The Journal of Supercritical Fluids 133 (2018) 479–485

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

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

Preparation of ibuprofen/hydroxypropyl-γ-cyclodextrin inclusion complexes using supercritical CO_2-assisted spray drying

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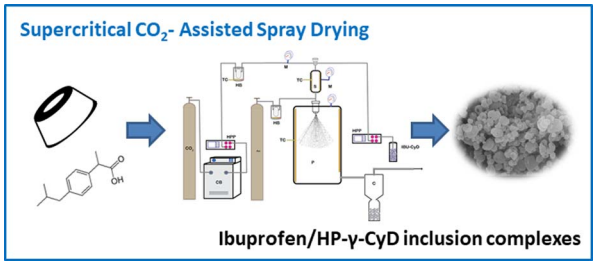
GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Cyclodextrin
Supercritical assisted atomization
Inclusion complex
Ibuprofen
SAA

ABSTRACT

Herein we report the formation of dry powder complexes of ibuprofen (IBU) and hydroxypropyl-γ-cyclodextrin (HP-γ-CyD) by supercritical CO_2-assisted spray-drying (SASD). SASD of HP-γ-CyD alone, IBU/HP-γ-CyD, as well as the physical mixture were prepared and characterized using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), X-ray diffraction (XRD), ultra-violet spectroscopy (UV), ^{13}C cross-polarization magic angle spinning nuclear magnetic resonance (^{13}C CP/MAS NMR), differential scanning calorimetry (DSC) and morphological studies. Results indicate the successful formation of amorphous inclusion complexes. SASD is a clean technology, suitable for processing thermolabile APIs, thus an interesting alternative to conventional spray drying and other methods of CyD solid complex formation.

1. Introduction

Cyclodextrins (CyDs) are cyclic oligosaccharides made up of repeating glucopyranose units linked by α-(1,4) glycosidic bonds in a ring formation. CyDs' importance in the pharmaceutical industry is largely due to their ability for host-guest molecular interactions (inclusion and non-inclusion complexes) with various active pharmaceutical ingredients (APIs). This enables CyDs to modify drug delivery properties such as aqueous solubility, physicochemical and physiological stability; and drug release/targeting behaviour *in vivo*. The formation of inclusion complexes is mediated by apolar attraction of lipophilic drug molecules to CyDs' interior cavities lined with ethereal carbons, while the orientation of their hydroxyl groups males their exterior surfaces hydrophilic [1,2].

Several methods have been reported for the preparation of solid drug-CyD complexes. Examples include spray-drying, lyophilization,

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https://doi.org/10.1016/j.supflu.2017.11.009
Received 11 September 2017; Received in revised form 12 November 2017; Accepted 14 November 2017
Available online 15 November 2017
0896-8446/

kneading, milling/co-grinding, co-evaporation, co-precipitation, microwave irradiation, etc. [3–5]. The choice of preparation method has been reported to affect the physicochemical properties and physiologic performances of CyD based drug delivery systems [5–7]. Supercritical fluid (SCF) technology has emerged as a very important method for various pharmaceutical processes, including CyD complex formation [8]. It utilizes dense gases with high compressibility, diffusivity and evaporation rate, which are tuneable under varying conditions of temperature and/or pressure, to facilitate the efficient manipulation of solvent effect on APIs and drug carriers. Also, SCF technology is greener, sustainable, low cost, non-toxic; and generally reduces the complexity of pharmaceutical unit operations during particle preparation or engineering [8,9]. Many types of SCF processes with specific merits and demerits have been advanced for pharmaceutical processes. Examples include: Rapid Expansion of Supercritical Solution (RESS), Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV), Gaseous Antisolvent (GAS), Particles by Compressed Antisolvent (PCA), Supercritical Antisolvent (SAS), Solution Enhanced Dispersion by Supercritical Fluids (SEDS), Supercritical Fluid-Assisted Atomization/Spray Drying (SAA/SASD), etc. [8].

Supercritical Assisted Atomization/Spray Drying has been described as one of the most effective micronization techniques for the production of spherical and amorphous micro and sub-microparticles [10]. First introduced by Reverchon and coworkers [11], the process uses CO_2 as a co-solute, that is, the supercritical CO_2 is solubilised into the liquid solution containing the drug-carrier system. This solution is then sprayed to a precipitator, at near atmospheric pressure, via a nozzle. The low surface tension (near zero) and viscosity of this expanded solution improve the atomization process by facilitating the production of droplets that are rapidly dried, preventing the organization of solute molecules into ordinate forms representative of crystals [10,12]. More recently, Cai and co-workers have shown that the introduction of a hydrodynamic cavitation mixer to SAA can enhance mass transfer in order to reduce processing time, and make the system more conducive for thermolabile materials such as biopharmaceuticals [13,14].

Since the turn of the millennium, several research groups have prepared solid drug-CyD complexes using different types of SCF technology [6,15–21]. The micronizing effect of SASD on CyD has been previously studied by Reverchon and Antonacci [20]. However, to the best of our knowledge, the description of SASD's utility in the preparation of solid drug-CyD complexes has not been reported in literature. Compared to conventional spray drying, SASD offers several advantages. Firstly, SASD allows for narrow and controlled particle size distribution required in the development of pulmonary and nanoparticulate drug delivery systems [22]. By acting as an efficient pneumatic agent, fast elimination of CO_2 from the primary droplets (decompressive atomization) during atomization leads to the production of smaller secondary droplets and particles [23]. Secondly, it is preferable for thermo-labile drugs since it utilizes lower operation temperature and eliminates the drying step required to reduce residual solvents present in spray dried particles to acceptable limits. Thirdly, when desired, the solubilisation effect of $scCO_2$ allows for effective cross-linking and/or intermolecular interactions between APIs and drug carrier systems in order to modify their physicochemical and physiologic properties [24–26]. Thus, when used to prepare solid drug-CyD complexes, $scCO_2$ can act as a co-solvent/co-solute in a CyD ternary system with huge possibilities for enhancing the formation of inclusion complexes.

In this study, we report the formation of solid complexes of ibuprofen (IBU) and hydroxypropyl-γ- cyclodextrin (HP-γ-CyD) by SASD. SASD of HP-γ-CyD alone and IBU/HP-γ-CyD, as well as the physical mixture were prepared and characterized using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), X-ray diffraction (XRD), ultra-violet spectroscopy (UV), ^{13}C cross-polarization magic angle spinning nuclear magnetic resonance (^{13}C CP/MAS NMR), differential scanning calorimetry (DSC) and morphological studies.

2. Experimental

2.1. Materials

(±)-Ibuprofen 20/35 (racemic α-methyl-4-[2-methylpropyl] benzene acetic acid, IBU) and CAVASOL® (hydroxypropyl-gamma-cyclodextrin, HP-γ-CyD) were kind gifts from Laboratórios Medinfar (Portugal) and Wacker Chemie AG (Germany), respectively. Ethanol (absolute anhydrous, 99.9% purity) was purchased from Carlo Erba Reagents. The water used in this study was purified with a Milli-Q water purification system (Water Max W1, Diwer Technologies). Industrial carbon dioxide (purity ≥ 99.93%)was purchased from Air Liquide. All compounds were used as received without further purification.

2.2. Methods

2.2.1. Preparation of IBU/HP-γ-CyD inclusion complex by SASD and physical mixture

Solid complexes of IBU and HP-γ-CyD were prepared by SASD. Based on previous studies [7,27–29], a molar ratio of 1:1 was used. Both compounds were dispersed in 60 mL of a hydroalcoholic solution 1:1 (v/v), vortexed and then sonicated in an ultrasound bath (Sonorex RK 100H) for 15 min to facilitate complete dissolution. The resulting complex solution was then filtered (80 μm filter). Two high-pressure pumps were used to deliver the complex solution (HPLC pump 305 Gilson) and the $scCO_2$ (HPLC pump K-501, Knauer) into a high-pressure static mixer saturator (3/16 model 37-03-075, Kenics Chemineer, 4.8 mm diameter, 191 mm length and 27 helical mixing elements) to facilitate the near equilibrium mixing of the $scCO_2$ and the complex solution. The CO_2 was first liquefied in a cryogenic bath, heated in an oil bath before entering the static mixer at a flow rate of 25 mL/min while the complex solution was fed into the static mixer at a flow rate of 2 mL/min. The pressure (12.8 MPa) was measured by a Setra pressure transducer and the temperature of the mixture, at the static mixer (65 °C) was controlled by a Shinko FCS-13A temperature controller. All operation parameters were selected based on previously optimized conditions in our laboratory and drug specific requirements found in literature. The mixture was then atomized through a nozzle with an internal diameter of 150 μm into the precipitator (an aluminium vessel that operates at near-atmospheric conditions). At the same time, a flow of previously heated compressed air (T = 120 °C) entered the precipitator to evaporate the liquid solvent. The temperature measured at the exit of the precipitation chamber was around 70 °C. The formed particles were then separated from the Air-CO_2-solvent flow by the high efficiency Büchi cyclone. A solution of HP-γ-CyD (without IBU) was also subjected to SASD using the same conditions. All powders were then collected and stored in a screw capped glass bottle prior analysis.

For the physical mixture (PM), regarded as control, IBU and HP-γ-CyD (1:1) were weighed into in flask and thoroughly mixed on a vortex, for 10 min. The particles obtained were also stored in a screw capped glass bottle prior analysis.

2.2.2. Morphological characterization

The morphology of the atomized particles as well of the physical mixture were observed by scanning electron microscopy (SEM) using a Hitachi equipment (model S-2400), with an accelerating voltage set to 20 kV. All samples were mounted on aluminium stubs using carbon tape and gold coated before analysis. Particle size distribution was determined using an optical particle analyser system (Morphologi G3 from Malvern Instruments Ltd., Malvern, UK). Atomized particles were characterized for mean particle size and particle size distribution by considering more than 30,000 particles. This characterization was performed in terms of the volume mean diameter (D_v) and the relative width of the distribution (span). The span is calculated using three measures, $D_{v,10}$, $D_{v,50}$, and $D_{v,90}$ (particle volume diameter corresponding to 10%, 50%, and 90% of the population, respectively) by the