Carbohydrate Polymers 87 (2012) 512–517

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

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

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ARTICLE INFO

*Article history:*
Received 16 June 2011
Received in revised form 29 July 2011
Accepted 4 August 2011
Available online 11 August 2011

*Keywords:*
Loratadine
β-CD
HP-β-CD
Inclusion complex
Mechanical grinding
Inclusion steps
Thermodynamic kinetics
Inclusion efficiency
Crystallinity
Amorphization

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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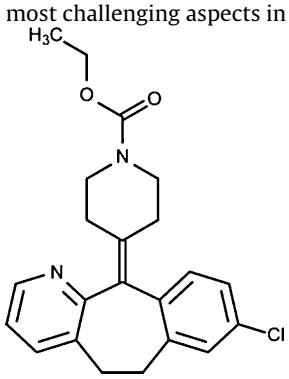
0144-8617/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2011.08.010

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 $\Delta H_{\text{LOR}}$ 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.