Reactive and Functional Polymers 105 (2016) 103–113

Contents lists available at ScienceDirect

Reactive and Functional Polymers

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

Adsorption and release studies of cefuroxime sodium from acrylic ion exchange resin microparticles coated with gellan

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ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 2 June 2016
Accepted 6 June 2016
Available online 7 June 2016

Keywords:
Ion exchange resin
Gellan
Cefuroxime sodium
Adsorption kinetic
Adsorption isotherm

ABSTRACT

Two types of microparticles based on acrylic ion exchange resin were prepared and used as macromolecular supports for the adsorption of an antibiotic (cefuroxime sodium salt) from aqueous solution. The first type of microparticles was synthesized by aqueous suspension copolymerization of acrylonitrile, ethylacrylate and ethylene glycol dimethacrylate followed by the aminolysis reaction of ternary copolymer with hydrazine hydrate. For the preparation of the second type of microparticles the gellan was selected to cover the surface of acrylic ion exchanger in order to increase the biocompatibility of these systems. Batch adsorption studies regarding the effects of various parameters such as, temperature, contact time, initial concentration of drug, drug:microparticles ratio and pH were studied. To study the adsorption kinetic mechanism, the Lagergren, Ho, Elovich and Weber-Morris particle diffusion models were applied and it was found that the adsorption of the drug could be described by pseudo first order equation (Lagergren model). The calculated values of thermodynamic parameters (ΔG, ΔH, ΔS) showed that the adsorption process was spontaneous and endothermic. The drug release process was found to be controlled by diffusion of drug molecules through polymer networks.

1. Introduction

Ion exchange resins are insoluble three-dimensional networks which have the property to exchange their mobile ions with the ions of similar charges, when they come in contact with an electrolyte solution [1]. Depending on the nature of the functional groups attached to the three-dimensional network, ion exchange resins can be classified as follows: cation, anion and amphoteric ion exchangers [2].

In recent years, ion exchange resins have represented an important research direction in the development of new advanced materials that can be used either to improve the existing pharmaceutical forms either to obtain the new sustained/controlled drug delivery systems [3,4].

The ion exchange resins present a wide spectrum of applications in medical and pharmaceutical fields due to their properties, such as physico-chemical stability, uniform size, spherical shape, the presence of functional groups, insolubility in any types of solvents over the whole range of pH and high loading capacity of drugs. Some of their applications include: water demineralization [5], drug purification [6], stabilization of vitamins [7], separation of proteins and peptides [8], extraction and purification of enzymes, hormones, alkaloids and amino acids, taste and odor masking [9], tablet disintegrants [10], sustained/controlled drug delivery systems for oral, nasal, transdermal and ophthalmic administration [11–13], implantation devices [14], cholesterol reducer and bile acid sequestrants (Colestipol – a weakly basic anion exchange resin and Cholestyramine – a strongly basic anion exchange resin) [15], adsorbents of toxins [16], smoking cessation program [17] and for the treatment of various disease like liver diseases, acute renal insufficiency (Kayexalate and Kionex-strongly acidic cation exchange resins), skin diseases, cardiac edema, etc. [18–21].

The usage of the ion exchange resin as polymeric carriers in pharmaceutical formulation has been proposed for the first time by Saunders and Chaudhary [22]. Nowadays, some ion exchange resins are available on the pharmaceutical market, such as Amberlite IRP 64, Amberlite IRP 88, Amberlite IRP 69, Duolite AP143, Ionamin and Tussionex [23,24]. Sometimes the release of drug from resins can be very fast, this process being prevented by coating the surface of the ion exchanger with different polymers, such as ethyl cellulose, poly(methyl methacrylate), hydroxypropyl methyl cellulose, Eudragit RS, paraffin, Carbopol 934, polyethylene imine [25–29]. In order to overcome this inconvenience

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http://dx.doi.org/10.1016/j.reactfunctpolym.2016.06.003
1381-5148/

and to increase the biocompatibility of the resin, in this paper is presented a new sustained drug delivery system obtained by coating the surface of ion exchange resin with an anionic polysaccharide namely gellan (GLL).

At industrial level, the gellan represents one of the most important extracellular heteropolysaccharide being obtained by aerobic fermentation of bacterium *Sphingomonas elodea* (*Pseudomonas elodea*) [30,31]. Discovered in 1978, this exopolysaccharide has been extensively studied being used in a wide range of applications starting from food and cosmetic industries and reaching to pharmaceutical and medical fields [32,33].

In our previous research we studied the interaction mode of cefotaxime sodium salt with two macromolecular supports based on ion exchange resins [34–36].

The novelty of this study consists in: (a) the synthesis of a novel ion exchanger prepared by aqueous suspension copolymerization of acrylonitrile, ethylacrylate and ethylene glycol dimethacrylate followed by aminolysis reaction with hydrazine hydrate and (b) the synthesis of a novel drug delivery system obtained by coating the surface of acrylic ion exchange resin with gellan in order to be used in rectal administration or in wound healing process. Because the drug was immobilized into polymeric matrix by adsorption, the knowledge of the equilibrium, kinetic and the mechanism of drug adsorption is relevant in the design of pharmaceutical dosage forms. The model drug used is a bactericidal cephalosporin antibiotic, namely cefuroxime sodium salt (CFR) which is active against Gram-negative and Gram-positive organisms. CFR is indicated for the treatment of infections of the ear, sinus, throat, lower respiratory tract, skin and soft tissue, urinary bladder and for treatment of the early stage of Lyme disease.

2. Experimental

2.1. Materials

The gellan gum (Gll) (Gelzan™, $M_w = 1 \times 10^6$ g/mol) was purchased from Sigma-Aldrich and was used as received. Acrylonitrile (AN), ethylacrylate (EA), ethylene glycol dimethacrylate (EGDMA), hydrazine hydrate, benzoyl peroxide (BOP), toluene and cefuroxime sodium salt ($M_w = 424.39$ g/mol) were purchased from Sigma Aldrich.

2.2. Synthesis of the acrylic ion exchange resin (H microparticles)

The acrylic copolymer was synthesized by radical suspension copolymerization technique in the presence of toluene (inert medium) and the benzoyl peroxide (polymerization initiator). The copolymerization reaction was carried out in a 0.5 L glass flask equipped with stirrer, reflux condenser and thermometer. The aqueous phase consisted of 250 mL deionized water, 10 g NaCl and 1 g of ammonium salt of poly(-styrene-co-maleic anhydride) as polymeric stabilizer. The organic phase consisted of 0.026 mol EGDMA, 0.1887 mol AN, 0.385 mol EA, 0.002 mol BOP and 35 mL toluene. The reaction was allowed to proceed for 30 min at 40 °C, 6 h at 70 °C and 4 h at 80–85 °C. After copolymerization reaction, the copolymer beads were washed with warm water, dried at room temperature, and then extracted with acetone in a Soxhlet apparatus to remove traces of residual monomers, linear oligomers and diluent. Finally, they were vacuum dried at 50 °C.

Aminolysis reaction was performed at 110–115 °C with hydrazine hydrate under reflux for 10 h in a glass round-bottomed flask equipped with stirrer, reflux condenser and thermometer. The copolymer:amine ratio was 1:5.5 (g/g). After the reaction, H microparticles were separated by filtration and washed with warm water. To convert the resin in Cl^- form, resin sample was equilibrated with 1 N HCl for 24 h and then washed with deionized water to remove HCl in excess. The exchange capacity of ion exchange resin was: $C_{sv} = 0.8265$ meq/mL or $C_{sg} = 2.4589$ meq/g.

2.3. Synthesis of microparticles based on acrylic ion exchange resin and gellan (HG microparticles)

The gellan solution was prepared by dissolving the polysaccharide in 1 N NaOH solution. 5 g of the acrylic ion exchange resin in Cl^- form (H microparticles) were placed in 500 mL of 1% gellan solution at 35–40 °C for 48 h under a permanent gentle stirring. Then the microparticles were removed from the gellan solution by filtration, rinsed with distilled water and centrifuged at 1000 rpm for 10 min. Finally, the HG microparticles were vacuum dried at 40 °C for 48 h.

The amount of gellan interacted with acrylic ion exchange resin was determined by the Eq. .(1):

$$\%\mathrm{Gll} = \frac{m_i - m_0}{m_0} \times 100 \quad (1)$$

where m_i is the mass of HG microparticles and m_0 is the mass of H microparticles.

It was found that 75% of the amount of gellan reacted with acrylic ion exchange resin.

2.4. Physico-chemical characterization of H and HG microparticles

FT-IR spectra were recorded on a Bruker Vertex FT-IR spectrometer at a resolution of 2 cm^{-1} in the range of 4000–400 cm^{-1} by KBr pellet technique. Thus, 0.03 g H and HG microparticles or gellan gum were firstly mixed and grounded with potassium bromide and then the fine powder was compressed into a disc. The discs were scanned and the characteristic peaks were recorded.

The surface morphology of adsorbent (H and HG microparticles) was examined by using an Environmental Scanning Electron Microscope type Quanta 200 at 25 kV.

The atomic force microscopy (AFM) experiments were performed using a Scanning Probe Microscope Solver Pro-M platform (NT-MDT, Russia) with a rectangular silicon cantilever NSG 10 and 203 kHz oscillation frequency, in air at ambient temperature (23 °C). The scan area was 10 μm × 10 μm, 256 × 256 scan point size image being thus obtained.

The thermal degradation of H and HG microparticles (4 mg of sample) was performed at a heating rate of 10 °C/min, in nitrogen atmosphere, using a METTLER TOLEDO TGA/SDTA 851 Derivatograph.

2.5. Adsorption batch experiments

To study the CFR adsorption onto H and HG microparticles, the batch technique was chosen as experimental method. Prior to use in the adsorption experiments the H and HG microparticles were placed in 250 mL beakers filled with deionized water and allow to swell for 24 h. After then, the supernatant was removed by decantation and the microparticles were centrifuged at 1000 rpm for 10 min. The study regarding the effect of pH on drug loading was carried out at various pH values ranging from 3 to 8. The pH values of the drug solutions were realized with chloride and phosphate buffer solutions. The optimum value for CFR adsorption onto microparticles was obtained at pH = 4 and the subsequent adsorption studies were realized at this value of pH. Also, a know amount of wet H and HG microparticles equivalent to 200 mg dry microparticles were introduced in 50 mL conical flasks filled with solution of 100 mg CFR at pH = 4. The conical flasks were placed in a thermostated shaker bath (Memmert M00/M01, Germany) and shaken at 180 rpm for different contact time ranging between 10 min and 24 h until equilibrium was reached. The flasks were than removed from the shaker and the samples were centrifuged at 1000 rpm for 10 min.

The influence of temperature has been evaluated by measuring the CFR adsorption at three temperature conditions: 298 K, 303 K and 313 K, respectively at a constant pH of 4. For the effect of drug concentration on drug loading the studies were carried out at various