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Adsorption and release studies of new cephalosporin from chitosan-*g*-poly(glycidyl methacrylate) microparticles

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ABSTRACT

Porous microparticles of chitosan-*g*-poly(glycidyl methacrylate) were obtained by grafting chitosan onto crosslinked networks based on glycidyl methacrylate and ethylene glycol dimethacrylate using suspension polymerization technique. A new cephalosporin from the indazole class prepared by acylation of 7-Aminodesacetoxycephalosporanic acid with mixed anhydride of 5-nitroindazole-1-yl-acetic acid was used as active principle. The cephalosporin-microparticle systems were characterized by FT-IR spectroscopy, SEM and AFM analysis. Batch experiments were carried out to study the influence of initial drug concentration, temperature, contact time, drug:microparticles ratio and pH on the adsorption process of cephalosporin onto porous crosslinked microparticles. Two-parameter and three-parameter isotherm models were used to evaluate the adsorption equilibrium. The values of diffusion coefficients indicate that the cephalosporin adsorption onto microparticles was controlled by both film diffusion and pore diffusion mechanisms. The analysis of the kinetic data of the release process indicate that the release mechanism of cephalosporin from microparticles corresponds to the anomalous transport mechanism.

1. Introduction

The increase of treatment efficiency, as well as the elimination of the side effects of drug caused either by over-doses either sometimes by their aggressiveness to both the disordered cells and the healthy ones are the major problems that medicine needs to solve.

Drug administration in free form, no matter if orally, parenterally, by instillations or ointments has the effect of continuous change of their concentration in the body or at the disease site. Short time after administration, the concentration of the active principle exceeds the one related to the therapeutic field, becoming toxic. Then, the concentration of drug quickly drops under the therapeutic field, which requires a new administration. This problem can be solved by the administration

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of drug immobilised on a polymeric support, when it is observed a variation of its concentration in the body after another kinetics. The drug is released gradually from macromolecular carrier ensuring a constant concentration in the body corresponding to the therapeutic value as well as an increase of the treatment effectiveness.

Among the various macromolecular carriers, the grafted chitosan copolymers obtained by several methods such as, grafting initiated by free radicals [1], grafting using radiation [2], enzymatic grafting [3], grafting via polycondensation [4], living cationic polymerization [5], soapless emulsion copolymerization [6], oxidative coupling [7] and ring opening [8] received an increased interest of the scientific community.

Chitosan-*grafted*-poly(acrylic acid) particles and microparticles of poly(acrylamide)-*grafted*-chitosan crosslinked with glutaraldehyde were prepared to encapsulate indomethacin [9], hydrophilic drugs or sensitive proteins [10] and nifedipine [11]. Also, the graft chitosan copolymers have potential to be used in dialysis [12] and present interesting properties for wound-healing and cardio-vascular applications [13].

Generally, the aim of drug delivery system administration focuses on the prevention of illnesses, improvement of some symptoms and the cure of various diseases such as, localized diseases by applying solutions and ointments or generalized diseases by administrating antibiotics. The β-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams) represent a category of drugs with a very wide spectrum in the therapy of bacterial infections [14].

Initially, the cephalosporins (CFS) have been isolated from cultures of bacteria *Cephalosporium acremonium* to give three types of compounds: the C and N cephalosporins having a similar structure with the penicillins and P cephalosporin, a steroid antibiotic with a similar structure to the one of the fusidic acid [15].

Subsequently, in 1964 the semi-synthetic cephalosporins were synthesized. The semi-synthetic CFS can be obtained by the introduction of different substitutes in position 3 of 7-ADCA structure [16]. Whatever was the method used for the synthesis of CFS, the final goal was to improve the antimicrobial and pharmaceutical properties, such as: broadening of the antibacterial spectrum, increasing of the stability towards acids or absence of side effects [17–19].

The originality of this work consists in the synthesis of the new porous polymer carriers and the new cephalosporin in order to obtain the drug delivery systems for potential applications in the treatment of infectious diseases. Also, the studies of the equilibrium, kinetic and the mechanism of cephalosporin adsorption, as well as the release studies from the porous macromolecular supports in form of microparticles obtained by grafting chitosan (CH) onto crosslinked network based on glycidyl methacrylate (GMA) and ethylene glycol dimethacrylate (EGDMA) were realized. Adsorption studies are very important to establish the performance of the adsorbents and hence for the selection of a sustained/controlled release system of active principle with highly efficiency.

2. Experimental

2.1. Materials

5-Nitroindazol, sodium chloroacetate, 7-Aminodesacetoxycephalosporanic acid and hydrochloric acid were purchased from Merck & Co.

Trimethyl acetic acid, dimethyl sulfoxide and chitosan (CH, M_w = 600,000 g/mol, degree of acetylation = 13.5%) were purchased from Fluka Chemical Company. Glycidyl methacrylate from Sigma Aldrich was distilled under reduced pressure. Ethylene glycol dimethacrylate, benzoyl peroxide (BOP), ammonium persulfate (APS), toluene, poly(vinyl alcohol) (PVA, M_w = 51,000 g/mol, degree of hydrolysis = 88%), triethylamine, cephalexin, sodium bicarbonate, sodium sulphate, acetic acid and butyl acetate were purchased from Sigma Aldrich.

2.2. Methods

2.2.1. Preparation of the porous microparticles

The porous crosslinked microparticles based on GMA (G_1 and G_2 microparticles) and microparticles based on chitosan-*g*-poly(glycidyl methacrylate) (C_1 and C_2 microparticles) were prepared by suspension polymerization technique described elsewhere [20,21].

It is known that, the reaction mixture of suspension polymerization is formed by two phases: aqueous phase and organic phase. In case of G microparticles the aqueous phase was formed by distilled water as dispersion medium and 1.5 wt.% PVA as a suspension stabilizer. In case of C microparticles the aqueous phase consists of 1.5 wt.% solution of PVA and chitosan. Also, in the aqueous phase of C microparticles a free radical initiator (APS) was added in order to create radicals on polysaccharide chain.

The organic phase for both types of microparticles was formed by GMA (90 mol% or 80 mol%), EGDMA (10 mol% or 20 mol %), BOP as free radical initiator of polymerization reaction of methacrylic monomers (2.5 wt.% with respect to the total amount of the monomers) and toluene as porogenic agent at a dilution of D = 0.5, where D = ml toluene/(ml toluene + ml monomers).

For C microparticles, the CH/methacrylic monomers ratio was 1:23 (w/w) and (BOP + APS) content was 2.5 wt.% with respect to the total amount of the monomers. The mixture of the monomers (GMA and EGDMA), BOP and toluene was added dropwise to the aqueous phase (PVA or PAV + CH) in a 500 cm^3 cylindrical reactor fitted with mechanical stirrer,