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Indomethacin-containing interpolyelectrolyte complexes based on Eudragit® E PO/S 100 copolymers as a novel drug delivery system

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ABSTRACT

Potential applications of a novel system composed of two oppositely-charged (meth)acrylate copolymers, Eudragit® EPO (EPO) and Eudragit® S100 (S100), loaded with indomethacin (IND) in oral drug delivery were evaluated. The particles based on drug-interpolyelectrolyte complexes (DIPEC), (EPO-IND)/S100, were prepared by mixing aqueous solutions of both copolymers at fixed pH. Particles of drug-polyelectrolyte complex (DPC), (EPO-IND) have a positive zeta potential, pointing to the surface location of free EPO chains and IND bound to EPO sequences. The formation and composition of both DPC and DIPEC were established by gravimetry, UV-spectrophotometry, capillary viscosity and elemental analysis. The structure and solid state properties of the formulated DIPEC were investigated using FTIR/NIR, Raman spectroscopy, XRPD and modulated DSC. DIPEC is a chemically homogenous material, characterized by a single T_g. DIPEC have an IR absorption band at 1560 cm^{-1}, which can be assigned to the stretching vibration of the carboxylate groups (S100, IND) that form ionic bonds with the dimethylamino groups of EPO. XRPD, NIR and Raman-shifts confirm that during the preparation of this formulation, IND is converted into its amorphous form. The release of IND from DPC EPO/IND (3:1) and DIPEC EPO/L100/IND (4.5:1:1) is sustained and is completed within 7 h under GIT mimicking conditions. However, S100 within DIPEC makes the release process slower making this system suitable for colon-specific delivery. Finally, DPC and DIPEC with indomethacin were used to prepare tablets, which can be potentially used as oral dosage forms for their slower indomethacin release in case of DIPEC which could be suitable for sustained delivery.

1. Introduction

The advantages of interpolymer complexes as polymeric carriers in oral controlled drug release have been reported elsewhere (Kemenova et al., 1991; Hartig et al., 2007; Khutoryanskiy, 2007; Lankalapalli and Kolapalli, 2009; Pillay et al., 2013; Bourganis et al., 2017. In the last years, our research group has developed polycomplex matrices based on interpolyelectrolyte complexes (IPECs) using different oppositely-charged Eudragit® copolymer combinations as new oral delivery systems able to deliver the drugs into site-specific gastrointestinal tract (GIT) regions (Mustafin and Kabanova, 2004, 2005; Moustafine et al., 2005, 2006, 2011; Moustafine et al., 2013; Moustafine and Bobyleva, 2006; Mustafin et al., 2010a, 2010b, 2011). Moreover, the advantages of Eudragit® copolymer combinations for controlled drug delivery purposes have been reported elsewhere (Siepmann et al., 2008; Obeidat et al., 2008; Sauer and McGinity, 2009; Alhnan and Basit, 2011; Bani-Jaber et al., 2011; Wulff and Leopold, 2014, 2016).

The comprehensive analysis of the effects of intermacromolecular interactions between chemically complementary Eudragits® on the drug release from oral drug delivery systems (DDS) was examined in recently published reviews (Gallardo et al., 2008; Mustafin, 2011; Moustafine, 2014; De Robertis et al., 2015). However, further studies are needed to address more complex systems involving oppositely-charged Eudragits® forming IPECs in the presence of ionic drugs. Only a few papers reported the possibility of using drug-interpolyelectolyte complexes (DIPEC) as

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three-component systems for development of drug delivery dosage forms (Palena et al., 2012, 2015; Bigucci et al., 2015).

Recently, a novel self-organized nanoparticulate carrier, based on drug – IPEC Eudragit® E100/L100 combination was successfully prepared using a simple aqueous dispersion method (Palena et al., 2012). In this study, the authors have reported that freeze-dried complexes were easily redispersed in water and DIPEC dispersions behaved as zwitterionic macromolecular systems that may change zeta potential values from negative to positive by changing the polymer composition. The authors have used atenolol, propranolol and metoclopramide as model drugs, which could be formulated using these nanoparticulate systems. Recently four additional anti-inflammatory drugs (salicylic acid, benzoic acid, ketoprofen and naproxen) were also studied (Palena et al., 2015). The DIPECs exhibited interesting properties useful for the design of nanoparticulate DDS for oral and topical administration.

Furthermore, a similar principle was successfully used in a chitosan/carboxymethylcellulose polyelectrolyte system via electrostatic interaction between the amino groups of chitosan and chlorhexidine (cationic drug) with the carboxyl groups of sodium carboxymethylcellulose, used for the preparation of vaginal inserts (Bigucci et al., 2015).

The objective of this study was the preparation and physico-chemical characterization of drug-interpolyelectrolyte complexes (DIPEC) as micro-sized particles formed between indomethacin and Eudragit® S100 with oppositely-charged Eudragit® EPO. These microparticles were found to be highly promising materials for designing pH-controlled systems for oral delivery to target the colon. Colon-specific drug delivery systems are of interest for the therapy of different local conditions such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer (Basit, 2005; Gazzaniga et al., 2006; Van den Mooter, 2006; Maroni et al., 2013; Amidon et al., 2015; Hua et al., 2015). Different approaches have been traditionally used in drug delivery for colon targeting, including the use of prodrugs, pH-responsive matrix systems, timed-release formulations, bioadhesive materials, microparticulate vehicles and enteric coatings (Amidon et al., 2015). Our approach involves the use of conventional enteric coating polymer Eudragit ® S100 that already provides gastric resistance properties; additionally, in our work we utilised the ability of this anionic polymer to form interpolyelectrolyte complexes with cationic Eudragit ® EPO. The functionality of both polymers provided an opportunity of forming polycomplex particles with indomethacin and formulate tablets with sustained drug release.

2. Materials and methods

2.1. Materials

Eudragit® E PO – a terpolymer of *N,N*-dimethylaminoethyl methacrylate (DMAEMA) with methylmethacrylate (MMA) and butylmethacrylate (BMA), (PDMAEMA-*co*-MMA-*co*-BMA) (molar ratio 2:1:1, MW 150 kDa) was used in this study as a cationic copolymer. Eudragit® S 100 (a copolymer of methacrylic acid (MAA) with methylmethacrylate (MMA), P(MAA-*co*-MMA) (molar ratio 2:1, MW 135 kDa)) was used as a polyanion. Different types of Eudragit® (EPO, S100) were generously donated by Evonik Röhm GmbH (Darmstadt, Germany). The copolymers were used after vacuum drying at 40 °C for 2 days. The solutions at different pH values, simulating the gastrointestinal conditions, were prepared for release tests by using hydrochloric acid, sodium phosphate tribasic dodecahydrate, potassium dihydrogen phosphate, and sodium hydroxide (Sigma-Aldrich, Bornem, Belgium). IND was used as a model anionic drug and was purchased from Sigma-Aldrich (Bornem, Belgium).

2.2. Methods

2.2.1. Preparation of solid DPCs and DIPECs with different macromolecular composition

The optimal conditions for the interaction between chemically complementary grades of a polycation (Eudragit® EPO) and a polyanion copolymer (Eudragit® S100) in the presence of ionized IND molecules were studied in aqueous salt media. EPO solutions were prepared by dissolving the copolymer in 1 M CH_3COOH. This solution was diluted with demineralized water to the desired volume and titrated with 1 M NaOH to the required pH 6.5. S100 and IND solutions were prepared by dissolving the copolymer and the drug in 1 M NaOH. This solution was diluted with demineralized water to the desired volume and titrated with 1 M CH_3COOH to the required pH 7.2. The EPO solutions were slowly poured into S100/IND solutions, and the mixture was stirred at 1000 r.p.m. for 2 days using a magnetic stirrer RET control visc-white (IKA®, Staufen, Germany). The solutions of copolymers and IND were mixed in different molar ratios. The yields of precipitate formed were first determined gravimetrically after centrifugation for 1 h at 5000 rpm at 5 °C in a SL16R laboratory centrifuge (Thermo Scientific, U.S.A.). The specific viscosity of the supernatant solution was determined using an Ubbelohde viscometer (Schott®, Germany) at 25.0 ± 0.1 °C. The quantity of the non-bonded IND present in the supernatant solutions and the encapsulation efficiency (EE) were investigated UV-spectrophotometrically at 266 nm (Evolution 220, Thermo Scientific, U.S.A.). For gravimetric determination, the sediment was dried under vacuum (vacuum oven VD 23, Binder, Germany) for 2 days at 40 °C until constant weight.

The optimal composition was prepared in a laboratory reactor system LR 1000 control equipped with pH-/temperature controlling units under continuous and simultaneous agitation at 10,000 r.p.m. using T25-digital Ultra-Turrax® homogenizer (IKA®, Staufen, Germany). The feeding rate was approximately 2 mL/min. After isolation of the precipitates of DPC and DIPEC particles from solutions, they were washed with ultrapure water (Smart2Pure UV/UF, Thermo Scientific, U.S.A.), frozen at −18 °C (Labconco® Shell Freezer, MO, U.S.A.) and subsequently freeze-dried for 2 days (Labconco® Freeze Dry System, FreeZone 1 L, MO, U.S.A.). The solid samples were stored in tightly-sealed containers at room temperature.

2.2.2. Elemental analysis

The composition of freeze-dried DPC (EPO/IND) and DIPEC (EPO/L100/IND) samples and physical mixtures were investigated by elemental analysis using a Thermo Flash 2000 CHNS/O elemental analyzer (Thermo Scientific, UK). Physical mixtures were obtained by mixing copolymer powders and IND at EPO: S100:IND molar ratio of 4.5:1:1.

2.2.3. Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR-spectra were recorded using a Nicolet iS5 FTIR-spectrometer (Thermo Scientific, U.S.A.) equipped with a DTGS detector. The untreated freeze-dried samples of solid DPC (EPO/IND), DIPEC (EPO/S100/IND) and physical mixtures were directly mounted over the iD5 smart single bounce ZnSe ATR crystal. The spectra were analyzed using OMNIC spectra software.

2.2.4. Near-infrared (NIR) spectroscopy

NIR-spectroscopy of freeze-dried samples of solid DPC (EPO/IND), DIPEC (EPO/S100/IND) and physical mixtures was performed using a Nicolet iS10 XT NIR/FTIR-spectrometer (Thermo Scientific, U.S.A.) equipped with Smart DRA diffusion reflection accessory. The spectra were analyzed using OMNIC spectra software.