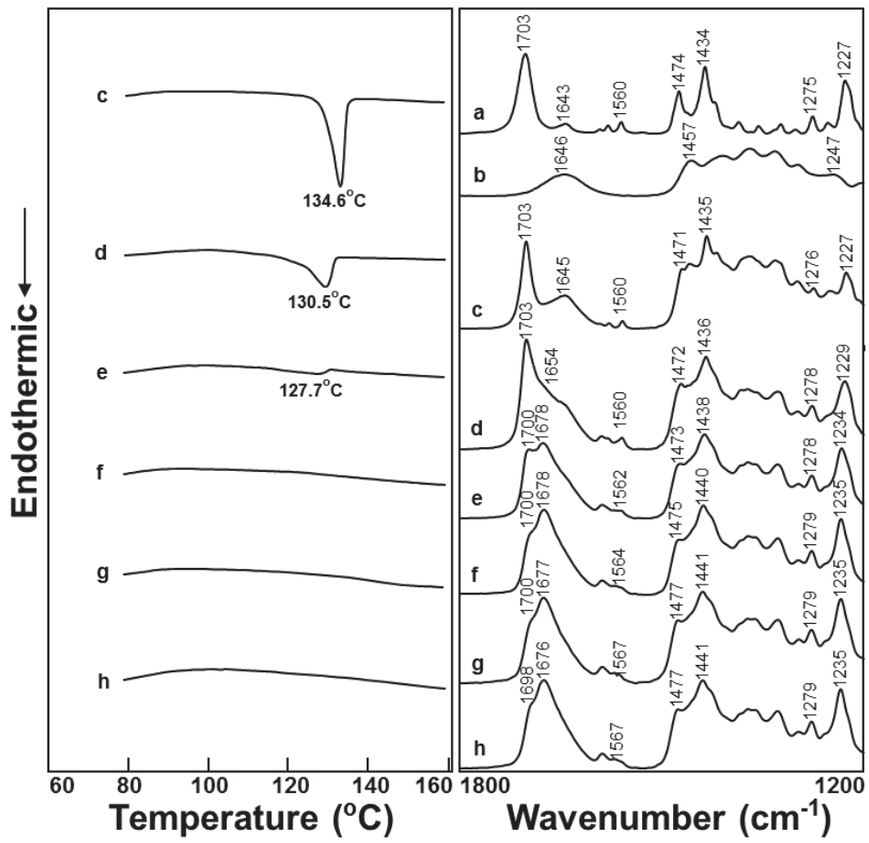


Fig. 2. The grinding-induced enthalpy changes and FTIR spectral shifts of the physical and ground mixtures of LOR/HP-β-CD with a 1:1 molar ratio. Key, a, LOR; b, HP-β-CD; Grinding time: c, o min; d, 3 min; e, 5 min, f, 7 min; g, 10 min, h, 15 min.

The effect of grinding time on the RDC_{LOR} in the absence or presence of β-CD or HP-β-CD is displayed in Fig. 3. Obviously, the crystallinity of LOR was reduced with the increase of grinding time. In addition, the HP-β-CD seems to be faster than that of the β-CD causing the reduction in crystallinity of LOR. The excess amount of HP-β-CD might improve the grinding effect than that of the β-CD used although there was the same molar ratio. Fig. 3 also demonstrates the apparent zero-order kinetics for the reduction in crystallinity of LOR in the presence of β-CD or HP-β-CD with grinding time.

3.2 Grinding-induced FTIR spectral shifts of LOR in the presence of β-CD or HP-β-CD

The FTIR spectral shifts for the physical and ground mixtures of LOR/β-CD or LOR/HP-β-CD at 1:1 molar ratio after grinding are also shown in Figs. 1 and 2. Several characteristic IR absorption bands for LOR, β-CD or HP-β-CD may be assigned as follows: 1703 cm^{-1} (C=O of ester), 1560, 1474 and 1434 cm^{-1} (stretching vibrations of benzene ring), 1227 cm-1 (C-O stretching) for LOR; 1644 or 1646 cm^{-1} (OH groups of the glucose moieties) for β-CD or HP-

β-CD, respectively (Nacsa et al., 2008, 2009; Zhao et al., 2003; Pedersen et al., 2005). In the LOR/β-CD mixture, four new peaks at 1675, 1478, 1440 and 1236 cm^{-1} were clearly observed after grinding for 15 min. The appearance of these new IR peaks might be due to the inclusion complex formation between LOR and β-CD. Once β-CD was replaced by HP-β-CD, however, the changes in FTIR spectra for LOR/HP-β-CD ground mixture were more pronounced.

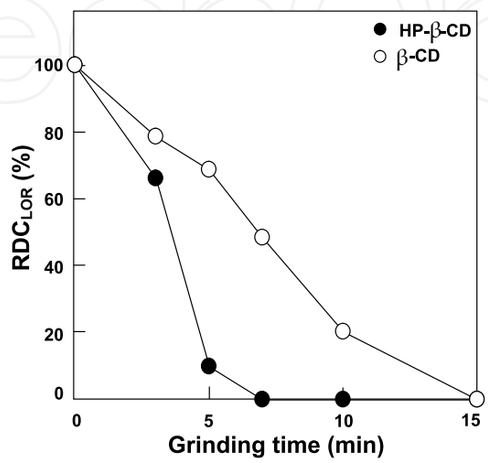


Fig. 3. The effect of grinding time on the RDC_{LOR} of LOR in the absence or presence of β-CD or HP-β-CD.

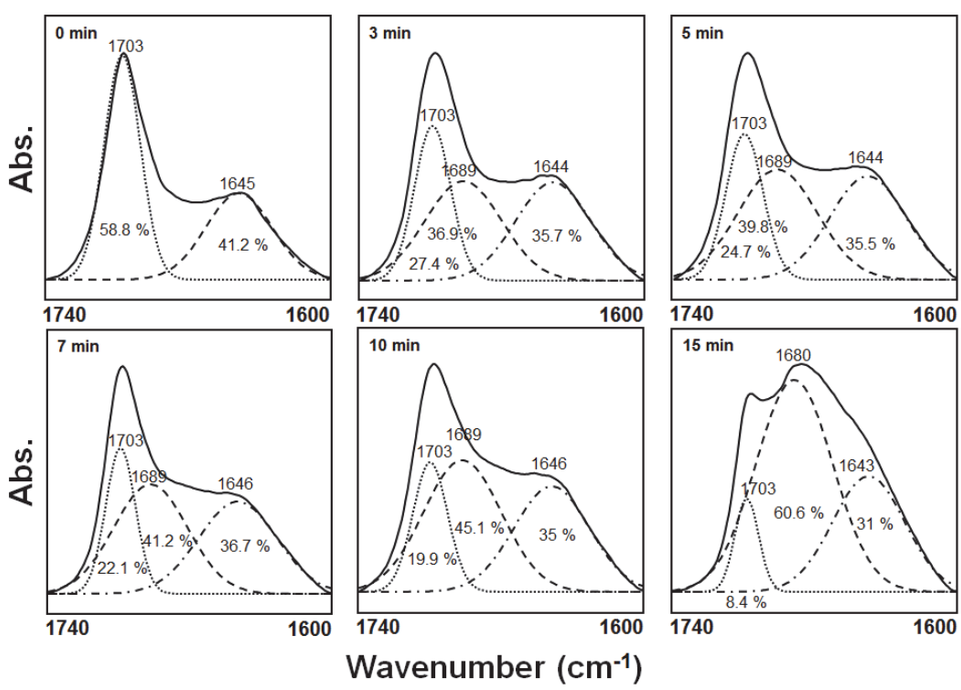


Fig. 4. The representative best-fitted FTIR spectra and the deconvoluted components for the physical mixture of LOR with β-CD before and after various grinding times.

After grinding for 5 min, a shoulder at 1678 cm^{-1} was observed. By increasing the grinding time, the shoulder at 1678 cm^{-1} was shifted to a predominant peak at 1676 cm^{-1}. In addition, the peak at 1229 cm^{-1} assigned to C-O stretching vibration was also shifted to 1235 cm^{-1}. The IR spectrum of 15 min-ground mixture was the same as the IR spectrum of the inclusion complex prepared by co-evaporation method reported in our previous study (Lin et al., 2010). Due to the inclusion complex formation, the characteristic bands at 1703 and 1227 cm^{-1} of LOR were down-shifted to 1676 cm^{-1} and up-shifted to 1235 cm^{-1}, respectively. Moreover, the structural benzene ring-related specific peaks at 1434, 1474, 1560 cm^{-1} were also shifted to 1441, 1477 and 1567 cm^{-1}, respectively. The progressive inclusion mechanism of LOR entering into the cavity of β-CD or HP-β-CD via grinding process was clearly evidenced.

The time-dependent inclusion complex formation of LOR/β-CD or LOR/HP-β-CD with a 1:1 molar ratio in the grinding process was estimated from the IR spectra by using the curve-fitting technique, as shown in Figs. 4 and 5. Obviously, the changes in IR spectra and the relative compositions of three components were obtained for both ground mixtures with the increase of grinding time. Three components were certainly estimated from the IR spectrum of each ground mixture, as compared with two components for LOR and one component for β-CD or HP-β-CD (Lin et al., 2010). Excluding the inherent peaks of LOR (1700-1703 cm^{-1}) and β-CD or HP-β-CD (1643-1646 cm^{-1}), the new peak formed after grinding might be attributed to the inclusion complex formation. In the LOR/β-CD ground mixtures, the best-fitting results indicate that the relative composition of the peak at 1703 cm^{-1} due to LOR was clearly reduced with the grinding time.

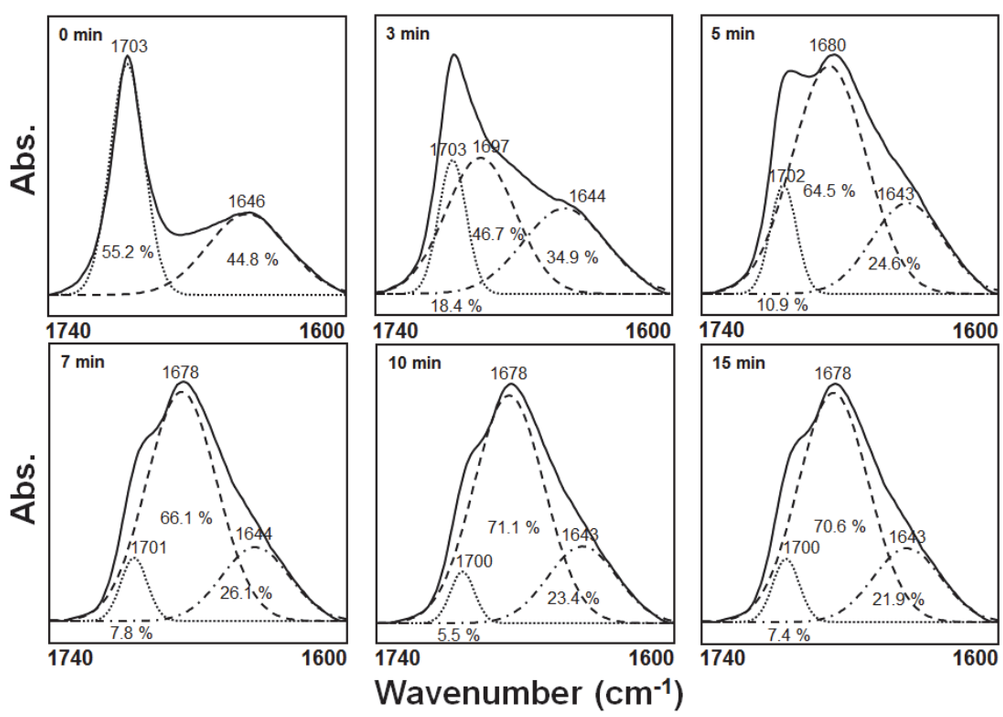
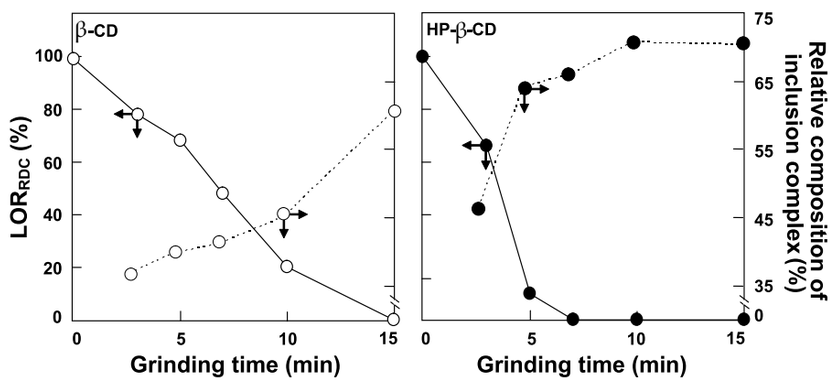


Fig. 5. The representative best-fitted FTIR spectra and the deconvoluted components for the physical mixture of LOR with HP-β-CD before and after various grinding times.

The unique IR peak at 1689 cm^{-1} was evidenced from the 3 min-ground mixture and also increased its relative composition slightly with grinding time. After grinding for 15 min, the peak position of inclusion complex formed was shifted from 1689 to 1680cm^{-1} and its relative compositions were increased from 36.9% to 60.6%. While in the LOR/HP-β-CD ground mixtures, the IR spectral peak at 1697 cm^{-1} was shifted to 1678 cm^{-1} in the grinding course from 3 to 15 min. Moreover, the relative composition of LOR/HP-β-CD inclusion complex was increased from 46.75 to 70.6% with the increase of grinding time.

Figure 6 indicates the relationship between the relative degree of crystallinity of LOR and the relative composition of inclusion complex in the grinding course. Obviously, the formation of inclusion complex for LOR/β-CD or LOR/HP-β-CD was significantly correlated with the reduction in LOR crystallinity under different grinding times. With the increase of grinding time, the crystallinity of LOR was gradually reduced but the inclusion complex formation was conversely enhanced. The possible inclusion mechanism of LOR/β-CD or LOR/HP-β-CD with the increase of grinding time might be proposed via the progressive reduction in LOR crystallinity at the initial and then gradual increase of amorphization of LOR, and finally the amorphized LOR molecule was included in the cavity of β-CD or HP-β-CD to form the inclusion complex.



Solid line: determined by DSC; dotted line: determined by FTIR

Fig. 6. The relationship between the relative degree of crystallinity of LOR and the relative composition of inclusion complex in the grinding course.

4. Conclusions

The results of present study indicate that the formation of inclusion complex for LOR/β-CD or LOR/HP-β-CD was significantly correlated with the reduction in LOR crystallinity. The apparent zero-order kinetics for the reduction in crystallinity of LOR in the presence of β-CD or HP-β-CD was obtained by increasing the grinding time. The inclusion complex of LOR/β-CD or LOR/HP-β-CD was easily formed with the increase of grinding time via the progressive changes in crystallinity and amorphization of LOR, and then entering the cavity of the β-CD or HP-β-CD molecule.

5. Acknowledgement

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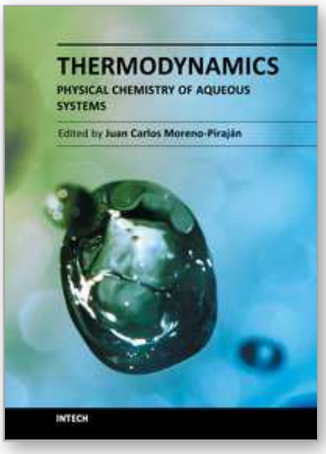

Thermodynamics - Physical Chemistry of Aqueous Systems

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