PHARMACEUTICS, PREFORMULATION AND DRUG DELIVERY

Structural Transformations During Swelling of Polycomplex Matrices Based on Countercharged (Meth)acrylate Copolymers (EudragitR EPO/EudragitR L 100-55)

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ABSTRACT: With a view to the application in oral controlled drug delivery systems (DDS), the design of new interpolyelectrolyte complexes (IPECs) between countercharged types of Eudragit® EPO (EPO) and Eudragit® L 100-55 (L100-55) was investigated. The formation and composition of four new IPECs between EPO and L100-55 were established by elementary analysis. The structure of the synthesized IPEC was investigated using FTIR spectroscopy and modulated-temperature differential scanning calorimetry. The binding ratio of a unit molecule of EPO with L100-55 was found to range between 1:2.75 ($Z = 0.36$) and 1:0.55 ($Z = 1.81$) while increasing the pH value from 5.5 to 7.0. As a result of electrostatic interaction between the copolymer chains, the glass transition temperature of the IPEC increased significantly. A large pH-sensitive swelling behavior was observed for different structures of the IPECs. The outcome of swelling and diclofenac sodium release from the polycomplex matrices confirm that they have great potential to be used as a controlled DDS in specified regions of gastrointestinal tract.
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Keywords: interpolyelectrolyte complexes; Eudragit® EPO; Eudragit® L 100-55; pH-dependent swelling behavior; oral drug delivery; FTIR; glass transition; polymeric drug carrier; controlled release; diclofenac sodium

INTRODUCTION

Depending on the pH, some (meth)acrylate copolymers can act as polyelectrolytes, which make them potentially suitable for drug delivery purposes, regulated by the number of charged and nonionized (ether) groups in the structure of these copolymers.[1–3] Some of them can be considered as polycations (Eudragit® types E, RL, and RS) and others as polyanions (Eudragit® types L, S, and FS). Combining countercharged (meth)acrylate copolymers appears to be an interesting field of investigation, providing advantages in the processing and modulation of release profiles.[4]

Direct compression was used to combine oppositely charged poly(meth)acrylates in matrix tablets production (RSPM/L100),[5] as well as wet granulation (aqueous and organic) (RS100/L12.5%)[6] and melt extrusion (RSPO/FS30D) processes.[7] These procedures show a synergistic effect on unexpected sustained release, which was stronger than the release profile of the same formulation with the individual copolymers. Moreover, solid dispersions (coprecipitates) of different drugs and countercharged poly(meth)acrylates are successfully used in matrix tablets production {RLPO(RSPO)/S100[L100, Eudragit® L 100-55 (L100-55)]},[8] (E100/S100).[9,10] Microspheres prepared by a solvent evaporation method with the copolymer combinations (RL100/L100-55),[11] [RS100/L100(L100-55)][12] showed a stronger sustained release.

It is well known that interaction between the ionic groups of copolymers can occur by blending anionic dispersions (L100, S100) with cationic

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dispersions (RL30D, RS30D), resulting in flocculation. To overcome this restriction, the pH of mixed dispersions can be adjusted by adding hydrochloric acid or sodium hydroxide.[1–3] Few publications are dealing with countercharged Eudragit® copolymers in organic and aqueous dispersed film coatings (RL100/L100/S100),[13] (RS30D/L100-55).[14] However, layering of the two oppositely charged poly(meth)acrylates, without preliminary mixing, was studied by different researchers. A colon delivery system was developed on the basis of L100. Before coating with L100, tablets were first subcoated with E100.[15] In contrast, E100 as overcoating was employed to layer an initial dose onto L100 containing films.[16] Recently, the influence of Eudragit® type EPO (EPO) in an L100-55 film coating applied by a dry coating technique to the miscibility in copolymer blends was investigated.[17,18] According to the results confirmed by FTIR and modulated-temperature differential scanning calorimetry (MTDSC), blends prepared with EPO and L100-55 were immiscible.[18] Possible interactions were also studied to see whether they occurred in trials where copolymers were applied in two different layers. Trials were performed to evaluate potential ionic interactions between RL30D (RS30D) and FS30D in a double-layer-coated pellet.[4,19] Using different analytical techniques (FTIR, DSC, and NMR), it was possible to show that no significant interaction between these oppositely charged copolymers was present.[19] Moreover, recently, novel sustained release of a tablet formulation using a binary mixture of E100 and L100 (S100) in their salt form was performed.[20,21] Results from swelling studies strongly supported the presence of ionic interaction between E100-citrate and L100-Na within polymer matrices that provide a pH-independent and sustained release behavior of a model drug from the tablets.

The interpolyelectrolyte reaction between two oppositely charged and pH-dependent poly(meth) acrylates could provide a base to manufacture matrix tablets with a different sustained release profile compared with pure copolymers and physical mixtures (PMs). It is known that possible interaction between them gives different properties of the copolymers because of the formation of interpolyelectrolyte complexes (IPEC).[22–24] The formation of IPEC by the cooperative reactions involving oppositely charged polyions is well known. Polycomplexes are a relatively new class of polymer carriers, which nowadays play an important role in creating new oral drug delivery systems (DDS).[25–29] Despite the large number of studies devoted to IPEC formation and properties, only a few of them attempt to investigate IPEC with copolymers participation, especially in constructing oral controlled DDS.[28]

The systematic investigations of involving countercharged types of Eudragit® in IPECs in aqueous mediums to modify their structure were performed by our group.[30–34]

Another method for preparing complexes between countercharged poly(meth)acrylates is by using organic solvents. Some authors have attempted to estimate the compatibility of different pairs of oppositely charged types of Eudragit® copolymers on the basis of intrinsic viscosity data for ternary copolymer–copolymer–solvent systems.[35] While mixing cationic (E100, RL100, RS100) with anionic (L100, S100) copolymers in various ratios in a common solvent, the formation of visible aggregates was observed. The behavior of the copolymer mixtures was the same in all selected solvents (methanol, ethanol, isopropanol, acetone, methylene chloride, ethyl acetate, and tetrahydrofuran). Although primary associated complexes between acid and basic (meth)acrylate copolymers were so stable that they did not dissociate upon dilution, the evaluation of observed aggregates was not performed.[35]

Polymers are considered compatible if attractive interactions among the functional groups of the macromolecules occur. Recently, the blends of EPO with polyacids including L100/S100 in methanol-chloroform mixture were examined.[36] Miscible blends were formed because of interactions between the functional groups of the blend constituents. The stoichiometry of EPO–polyacid complexes is important in the selection of blend compositions that exhibit the desired pH-dependent swelling properties in simulated gastric and intestinal fluids.

Formation of precipitates by mixing countercharged (meth)acrylate copolymers in isopropanol–acetone mixture (60:40) was reported by Gallardo et al.[37] Characterization of complexes formed by the cationic (EPO) and four anionic (L100-55/L100/S100/FS) copolymers with different percentages of carboxylic groups confirmed the existence of possible ionic interactions between copolymers.[38] From the nitrogen content of the precipitated complexes EPO/L100-55, the authors concluded that the composition corresponds to a combination of a complete reaction between the copolymers and a stoichiometric reaction.[39]

Complexes based on countercharged Eudragit® copolymers in both organic and aqueous solutions have been extensively investigated in recent years. However, only limited research has been directed toward detailed investigations of structural and compositional microenvironment transformations during swelling and release evaluation.[40,41]

The objective of this study was to investigate some fundamental physicochemical characteristics of new IPECs made up of EPO and L100-55 in aqueous