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Mechanical grinding effect on thermodynamics and inclusion efficiency of loratadine–cyclodextrin inclusion complex formation

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ABSTRACT

The interaction of poor water-soluble drug loratadine (LOR) with β-cyclodextrin (β-CD) or hydroxypropyl-β-cyclodextrin (HP-β-CD) in aqueous or solid state was investigated. Mechanical grinding effect on the inclusion steps, thermodynamic kinetics and inclusion efficiency of inclusion complex formation of LOR with β-CD or HP-β-CD was quantitatively investigated by DSC and FT-IR microspectroscopy with curve-fitting analysis. The phase solubility profiles of LOR with β-CD and HP-β-CD were classified as A_L-type phase diagram. The grinding-induced reduction in LOR crystallinity in the presence of β-CD or HP-β-CD was found to be apparent zero-order kinetics. The inclusion efficiency of solid inclusion complex for LOR/β-CD or LOR/HP-β-CD was significantly correlated with the reduction in LOR crystallinity and the grinding time. The mechanism of inclusion complex formation for LOR/β-CD or LOR/HP-β-CD was proposed through the progressive reduction in LOR crystallinity, the promoted LOR amorphization, and molecular inclusion processes in the continuous energy input process of mechanical grinding.

1. Introduction

Mechanical grinding process is one of the most common unit operations in pharmaceutical industry by grinding the solid drugs via the mechanical forces to pulverize the large solid drug particles to fine powders or to create new molecular or supramolecular assemblies of drugs with or without additives (Fernandez-Bertran, 1999; Hickenboth et al., 2007). The mechanical activation of solid-state grinding can not only prepare the amorphous solids, polymorphs, and solid dispersions but also cause drug–drug or drug–excipient interaction, resulting in the modification of physico-chemical properties, dissolution rate and bioavailability of drugs (Boldyrev, 2004; Chieng, Aaltonen, Saville, & Rades, 2009; Janssens & Van den Mooter, 2009). During the drug–excipient interaction studies, inclusion complex formation between drug and cyclodextrins (CDs) has been playing a very important role in formulation design for water-insoluble drugs (Jackson, Young, & Pant, 2000; Loftsson, Jarho, Másson, & Järvinen, 2005). The effect of mechanical grinding on the polymorphic transformation, drug–excipient interaction and inclusion complex formation of drugs had been investigated in our previous studies (Cheng, Wang, & Lin, 2008; Hsu, Ke, & Lin, 2010; Lin & Perng, 1992; Lin, Cheng, & Wang, 2006; Lin, Hsu, & Sheu, 2010).

For several years cyclodextrins (CDs) have been paid much attention and interest for their ability to form inclusion complexes with many drug molecules by including a whole drug molecule, or some part of it, into the cavity of CDs (Loftsson et al., 2005; Stella & Rajewski, 1997; Valle, 2004). This unique molecular encapsulation technique to form an inclusion complex of drug has been proven to be successful in altering the physico-chemical and biopharmaceutical properties of many drugs, such as irritation, bitterness, volatilization, stability, solubility and dissolution, leading to significant improvement of formulation design and enhancement of bioavailability of drugs (Davis & Brewster, 2004; Laza-Knoerr, Gref, & Couvreur, 2010; Loftsson et al., 2005; Stella & Rajewski, 1997; Valle, 2004). Thus, CDs have been extensively applied to the pharmaceutical dosage form development for various drugs. This may reflect the steady increase in many drug/CD products available on the global pharmaceutical market (Davis & Brewster, 2004; Laza-Knoerr et al., 2010; Loftsson et al., 2005; Stella & Rajewski, 1997; Valle, 2004).

Loratadine (LOR) is a drug commonly used to temporarily relieve the symptoms of hay fever and other allergies (Van Cauwenberge, 2002; Walsh, 2002). LOR is also available in

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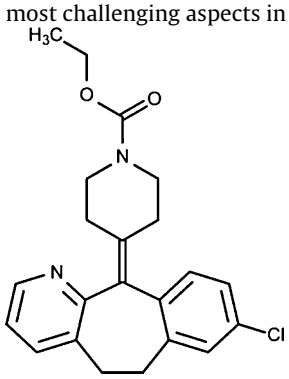
combination with pseudoephedrine as an OTC medicine in the relief of symptoms associated with allergic rhinitis and common cold (Grubbe, Lumry, & Anolik, 2009). However, a large intra or inter subject variability of LOR after oral administration has been reported to correlate with the poor water-soluble property and dissolution rate-limited absorption of LOR (Khan et al., 2004; Ramirez et al., 2010). Therefore, the solubility behavior of LOR remains one of the most challenging aspects in formulation design.



Various methods to prepare the solid inclusion complex of drug/CD binary system have been widely attempted to carry out in a solution or slurry using coprecipitation, evaporation, freeze drying, spray drying, or supercritical fluid process; in a paste using kneading method; or in a solid using mechanical grinding method (Davis & Brewster, 2004; Laza-Knoerr et al., 2010; Loftsson et al., 2005; Stella & Rajewski, 1997; Valle, 2004). The mechanical grinding is simple, inexpensive, solventless, easy to operate and scaleable (Boldyrev, 2004; Fernandez-Bertran, 1999; Hickenboth et al., 2007), it was selected as a suitable tool to prepare the inclusion complex of LOR/CDs in this study. Here, the interaction between LOR and β-CD or HP-β-CD in the aqueous or solid state was examined. The effect of mechanochemical grinding on the progressive steps of inclusion complex formation of LOR with β-CD or HP-β-CD was quantitatively investigated by differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) microspectroscopy with curve-fitting analysis. The thermodynamic kinetics and inclusion efficiency of LOR with β-CD or HP-β-CD to form an inclusion complex by grinding were also studied. Moreover, the inclusion mechanism of LOR incorporating into the cavity of β-CD or HP-β-CD through a grinding process was proposed.

2. Experimental

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. Microcrystalline cellulose (MMC PH101, FMC Co., Philadelphia, PA), hydroxypropyl methylcellulose 4000 (HPMC, Shin-Etsu Chem. Co. Ltd, Tokyo, Japan) and dextran 40 (dextran, Sigma Chemical Co., St. Louis, USA) were used. All the other materials were of analytical reagent grade.

2.2. Solubility studies

Phase solubility studies of LOR in the presence of β-CD or HP-β-CD were carried out in water according to the method described by Higuchi and Connors (1965). An excess amount of LOR was separately added to each 10 ml of aqueous solution containing different concentrations of β-CD or HP-β-CD, and then shaken for 72 h at room temperature. After 72 h, all the suspensions were filtered through 0.45 μm membrane filters. Each filtrate was appropriately diluted with 50% alcoholic water and measured by UV spectrophotometer at 248 nm. There was no any interference coming from β-CD or HP-β-CD to interfere the spectrophotometric assay. Each experiment was performed in triplicate and the mean was obtained. The apparent stability constant (*Kc*) of the LOR/β-CD or LOR/ HP-β-CD inclusion complex was calculated from the slope and intercept of the straight line of the phase-solubility diagram (Valle, 2004), according to following Eq. (1):

$$Kc = \frac{\text{slope}}{\text{intercept}(1 - \text{slope})} \quad (1)$$

where the intercept represents the equilibrium solubility of LOR in the absence of β-CD or HP-β-CD.

2.3. Preparation of the solid inclusion complex of LOR and β-CD or HP-β-CD

The solid inclusion complex of LOR and β-CD (LOR/β-CD) or LOR and HP-β-CD (LOR/HP-β-CD) with 1:1 molar ratio was prepared by solvent evaporation method. Each above physical mixture was respectively dissolved in 80% or 95% ethyl alcohol and then evaporated at room temperature. The dried samples were washed with acetone cooled and then dried at 50 °C.

2.4. Preparation of ground mixtures of LOR with different additives

The ground mixtures of LOR with different additives (MMC, HPMC, dextran, β-CD or HP-β-CD) in a weight ratio of 1:1 were respectively prepared in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) with 15 Hz oscillation frequency. About 0.2 g powder sample was placed in a 25 ml volume stainless steel milling jar containing two 15 mm diameter stainless steel balls by grinding for 30 min. In addition, each ground mixture of LOR/β-CD or LOR/HP-β-CD in the 1:1 molar ratio was also separately prepared. In the grinding process, the sample was withdrawn at the prescribed intervals for further examination (Cheng, Wang, et al., 2008; Hsu et al., 2010; Lin & Perng, 1992; Lin et al., 2006, 2010).

2.5. Differential scanning calorimetric study

Temperature and enthalpy of each sample were determined by using a differential scanning calorimetry (DSC, TA Instruments, Inc., New Castle, DE) at a heating rate of 3 °C/min with an open pan system in a stream of N_2 gas. There was no oxidation or decomposition phenomenon observed in these determining conditions before the melting of LOR. The enthalpy of an endothermic peak in the DSC curve was calculated by integrating the peak area corresponding to a given endothermic transition. Since the degree of crystallinity was correlated with the melting enthalpy (Bettinetti et al., 1999; Mura, Maestrelli, Cirri, Furlanetto, & Pinzauti, 2003), the relative degree of crystallinity of LOR (RDC_{LOR}, %) in the physical and ground mixtures sampled at a prescribed grinding time was estimated by the ratio between the melting enthalpy of the LOR obtained for in each ground sample and that of the starting physical mixture (or pure LOR) (Mura et al., 2003), according to following Eq. (2):

$$\text{RDC}_{\text{LOR}}(\%) = \frac{\Delta H_{\text{sam}(t)}}{\Delta H_{\text{LOR}}} \times 100 \quad (2)$$

where $\Delta H_{\text{sam}(t)}$ and ΔH_{LOR} are the melting enthalpies of LOR calculated from the DSC curve of the ground mixture after t min of mechanical grinding, and the starting physical mixture (or pure LOR), respectively.

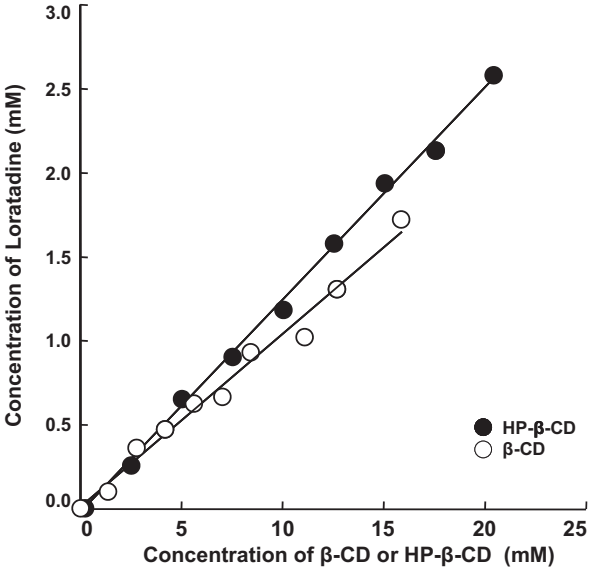


Fig. 1. Phase solubility diagram of LOR with β-CD or HP-β-CD in water at 25 °C.

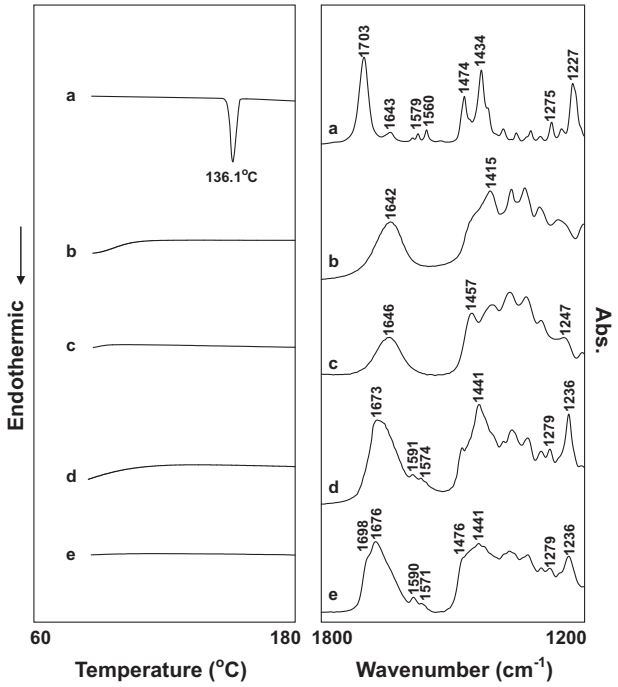


Fig. 2. The DSC curves and FT-IR spectra of raw material of LOR (a), β-CD (b) or HP-β-CD (c), and the solid inclusion complex of LOR/β-CD (d) or LOR/HP-β-CD (e) after solvent evaporation. Key: β-CD or HP-β-CD was previously dried at 100 °C for 10 min.

2.6. Curve-fitted FT-IR determination

All the samples were separately examined by an Fourier transform infrared (FT-IR) microspectroscopy (IRT-5000-16/FT-IR-6200, Jasco Co., Tokyo, Japan) equipped with a mercury cadmium telluride (MCT) detector via a transmission technique (Cheng, Wang, et al., 2008; Hsu et al., 2010; Lin et al., 2006). All the FT-IR 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 FT-IR spectra by a curve-fitting algorithm with a Gaussian–Lorenzian function, as described in our previous studies (Cheng, Lin, & Wang, 2008; Hu, Wang, Chen, & Lin, 2002). The curve-fitting program was combined with a nonlinear deconvolution technique to probe the nature and extent of structural changes in the IR spectra of different samples. The best curve-fitting procedure was performed by iterative fits toward a minimum standard error. The relative composition of a component was computed to be the fractional area of the corresponding peak, divided by the sum of areas of all the peaks.

3. Results and discussion

3.1. Phase solubility study

The solubility diagram of LOR with β-CD or HP-β-CD in water at 25 ± 0.5 °C is shown in Fig. 1. Obviously, the apparent solubility of LOR in water was linearly increased with an increase of the β-CD or HP-β-CD concentrations used. Both phase solubility diagrams can be classified as A_L-type phase diagram, according to the classification of Higuchi and Connors (1965), indicating that the soluble inclusion complex for LOR/β-CD or LOR/HP-β-CD possessed a 1:1 binding stoichiometry. The apparent stability constant (*Kc*) was estimated from the slope of the linear plot of phase solubility diagram according to Eq. (1). The value of *Kc* for LOR/β-CD or LOR/HP-β-CD complex was $2.17 \times 10^4\ M^{-1}$ or $2.22 \times 10^4\ M^{-1}$, respectively. The high *Kc* value reveals that the LOR/β-CD or LOR/HP-β-CD inclusion complex was a quite stable complex. Since two stability constants were of the same order of magnitude for both complexes, implying that the hydroxypropyl derivative of β-CD did not influence the inclusion ability of CD cavity for HP-β-CD. However, a high aqueous solubility of HP-β-CD may be much more feasible than that of β-CD for pharmaceutical applications.

3.2. Characterization and identification of raw materials and solid inclusion complexes

The DSC curves and FT-IR spectra of LOR, β-CD, HP-β-CD, and the solid inclusion complex of LOR/β-CD or LOR/HP-β-CD after solvent evaporation are shown in Fig. 2. Obviously, one endothermic peak at 136.1 °C (enthalpy of 89.8 J/g) due to the melting of LOR was observed in the DSC thermogram of pure LOR, which was consistent with other report (Ramos & Cavalheiro, 2007). The FT-IR spectrum of pure LOR is also displayed in Fig. 2a. Several characteristic IR absorption bands and their assignments for LOR are displayed as follows: 1703 cm^{-1} (C=O stretching of ester), 1560, 1474 and 1434 cm^{-1} (stretching vibrations of benzene ring) and 1227 cm^{-1} (C–O stretching) (Nacsa, Ambrus, Berkesi, Szabó-Révész, & Aigner, 2008; Nacsa, Berkesi, Szabó-Révész, & Aigner, 2009). There was lack of endothermic peak within the temperature range of 30–160 °C for pure β-CD and HP-β-CD after pre-drying at 100 °C. The dominant IR spectral peak at 1642 or 1646 cm^{-1} may be attributed to the OH groups in the glucose moieties of β-CD or HP-β-CD (Pedersen et al., 2005). Fig. 2d and e indicates the DSC curves and FT-IR spectra of the solid inclusion complex for LOR/β-CD or LOR/HP-β-CD after solvent evaporation. It is apparent that there was no any endothermic peak observed in the DSC curves for both solid inclusion complexes, implying that LOR was included into the cavity of β-CD or HP-β-CD. In addition, three predominant IR peaks at 1673, 1441 and 1236 cm^{-1} or at 1676, 1441 and 1236 cm^{-1} were observed in the FT-IR spectrum of LOR/β-CD or LOR/HP-β-CD inclusion complex, respectively. The disappearance of an endothermic peak in the DSC curve and the appearance of new IR spectral peaks might explain the inclusion complex formation between LOR and β-CD or HP-β-CD. Due to the inclusion complex formation, the characteristic band at 1703 cm^{-1} of LOR was down-shifted to 1673 or 1676 cm^{-1}; and at 1434 and 1227 cm^{-1} were upper-shifted to 1441 and 1236 cm^{-1} for both inclusion complexes, respectively.

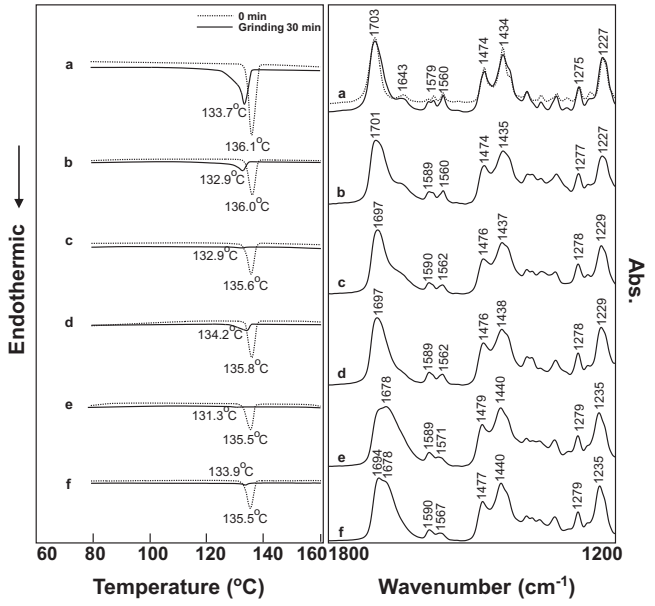


Fig. 3. The effect of mechanical grinding process on the changes in the DSC curves and FT-IR spectra of the physical mixture (weight ratio of 1:1) of LOR with different additives. Key: additives: a, pure LOR; b, MCC; c, HPMC; d, dextran; e, β-CD; f, HP-β-CD.

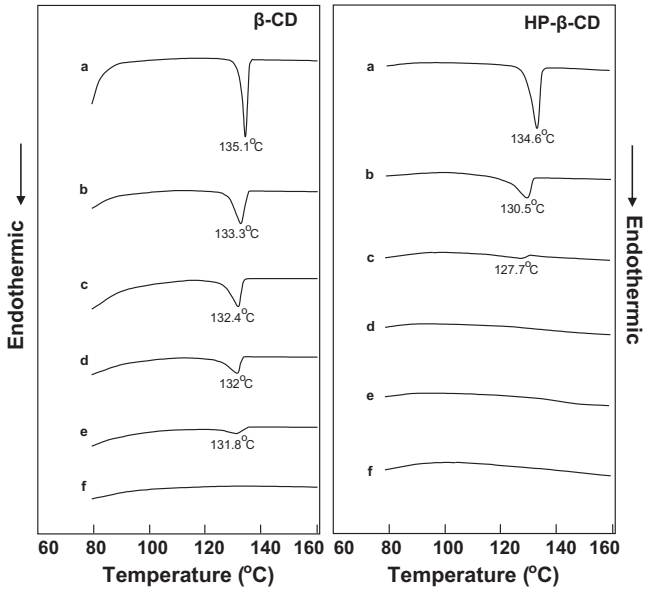


Fig. 4. Changes of DSC curves for the physical mixture of LOR with β-CD or HP-β-CD (1:1 molar ratio) before and after different grinding times. Key: grinding time: a, 0 min; b, 3 min; c, 5 min; d, 7 min; e, 10 min; f, 15 min.

3.3. Grinding effect on the physical mixtures of LOR with different additives

The effect of mechanical grinding process on the changes in the DSC curves and FT-IR spectra of the physical mixture (weight ratio of 1:1) of LOR with different additives is demonstrated in Fig. 3. There was no IR spectral change for pure LOR before and after grinding for 30 min, although the endothermic peak was shifted from 136.1 to 133.7 °C and the enthalpy was also slightly reduced. This reveals that there was no polymorphic change but somewhat amorphization of LOR obtained after grinding for 30 min. By co-grinding the LOR with MCC, HPMC or dextran, the FT-IR spectrum of each ground mixture was unchanged by comparing with the FT-IR spectrum of pure LOR but a significant alteration in each DSC curve was found. A marked amorphization of LOR caused by co-grinding with additives might be responsible for this result, which agreed with the results of the other investigations (Bogner & Bahl, 2006; Colombo, Grassi, & Grassi, 2009; Vogt, Kunath, & Dressman, 2008). However, it is interesting to note that significant changes were found in the DSC curves and FT-IR spectra after co-grinding the LOR with β-CD or HP-β-CD (Fig. 3e and f). The disappearance of DSC endothermic peak and the appearance of several new FT-IR spectral peaks at 1678, 1440, 1235 cm^{-1} might be explained by the inclusion complex formation, as compared with the data shown in Fig. 2.

3.4. Grinding-induced enthalpy changes of LOR in the presence of β-CD or HP-β-CD

According to the above result, it is worth to investigate the progressive steps of inclusion complex formation for LOR with β-CD or HP-β-CD under the mechanical grinding process. Changes of DSC curves for the physical mixture of LOR/β-CD or LOR/HP-β-CD (1:1 molar ratio) before and after different grinding times are shown in Fig. 4. It is apparent that a sharp endothermic peak at 135.1 or 134.6 °C due to the melting of LOR was observed in the DSC curve of the physical mixture of LOR/β-CD or LOR/HP-β-CD before grinding. Once the mechanical grinding process was performed, the sharp endothermic peaks in the DSC curves for both physical mixtures became weaker and broader with an increase in grinding time. The melting peak of LOR disappears after 15 or 7 min for LOR/BCD or LOR/HP-B-CD mixture, respectively, probably due to the amorphization and/or inclusion complex formation after mechanical grinding (Chowdary & Srinivas, 2006; Giordano, Novak, & Moyano, 2001; Willart & Descamps, 2008). It is found that HP-β-CD seemed to be more efficient than the β-CD to fast reduce the peak intensity of LOR in the DSC curve after grinding.

By grinding the physical mixture of drug and CDs, two possible mechanisms can be hypothesized in the course of grinding. The first is the reduction in drug crystallinity due to the co-grinding effect with additive; the second will be the formation of inclusion complex. Once the drug was amorphized or embedded into the

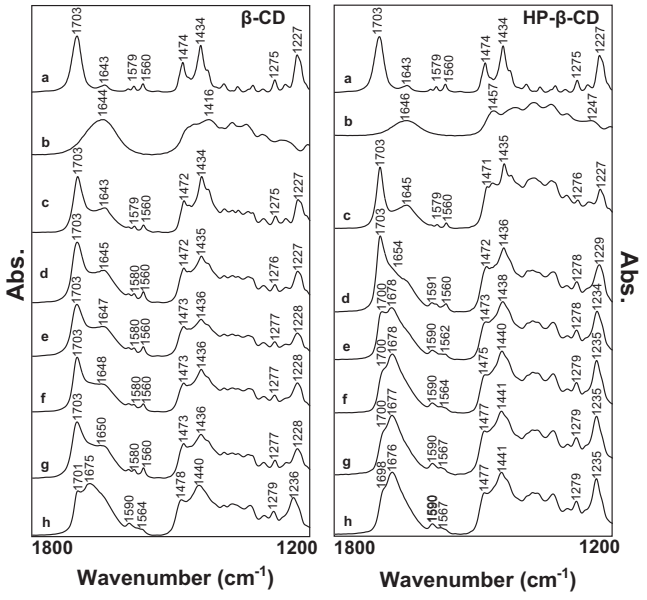


Fig. 5. The grinding effect on the FT-IR spectral shifts of the physical mixture of LOR and β-CD or HP-β-CD at 1:1 molar ratio after different grinding times. Key: a, pure LOR; b, pure β-CD or HP-β-CD. Grinding time: c, 0 min; d, 3 min; e, 5 min; f, 7 min; g, 10 min; h, 15 min.

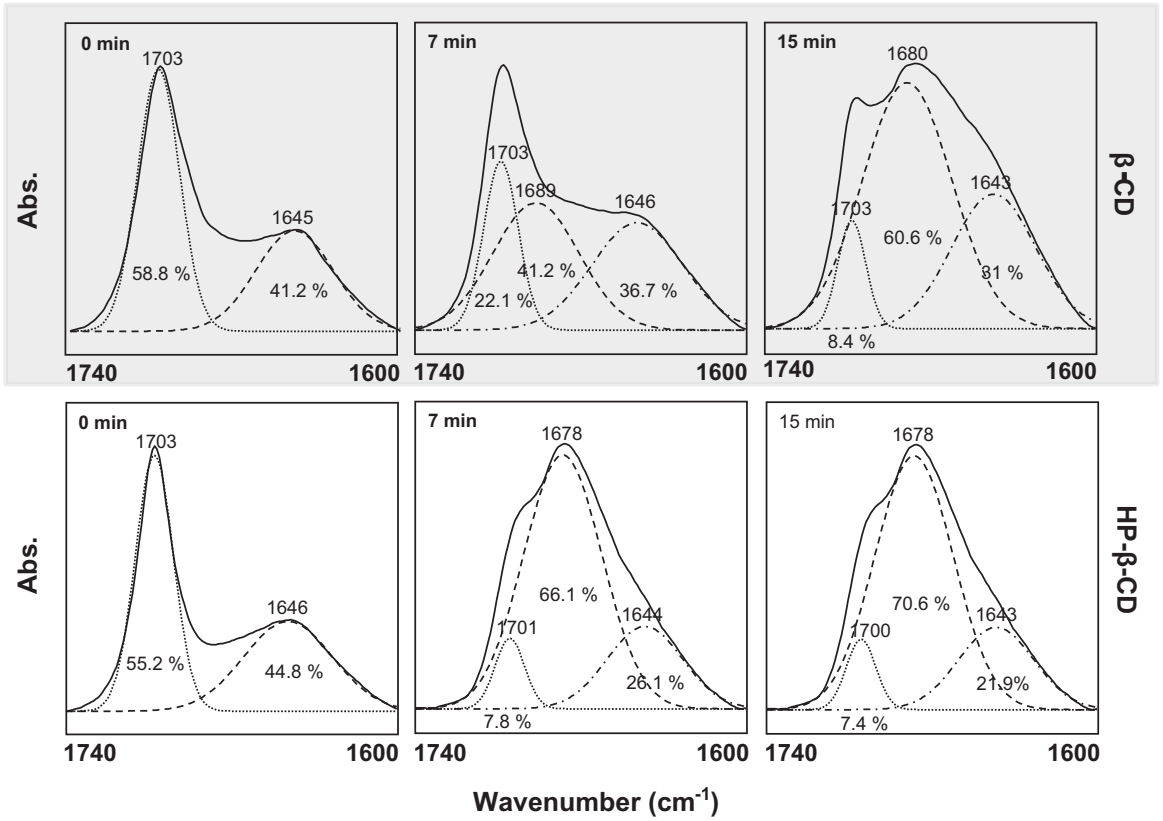


Fig. 6. The representative best-fitted FT-IR spectra and the deconvoluted components for the physical mixture of LOR with β-CD or HP-β-CD before and after various grinding times.

CD cavity to form an inclusion complex, its endothermic peak in the DSC curve generally shifted to a lower temperature or disappeared (Al-Marzouqi, Elwy, Shehadi, & Adem, 2009; Cirri, Rangoni, Maestrelli, Corti, & Mura, 2005). Here, the decrease of the enthalpy value of LOR in the ground mixture was difficult to differentiate from the origin belonging to the amorphization of LOR or the inclusion complex formation of LOR/CDs after grinding. Thus, the total enthalpy change caused by mechanical grinding process might be examined by Eq. (2). It clearly indicates that 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 to cause the reduction in LOR crystallinity. An excessive amount of HP-β-CD used might improve the grinding effect than that of the β-CD used although there was the same molar ratio. The grinding-induced reduction in LOR crystallinity in the presence of β-CD or HP-β-CD was also found to be apparent zero-order kinetics.

3.5. Grinding-induced inclusion efficiency of LOR in the presence of β-CD or HP-β-CD

The grinding effect on the FT-IR spectral shifts of the physical mixture of LOR/β-CD or LOR/HP-β-CD at 1:1 molar ratio after different grinding times is illustrated in Fig. 5. It clearly indicates that the FT-IR spectral peaks at 1675 (1676), 1478 (1477), 1440 (1441), 1236 (1235) cm^{-1} were gradually observed in the ground mixture of LOR/β-CD or LOR/ HP-β-CD with the increase of grinding time. The appearance of these IR peaks shifted might be due to the inclusion complex formation occurred in LOR/β-CD or LOR/HP-β-CD mixture after mechanical grinding for 15 min, as evidenced in Fig. 2.

In order to confirm the molecular encapsulation efficiency of LOR in the cavity of β-CD or HP-β-CD caused by mechanical grinding, the curve fitting technique of spectral analysis was used to examine the inclusion efficiency of LOR in the presence of β-CD or HP-β-CD by estimating the number of bands, and their positions and compositions in the FT-IR spectra (Cheng, Lin, et al., 2008; Hu et al., 2002). In the present study, the IR spectral region of 1740–1600 cm^{-1} was selected due to the most marked alteration in this region. The representative best-fitted FT-IR spectra and the deconvoluted components for the physical mixture of LOR/β-CD or LOR/HP-β-CD before and after various grinding times are indicated in Fig. 6. It clearly finds that three components were contained in the IR spectrum of LOR/β-CD or LOR/HP-β-CD ground mixture. The component for the IR peak position at 1703–1700 cm^{-1} or at 1646–1643 cm^{-1} belonged to the contribution of LOR, or β-CD (HP-β-CD), respectively. The new peak position at 1689–1680 or at 1678 cm^{-1} might be due to the contribution of LOR/β-CD or LOR/HP-β-CD inclusion complex. After co-grinding the LOR/β-CD mixture for 15 min, the peak position of the inclusion complex formed was located at 1680 cm^{-1} with a relative composition of 60.6%. While the peak position of the LOR/HP-β-CD inclusion complex after 15 min-grinding was located at 1678 cm^{-1} with a relative composition of 70.6%. This strongly implies that the curve fitting technique for IR spectral analysis may be a useful method to determine the inclusion efficiency of drug embedded in the inclusion complex after mechanical grinding.

The relationship between the relative degree of LOR crystallinity and the relative composition of inclusion complex after different grinding times is revealed in Fig. 7. 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. The more the loss of LOR crystallinity formed the higher the amount of inclusion complex obtained. Thus, the molecular encapsulation of LOR into the cavity of β-CD or HP-β-CD to form a LOR/β-CD or LOR/HP-β-CD inclusion complex in

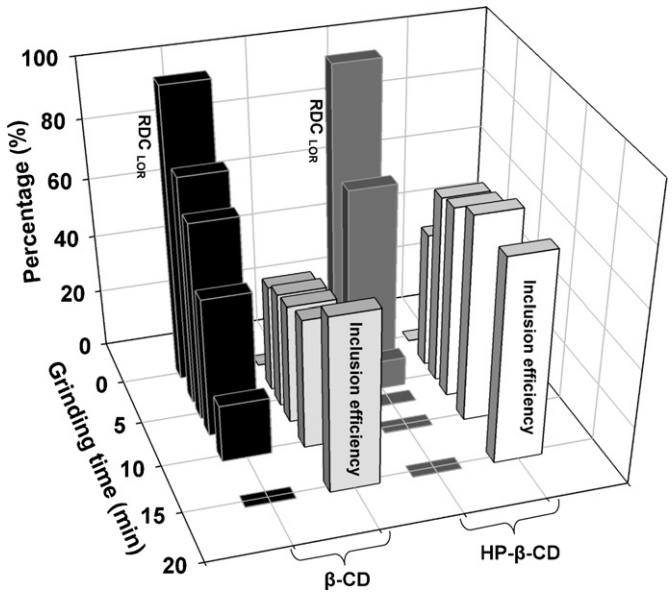


Fig. 7. The relationship between the relative degree of crystallinity of LOR and the relative composition of inclusion complex after different grinding times.

the course of grinding was proposed as the following steps: The progressive reduction in LOR crystallinity and the promoted LOR amorphization were previously caused by mechanical grinding. Then, the amorphized LOR molecule was sucked up into the cavity of β-CD or HP-β-CD to form the inclusion complex in the continuous energy input process of mechanical grinding (Govindarajan & Suryanarayanan, 2006).

4. Conclusions

The inclusion complex formation of LOR/β-CD or LOR/HP-β-CD binary system was significantly correlated with the reduction in LOR crystallinity caused by mechanical grinding. The grinding-induced reduction in LOR crystallinity in the presence of β-CD or HP-β-CD was also found to be apparent zero-order kinetics. The inclusion complex of LOR/β-CD or LOR/HP-β-CD was easily formed with the grinding time through the gradual reduction in LOR crystallinity, the promoted LOR amorphization, and inclusion processes.

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