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Analysis of physicochemical properties of ternary systems of oxaprozin with randomly methylated-ß-cyclodextrin and L-arginine aimed to improve the drug solubility

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ABSTRACT

The influence of L-arginine on the complexing and solubilizing power of randomly-methylated-β-cyclodextrin (RameβCD) towards oxaprozin, a very poorly soluble anti-inflammatory drug, was examined. The interactions between the components were investigated both in solution, by phase-solubility analysis, and in the solid state, by differential scanning calorimetry, FTIR and X-ray powder diffractometry. The morphology of the solid products was examined by Scanning Electron Microscopy. Results of phase-solubility studies indicated that addition of arginine enhanced the RameβCD complexing and solubilizing power of about 3.0 and 4.5 times, respectively, in comparison with the binary complex (both at pH ≈ 6.8). The effect of arginine was not simply additive, but synergistic, being the ternary system solubility higher than the sum of those of the respective drug-CD and drug-arginine binary systems. Solid equimolar ternary systems were prepared by physical mixing, co-grinding, coevaporation and kneading techniques, to explore the effect of the preparation method on the physicochemical properties of the final products. The ternary co-ground product exhibited a dramatic increase in both drug dissolution efficiency and percent dissolved at 60 min, whose values (83.6 and 97.1, respectively) were about 3 times higher than the sum of those given by the respective drug-CD and drug-aminoacid binary systems. Therefore, the ternary co-ground system with arginine and RameβCD appears as a very valuable product for the development of new more effective delivery systems of oxaprozin, with improved safety and bioavailability.

1. Introduction

Oxaprozin (3-(4,5-diphenyl-1,3-oxazol-2-yl) propanoic acid) is a non-steroidal anti-inflammatory drug (NSAID) endowed with analgesic and antipyretic properties, mainly utilized to treat inflammatory conditions, in particular osteoarthritis and rheumatoid arthritis and to alleviate moderate pain. Moreover, it can also have a protective effect against the development of cancer or Alzheimer's disease [1]. However, owing to its high permeability but very low water solubility, oxaprozin is classified as a Class II drug, according to the Biopharmaceutic Classification System (BCS) [2]. Its very poor aqueous solubility may give rise to formulation problems and also limit its actual therapeutic effectiveness, causing variable bioavailability, and enhancing the appearance of adverse effects, such as in particular gastro-duodenal mucosal injury [3].

Cyclodextrin (CD) complexation has been widely and successfully exploited as an efficient tool for improving the biopharmaceutical properties of several drugs, including different NSAIDs, in particular through an increase in dissolution and in absorption rate, a decrease in gastrointestinal irritancy, and a masking of their bitter taste [4–8]. Careful studies are necessary for a rational selection of the most effective CD to use and for and adequate physical-chemical characterization of the developed drug-CD system [9–12]. In a previous study we compared the complexing and solubilizing abilities towards oxaprozin of different cyclodextrins (CDs), both natural and chemically-modified, and pointed out the greatest effectiveness of the randomly-methylated-βCD (RameβCD) [13]. However, it has to be taken into account that the amount of CDs that can be used in pharmaceutical dosage forms is limited by various problems, such as their high molecular weight, with the subsequent increased bulk of the solid formulations, and, particularly in the case of the methylated derivatives, risks of potential toxicity [14]. The addition of a third component, able to increase the complexing and solubilizing power of CDs, thus reducing the

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amount needed to achieve the desired drug solubilizing effect, is an interesting approach to overcome these drawbacks [15]. For example, the addition of small amounts of suitable hydrophilic polymers to the complexation medium was effective in increasing the CD solubilizing efficiency by multicomponent complex formation [16–19]. In particular, we explored in deep the influence of chitosan on CD complexing and solubilizing effect towards drugs [20], and we recently found that the addition of such polymer (at 0.0625% w/v) enabled an about four times improvement of the RameβCD solubilizing power towards oxaprozin [21]. Otherwise, it has been reported that some low molecular weight hydroxy-acids can strongly enhance the CD solubilizing capacity toward basic drugs, probably as a consequence of the joined effect of inclusion complexation and salt formation [22–25]. Likewise, ternary complexation involving salt formation with organic or inorganic cations was successfully applied to improve the CD solubilizing capacity towards acidic drugs [26,27]. In this regard, the use of basic aminoacids as counter-ions for ternary complex formation with CD and acidic drugs proved to be particularly effective [28–231]. Moreover, the use of aminoacids as counter-ions enables a reduction of the marked burning sensation and of the soapy taste given, when dissolved in water, by the CD complexes with NSAIDs as sodium salts [27].

Therefore, considering these premises, it seemed of interest to explore the possible effect of L-arginine, a basic aminoacid, in enhancing the complexing and solubilizing abilities of RameβCD toward oxaprozin. This would allow a more efficient and safer use of this methylated CD, in view of the future development of new more effective delivery systems of this NSAID based on such ternary system.

Studies for characterization of interactions in solution between RameβCD, arginine and oxaprozin were performed by phase-solubility analyses in aqueous solutions at different pH values. Moreover, equimolar oxaprozin-RameβCD-arginine solid systems, prepared by different techniques, were characterized for solid-state interactions (by Differential Scanning Calorimetry, FTIR, X-ray powder diffractometry), and dissolution properties, in comparison with the corresponding drug-CD or drug-arginine binary systems. The morphological characteristics of the different products were examined by scanning electron microscopy.

2. Materials and methods

2.1. Materials

Oxaprozin (OXA) (Mw 293.317, pKa 4.3), was kindly donated by S.I.M.S. (Florence, Italy) and used as received. Randomly substituted methyl-β-cyclodextrin (RameβCD) with an average molar substitution degree per anhydroglucose unit of 1.8, was a kind gift from Wacker-Chemie GmbH (München, Germany), L-arginine (ARG) was from Sigma Chemical Company (St Louis, MO, USA). All other reagents were of analytical grade.

2.2. Solubility studies

Solubility measurements of OXA alone or as equimolar mixture with ARG, equimolar complex with RameβCD and equimolar ternary system with CD and ARG were carried out by adding an excess amount of drug or each product to 10 mL of buffered (pH 5.5, 6.8 and 7.4 phosphate buffer), or unbuffered aqueous solutions in sealed glass vials preserved from the light and magnetically stirred (500 rpm) at 25 ± 0.5 °C. Aliquots were periodically withdrawn with a syringe-filter (0.45 μm pore size), and spectrometrically assayed for drug content at 285.2 nm (UV–vis 1600 Shimadzu spectrophotometer, Tokyo, Japan) until equilibrium. It has been verified that the presence of RameβCD and/or ARG did not interfere with the drug assay. The pH at equilibrium was checked in all the suspensions. Each test was repeated four times (coefficient of variation C.V. < 3%).

2.3. Phase-solubility studies

Excess amounts of OXA or OXA-ARG equimolar combination were added to 10 mL of pH 5.5 phosphate buffer, or unbuffered aqueous solutions, containing increasing concentrations of RameβCD in the 0–25 mM concentration range. The vials were sealed preserved from the light and electromagnetically stirred (500 rpm) at 25 ± 0.5 °C. Aliquots were withdrawn every 24 h until equilibrium (72 h), filtered (0.45 μm pore size), and spectrometrically assayed as described above. The pH at equilibrium was about 5.5 and 6.8 for binary and ternary systems, respectively. Each test was performed in triplicate (C.V. < 4%). Analogous phase-solubility studies were also performed, under the same experimental conditions, on OXA-RameβCD binary systems in pH 6.8 phosphate buffer solutions (i.e. the same pH of unbuffered aqueous solutions of OXA-ARG combinations with RameβCD). Diagrams were constructed by graphing the apparent solubility of OXA against the CD concentration in the sample.

2.4. Preparation of solid systems

Equimolar binary (OXA-RameβCD) or ternary (OXA-ARG-RameβCD) solid systems, were prepared by different methods. Physical mixtures (PM) were obtained by 15 min tumble mixing weighed amounts of the individual components (75–150 μm sieve granulometric fraction). Co-ground products (GR) were prepared by ball-milling PM 30 min at 24 Hz in a high-energy vibrational micro-mill (Mixer Mill MM 200, Retsch GmbH, Düsseldolf, Germany). Coevaporated products (COE) were prepared by coevaporation in a rotary evaporator (Laborota 4000, Heidolph, Milan, Italy) of 1:1 v/v ethanol–water solution of PM. Kneaded products (KN) were prepared by adding a small volume of ethanol to the PM, kneading thoroughly with a pestle to obtain homogeneous slurry and continuing until all the solvent was removed.

2.5. Differential scanning calorimetry (DSC)

DSC analyses of the single components or the different binary and ternary products were performed using a Mettler TA4000 Star^e system (Mettler Toledo, Greifensee, Switzerland) equipped with a DSC 25 cell. Weighed samples (5–10 mg, Mettler M3 Microbalance) were scanned in pierced Al pans at 10 °C/min from 30 to 200 °C under static air.

2.6. Fourier transformed infrared spectroscopy (FTIR)

The FTIR spectra of the individual components and of their equimolar physical mixtures and co-ground products were obtained by a Perkin-Elmer Mod. 1600 spectrometer (Wellesley, USA). All samples were prepared by the KBr disc method and scanned in the 3000–400 cm^{-1} region at 2 cm^{-1} resolution.

2.7. X-ray powder diffractometry (XRPD)

The XRPD patterns of the individual components and of the different binary and ternary solid products were obtained with a theta–theta Bruker D8-advance instrument (Silberstreifen, Germany) using a Cu Kα radiation and a graphite monochromator, at a 40 mV voltage and 55 mA current. All samples were examined at room temperature in the 5–35° 2θ range, at a scan rate of 0.05°/s.