Journal of Drug Delivery Science and Technology 35 (2016) 34–39

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Efficiency of "cyclodextrin-ibuprofen" inclusion complex formation

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ARTICLE INFO

Article history:
Received 23 February 2016
Accepted 15 April 2016
Available online 15 June 2016

Keywords:
Cyclodextrin
Ibuprofen
Inclusion complex
Ball milling
Efficiency of drug encapsulation

ABSTRACT

A modified method for ibuprofen/β-cyclodextrin (IBU/β-CD) complex formation, based on ball milling (BM) under controlled conditions was developed and its efficiency with respect to the drug encapsulation yield was compared with the well-known kneading and solid dispersion synthetic approaches. Quantitative evaluation of the efficiency of drug-cyclodextrin interaction applying various methods and experimental conditions as well as characterization of the inclusion complexes were carried out by X-ray diffraction (XRD), differential scanning calorimetry (DSC), thermogravimetry (TG), scanning electron microscopy (SEM), infrared (IR) and nuclear-magnetic resonance (^{1}HNMR) spectroscopy. It was found that the yield of the formed IBU/β-CD complex varies in a large range, depending on the techniques applied. The degree of complexation between IBU and β-CD using the proposed optimized BM method is very high and close to the complete inclusion complex formation achieved by a modified solid dispersion method. Furthermore, using DSC, TG and ^{1}HNMR we proved that the ibuprofen molecules enter the β-CD hydrophobic cavities replacing completely the water molecules present naturally inside, which we determined to be 7.

1. Introduction

The research and market interest in natural cyclodextrins (CDs) and their derivatives continues to grow. The natural α-, β- and γ-cyclodextrins are cyclic oligosaccharides produced after enzymatic degradation of starch in presence of Bacillus macerans. They consist of 6, 7 or 8 alpha-1,4- linked alpha-D-glucopyranose units which are in "chair conformation" so that the molecules are shaped like a truncated cone. The primary and secondary hydroxyl groups are located on the outer edges of the cone making the external molecular surface hydrophilic. The unique feature of the cyclodexrin molecular structure is the presence of a central apolar cavity with small number of water molecules located in it. This structure determines cyclodextrin's ability to form inclusion compounds with wide range of solid, liquid and gaseous hydrophobic compounds [1,2].

There are many new applications of cyclodextrins in pharmaceutics [2–17], food [17,18], cosmetics [19–25]; in environmental protection, biotechnology [2], cell biology [2], biosensing [2] etc. Among all three CDs β-CD has the lowest aqueous solubility (1.85 g/100 mL H_2O) and is the most used cyclodextrin in the pharmacy, because of its structure, cavity size and price [26,27].

Ibuprofen ((RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid) is a nonsteroidal anti-inflammatory drug (NSAID). There are many reports on Ibuprofen (IBU) complexes with β-cyclodextrin and its derivatives. These inclusion compounds are widely used and made to increase Ibuprofen water solubility [28–30]. Variety of methods had been applied for the synthesis of the inclusion compounds such as kneading [31–34], solid dispersion [35], spray/freeze drying [28,32–38], supercritical carbon dioxide [38,40,41], [42,43,44], microwave treatment [39,45–48], sealed-heating [31,38,39], co-evaporation [31–33,38], co-grinding [31,34]. Mechanochemical synthesis or co-grinding has been reported as well [49–51], however there are no studies comparing wet and dry ball milling synthesis of inclusion compounds between β-CD and ibuprofen. In general the ball milling synthetic approach has a lot of benefits – controlling the particles size, improving ibuprofen solubility and stability and even amorphization of the product (XRD, DSC, SEM) [52–54]. Also the method is easy, cheap, environmental friendly and can be apply in an industrial scale.

Phase-solubility technique for determination of the stoichiometric ratio of the inclusion compounds according Higuchi & Conners [55] is presented as well. Most of the authors report of a ratio drug:β-CD = 1:1 [28,29], but there are also papers reporting ratios such as 1:3 and 2:3 at room temperature (23 °C) and at 37 °C respectively [30]. It is worth noting that the available results show

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http://dx.doi.org/10.1016/j.jddst.2016.04.006
1773-2247/

some discrepancy with respect to the productivity of the synthetic methods. Even sometimes reliable proofs for the complete complex formation are missing. Therefore, the present work aims at comparing the efficiency of several synthetic methods for ibuprofen encapsulation into β-CD, realized by a number of appropriate microstructural, thermal and spectroscopic techniques. For this purpose a modified mechanical micronization of IBU via complexation with beta-cyclodextrin in a ball mill was developed and its complexation efficiency in comparison to kneading and co-evaporation methods was analyzed. Ibuprofen has been chosen as a model drug because of its hydrophobicity and low water solubility. Additionally, some valuable quantitative information concerning the mechanism of the complex formation was presented.

2. Experimental part: methods and materials

2.1. Materials

2-(4-isobutylphenyl)-propionic acid Ibuprofen 50 (catalytic process) was purchased from BASF AG, Germany and β-cyclodextrin - from Wacker Chemie AG, Germany. All other reagents used were of analytical grade.

2.1.1. Phase solubility studies

The phase solubility studies were conducted according to the method of Higuchi and Connors [55]. Excess amounts of the drug (Ibuprofen) were added to nine flasks containing 50 mL of aqueous solutions having different β-CD concentrations (0, 1, 2, 3, 4, 5, 6, 8 and 12 $\times$ 10^{-3} M). The samples were shaken at 25 °C in thermostatically controlled mechanical shaker (Orbital Shake-Incubator, ES-20, Biosan) for 22 h. Following equilibrium, an aliquot was filtered using a 0.45 μm membrane filter. All samples were analyzed by using UV/Vis (Specord) technique.

2.2. Preparation of ibuprofen – β-CD solid complex

2.2.1. Kneading

Kneading was carried out in a mortar with a pestle by adding ethanol – water solution 1:1(v/v) to powder mixture of IBU/β-CD = 1:1 (M/M). The mass was triturated for 45–50 min and after that dried in an oven at 42 °C for a day.

2.2.2. Solid dispersion technique (SD)

IBU/β-CD solid dispersions were prepared in a ratio 1:1 (M/M) by common solvent method.

2.2.3. SD_1

β-CD dissolved in water were gradually added to solution of IBU in ethanol by stirring (electromagnetic stirrer) until a homogenous solution was formed. The solvent was removed in open-air and the solid residue slowly dried in an oven at 42 °C for about 22 h.

2.2.4. SD_2

Modification of Method 1 - The final IBU/β-CD (1:1 M/M) solution was alkalized with ammonia and the solvent removed by rotary vacuum evaporator. The solid residue was dried in an oven at 42 °C for 8 h.

2.2.5. Physical mixture (PhM)

The PhM was prepared in ratio IBU/βCD/1:1 (M/M) in a mortar with a pestle by grinding of the powder mixture for 10 min.

2.2.6. Ball milling

Three procedures of milling was used to prepare IBU/β-CD 1:1 (M/M) solid complex in planetary mill Fritch 6, at ball to powder ratio 4:1 (4 balls of 1 g each one to 1 g powder), varying the milling intensity and duration.

2.2.7. BM_1

0.306 g of Ibuprofen and 1.7 g β-CD (IBU/β-CD 1:1 M/M) were mixed and ball-milled under dry ball-milling conditions at 100 rpm for 5 min, 25 min, 1 h and for 2 h with 300 rpm.

2.2.8. BM_2

Powder mixture of Ibuprofen (0.15 g) and β-CD (0.85 g) (IBU/β-CD 1:1(M/M)) was ball-milled in presence of 0.5 mL aqueous ethanol solution (H_2O/C_2H_5OH (1/1 v/v)). The sample was milled at 300 rpm for 50 min.

2.2.9. BM_3

Powder mixture of Ibuprofen (0.15 g) and β-CD (0.85 g) (IBU/β-CD 1:1 M/M) was ball-milled at 300 rpm for 50 min and every 10 min 0.1 mL (2 drops) of aqueous ethanol (H_2O/EtOH 1:1 v/v) were added.

2.3. Characterization of the complex

2.3.1. Differential scanning calorimetry (DSC) and thermogravimetry (TG)

The thermal behavior and stability of the pure substances and inclusion complexes were characterized by Perkin-Elmer DSC - 2C and TG - 2. Samples were heated from room temperature (25 °C) to 200 °C with a scanning rate of 10 °C/min.

2.3.2. Scanning electron microscopy (SEM)

The morphology and particle size of the inclusion complexes were observed by SEM, JEOL JSM-5510.

2.3.3. X-ray diffraction (XRD)

Bruker D8 Advance diffractometer with Cu-Kα radiation was used for the samples microstructure determination.

2.3.4. Infra-red absorption spectroscopy (IR)

Nicolet™ FT-IR Spectrometer, Thermo-Electron Corporation, according to the KBr disk method.

2.3.5. Nuclear magnetic resonance (^{1}HNMR)

Bruker Avance III 500 Mhz, 54 mm ASCEND magnet with 11.7 T strength of the magnetic field.

3. Results and discussion

The phase solubility diagram for ibuprofen as a function of β-CD concentration at 25 °C, shown in Fig. 1, can be classified as Bs type, according to Higuchi and Connors [55], because of precipitation of the insoluble complex at high concentrations of the carrier [56]. The maximum amount of ibuprofen dissolved reached a constant concentration at 4 $\times$ 10^{-3} M β-CD. The slope of the linear part of the phase solubility plot is lesser than unity. This fact assumes drug/ligand 1:1(M/M) or 1:3 (M/M) stoichiometry.

Further ^{1}HNMR study in D_2O was carried out to prove the stoichiometry of the IBU/β-CD complex in solution. The results were in accordance with those reported by M. di Cagno et al. [57] and verify substrate/ligand ratio 1:1(M/M) in solution. Thus, all IBU/β-CD complexes object of the present study were prepared in 1:1 M/M ratio.

It is well known that the ball-milling is well approved method not only for production of nano-powders, but also a method for solid state synthesis, especially when non-covalent bonds are created between the reacting components of the powder mixture.