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A Comparative Study of Naproxen – Beta Cyclodextrin Complexes Prepared by Conventional Methods and Using Supercritical Carbon Dioxide

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Abstract

Naproxen is a poorly soluble anti-inflammatory drug, the solubility of which can be enhanced by complexation with beta-cyclodextrin. Besides that, the inclusion complex reduces the incidence of gastrointestinal side effects of the drug. The aim of this work was to compare the physicochemical characteristics of the solid complexes prepared by traditional methods (kneading, freeze-drying and spray-drying) and using a supercritical fluid technology. The unusual solvent properties of carbon dioxide above their critical temperature and pressure were exploited in order to prepare inclusion compounds. Complexes prepared using supercritical fluid technology showed similar properties to those of freeze-drying and spray-drying complexes as proved by DSC, FT-IR and UV.

Introduction

Naproxen is one of the most efficient nonsteroidal anti-inflammatory drugs (NSAIDs) of the family of the aryl-propionic acids with anti-inflammatory, analgesic and antipyretic properties and is widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain in musculoskeletal disorders. However, gastrointestinal ulcerative damages are common adverse drug reactions, consequence of both systemic inhibition of cyclooxygenase enzyme reducing the prostaglandin production and local tissue irritation, when it is orally administered. Since naproxen is poorly water soluble, gastric ulceration seems to be caused by slowly drug dissolution which provides high local drug concentration that gets in contact with the gastric mucosa. An increase in the dissolution and absorption rates reducing the contact time between the drug and the mucosa may result in a reduction of drug induced gastric undesirable effects. This better tolerability could be reached by drug complex formation with cyclodextrins.

Cyclodextrins (CDs) are cyclic water soluble oligosaccharides containing glucopyranose units bonded together by α-(1,4) linkages, obtained from enzymatic conversion of starch. Among them, the most commercially and economically available is β-CD, which is comprised of 7 units of glucopyranose. Thus, β-CD was chosen for this study. Complex formation or inclusion complexation occurs when the CD molecule partially or fully entraps a guest compound in its hydrophobic cavity. In this case the guest is the drug molecule naproxen.

There are several methods for the synthesis of CD-guest complexes depending on the properties of the included compound, such as, kneading, neutralisation, grinding, co-precipitation, heating in a sealed container and freeze-drying [1]. In general, complexes are prepared by the addition of an excess of the drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated, under continuos agitation, at the desired temperature for periods of up to one week, and then filtered or centrifuged to form a clear drug-cyclodextrin complex solution. For the preparation of solid complexes, the water is removed from aqueous solution by evaporation (for example, spray drying) or sublimation (for example lyophilization) [2].

The aim of this work was to compare the physicochemical characteristics of the naproxen-β-CD solid complexes prepared by three traditional methods (kneading, freeze-drying and spray-drying) and using supercritical fluids as an alternative method. Supercritical carbon dioxide have been used as a solvent in the food industry for many years, for example in decaffeination of coffee, and now is finding more acceptance in the pharmaceutical industry, replacing environmentally unfriendly, unsafe and expensive solvents.

Supercritical fluid technology is a unique concept that exploits the solvent properties of supercritical fluids above their critical temperature and pressure conditions. Near the critical point, supercritical fluids possess liquid-like densities and gas-like transport properties [3].

While much work has concentrated on the use of cyclodextrins in supercritical chromatography, only two other studies have looked about the application of supercritical carbon dioxide to the cyclodextrin-drug compounds as far

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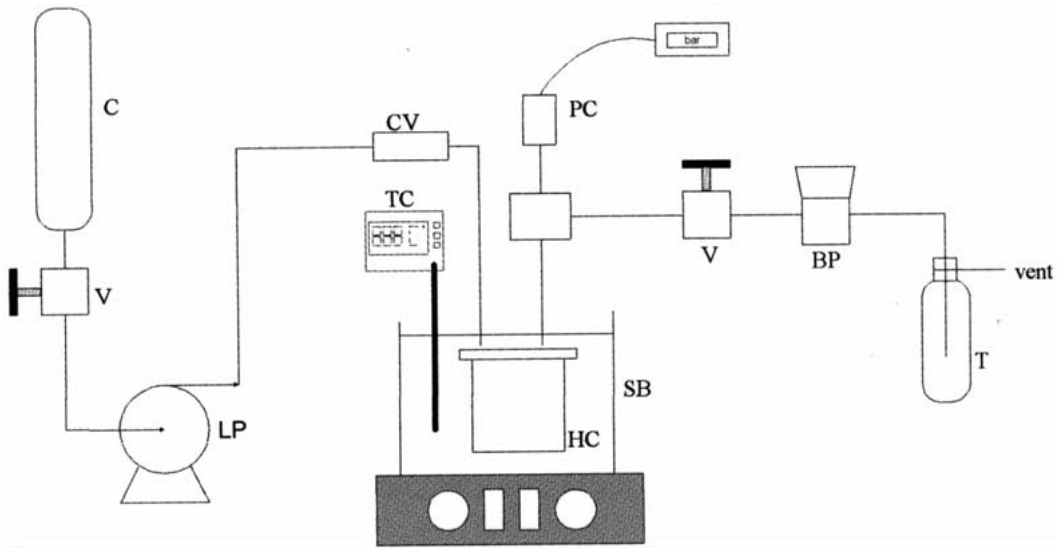

Figure 1. Schematic diagram of the apparatus. C – gas cylinder; V – valves; LP – liquid pump; CV – check-valve; HC – high-pressure cell; SB – thermostatted silicone bath; PC – pressure transducer; BP – back-pressure regulator; T – cold trap; TC – temperature control.

as our knowledge. In 1996, Giordano and co-workers [4] studied the supercritical fluid extraction to extract acetaminophen from its complex with β-CD but did not achieved formation of inclusion compounds and in 1999 Van Hees *et al*. [5] used a supercritical extractor apparatus to prepare piroxicam-β-CD inclusion compound. In this study a new experimental supercritical unit was developed and tested.

Experimental

Materials

β-CD were obtained from Wacker-Chemie and naproxen was generous gift from Janssen Cilag and were used as received. Carbon dioxide was supplied by Carburos Metalicos with a purity of 99.999% (SCF grade). All other chemicals were reagent grade and used without further purification.

Preparation of the physical mixture

The physical mixtures of naproxen and β-cyclodextrin were prepared in a 1 : 2 molar ratio by simple blending in a vial for 30 minutes.

Preparation of naproxen-β-cyclodextrin solid inclusion complexes

Kneading. Amounts of naproxen and β-cyclodextrin with molar ratios of 1 : 2 were wetted in a mortar with the same weight of 50% ethanol/water mixture and thoroughly mixed for 45 min until a dense paste was formed after the solvent had evaporated. These pastes were dried in an oven at 50 °C until constant weight and then pulverized in a mortar.

Freeze-drying. Amounts of naproxen and β-cyclodextrin with molar ratios of 1 : 2 were dissolved in deionized water. Little quantities of ammonium hydroxide (25%) were used in order to obtain limpid solutions before drying. Once solutions were transparent, were stirred by a magnetic stirrer at room temperature for 24 h and then frozen and lyophilised (Chirst alpha 1–4 apparatus).

Spray-drying. The technique was as described above. The 24 h stirred solutions were atomized into a drying chamber with a spray nozzle. The spray-dryer (Buchi mini spray dryer B-191) was operated under the following conditions: inlet temperature 130 °C; outlet temperature 88 °C; sample feeding speed 3.3 ml/min.

Using supercritical fluid. A high-pressure experimental apparatus was built. As naproxen is poorly soluble in supercritical carbon dioxide ethanol was used as co-solvent. A mixture of CO_2 and ethanol (2.5%) was previously prepared in a stainless steel cylinder. The 140 ml high-pressure cell was charged with a 1 : 2 mixture of naproxen (115 mg) and beta-cyclodextrin (1136 mg). The cell was immersed in a thermostatted silicone bath (62 °C) and was internally stirred with a Teflon magnetic bar, which is an efficient stirring device. The mixture in the cylinder was pumped into the system by means of a liquid pump up to the desired pressure (160 bar). The naproxen and cyclodextrin mixture was in contact with the supercritical carbon dioxide and 2.5% ethanol mixture. At the end of the experiment, the system was slowly vented in a continuous mode. The powder obtained was washed with fresh high-pressure CO_2 to remove the ethanol before depressurising. In Figure 1 a schematic diagram of the system is represented.

Differential scanning calorimetry

DSC was performed by a Mettler TA4000 apparatus equipped with a DSC 25 cell. Samples were weighted in aluminium pans with a perforated lid, and scanned at 5 °C min^{-1} between 30 °C and 270 °C.

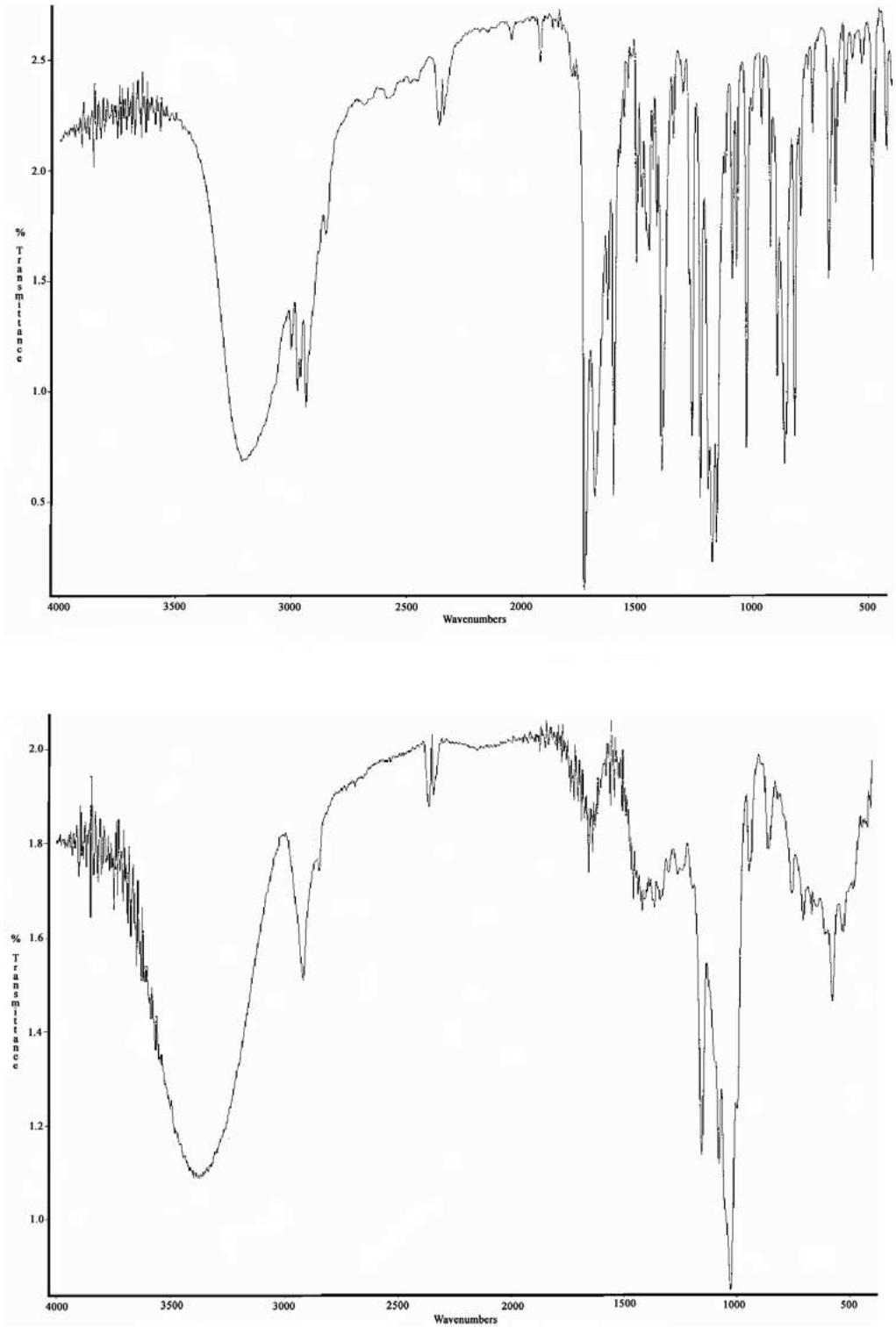

Figure 2. FT-IR spectrum from pure naproxen and complex naproxen : beta-cyclodextrin (1 : 2) obtained by supercritical carbon dioxide with co-solvent.

FT-IR spectroscopy experiments

The Fourier transform IR (FT-IR) spectra were recorded on a ATI Mattson Genesis Series FTIR spectrometer from KBr discs in the 4000–500 cm^{-1} region.

Ultra-violet

UV spectra were performed by an Hitachi U-200 in the range of 230–380 nm. Fixed wavelength measurements were done at 271 nm.

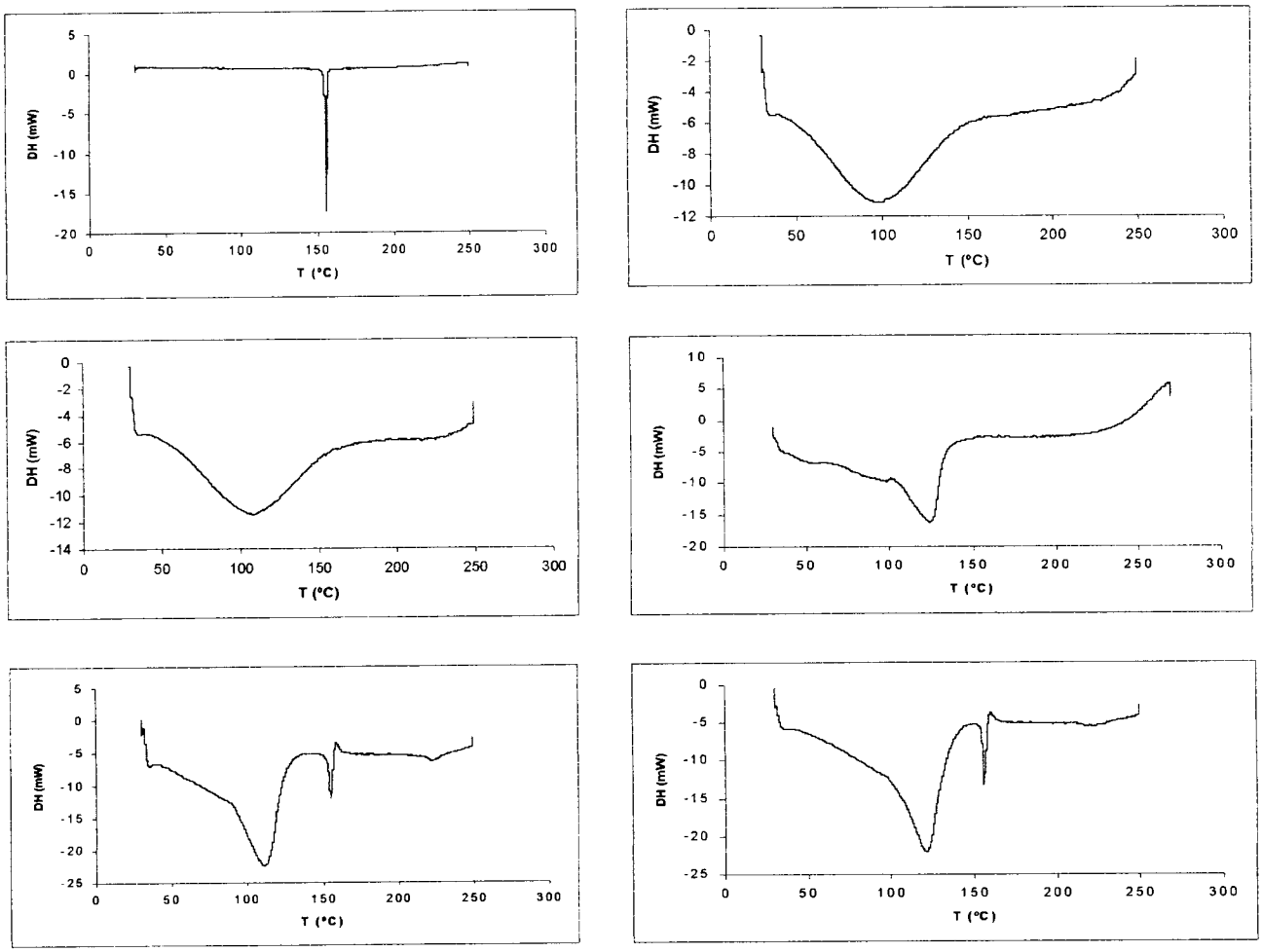

Figure 3. DSC thermograms from upper to the right: pure naproxen; Lyophilised complex Nap : betaCD (1 : 2); Spray-dried complex Nap : betaCD (1 : 2); Supercritical CO_2 complex Nap : betaCD (1 : 2); Kneading Nap : betaCD (1 : 2); Physical mixture Nap : betaCD (1 : 2).

Results and discussion

The complexation and mixture of naproxen with β-CD increases the aqueous solubility of naproxen which is very low, in the range of 3×10^{-5} M, as reported in the literature. [6]. Since this drug is a weak acid the nonionized (HNAP) and the ionized (NAP^-) species of naproxen could be present in solution and both could be included within CD cavity. During the freeze-dried and spray-dried complex preparation the pH changed from 3.9 to 7.9 with the ammonia addition resulting a predominance of the ionized form in the medium.

The use of different analytical techniques enables us to characterise and compare the physicochemical properties of the solid complexes prepared. IR and UV spectroscopy and thermal analysis were carried out.

All the solid inclusion complexes were white powders with different densities. Freeze-drying method conducted to the free-flowing, fluffy powder. Spray-drying and supercritical carbon dioxide methods resulted in lower production yields.

The FT-IR drug spectrum presents a band at about 1730 cm^{-1} due to the carbonyl stretching. This is in agreement with literature [7, 8] Spectroscopic changes can be observed in the complexes prepared by freeze-drying, spray-drying and using supercritical carbon dioxide (Figure 2), in comparison to the drug spectra, in that region. Carbonyl band has changed the intensity and has slightly shifted suggesting complex inclusion of that part of the molecule. For the powder prepared by kneading, changes were not observed, in fact its spectrum is almost superimposed to that of the physical mixture.

The DSC curves of pure components and respective drug-carrier 1 : 2 molar ratio systems prepared by the different methods are shown in Figure 3.

The thermal curve of naproxen showed the typical drug melting endotherm at 156 °C indicated its crystalline anhydrous state. Liberation of crystal water from β-CD was observed as an endothermal effect peaked around 100 °C. In the physical mixtures and in the systems obtained by kneading, the drug melting peak is present, suggesting that this method does not give complete encapsulation. The complete disappearance of the drug endothermal effect was instead observed for systems obtained by freeze-drying, spray-drying and using supercritical carbon dioxide showing evidence of complex formation. The UV spectra of the complexes prepared confirmed the presence of the drug substance showing its characteristics absorption bands.

It was shown that the properties of the solid complexes of naproxen with β-CD are influenced by the preparation method. The new experimental supercritical fluid unit built to prepare naproxen-β-CD (1 : 2 molar ratio) solid complexes avoids the use of dangerous ammonium hidroxide as solvent. Thus, residual solvent removal is not necessary. This technology in an interesting approach in order to prepare complexes with fewer processing steps.

Acknowledgements

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