Interaction Between Eudragit® E100 and Anionic Drugs: Addition of Anionic Polyelectrolytes and Their Influence on Drug Release Performance

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ABSTRACT: In this work, we report results concerning the study of solid complexes compounded by a cationic polymethacrylate (Eudragit® E100, Eu) and mesalazine (M) (Eu–M_x complex). The influence of an anionic polyacrylic acid polymer (carbomer, C) on dissolution behavior of M from the complex was evaluated (Eu–M_xC_y complex). The dissolution profiles and solvent front movements of solid matrices in different media (water, buffer pH 7.4, 0.9% NaCl) were investigated and ionic interactions among Eu, M, and C were determined through Fourier transform infrared (FT-IR) spectroscopy. For Eu–M_x complexes, the affinity between M and Eu modulated the delivery of free M in solution, with the dissolution media affecting the delivery rate mainly due to an ionic interchange process between M and anionic electrolytes (i.e., Cl^-). FTIR spectroscopy allowed the ionic interaction between Eu and M to be verified. The addition of C (Eu–M_xC_y) influenced the dissolution behavior of these matrices. As the amount of C was increased, the release mechanism changed from diffusion (Eu–M_{50}) or anomalous (Eu–M_{100}) to zero order (Eu–M_xC_{50}). This variation in rate delivery was also affected by the dissolution media, as occurred with Eu–M_x complexes. The formation of the gel layer during the dissolution process, as consequence of Eu–M_xC_y matrices hydration, was influenced by C amount and dissolution media. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:4664–4673, 2011

Keywords: polyelectrolytes; complexation; diffusion; Eudragit; carbomer; mesalazine; controlled release and dissolution rate

INTRODUCTION

The complexation of polyelectrolytes (PEs) with ionizable drugs is a very common strategy used in the design of different pharmaceutical dosage forms that need to provide modified drug release,[1–3] with this strategy having permitted formulation difficulties, such as taste masking,[4] drug compatibility,[5]and drug stability improvement,[6] to be overcome.

The main advantages of PE–drugs complexes in comparison to their physical mixtures (PMs) are increasing in apparent solubility of low solubility drugs, increasing stability, resistance to enzymatic attack, and feasibility for drug release modulation.

The interaction between PE and these drugs is the relevant factor that defines the features of the delivery system and many reports on this topic can be found in the literature, especially those referring to anionic PE–basic drugs complexes.[7–9] However, detailed information about the factors involved in the nature of basic PE–acidic drugs (BPE–ADs) interactions is scarce.

The BPE–AD complexes are not common and the basic polymethacrylates (Eudragit® E100, Eu)[10] are among the few BPEs able to interact with ADs. In aqueous dispersion, the drug sorption by the BPE is essentially the consequence of an acid–base interaction between the tertiary amino groups (-NR_2) and the acidic group of the AD. Therefore, it is predictable that drug properties such as acid strength, hydrophilicity, and solubility can influence the physical–chemical characteristics of these complexes.

In a previous work, we obtained complexes of Eu with different ADs[11] and observed that the solubility

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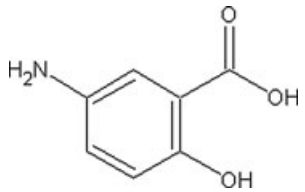

Scheme 1. Chemical structure of mesalazine.

of the drugs had a direct influence on the complex solubility and hence on drug release. In the case of mesalazine (M, Scheme 1), which showed a high aqueous solubility (1 mg/mL, 25°C), release from the solid complex was practically immediate. However, we also verified that the drug remained attached to the polymer in solution because M was slowly released through a semipermeable membrane. This indicated that the polymer–drug interaction regulated the release of free drug toward the media.

The use of hydrocolloid polymers with the aim of modulating drug release has been well described,[12,13] with water uptake and the swelling properties of these materials being the key properties that influence drug release from the solid matrix. Among the most used polymer are polyacrylic acid derivatives, with carbomer (C), an acidic polymer having been intensely studied as modulator of drug release.

Considering that M showed an immediate release from particulate Eu–M complexes, the aim of this work was to evaluate the influence on drug release of the incorporation of different proportions of C to the solid complex matrices. Swelling, water uptake, and the influence of the dissolution media were also evaluated.

MATERIALS AND METHODS

Materials

Poly [butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate] 1:2:1 (Eu) (Eudragit® E100, pharmaceutical grade; Röhm Pharma, Steinheim, Germany) was a gift from Etilfarma SA (Buenos Aires, Argentina). Mesalazine (M) (PA grade; Fluka, Stockholm, Sweden) and carbomer 934-P (C) (Carbopol 934-P NF; BF-Goodrich Company, Cleveland, Ohio) were also used. All other materials were of analytical grade.

Methods

Preparation of Eu–M Complex

Pretreatment of Eu. Before complexation with M, solid Eu was milled and sieved through 40 and 70 mesh sieves. The equivalent amino groups per gram of Eu (3.096×10^{-3}) were assayed by acid–base titration.[14,15]

Eu–M_x Solid Complex. It was prepared by dissolving Eu and the appropriate amount of M in acetone, in order to neutralize 50% or 100% of the amino groups of Eu. The solid complexes were precipitated after solvent evaporation at room temperature. "*x*" indicates the percentage of amino groups neutralized in the notation Eu–M_x. In this way, we obtained free flowing solids in which, for example, when Eu was 50% neutralized with M, we obtained the Eu–M_{50} complex.

Characterization of Solid Complexes. Fourier transform infrared (FTIR) spectra were measured using a Nicolet 5SXC FT-IR Spectrometer (Thermo Scientific, Madison, WI, USA) using KBr disks.

Manufacture of Eu–M_x and Eu–M_xC_y Compressed Matrices

The solid particulate complex was compressed in a single-punch (13 mm, flat) eccentric press (Delfabro HPH 15; San Francisco, Córdoba) under 2500 kg/cm^2 for 5 s, resulting in 12.8-mm thick tablets, which weighed 150 mg. These compressed tablets increased in weight with the addition of the respective amounts of C. To prepare the solid matrix of the complex–polymer combination to 150 mg of the Eu–M_x complex, 10, 30, or 50 mg of C were incorporated in the blend, homogenized in a mortar, and then compressed. In the notation Eu–M_xC_y, "*y*" indicates the amount (mg) of polymer added in the matrix. For example, when 50 mg of C was added to 150 mg of the Eu–M_{50} complex, 200 mg of powdered Eu–$M_{50}C_{50}$ was obtained.

The powdered PM used for comparative analysis was compounded by Eu (120 mg), M (30 mg), and C (50 mg).

Water Uptake

The liquid uptake kinetics of the tablets was evaluated by using a modified version of the apparatus described elsewhere.[16–18] Distilled water, 0.9% NaCl solution, and phosphate buffer solution (PBS, 0.2 M, pH 7.4) were used. This assay was performed for Eu–M_{50}, Eu–M_{100}, Eu–$M_{100}C_{50}$, and Eu–$M_{50}C_{50}$ matrices.

Drug Delivery Measurement

Delivery kinetics of M from solid matrices were measured using a USPXXIV dissolution apparatus 2 (Hanson Research, Kent City, Michigan) at 100 rpm at 37°C, using 900 mL of dissolution medium (water, 0.9% NaCl aqueous solution and PBS). Samples of 5 mL were withdrawn at predetermined time intervals and the M concentration was spectrophotometrically (λ = 302.8 nm) determined (in triplicate).