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Research Article

Study of the Potential of Amphiphilic Conetworks Based on Poly(2-ethyl-2-oxazoline) as New Platforms for Delivery of Drugs with Limited Solubility

Bistra Kostova,[1] Krasimira Ivanova-Mileva,[2] Dimitar Rachev,[1] and Darinka Christova[2,3]

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Abstract. Thermoresponsive amphiphilic conetworks comprising poly(2-ethyl-2-oxazoline) (PEtOx), 2-hydroxyethyl methacrylate, and 2-hydroxypropyl acrylate segments have been studied as new platforms for delivery of drug with limited solubility. Series of conetworks of varied composition were synthesized and swelling kinetics in aqueous media and ethanol were followed. The platforms were loaded with the hydrophobic drug ibuprofen by swelling in its ethanol solution. The structure and properties of the drug carriers were investigated by scanning electron microscopy and differential scanning calorimetry. The release kinetics profiles of ibuprofen from the studied platform were established. The investigation proved the feasibility of the PEtOx-based amphiphilic conetworks as highly effective platforms for sustained ibuprofen delivery.

KEY WORDS: amphiphilic conetworks; drug delivery systems; polyoxazolines; termoresponsive polymers.

INTRODUCTION

Development and enhancement of controlled release systems is the main challenge of contemporary pharmaceutical science and technology. In this regard, stimuli-responsive polymers and hydrogels are of particular importance (1). The ability of these systems to respond to stimuli such as temperature, pH, ionic strength, and electric field could enhance the efficiency of drug loading and release, and optimize the delivery of therapeutic molecules to a specific target area (2–6). Temperature is among the most commonly used external stimuli in the responsive polymer systems. At a certain temperature, known as lower critical solution temperature (LCST), linear thermoresponsive polymers undergo sol–gel phase transition (7,8). Accordingly, the cross-linked thermoresponsive hydrogels collapse when attaining the volume phase transition temperature (9). These features could be used in several major biomedical areas, including effective drug loading by applying temperature variations; modulation of the release rate trough temperature-triggered changes of the polymer configuration, efficient control on the drug delivery properties by using physiological temperature at the application site; targeted drug delivery to relevant areas with altered thermal characteristics; etc.

Numerous thermoresponsive polymers have been studied aiming at application in modern pharmaceutical science and technology (6,10). Poly(*N*-isopropylacrylamide) is perhaps the most well-known member of the class of responsive polymers which undergoes a sharp coil-to-globule phase transition in aqueous solution at about 32°C (11–15). Triblock copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide), also known as Pluronic® (BASF) or Poloxamer® (ICI), represent another widely studied group of thermoresponsive polymers (16–18). Research continues to focus on improving the well-known polymers and develop and test novel smart polymers and copolymers with various architectures as sustained drug delivery systems (19).

Polyoxazolines have been the subject of a considerable research interest since the 1960s (20,21) but only recently have attracted the attention as versatile biomaterials (22,23). One of the principal application areas is drug and gene delivery systems, such as thermoresponsive micelles and vesicles (24–29). Investigations of the biocompatibility of polyoxazolines as an alternative to the widely applied in protein and drug delivery PEO have been carried out (30). In addition, recent cytotoxicity studies on poly(2-ethyl-2-oxazoline) (PEtOx) and on series of di- and triblock copolymers comprising various poly(2-alkyl-2-oxazoline) segments have proved the biocompatibility of hydrophilic polyoxazolines even at high polymer concentrations (31,32).

Amphiphilic conetworks based on end-linked polymers represent an emerging class of materials with unique properties and great application potential as drug delivery carriers (33,34). Among them, only few examples of polyoxazoline-based hydrogels have been studied as drug carriers (22,35,36). Recently, PEtOx/poly(acrylic acid) hydrogels have been synthesized by using γ-rays-induced polymerization and cross-linking in order to investigate their drug release behavior at

[1] Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Medical University-Sofia, 2 Dunav Str, 1000 Sofia, Bulgaria.
[2] Institute of Polymers, Bulgarian Academy of Sciences, Akad. G. Bonchev Str. 103A, 1113 Sofia, Bulgaria.
[3] To whom correspondence should be addressed. (e-mail: dchristo@polymer.bas.bg)

different pH values (37). Drug release profiles of hydrogels loaded with ibuprofen as a model drug has been studied at pH 1 and 7 aiming at colon-specific drug delivery application.

In a previous paper, the synthesis and properties in aqueous media of new amphiphilic thermoresponsive materials based on PEtOx were reported (38,39). Series of conetworks were obtained by applying UV-induced radical copolymerization of PEtOx macromonomers with 2-hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl acrylate (HPA), or methyl methacrylate as comonomers. It was shown that basic properties of the conetworks such as swelling degree in solvents of different polarity and temperature of the phase transition in swollen state can be easily controlled over a broad range. This was achieved by varying the molecular mass and the content of the PEtOx precursor, its content in the copolymer composition, as well as the nature of the comonomer.

The aim of this work was to evaluate the potential of PEtOx-based amphiphilic conetworks as platforms for sustained delivery of drugs with low solubility in aqueous media. For this purpose, conetworks derived from bifunctional PEtOx macromonomer of relatively high molar mass in combination with HEMA or HPA as comonomers were selected. Poly(2-hydroxyethyl methacrylate) (PHEMA) was selected because of its high swelling in water and its hydrophilicity which is similar to those of PEtOx. Moreover, both PHEMA and PEtOx exhibit solubility parameter of ~26 $MPa^{1/2}$ (40,41). Poly(hydroxypropyl acrylate) (PHPA) is relatively more hydrophobic, with a reported LCST of 16°C (42) in contrast to PEtOx, which undergoes phase transition in water at 65–80°C depending on the molar mass. Consequently, in physiological conditions, PEtOx-PHPA conetworks will be partially collapsed due to the contracted PHPA chains, whereas both the segments in PEtOx-PHEMA conetworks will be in extended conformation. Inclusion in the network structure of thermoresponsive segments such as PEtOx and PHPA will provide opportunity to finely tune the hydrophilic–hydrophobic balance at different temperatures and hence to modulate the drug loading capacity and release kinetics of the conetworks.

Ibuprofen, a drug of systematic IUPAC name (RS)-2-(4-isobutylphenyl) propionic acid, was chosen as a model hydrophobic drug. It is a nonsteroidal antiinflammatory drug assessed to be a Biopharmaceutical Classification System class II drug with pK_a in the range of 4.5–4.6 and very low solubility in water (43).

MATERIALS AND METHODS

Materials

Monomers HEMA (Aldrich, 99%) and HPA (Aldrich, 95%) were purified by distillation in the presence of a radical inhibitor, phenothiazine (Aldrich). 2-Ethyl-2-oxazoline (EtOx) (Aldrich, 99%) was refluxed over CaH_2/KOH and distilled prior to use. Initiators, 1,4-dibromo-2-butene (Aldrich, 99%) and 2,2′-azobis(2-methylpropionitrile), were dried in vacuum before use. Acetonitrile (Aldrich, 99.9%, HPLC grade) was purified by distillation over calcium hydride. All other reagents and solvents were used as received, unless otherwise specified. Ibuprofen was provided by BASF Chemtrade GmbH (Germany).

Network Synthesis

Segmented polymer networks were prepared by UV polymerization of HEMA or HPA in the presence of PEtOx bis-macromonomer as described previously (39). The bis-macromonomer used in this study—PEtOx-diacrylate of molar mass 10,200 g/mol (NMR) and end-group functionality 1.98—was synthesized according to the known procedure (44). To obtain the platform networks, the chosen amount of the bis-macromonomer was dissolved in corresponding amount of the comonomer (HEMA or HPA) in order to achieve the desired PEtOx-to-comonomer mol ratio. Then, the solution was flushed with nitrogen for 15 min. The initiator 2,2′-azobis(2-methylpropionitrile) (0.5% with respect to the comonomer) was added and the reaction mixture was stirred under nitrogen until homogeneity was reached. Finally, the reaction mixture was transferred in glass mold of thickness 1 mm and irradiated with UV light (360 nm; 10 mW/cm^2) for 30 min. The network films obtained were dried at 70°C under vacuum for 5 h. After cooling, the networks were repeatedly soaked in distilled water for 24 h to remove residues of unreacted reagents and finally dried in vacuum at 70°Ch to constant weight.

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 for 24 h in ethanol solution of ibuprofen of concentration 250 mg/ml. Then, the platforms swollen to equilibrium were carefully taken out, the excess of the solution on the surface was removed by blotting with filter paper, and the 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.

Characterization of the Drug Delivery Carriers

Network Swelling Kinetics

Swelling studies for all prepared platforms were done gravimetrically. A disk cut from the network film was weighed, transferred into a test tube with the corresponding media: water buffer solution with pH7.2 or ethanol, and then placed in a thermostat at the desired temperature. At regular intervals, the platform was taken out, the excess solvent was removed from the surface with tissue paper, and the platform was weighed 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 Eq. (1), where W_d is the initial weight of the dry sample and W_s is the weight of the sample swollen to equilibrium. For each sample, the average values of Q were calculated from the data obtained from two parallel examinations; the deviations did not exceed 3.5%.

$$Q(\%) = \frac{W_s - W_d}{W_d} \times 100, \quad (1)$$

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analyses were carried out on a PerkinElmer DSC 8500 equipment. The

samples were subjected consecutively to a heating, cooling, and second heating experiment at scanning rate of 10°C/min in nitrogen atmosphere.

Scanning Electron Microscopy

The scanning electron micrographs were taken on a JEOL JSM-5510 apparatus (Japan). Prior to analysis, the samples were fractured in liquid nitrogen and then freeze-dried. All scanning electron microscopy (SEM) images were obtained from the gold-coated surfaces (Sputter Coater Jeol Fine Coater 1200, Japan) using 6 to10 kU electron energy beams. The samples' cross-sections were examined.

In Vitro Drug Dissolution Studies

Drug release kinetics was evaluated using a dissolution test apparatus (Erweka DT 600, Hensenstmm, Germany). The platforms are light, fragile when highly swollen and of low ibuprofen dose. In order to ensure adequate release kinetics investigation, USP basket method was selected at the following conditions: basket rotation speed of 50 rpm, 400 ml dissolution medium at pH value 7.2 and 37±0.5°C. The dissolution progress was monitored by withdrawing 5 ml filtered samples (0.45 μm filter) at preselected intervals (up to 14 h). 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). The cumulative percentage of drug release was calculated as the average of three parallel determinations used in the data analysis. The standard deviations did not exceed 2%.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Platforms

It is well known that loading a polymer carrier with particular drug is strongly influenced by a number of factors such as: the nature and swelling characteristics of the carrier, its hydrophilic–lipophilic balance, its ability to immobilize and sustain the drug molecules, interactions between polymer chains and drug molecules, etc. In this regard, amphiphilic conetworks are promising candidates for drug delivery systems, as the main properties of this kind of materials could be easily control by varying the constituents and copolymer composition (45,46). In order to evaluate the potential of PEtOx-based conetworks as drug delivery systems, four samples of different composition have been synthesized and tested as platforms for sustained release of ibuprofen. The main characteristics of the conetworks obtained are summarized in Table I.

Swelling kinetics of the platforms was followed in buffer (pH7.2) at 20 and 37°C, as well as in ethanol (Figs. 1, 2, and 3). Swelling in ethanol was of particular importance because of the excellent solubility of ibuprofen in this organic solvent. As shown in Fig. 1, the investigated platforms can take up from 300 to 1,000% ethanol depending on the composition. The systems reach their equilibrium within 7 h. Such high swelling degrees in ethanol suggests the possibility of loading the platforms with ibuprofen by a simple and convenient procedure.

From the kinetic data presented in Figs. 2 and 3, it can be clearly seen that the platform PL-1 swells in the greatest extent in buffer, irrespective of the temperature. The degree of swelling of the PL-1 is very high and at 20°C goes up to 1,500%. This behavior is logical, considering that the network contains the highest fraction of hydrophilic PEtOx (70%) and that the counterpart PHEMA is known for its high water affinity. It is worth noting that reducing the PEtOx content by only 20% (PL-2) leads to a drastic decrease in the equilibrium swelling degree (to 420%) at the same temperature (Table I and Fig. 2). This change may be assigned to the lowered content of PEtOx cross-links and subsequent increased possibility of long PHEMA segments to form intermolecular hydrogen bonds. Therefore, the content of PEtOx is considered the main factor influencing the swelling degree of the studied platforms. The behavior of the platforms based on PHPA and PEtOx is different: again the platform with higher content of PEtOx (PL-3) swells to a higher extent than PL-4 but less than the corresponding PHEMA network (PL-1). This is explained by the thermoresponsive properties of PHPA segments: PHPA exhibits LCST of 16°C, therefore at temperatures over 16°C the PHPA segments collapse, which prevents complete hydration and expansion of hydrophilic PEtOx segments in the network. Although the difference in the PEtOx content between PL-3 and PL-4 is much higher (40%) compared to those between PL-1 and PL-2, the difference in the swelling degree is less significant. The equilibrium swelling degrees of the platforms based on PHEMA are always higher than those of the platforms based of the PHPA (at comparable content of PEtOx), which is due to the superior hydrophilicity of PHEMA compared to PHPA.

When retained in buffer at 37°C, the platforms revealed equilibrium swelling degrees approximately two times lower compared to the state at 20°C (Table I; Fig. 3). That is, in physiological conditions, all studied networks will be to some

Table I. Swelling Characteristics of the Platforms at Different Environmental Conditions

		Equilibrium swelling,%		
		In buffer solution (pH7.2)		
Sample code	Network composition[a]	At 20°C	At 37°C	In ethanol at 20°C
PL-1	$PHEMA_{30}$-*l*-$PEtOx_{70}$	1,500	780	1,050
PL-2	$PHEMA_{50}$-*l*-$PEtOx_{50}$	420	180	320
PL-3	$PHPA_{30}$-*l*-$PEtOx_{70}$	880	440	830
PL-4	$PHPA_{70}$-*l*-$PEtOx_{30}$	340	165	415

[a] The values after the polymer abbreviations indicate the weight fractions of the corresponding components by feed; "*l*" stands for "linked by"

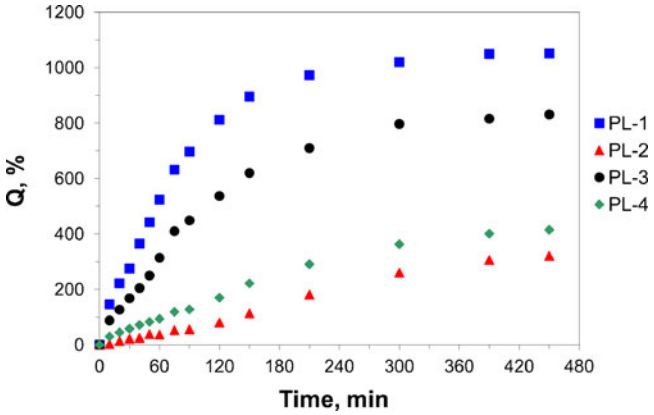

Fig. 1. Swelling kinetics of the platforms in ethanol

extent collapsed, and consequently more hydrophobic. This is especially important with regard to the development of efficient carrier for a hydrophobic drug such as ibuprofen. Control over the drug release of platforms which structure is fully expanded *in vivo* conditions is difficult since the drug substance would be released rapidly after administration. The complete collapse of the platform structure hampers the diffusion of the drug molecules and the active substance would not be released in the necessary rate and degree. Therefore, the partly collapsed conformation of the platform studied here is expected to be favorable for a sustained release of hydrophobic drug molecules.

Drug Loading

The ability of the studied platforms to swell significantly in ethanol which is a good solvent for ibuprofen was used for achievement of the drug loading. The test disks cut from the networks were soaked in concentrated ethanol solution of ibuprofen and then the solvent was evaporated. In this way, a series of extremely high-loaded drug delivery systems, containing 60–80% by weight (50 to 80 mg per test disk) ibuprofen, were prepared (Fig. 4). The structure of the obtained ibuprofen-loaded platforms is schematically presented in Fig. 5.

As expected, both platforms with higher degree of swelling in ethanol (PL-1and PL-3) include higher amount of ibuprofen (Fig. 3). The lower content of PEtOx in the platforms PL-2 and PL-4, which was shown to significantly reduce their

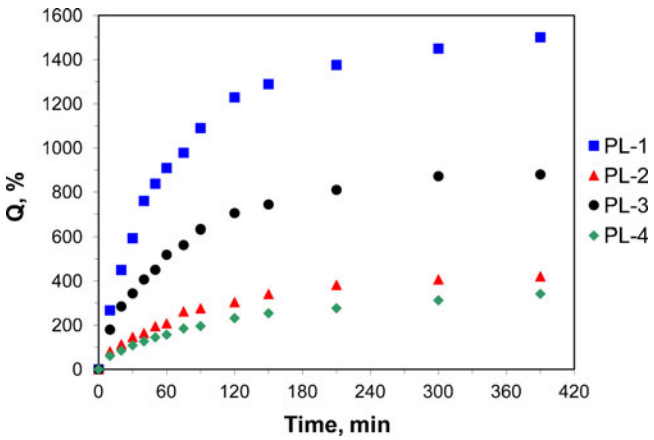

Fig. 2. Swelling kinetics of the platforms in buffer (pH7.2) at 20°C

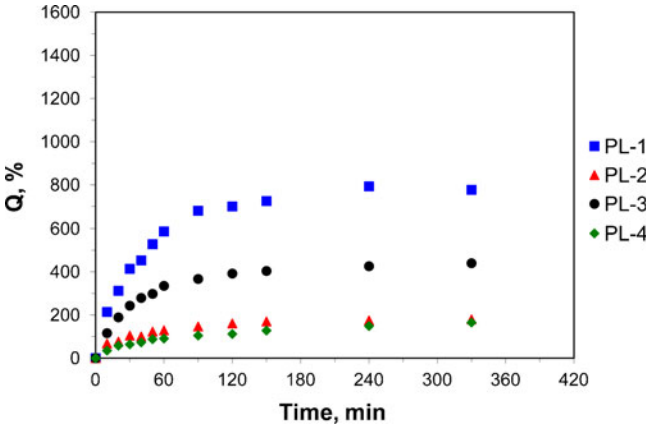

Fig. 3. Swelling kinetics of the platforms in buffer (pH7.2) at 37°C

swelling in ethanol, does not influence the level of ibuprofen loading to the same extend. Although PL-2 and PL-4 swell approximately three times less in ethanol compared to PL-1 and PL-3, the drug incorporation is still high, 65 and 58%, respectively. The fact that the drug loading capacity of the selected four platforms is high can be explained with the proper hydrophilic–hydrophobic balance of the conetworks in combination with suitable network density, which favors ibuprofen entrapping.

SEM Studies of the Platforms

The aim of the SEM study was to visualize the internal structure of the platforms before and after loading of the active substance. Figure 6a, b shows the fracture of the pure PL-3 platform in swollen state after freeze-drying. As it can be seen from the SEM images of different magnification, the platform is characterized by a folded structure with numerous well-formed cavities and channels. The surface of the walls is smooth. The micrograph C in Fig. 6 of the loaded PL-3 clearly shows that after the incorporation the ibuprofen molecules crystallize uniformly in the whole interior of the platform structure. The magnification of the fracture (Fig. 6d) makes

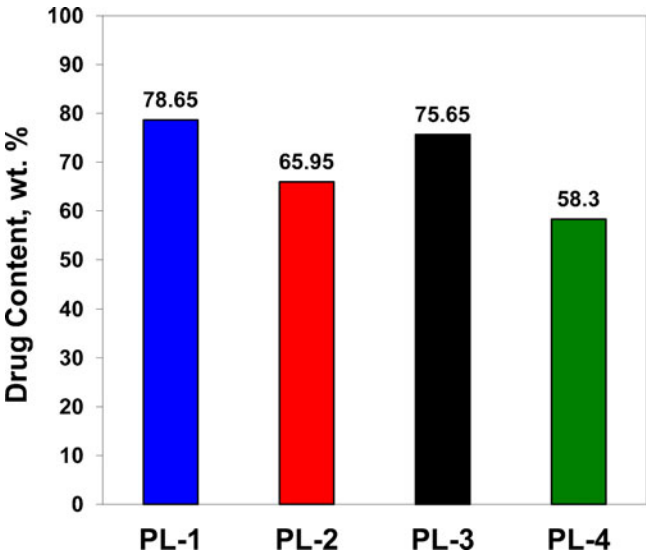

Fig. 4. Drug content in the dried platforms

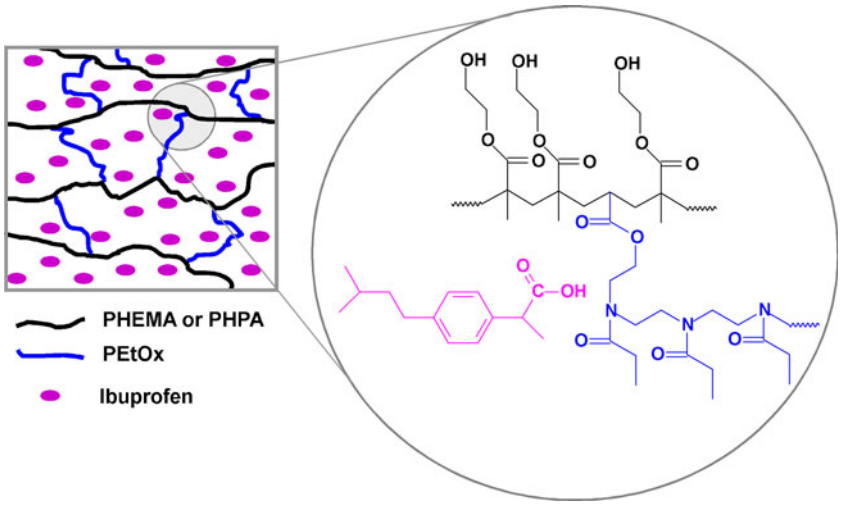

Fig. 5. Schematic illustration of the structure of ibuprofen-loaded platform

it obvious that, although integrated into the cavities and channels of the platform, ibuprofen crystals form clearly separated (independent) microstructures. Similar structure was observed in all loaded platforms.

Investigation on the Thermal Properties of the Platforms

DSC analysis of the developed drug delivery systems was carried out by performing consecutively heating, cooling, and second heating of the samples at scanning rate of 10°C/min in nitrogen atmosphere. Melting endotherm peaks were registered for all studied systems during the first heating. During the cooling, however, no crystallization was observed for ibuprofen neither entrapped in the platforms nor in pure state. As a consequence, no melting endotherms were registered during the second heating of the samples.

The overlaid thermograms (first heating) of pure ibuprofen and of two of the loaded platforms are shown in Fig. 7. Pure ibuprofen is characterized by a sharp melting endotherm with onset at 77°C and peak maximum at 82.3°C (ΔH=122 J/g). As seen from Fig. 7, the inclusion of the drug in the platform results in a significant decrease in the temperature at which the ibuprofen melting starts: from 74°C for pure substance to 35.4 and 52.7°C in the case of PL-1 and PL-3, respectively. The onset temperature decreases too (Table II).

These data clearly show that there is interaction between loaded ibuprofen and the platform, which most likely consists

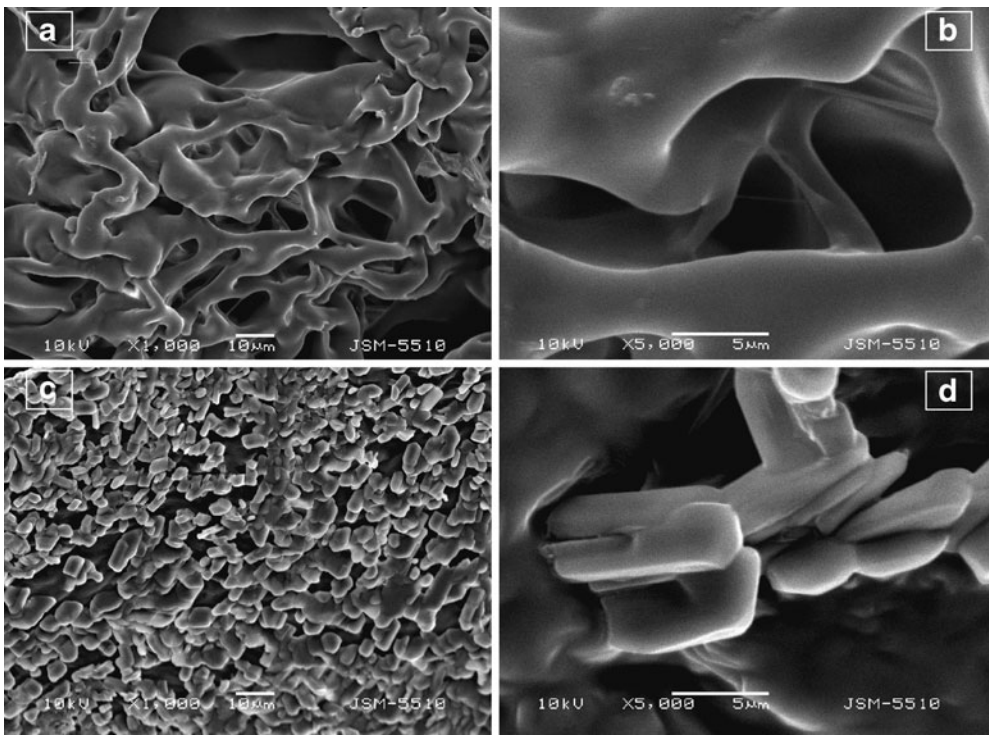

Fig. 6. SEM micrographs of: **a**, **b** fracture of pure PL-3 swollen in ethanol to the equilibrium and freeze-dried; **c**, **d** fracture of PL-3 swollen in ethanol solution of ibuprofen to the equilibrium and freeze-dried

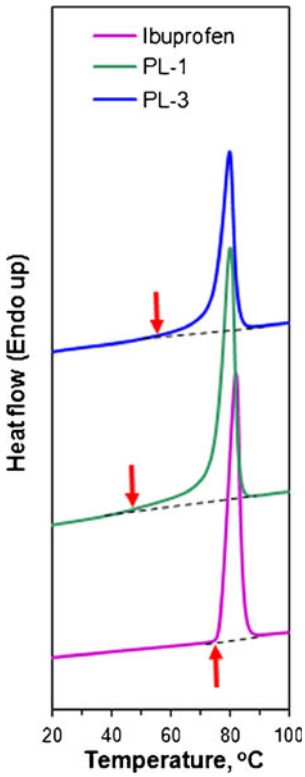

Fig. 7. DSC thermograms (first heating) of platforms PL-1 and PL-3, loaded with ibuprofen compared to the thermogram (first heating) of the pure ibuprofen

of H-bonding between hydroxyl proton of the carboxyl group of ibuprofen and carbonyl functions in the platforms. Consequently, the distortion of the ibuprofen crystal structure in the platforms can facilitate the drug dissolution.

In Vitro Drug Dissolution Studies

Kinetic curves of ibuprofen released from the investigated platforms and dissolution profile of pure ibuprofen at 37°C in buffer (pH7.2) are presented in Figs. 8 and 9. It can be clearly seen that the pure drug is completely dissolved within 20 min whereas all four platforms are able to control the ibuprofen release.

Platforms PL-1 and PL-2 based on PHEMA display more rapid release of ibuprofen attaining 98% for PL-1 and 77% for PL-2 within 14 h (Fig. 8). This is expected for platform PL-1 considering its hydrophilicity and high swelling in buffer pH7.2 at 37°C. Although the platform PL-2 exhibits significantly lower swelling at the same conditions (Fig. 3), the rate of ibuprofen release does not

Table II. Thermal characteristics of ibuprofen melting obtained by DSC during first heating

Sample	Start of the melting process, °C	Melting onset, °C	Maximum of the melting peak, °C	ΔH, J/g
Pure ibuprofen	74.0	77.0	82.3	122
PL-1	35.4	75.0	80.3	72
PL-3	52.7	74.8	80.1	60

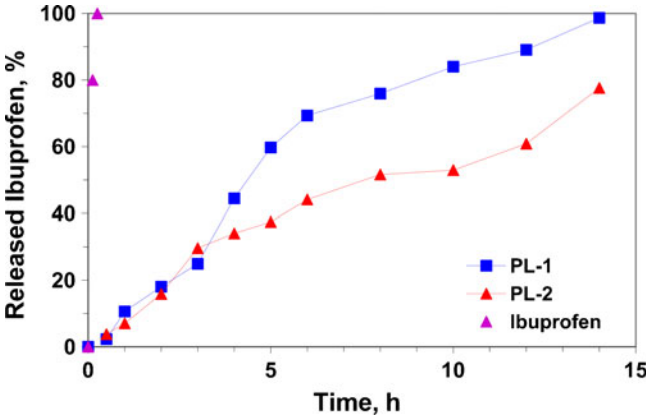

Fig. 8. Release kinetics of ibuprofen from loaded PL-1 and PL-2 platforms and dissolution profile of pure ibuprofen at pH7.2 (37°C)

differ substantially from those of PL-1 during the first 3 h (Fig. 8). This is due to the fact that in the beginning of the dissolution experiment the surface of PHEMA-PEtOx platforms is well hydrated. This facilitates the fast release of molecules from the surface of the ibuprofen crystals independently of the network composition. After the third hour, the release rate of PL-1 increases compared to Pl-2, assigned to the higher swelling degree of PL-1.

The PL-3 and PL-4 based on PHPA showed significant differences in the rate and degree of ibuprofen release compared to PHEMA-based platforms. As can be seen in Fig. 9, PL-3 and PL-4 exhibit low release rate until the third hour, which can be explained with the partially collapsed conformation of the platforms' networks at the experimental conditions. As it was already emphasized, PHPA is a thermoresponsive polymer with phase transition temperature of about 16°C. Obviously, at 37°C, PHPA segments in PL-3 and PL-4 are collapsed, the penetration of the buffer solution in the interior of the networks is hindered, and this prevents the release of the ibuprofen molecules out of the platform in the beginning of the dissolution experiment.

After the third hour, the amount of the released ibuprofen from both PL-3 and PL-4 platforms increases with almost constant rate (Fig. 9) which was proven by linear regression analysis of the data from the 3rd to 14th hour to zero-order

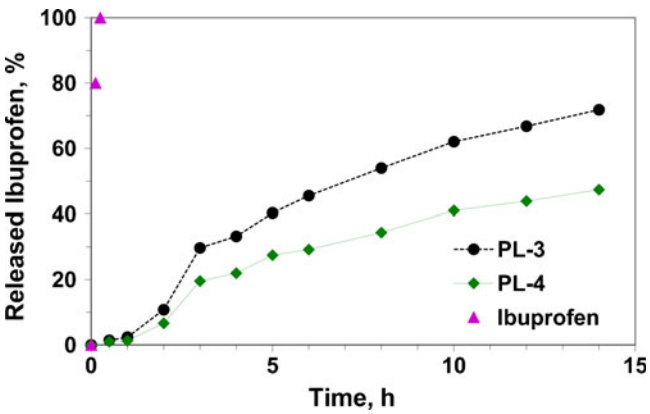

Fig. 9. Release kinetics of ibuprofen from loaded PL-3 and PL-4 platforms and dissolution profile of pure ibuprofen at pH7.2 (37°C)

kinetics (obtained correlation coefficients: R^2=0.9884 for PL-3 and R^2=0.9902 for PL-4). The increase in the amount of the released ibuprofen observed is due to the gradual hydration of the PEtOx chains. Here, again, the platform with higher PEtOx content (i.e., of higher swelling degree) PL-3 reaches higher drug release compared to PL-4.

It is noteworthy that both PL-3 and PL-4 platforms containing PHPA exhibit much more regular drug release kinetics compared to the systems based on PHEMA. This can be explained by taking into account the thermoresponsive character of the studied platforms and the status of the each conetwork at the experimental release conditions. PHPA-containing platforms, which are partially collapsed at 37°C, obviously maintain better sustained release of ibuprofen than the corresponding PHEMA analogues.

CONCLUSIONS

Two types of amphiphilic thermoresponsive PEtOx-based conetworks have been studied as novel drug delivery systems: one including PHEMA and another one comprising PHPA. The platforms exhibited high swelling degree in aqueous solutions as well as in ethanol, which allowed them to be effectively loaded with the hydrophobic drug ibuprofen. In this way, drug delivery systems containing very high drug quantity—up to 78% by weight—have been obtained. The SEM studies revealed that the ibuprofen crystallizes uniformly in the whole conetwork structure, whereas the results from the DSC investigation referred to the existence of interaction between loaded drug and the platform, most likely H-bonding. It has been proven that all the investigated conetworks are able to maintain sustained release of ibuprofen. The established drug release kinetics of the studied platforms, however, differ significantly, which could be further explored in the development of drug delivery systems for specific applications.

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