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Enhanced intestinal permeability and oral bioavailability of enalapril maleate upon complexation with the cationic polymethacrylate Eudragit E100

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ABSTRACT

The low bioavailability of enalapril maleate associated to its instability in solid state motivated the development of a polyelectrolyte-drug complex between enalapril maleate and the cationic polymethacrylate Eudragit E100. The solid complexes were characterized by DSC–TG, FT-IR and X-ray diffraction. Their aqueous dispersions were evaluated for drug delivery in bicompartimental Franz cells and electrokinetic potentials. Stability in solid state was also evaluated using an HPLC–UV stability indicating method. Absorption of enalapril maleate was assessed thorough the rat everted gut sac model. In addition, urinary recovery after oral administration in rats was used as an indicator of systemic exposition. The solid materials are stable amorphous solids in which both moieties of enalapril maleate are ionically bonded to the polymer. Their aqueous dispersions exhibited controlled release over more than 7 h in physiologic saline solution, being ionic exchange the fundamental mechanism that modified the extent and rate of drug release. Intestinal permeation of enalapril maleate was 1.7 times higher in the presence of the cationic polymer. This increase can be related with the capacity to adhere the mucosa due to the positive zeta potential of the complexes. As a consequence bioavailability was significantly improved (1.39 times) after oral administration of the complexes. In addition, no signs of chemical decomposition were observed after a 14 months period. The results indicated that the products are new chemical entities that improve unfavorable properties of a useful drug.

1. Introduction

Polyelectrolytes (PE) under the form of ionic exchange resins (insoluble PE) or dispersible hydrophilic polymers (soluble PE) have been largely used in pharmaceutical formulations (Anand et al., 2001; Guo et al., 1998; Heller, 1995; Jantzen and Robinson, 1996). Examples of such polymers include DNA (Van de Wetering et al., 1998; Wang et al., 2011), proteins (Kratz, 2008), carbomer (Parojčić et al., 2004), alginic acid (Tønnesen and Karlsen, 2002), hyaluronic acid (Dollo et al., 2004), carrageenan (Pavli et al., 2011), certain derivatives of cellulose polymers (Gallo et al., 2013; Ramírez Rigo et al., 2004), chitosan and other cationic polymethacrylates (Hamman, 2010; Kojima et al., 2012).

The ionic interaction between PE and acid or basic drugs (D) is a valuable resource to obtain new materials with physicochemical, pharmaceutical and biopharmaceutical properties different from those of their precursors. The ionic (PE–D) complexes can be obtained in a wide variety of qualitative and quantitative compositions as aqueous dispersions or in solid state. According to the properties of the newly formed chemical entity, the PE–D interaction can improve the drug stability in solution (Esteban et al., 2009; Jimenez-Kairuz et al., 2004), the permeability through biological membranes (Bonferoni et al., 2008), the apparent solubility in the vehicle (Dai et al., 2007) or modulate the release of drugs (Guzmán et al., 2012; Jimenez-Kairuz et al., 2005; Ramírez Rigo et al., 2006, 2009). Therefore these products are useful to develop drug delivery systems (Bermúdez et al., 2008; Kindermann et al., 2011; Vilches et al., 2002). Drugs recognized as safe and effective, but with some unfavorable physicochemical or biopharmaceutical properties, are good candidates to be loaded on a PE.

Within this framework, the maleate salt of Enalapril (EnM) was selected to develop PE–D complexes. EnM is the first choice in the

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treatment of hypertension and congestive heart failure. It is a prodrug that is administered in daily oral doses of 5–20 mg, being the maximum tolerated dose 40 mg per day (Clinical Pharmacology, 2011). Approximately 55–75% of the dose of EnM is rapidly absorbed through the digestive tract in healthy individuals and hypertensive patients (Tabacova and Kimmel, 2001). According to the biopharmaceutical classification system, EnM was provisionally classified as a class III drug because of its high solubility relative to the dose and low intestinal permeability (Pretorius and Bouic, 2009).

Transdermic formulations have been developed as a strategy to increase the bioavailability of EnM (Li and Nguyen, 2003) although the oral route is the preferred method of administration (Parente Dueña et al., 1999).

This prodrug is metabolized mainly in the liver where it is hydrolyzed by esterases to enalaprilat, its active metabolite. The therapeutic effects appear between 1 and 2 h after a single oral dose of enalapril, and they persist for 12–24 h. Excretion of both enalapril and enalaprilat is primarily renal and 61% of the dose (43% enalaprilat, 18% enalapril) is recovered in urine (Tabacova and Kimmel, 2001).

Another important aspect to consider is that EnM salt exhibits marked problems of compatibility (stability) with excipients generally used in solid formulations like microcrystalline cellulose, magnesium stearate, calcium phosphates, starch, sodium starch glycolate, crospovidone and croscarmellose sodium, a feature that is relevant in formulation stages (Bharate et al., 2010; Marcal Lima et al., 2008; Patel and Davila, 2005; Rezende et al., 2008). Moreover, water content and temperature have a large influence on drug stability. The degradation of EnM leads through two main degradation products, enalaprilat and diketopiperazine, which are formed by hydrolysis of the ethyl ester moiety and by intramolecular cyclization of the drug, respectively (Simončič et al., 2007). The use of excipients that have proved to be compatible with EnM (Novartis, 2005; Rezende et al., 2008) or the formation of cyclodextrin inclusion complexes (Zoppi et al., 2008) are pharmaceutical strategies used to increase the stability of EnM in solid formulations.

The acidic and basic groups which are present in the structure of enalapril (En) (Fig. 1a) enable it to interact with anionic and cationic PE. However, when it is salified with the maleate counterion (M), a cationic PE would have the ability to ionically interact with both moieties of the salt. On this basis, the cationic PE Eudragit® E100 (EU) was selected to design a complex for oral administration.

The EU is a copolymer based on dimethylaminoethylmethacrylate and neutral methacrylic esters (Fig. 1b). It is soluble in aqueous media up to approximately pH 5 and it is mainly used in pharmaceutical technology as a tablet coating excipient. After oral ingestion, EU was not absorbed and was excreted unchanged with the feces. Daily permissible intake limits for polymethacrylate derivatives are 2–20 mg/kg body weight (Rowe et al., 2006).

Cationic polymethacrylate-acid drug complexes have been obtained with different monofunctional poorly water-soluble drugs in order to improve their apparent solubility (Baena et al., 2011; Guzmán et al., 2012; Kindermann et al., 2011, 2012; Quinteros et al., 2008). In addition, a study of the stability of films obtained by solvent evaporation on an aluminum support of ethanolic dispersions of mixtures of EnM and EU at different weight ratios of 1:1, 1:2, 1:3 has been reported. The stability of the drug in these films depended on the proportion of EU present in the mixture, indicating an inverse relationship between the amount of EU and the appearance of the degradation product (Wang et al., 2004). This point will be further addressed in this report.

Although there have been some interesting contributions regarding this subject, no product has been developed from EnM and PE that improves the unfavorable properties described for this drug (low bioavailability and low chemical stability). With this motivation, the aim of this article was to describe the preparation and the physicochemical, pharmaceutical and biopharmaceutical characterization of a new particulate material based on a $(EU–EnM)_x$ complex.

2. Materials and methods

2.1. Materials

The following materials were used as received from the supplier: EU (poly (butyl methacrylate-co-(2-dimethyl aminoethyl) methacrylate-co-methyl methacrylate) 1:2:1) (Pharmaceutical Grade, Rohm, Germany), EnM (Pharmaceutical Grade, Parafarm, Argentina, melting point: 147.4–149.6 °C), maleic acid (PA grade, Aldrich, USA, melting point: 130.0–131.4 °C), HCl and NaOH solutions (1 M, Anedra, Argentina), methanol, acetonitrile, water (HPLC grade, Sintorgan, Argentina). The EnM and enalaprilat HPLC standards were kindly provided by Roemmers Laboratory (Argentina). All other reagents and solvents were *pro-analysi* grade.

2.2. Preparation of $(EU–EnM)_x$ complexes in solid state

The subscript × indicates the percentage of amino groups of EU neutralized by the $–COO^-$ group of enalapril.

EU was milled in a mortar and sieved through 40 and 70 mesh sieves (ASTM, Zonytest, Argentina). The equivalents of amino groups per gram of EU (3.10×10^{-3}) were assayed by direct acid–base titration.

A series of complexes were prepared in a mortar by dissolving 3.5 g of EU and the appropriate amount of EnM in 10 mL of ethanol (96°). During mixing, spontaneous evaporation at room tempera-

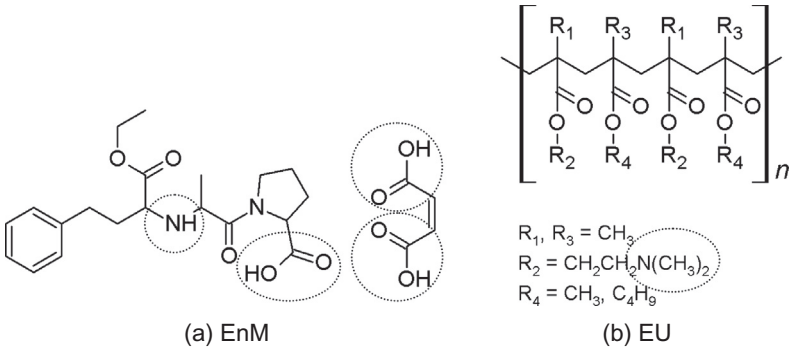

Fig. 1. Structural formula of (a) EnM and (b) EU showing their acidic and basic funtional groups.