Materials Science and Engineering C 72 (2017) 405–414

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Physicochemical characterization of *in situ* drug-polymer nanocomplex formed between zwitterionic drug and ionomeric material in aqueous solution

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ARTICLE INFO

Article history:
Received 3 October 2016
Received in revised form 10 November 2016
Accepted 21 November 2016
Available online 26 November 2016

Keywords:
Interfacial nano-complex
Ampicillin
Zwitterionic drug
Eudragit E
Cationic polymer

ABSTRACT

Biocompatible polymeric materials with the potential to form functional structures, in association with different therapeutic molecules, in physiological media, represent a great potential for biological and pharmaceutical applications. Therefore, here the formation of a nano-complex between a synthetic cationic polymer and model drug (ampicillin trihydrate) was studied. The formed complex was characterized by size and zeta potential measurements, using dynamic light scattering and capillary electrophoresis. Moreover, the chemical and thermodynamically stability of these complexes were studied. The ionomeric material, here referred as EuCl, was obtained by equimolar reaction between Eudragit E and HCl. The structural characterization was carried out by potentiometric titration, FTIR spectroscopy, and DSC. The effect of pH, time, polymer concentration and ampicillin/polymer molar ratio over the hydrodynamic diameter and zeta potential were established. The results show that EuCl ionomer in aqueous media presents two different populations of nanoparticles; one of this tends to form flocculated aggregates in high pH and concentrations, by acquiring different conformations in solution by changing from a compact to an extended conformation. Moreover, the formation of an *in situ* interfacial polymer-drug complex was demonstrated, this could slightly reduce the hydrolytic degradation of the drug while affecting its solubility, mainly under acidic conditions.

1. Introduction

Biocompatible polymeric materials that could form functional nanostructures in physiological media represent a great opportunity for application in pharmaceutical, biological and environmental fields [1,2]. Some polymeric materials which exhibit these kind of properties are the copolymers derived from amino-alkyl methacrylate, commercially known as Eudragit E [3,4]. These materials have been widely used in the pharmaceutical field as coating agents to protect the active pharmaceutical ingredients (APIs) against several external factors such as humidity, heat, oxygen and light, therefore enhancing their chemical stability [5–7]. They have also been used to increase the solubility of poorly soluble APIs [4,8], to enhance the permeability of some drugs [9], to improve some organoleptic properties [6,10] and, to control the release of drugs as response to the pH [11–17]. For the other hand, it is well known that the chemical integrity of polymeric material with monomeric unites corresponding to alkyl-ester and alkyl-amino-ester groups [18] as Eudragit E, are strongly affected by influence of H^+ concentration in media [12,19,20], in a similar process as described in Fig. 1.

Depending on the DMAE ionization degree and the number of esterified groups in the polymer side chain, there is the possibility of having different kinds of interactions among the polymer, the solvent, other compounds and with itself. When a high ionization degree is presented the polymer is quite solvated, on the other hand with a major number of alkyl-esterified groups it is possible to form hydrophobic pseudo-phase in aqueous media [21], where different types of organic molecules, could be associated or solubilized, such as drugs or pharmaceutical excipients. These interactions significantly could affect the solubility of those compounds or improve the chemical stability, phenomena very important in the pharmaceutical formulation and design process [2,8,9,17,22–24].

Is for that reason that the current study focused on a) To obtain an ionomeric material from Eudragit E and characterize its behavior in aqueous media. b) To characterize the formation of *in situ* drug-polymer complexes in aqueous media between the produced ionomer and a model zwitterionic drug; c) To evaluate the effect of the complexation on the chemical stability and the solubility of the drug in different physiological simulated conditions, *e.g.* gastric pH 1.2 and plasma pH 7.4, As a model drug in this work, we used ampicillin trihydrate

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http://dx.doi.org/10.1016/j.msec.2016.11.097
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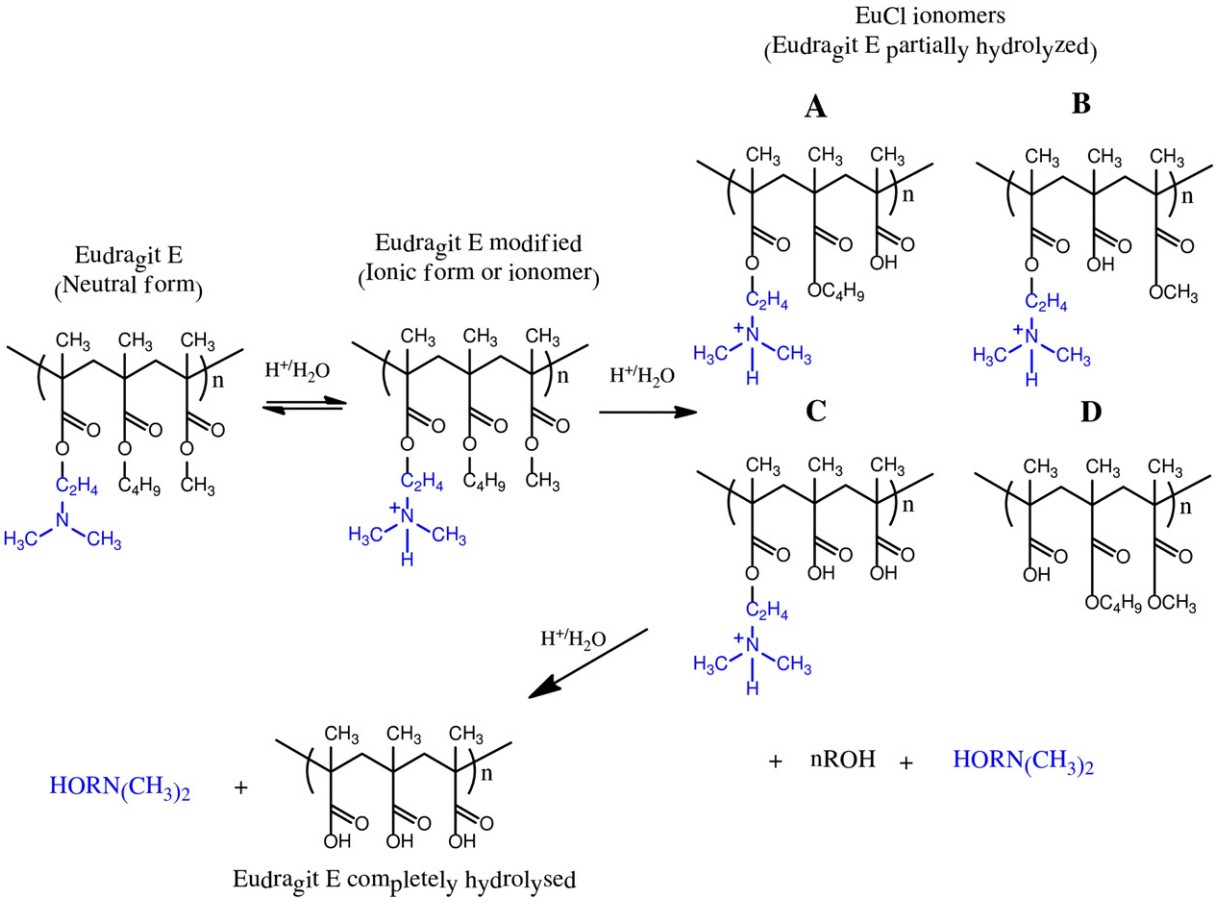

Fig. 1. Scheme of Eudragit E in acidic conditions and its respective ionomeric products. The dimethylamine alkyl substituent (DMAE) in the side chain of the polymer is highlighted.

(Fig. 2). This drug is a β-lactam antibiotic characterized by a high chemical degradability and a variation of the solubility depending on the pH [25].

2. Materials and methods

2.1. Materials

Ampicillin trihydrate (Fersinsa Gb) and Eudragit E PO with a molecular weight around 150 kDa (Evonik) were provided by Tecnoquímicas S.A. laboratories and Alamapal from Colombia respectively and were used as received. HCl, $HClO_4$, NaOH, KCl, KH_2PO_4 and K_2HPO_4 were obtained from Merck and used as received. Ultra-pure water was produced with a water purification system (Millipore Elix Essential), with an average conductivity value of 1 μS/cm. Buffer solution pH 5.0, citric acid/sodium citrate (Fluka) was used as received, while the buffer solutions with values of pH 1.2 and pH 7.4 with the ionic strength of 0.15 M, were prepared using mixtures of HCl/KCl, and KH_2PO_4/K_2HPO_4, respectively. KCl was used to adjust the ionic strength.

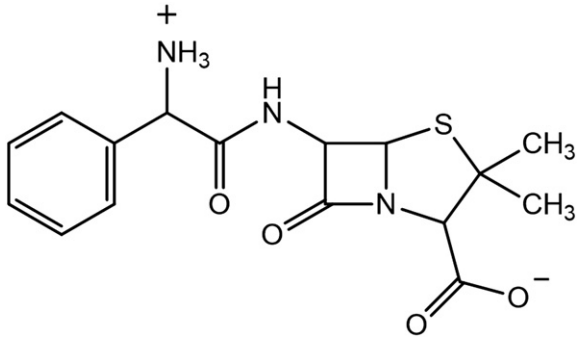

Fig. 2. Zwitterionic structure of trihydrate ampicillin.

2.2. Production and characterization of the ionomer

Briefly, modified Eudragit E was produced as from Eudragit E PO copolymer, here referred as Eu, which was reacted with HCl in aqueous solution at a higher DMAE to HCl molar ratio (Fig. 1). For this, 50 g of polymer powder were suspended in one liter of 0.39% (v/v) HCl solution. The reaction was carried out at room temperature for one hour with moderate agitation. Then, the polymeric solution was dialyzed using a cellulose membrane (Sigma Chemical Co) 12 kDa cut off, until a constant conductivity value was reached. Finally, the polymer material was lyophilized on a dryer Eyela freezer (model FDU 1110) to obtain the ionomer material referred as EuCl.

2.2.1. Potentiometric titration

Eudragit E polymer and the EuCl ionomer were titrated with $HClO_4$ dissolved in acetic acid and an aqueous solution of NaOH to determine the number of DMAE and carboxyl acid groups (COOH) present in the polymer molecule. The DMAE groups in the Eu polymer and EuCl polymer obtained were determinate from the alkali value (AV), which states how many mg of KOH are equivalent to the basic groups contained in 1 g of dry substance (DS), as shown in Eqs. (1) and (2).

$$\%(DMAE)groups = AV\left(\frac{mgKOH}{gDS}\right) \times 0.1286 \quad (1)$$