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β-cyclodextrin hinders PLGA plasticization during microparticle manufacturing☆

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ABSTRACT

Macromolecules, such as poly(lactide-co-glycolide), have nowadays a pivotal role in drug delivery technologies. To have a precise and predictable control of the drug release kinetics in a delivery system, polymer physico-chemical characteristics must be deeply investigated together with all the other components of the device, including the active pharmaceutical ingredient/s. In fact, drug-polymer interaction may result in drastic changes of polymer characteristics. Plasticization, by changing polymer mechanical properties and diffusion coefficients, may seriously compromise device performances.

We investigated the possibility to hinder the plasticizing effect of ketoprofen on poly(lactide-co-glycolide) (PLGA) during microparticle preparation. To this aim, ketoprofen was included in β-cyclodextrin and then encapsulated in PLGA.

The formation of the inclusion complex was confirmed by X-ray and FT-IR data, and UV–Vis analysis showed that ~85% of ketoprofen was included in the cyclodextrins. Molecular dynamics forecasted the enthalpy-driven formation of 4 inclusion complexes with hydrogen bonding playing an important role on their stability. PLGA microparticles were prepared using the solvent diffusion/evaporation method with encapsulation efficiency higher than 60%, without polymer plasticization.

We proved that ketoprofen/β-cyclodextrin inclusion complex allowed to hinder the plasticizing effect of ketoprofen on PLGA during microparticle preparation. The inclusion of ketoprofen within β-cyclodextrin hindered its physical interaction with the polymer chains thus avoiding plasticization.

1. Introduction

Biocompatible biodegradable polymers have, nowadays, a significant role in medical and pharmaceutical sciences. Among the different synthetic polymers investigated and proposed for drug delivery, homo- and heteropolymers prepared by condensation of lactic and/or glycolic acid are, at the moment, the most successful. Borne as absorbable materials for internal sutures in the seventies [1], these polyesters have been massively studied for drug delivery in the last 30 years. Tablets [2], pellets [3,4], microparticles [5], nanoparticles [6], slabs, and *in situ* forming devices [7] have been formulated using these macromolecules. Their application in regenerative medicine as scaffolding material and/or drug delivery systems is also under evaluation [8–11].

Poly(lactide) (PLA) or poly(lactide-co-glycolide) (PLGA) are partially crystalline or completely amorphous polymers depending on their composition. Due to the amorphous state or the presence of amorphous regions in between crystallites, their glass transition temperature (*Tg*) becomes a fundamental parameter to monitor and to control (especially in totally amorphous materials). A modification in *Tg* value during manufacturing may drastically change device performances (e.g., release kinetics and mechanisms, tensile strength). In the specific case of drug delivery systems, the diffusion coefficients of small molecules through the

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polymer matrix may increase by several orders of magnitude going from glassy to rubbery state [12].

Physical interaction of small organic molecules, macromolecules or even inorganic compounds (e.g., active pharmaceutical ingredients, excipients) with the polymer chains may reduce or increase the *Tg*. A substance that mixed to a polymer reduces its *Tg* is generally called plasticizer while an antiplasticizer is a substance that increases *Tg* [13,14]. Pharmaceutically relevant polymers may need addition of plasticizers to facilitate the manufacturing process or to obtain the desired characteristics [15,16]. However, in some cases, the plasticizing effect may be undesired [17,18].

It has been reported that different non-steroidal anti-inflammatory drugs, such as acetyl salicylic acid derivatives [19], ketoprofen [17,18,20], and ibuprofen [21–23], act as plasticizers when mixed with hydrophilic or hydrophobic polymers. This effect limits not only the possibility to obtain the desired release kinetics, customizable choosing the right molecular weight, lactic/glycolic acid ratio (in the specific case of PLA/PLGA), end-chain, and device characteristics (e.g., size, porosity) but also the possibility to manufacture correctly such a device.

Polymer plasticization has been largely studied to allow easier manufacturing, but the problems deriving from undesired plasticization (e.g., drug-polymer interaction), have been largely ignored in drug delivery science and technology. This is surely due to an incomplete understanding of the phenomenon and to inadequate theories and models available at the moment [24]. The addition of excipients to modulate drug release is a common practice [16,21] but few attempts to hinder polymer plasticization have been reported [21].

Ketoprofen loaded PLA/PLGA microparticles have been previously formulated using the solvent diffusion-evaporation technique. Due to ketoprofen and water [25] plasticizing effects, the production of PLA/PLGA microparticles was not possible with low-molecular-weight polymers (low *Tg* value) using the mentioned method [18].

It was hypothesized that, by hindering the physical interaction between ketoprofen and polymer chains, plasticizing effect could be eluded during microparticle preparation. To test this hypothesis, ketoprofen was included in β-cyclodextrins (βCDs) and the inclusion complex was encapsulated in low-molecular-weight PLA/PLGA.

2. Materials and methods

2.1. Materials

Polymers poly(D,L-lactide-co-glycolide) 50:50 RG 502 (Mw ~ 10 kDa), RG 502H (Mw ~ 10 kDa), and poly(D,L-lactide) RG 202H (Mw ~ 10 kDa) were purchased from Boehringer Ingelheim (Ingelheim, Germany). Ketoprofen was kindly supplied by Bidachem S.p.A. (Bergamo, Italy). βCDs were obtained from Fluka Chemical (Milan, Italy), KBr and (hydroxypropyl) methylcellulose (viscosity of 80–120 cP, aqueous solution 2% w/v) were obtained from Sigma Aldrich Chemical Co. Ltd. (Milan, Italy). Dichloromethane and acetonitrile (HPLC grade) were purchased from J. T. Baker (Milan, Italy). Ultrapure water was obtained from Human Power 1 system (Human Corporation, Caserta, Italy). All the other materials employed were of the highest purity grade commercially available.

2.2. Preparation and characterization of the inclusion complex

2.2.1. Inclusion complex preparation

Inclusion complex was prepared using the kneading method at two different βCD:ketoprofen stoichiometric ratios, 1:1 and 2:1. The two starting materials were mixed in a mortar and wetted with a minimum volume of ethanol/water (1:1 v/v) and kneaded for 10 min. The mixture was exsiccated under vacuum for 3 days to obtain the inclusion complex as dry powder [26].

2.2.2. UV–Vis spectrophotometry

The inclusion complexes were analyzed UV–Vis spectrophotometry (λ, 254 nm) to quantify both free and total ketoprofen content using an Agilent 8453 spectrophotometer. To evaluate total ketoprofen content in the inclusion complex, 10 mg of powder were solubilized in 10 mL of a mixture of acetonitrile:water, 1:1 v/v. To determine the free ketoprofen, 10 mg of inclusion complex were dispersed in 10 mL of dichloromethane and the suspension obtained was filtered using Teflon filter (0.2 μm-Lida, Kenosha). The solution obtained after filtration was analyzed to determine the free ketoprofen content [27].

2.2.3. Morphological analysis

Morphological characterization was performed by scanning electron microscopy (SEM) using a Philips XL30 SEM (Philips Electron Optics, Heindoven, Netherlands). Samples were prepared by placing inclusion complex powder, physical mixtures, βCD and ketoprofen powder onto an aluminum stub covered by a carbon double sided adhesive disc. Samples were coated with gold prior to imaging (EMITECH K-550 sputter coater Ashford, Kent, UK). Coating was carried out at 20 mA for 4 min.

2.2.4. Thermal analysis

Differential scanning calorimetry (DSC) data were acquired by a calorimeter DSC821e (Mettler Toledo, Greifensee, Switzerland) equipped with a refrigerated cooling system. The system was calibrated by an indium standard. Samples (exactly weighed) were sealed in aluminum pans and submitted to a heating cycle from 25 °C to 100 °C at 10 °C/min. Data were elaborated by the STARe software (Mettler Toledo, Griefen-see, Switzerland), and the results were expressed as the mean of 3 independent measures.

2.2.5. X-ray powder diffraction analysis

X-ray powder diffraction spectra were recorded by a Philips 1710 powder X-ray diffractometer using Cu Kα radiation, a voltage of 40 kV and a 30 mA current. The diffractometer had a PW1820 goniometer and a graphite monochromator for diffracted rays. Spectra were recorded using the step scanning method (step size 0.03°) and elaborated using the PC-APD software. Samples were prepared using the lateral loading method to minimize the preferential orientation.

2.2.6. FT-IR analysis

Samples were prepared by mixing the powder with KBr and compressing the mixture with a hydraulic press (Perkin Elmer, Beaconsfield, United Kingdom) (13-mm diameter die; compression force, 5 tons; time, 1 min). FT-IR spectra were recorded on a Jasco FT-IR-410, 420 Herschel spectrometer (Jasco Corporation Tokyo, Japan).

2.2.7. Molecular dynamics simulations

βCD and R- and S-ketoprofen were sketched using the Maestro interface (Maestro, version 9.9, Schrödinger, LLC, New York, NY, 2014) and submitted to mixed torsional/low-mode conformational sampling using MacroModel (MacroModel, version 10.5, Schrödinger, LLC, New York, NY, 2014). OPLS-2005 [28] was used as force field and GB/SA as solvation treatment [29]. Only global minima were retained from the conformational search and were used for the following analysis. The 2 ketoprofen enantiomers were manually docked into βCD in both orientations and the resulting