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# Development and characterization of fast dissolving tablets of oxaprozin based on hybrid systems of the drug with cyclodextrins and nanoclays

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ABSTRACT

Previous studies highlighted an increase of the randomly-methylated-ß-cyclodextrin (RAMEB) solubilizing power towards oxaprozin when used in combination with L-arginine (ARG) or sepiolite nanoclay (SV). Therefore, the aim of this work was to investigate the possibility of maximising the RAMEB solubilizing efficacy by a joined approach based on the entrapment in SV of the drug-RAMEB-ARG complex. The quaternary nanocomposite was prepared by different techniques and characterized for solid state and dissolution properties, compared to ternary drug combinations with RAMEB-ARG, RAMEB-SV or ARG-SV. The dissolution rank order was drug-RAMEB-ARG-SV>>drug-RAMEB-ARG≈drug-RAMEB-SV>>drug-ARG-SV. The new hybrid nanocomposite enabled an increase from 60 up to 90% of oxaprozin dissolution parameters compared to the ternary systems with RAMEB-ARG and RAMEB-SV. Moreover, the lowest solubilizing efficacy of ternary systems with ARG-SV evidenced the specific synergic effect of both ARG and SV with RAMEB in enhancing oxaprozin dissolution properties. The superior performance of the quaternary nanocomposite was maintained after incorporation in a tablet formulation. In vivo studies on rats proved that the developed fast-dissolving tablet formulation, containing oxaprozin as cofused system with RAMEB, ARG and SV was more effective than the marketed tablet in terms of faster and more intense pain relieving effect in the treatment of adjuvant-induced arthritis.



## Introduction

The low dissolution rate in gastrointestinal fluids of poorly-soluble drugs is a crucial factor limiting their absorption rate and bioavailability (Vemula et al., 2010; Sharma et al., 2009). Therefore, the search for suitable approaches able to overcome such a critical drawback remains as one of the most challenging aspects in the development of new oral drug delivery systems (Yellela, 2010; Kumar et al., 2011).

Oxaprozin, a non-steroidal anti-inflammatory drug mainly utilized to treat inflammatory conditions, including rheumatoid arthritis, is currently available on the market as 600 mg oral conventional tablets, with an usual daily dosage of 1.2 g. It is labelled in Class II of BCS (Biopharmaceutics Classification System), due to its high permeability but very poor water-solubility (Yazdanian et al., 2004). In particular, despite its acidic character, it fulfils the BCS low solubility criteria over the entire gastrointestinal pH range from 1.2 to 7.4 (Yazdanian et al., 2004), indicating that its oral absorption is most likely limited by its poor solubility and dissolution in the entire gastrointestinal region. Therefore, the development of a new tablet formulation with improved oxaprozin solubility and dissolution rate would allow to enhance its bioavailability and reduce its dosage and dose-related side-effects (Rothstein, 1998).

Cyclodextrins have been widely and successfully used as carriers to improve the solubility and bioavailability of several poorly soluble drugs (Uekama et al., 1998; Loftsson and Duchêne, 2007). Moreover, cyclodextrin complexation can provide

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additional advantages, including taste masking, dose lowering and side effects reduction, particularly beneficial in the case of anti-inflammatory drugs (Otero Espinar et al., 1991; Ann et al., 1997; Elkheshen et al., 2002; Muraoka et al., 2004).

Based on these premises, in a previous study we investigated the performance of different cyclodextrins in improving oxaprozin dissolution properties, and we individuated the randomly methylated ß-cyclodextrin (RAMEB) as the most effective one (Maestrelli et al., 2009). However, the amount of methylated cyclodextrins actually usable in pharmaceutical formulations is restricted by problems of potential dose-related toxicity (Boudemarat et al., 2005; Ulloth et al., 2007; Kiss et al., 2010). For this reason, it would be very important to find proper ways to increase the solubilizing efficacy of such cyclodextrin derivative, and then reduce the necessary amount to use.

Ternary complexation involving salt formation with suitable cations, including basic aminoacids, has been suggested as a possible approach to improve the cyclodextrin solubilizing power towards acidic drugs (Redenti et al., 2001; Mura et al., 2005; Figueiras et al., 2010). In particular, we have found recently that the equimolar ternary system of oxaprozin with RAMEB and arginine exhibited a very marked increase in dissolution efficiency with respect to the corresponding binary system without the basic aminoacid (Mennini et al., 2016).

Alternatively, combined strategies based on drug-cyclodextrin complexation and complex entrapment into various carriers such as solid-lipid (Cavalli et al., 1999) or polymeric (Vega et al., 2013) nanoparticles, liposomes (Bragagni et al., 2010; Maestrelli et al., 2010), niosomes (Marianecci et al., 2015), micelles (Li et al., 2010), microemulsions (Mura et al., 2014) or nanostructured lipid carriers (Cirri et al., 2012) proved to be able to enhance the performance of both kinds of nano-carriers, overcoming or reducing the problems related to their use. In this regard, we have experimented recently a new combined approach, by developing a hybrid system, based on loading the oxaprozin-RAMEB complex into nanoclays, with the aim of joining and, possibly, potentiating the relative benefits of both carriers in a single drug delivery system (Mura et al., 2016). The particular interest in the use of inorganic matrices as drug carriers was due to their biocompatibility and high entrapment power (Aguzzi et al., 2007; Viseras et al., 2010), together with their ability to provide increased drug dissolution properties, sustained release, improved drug stability (Ambrogi et al., 2001, 2003; Zheng et al., 2007; Rojtanatanya and Pongjanyakul, 2008; Perioli et al., 2011). The developed "oxaprozin in RAMEB in sepiolite" ternary system allowed to double the % of drug dissolved with respect to the complex as such (Mura et al., 2016).

Therefore, considering the interesting results obtained either by ternary complexation of oxaprozin with RAMEB and arginine (ARG) (Mennini et al., 2016) or by the combined use of RAMEB and sepiolite (SV) (Mura et al., 2016), in the present work we considered it worthy of interest to join these different strategies in an only system, to maximise the RAMEB performance.

Moreover, in order to evaluate the influence of the preparation method on the performance of the final product, ternary and quaternary combinations of the drug with RAMEB, ARG and SV were prepared by cofusion, cogrinding or coevaporation and characterized for solid state (by Differential Scanning Calorimetry and X-ray powder diffractometry analyses) and dissolution properties. The best systems were selected for the development of tablets, which were evaluated for technological properties and dissolution behaviour. The most effective tablet formulation was finally selected for in vivo studies on rats, to evaluate its therapeutic efficacy in the treatment of induced rheumatoid arthritis compared to the marketed OXA tablet formulation.

## Materials and methods

### 2.1. Materials

Oxaprozin (OXA) (4,5-diphenyl-2oxazole propionic acid) was kindly provided by S.I.M.S. (Firenze, I) and used as received. Amorphous randomly substituted methyl-ß-cyclodextrin (RAMEB), average MS 1.8, was donated by Wacker-Chemie GmbH (München, Germany). Sepiolite (SV) was from Vicalvaro (Spain). L-arginine (ARG) was from Sigma Chemical Company (St Louis, MO, USA). Microcrystalline cellulose (Emcocel® 90 M) was purchased from Penwest Pharmaceuticals Oy (New York, U.S.A.). Magnesium stearate was obtained from Aldrich Chemie GmbH (Steinhelm, Germany). Sodium starch glycolate (Explotab®) was from JRS Pharma (Rosenberg, Germany). Tablets of oxaprozin commercially available in Italy (Walix®) were from Fidia Farmaceutici, S.p.A. All other chemicals and solvents were of reagent grade and used without further purification.

### 2.2. Phase-solubility studies

Phase-solubility studies of OXA with RAMEB alone (Maestrelli et al., 2009), or in the presence of ARG (1:1 mol:mol) (20 Mennini et al., 2016) were previously performed. Therefore, in order to evaluate the effect of the presence of SV on such systems, excess amounts of OXA (100 mg) combined with SV (1:4 w/w) or ARG (1:1 mol:mol) and SV (1:4 w/w) together, were added to 10 mL of pH 5.5 phosphate buffer solutions, containing increasing concentrations of RAMEB (0–25 mM) in sealed glass containers preserved from the light and electromagnetically stirred (500 rpm) at $25 \pm 0.5\,^{\circ}C$. Aliquots were withdrawn every 24 h with a filter syringe (0.45 μm pore size) until equilibrium (72 h), and spectrometrically assayed for drug content at 285.2 nm (UV–vis 1600 Shimadzu spectrophotometer, Tokyo, Japan). Each test was performed in triplicate (C.V. <4%). The apparent stability constants ($K_{1:1}$) of the complexes were calculated from the slope of the straight line portions of the phase-solubility diagrams (Higuchi and Connors, 1965).

### 2.3. Preparation of drug-carrier systems

OXA-RAMEB-SV, OXA-RAMEB-ARG, OXA-ARG-SV and OXA-RAMEB-ARG-SV interaction products were obtained by different methods:

1-Physical mixing: physical mixtures (PM) were obtained by 15 min blending in a turbula mixer the single components previously sieved (75–150 μm sieve fraction);

2-Cofusion: PMs were heated 20 min at 200 °C, and then let solidify to room temperature in a desiccator (cofused products, COF);

-Co-grinding: PMs were ball-milled in a high-energy vibrational micro-mill (Mixer Mill MM 200, Retsch GmbH, Düsseldolf, Germany) at 24 Hz for 30 min (coground-products, GR);

-Coevaporation: PMs were dissolved/dispersed in a 60:40 v/v ethanol-water mixture and then the solvent was removed in a rotary evaporator (Laborota 4000, Heidolph, Milan, Italy) (coevaporated products, COE).

Based on previous studies, regardless of the preparation method used, RAMEB and ARG were always added in equimolar ratio with the drug (Mennini et al., 2016), while SV was added at 1:4 w/w ratio (Mura et al., 2016).

### 2.4. Solid state characterization of drug-carrier systems

The solid state properties of the pure components and of their different combinations were characterized by: