EVALUATION OF CATIONIC COPOLYMER NETWORK AS SUSTAINED IBUPROFEN DELIVERY SYSTEM

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Abstract. One of the main approaches to increase the therapeutic effectiveness of the controlled drug delivery systems is the development of new polymeric carriers designed to match the specific properties of a given drug molecule. In present paper properties of a newly synthesized polymer network based on cationic poly{[2-(acryloyloxy)ethyl]-trimethylammonium chloride} (PAETAC) was evaluated as a drug-delivery system of ibuprofen for potential dermal administration. The properties of the cationic network used were characterized by FTIR spectroscopy and swelling kinetics in various solvents. Ibuprofen release profile established in PBS at 37 °C proved the ability of the investigated cationic PAETAC-based carrier to maintain steady ibuprofen release up to 24 hours without initial burst effect.

Keywords: polymer carriers, drug delivery systems, sustained drug delivery

Introduction

Development and enhancement of controlled drug delivery systems is a foremost challenge of contemporary pharmaceutical science and technology [1,2]. The main priority nowadays is to improve the targeting performance and efficiency of drug release systems, which could be achieved by applying the principles of macromolecular design in order to create polymeric carriers that meet the specific requirements for medications [3,4]. In this regard, application of polyelectrolytes, and polycations in particular gives unique possibilities [5,6]. The prospects of cationic polymers to be used as drug carriers rely on well-defined composition and controlled macromolecular architecture [7,8]. Quaternary ammonium polymers are of increasing interest as drug carriers due to the specific properties, strongly dependent on the density and distribution of positive charges along the macromolecular chains as well to various interactions with biomolecules and substances [9]. Consequently, changes of the polymer chain conformation in physiological conditions could be utilized for the purposes of sustained drug delivery and drug targeting.

The aim of this investigation was to evaluate the potential of a new cationic copolymer network composed of cationic poly{[2-(acryloyloxy)ethyl]-trimethylammonium chloride} (PAETAC) and poly(oxiethylene) (PEO) segments as carrier of ibuprofen for drug delivery system. The targeted drug ibuprofen is a nonsteroidal anti-inflammatory drug of Class 2 according to BCS, showing pK_a of 4.5-4.6 and very low solubility in aqueous media [10].The properties of the cationic network used were thoroughly investigated by FTIR spectroscopy and swelling experiment. Ibuprofen loading was carried out trough swelling of the network in ethanol solution and release profile of the developed drug delivery system was studied in PBS at 37 °C.

Materials and Methods

Materials

The monomer 2-(acryloyloxy)ethyl]-trimethylammonium chloride (AETAC; 80 wt. % in H_2O) and initiator 4,4‘-azobis(4-cyanovaleric acid) (≥98%) were purchased from Sigma-Aldrich (Seelze, Germany). The crosslinker poly(ethylene glycol) diacrylate (PEG-diacrylate; average M_n~600) was also obtained from Sigma-Aldrich. Ibuprofen was provided by BASF Chemtrade GmbH (Germany). All other solvents and reagents used were of standard laboratory reagent grade.

Network synthesis

Copolymer network was synthesized by radical polymerization of AETAC in the presence of PEG-diacrylate as macromolecular crosslinker. To obtain copolymer network hydrogel, chosen amount of PEG-diacrylate was dissolved in corresponding amount of AETAC aqueous solution. The solution was flushed with nitrogen for 30 min and the initiator 4,4'-azobis(4-cyanovaleric acid) (0.5 % with respect to the comonomers) was added. The reaction mixture was stirred under nitrogen for additional 10 min, and transferred in a mould of thickness 1 mm and finally placed in an oven at 60 °C for 7 hours. The hydrogel network obtained was repeatedly soaked in deionized water to remove non-reacted monomers and initiator residues, and finally dried in vacuum at 70 °C to constant weight.

The copolymer composition of the obtained segmented network (PAETAC 80 %-wt.; PEO 20%-wt.) was determined on the basis of the initial reagents' concentrations and yield.

Network swelling kinetics

Swelling studies for all prepared systems were done gravimetrically. Disks cut from the network film were transferred to the beaker containing excess of corresponding media (water, PBSpH 7.4 or ethanol) and thermostated. At regular intervals, the samples were taken out for weight measuring and then returned to the medium. The swelling was continued until a constant weight was attained. The equilibrium degree of swelling, Q; was calculated from the following equation: $Q = 100(w\text{-}w_o)/w_o$ (in %); where $\mathbf{w_o}$ is the initial weight of the dry sample and **w** is the weight of the swollen sample at the time.

Drug loading

Test samples for drug loading experiments were prepared by cutting uniform disks (0.6 cm in diameter) from the dry network films. The disks were immersed in ethanol solution of ibuprofen of concentration 250 mg/mLfor 24 h. Then the hydrogels swollen to equilibrium were taken out, the excess of the solution on the surface was blotted out with filter paper and the loaded disks were dried under vacuum to constant weight.

The amount of loaded drug for each sample was calculated from the weight of the dry sample before and after loading.

Fourier transform infrared spectroscopy

Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectra were recorded using an IR Affinity-1 spectrophotometer (Shimadzu Co., Kyoto, Japan) equipped with a MIRacle™ ATR accessory (diamond crystal; PIKE Technologies, USA) providing depth of penetration of the IR beam into the sample of about 2 μm. All samples were scanned over wavenumber range of 4000 - 500 cm^{-1} performing 50 scans at a resolution of 4 cm^{-1}.

In vitro drug dissolution studies

Drug release kinetics was evaluated using a dissolution test apparatus (Erweka DT 600, Hensenstmm, Germany). The USP basket method was selected. The test was carried out at basket rotation speed of 50 rpm, maintained at 37 ± 0.5 °C, in 400 mL dissolution medium at pH value 7.4. The dissolution progress was monitored by withdrawing 5 ml filtered samples (0.45μm filter) at preselected intervals up to 24 hours. The content of ibuprofen in the sample solutions was determined by measuring the UV absorbance of the samples at 266 ± 2 nm using a Hewlett-Packard 8452 A Diode Array spectrophotometer (New Jersey, USA).

Results and discussion

Network synthesis

The cationic hydrogel network to be evaluated as a drug carrier was synthesized by free radical polymerization. Polymerization of AETAC was conducted in aqueous media at 60 ºC in presence of poly(ethylene glycol) diacrylate as a macromolecular crosslinker and using 4,4'-azobis(4-cyanovaleric acid) as a water soluble initiator. The structure of the obtained copolymer comprising cationic PAETAC segments crosslinked with neutral hydrophilic PEO chains is shown in Figure 1.

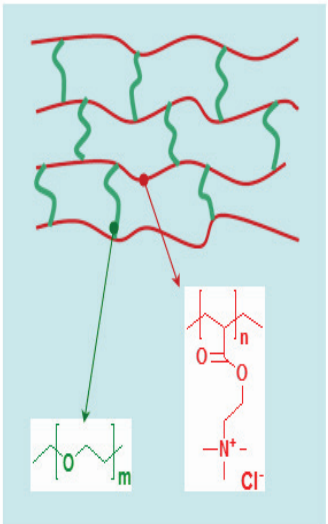

Figure 1. Schematic representation of the structure of PAETAC-PEO segmented network.

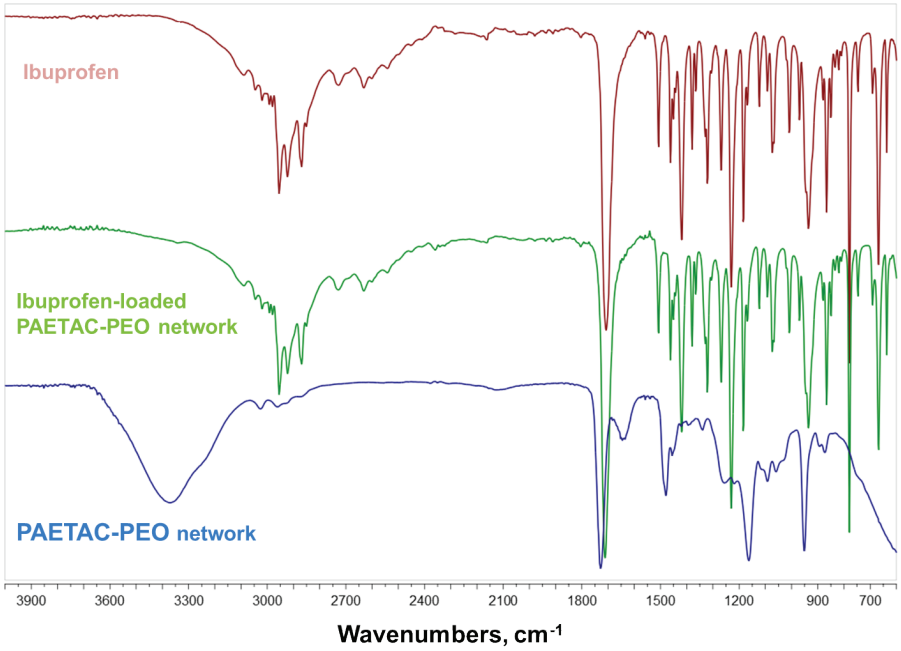

Figure2. FTIR spectra of: ibuprofen (up); segmented cationic network (down) and ibuprofen-loaded network (middle)

The main characteristics of the network were evaluated by spectroscopic investigations and swelling experiments.

Fourier transform infrared spectroscopy

The composition of the purified PAETAC-PEO copolymer network was confirmed by FTIR spectroscopy (Fig.2). Infrared spectrum of the network (PAETAC-PEO) shows the characteristic bands for PAETAC chains: strong carbonyl band–O–C(=O)– at 1728.22cm^{-1}and C–N stretching vibrations at 1163.08 cm^{-1}. The band at 954 cm^{-1} is the definite vibration absorption peak of the quaternary ammonium ion –N^{+}(CH$_3$)$_3$.Weak band at 1091.71 cm^{-1} assigned to the C–O–C vibrations confirms the presence of PEO crosslinks in the structure.

In Figure 2, the IR spectrum of the ibuprofen-loaded copolymer network is compared to the spectrum of pure ibuprofen as well.Strong characteristic carboxyl band at 1707 cm^{-1}of pure ibuprofen substance is well expressed. In the spectrum of ibuprofen-loaded network, this band appears at 1710 cm^{-1} and together with the bands at 1203 cm^{-1} and 779 cm^{-1} confirms that the cationic network is highly loaded with ibuprofen.

Network swelling kinetics

The network swelling kinetics in various solvents was followed at different temperatures: in deionized water at 20 ºC, in ethanol at 20ºC, and in phosphate buffer m pH 7.4 at 37 ºC and obtained results are presented in Figure 3. Swelling in deionized water is a standard test for evaluation of hydrophilic crosslinked polymers. As shown in Fig.3, the investigated network imbibes huge amount of water and reaches the equilibrium swelling degree of 9750 % within 6 hours. Such enormous swelling in aqueous media is due to the cationic nature of the polymer network composed of 80 % quaternary ammonium monomer loosely crosslinked with short PEO chains.Swelling in ethanol is of particular importance because of the excellent solubility of ibuprofen in this organic solvent. The investigated network swells considerably in ethanol taking up about 1530 % ethanol within 6 hours. This explains the high loading capacity of the network with the drug in ethanol solution. The 81.5% wt. loading capacity in ethanol was achieved.

The network swelling kinetics in phosphate buffer medium at 37ºC revealed much lower swelling degree compared to the swelling in deionized water (Fig. 3). Due to the cationicnature of the copolymer an equilibrium swelling of 2070 % was attained in PBS at pH 7.4 within 6 hours. This relatively high degree of swelling and the profile of the registered swelling curve indicate that the tested cationic networks could be successfully applied in drug delivery of ibuprofen. It is expected that the release of hydrophobic substancefrom such system will be dependent mainly onthe swelling of the network.

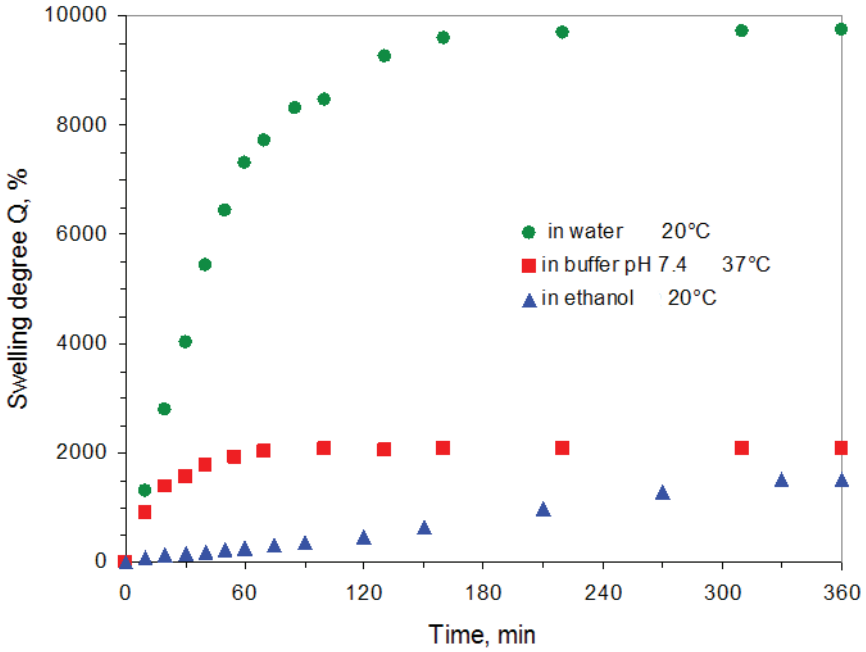

Figure3. Swelling kinetics of the investigated cationic copolymer network in water and ethanol at 20ºC and in BS pH 7.4 at 37 ºC.

In vitro drug dissolution studies

In vitro ibuprofen release kinetics from the investigated cationic copolymer network was followed within 24 hours. The dissolution profile in phosphate buffer solution (pH 7.4)at 37ºCis shown in Figure 4.

From the results presented in Fig. 4 it can be outline that the investigated cationic network is able to implement sustained ibuprofen release within a day. There is no indication for pronounce burst effect in the in the initial phase of the dissolution process. Released ibuprofen at 1 hour is about 11%, at 8 hour – about 48%, and at 24 hours – 83%. These results correlate well with swelling behavior of the network in buffer at similar experimental conditions (Fig. 3) despite of the high ibuprofen concentration in the network due to the high loading efficiency. As a result from the dissolution experiment it is evident that the studied system has a pronounced potential in sustained ibuprofen release and can be further optimized for dermal application.

Conclusions

Segmented cationic network of composition 80 %-wt. PAETAC and 20%-wt. PEO was successfully evaluated as an ibuprofen carrier. Survey of swelling kinetics of the network in various media showed very high swelling capacityin ethanol resulting in enhanced ibuprofen loading. In vitro release kinetics of ibuprofen from the network revealed stable performance of the system with gradual dissolution of the drug substance. Ibuprofen-loaded PAETAC-PEO network demonstrated sufficient drug release rate and extending up to 83% for 24 hours, without indication for initial burst effect.

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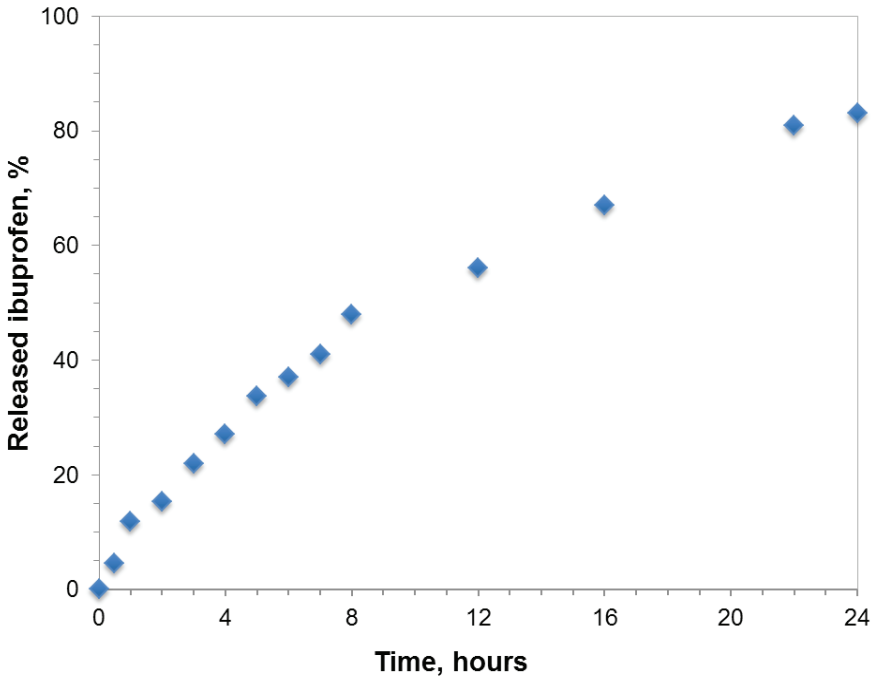

Figure 4. Ibuprofen release kinetics in PBS pH 7.4 at 37 ºC.

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