Research Article

The Study of Release of Chlorhexidine from Preparations with Modified Thermosensitive Poly-N-isopropylacrylamide Microspheres

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Received 11 October 2011; Accepted 20 November 2011

Academic Editor: Doron J. Aframian

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The aim of this study was to investigate and compare the release rates of chlorhexidine (CX) base entrapped in the polymeric beads of modified poly-N-isopropylacrylamides (pNIPAMs) at temperatures below and over the volume phase transition temperature (VPTT) of synthesized polymers: pNIPAM-A with terminal anionic groups resulting from potassium persulfate initiator, pNIPAM-B with cationic amidine terminal groups, and pNIPAM-C comprising anionic terminals, but with increased hydrophobicity maintained by the N-tert-butyl functional groups. The preparations, assessed in vitro below the VPTT, release an initial burst of CX at different time periods between 120 and 240 min, followed by a period of 24 h, when the rate of release remains approximately constant, approaching the zero-order kinetics; the release rates for the polymers beads are as follows: pNIPAM-C > pNIPAM-B > pNIPAM-A. The pattern of release rates at temperature over the VPTT is as follows: pNIPAM-C > pNIPAM-A > pNIPAM-B. In the presence of pNIPAM-C, the duration between the start of the release and the attained minimal inhibitory concentration (MIC) for most of the microbes, in conditions over the VPTT, increased from 60 to 90 min. The release prolongation could be ascribed to some interactions between the practically insoluble CX particle and the hydrophobic functional groups of the polymer.

1. Introduction

Chlorhexidine (CX), the known and widely applied antimicrobial agent, still is identified as the so-called “gold standard” in many applications, including oral and skin health applications, as well as some other skin and mucosal applications [1]. Researchers are evaluating numerous systems for controlled delivery of CX to the place of the interest, that is, mucosa of oral cavity, or skin surface. Yue et al. prepared, by single emulsion, solvent evaporation technique microparticles of poly(dL-lactic-co-glycolic acid) containing CX-free base, CX digluconate, and their association or inclusion complex with methylated-beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin [2]. Some authors proposed urethane dimethacrylate-triethylene glycol dimethacrylate resin system with some success [3]. Early works included carriers based on acrylic strip [4] and chip of cross-linked collagen [5]. Also natural polymers as xanthan [6] or silk fibroin/gelatin hybrid films [7] were evaluated for loading CX.

The approach to effectively use microspheres for CX delivery to the place of proper activity was evaluated originally by Egbaria and Friedman [8], who evaluated the antibacterial activity of human albumin microspheres containing CX dihydrochloride against bacteria of urinary tract. The microspheres composed of chitosan were soon evaluated for preparation of buccal tablets with CX, acting on the oral mucosa [9]. Wu and Lee [10] applied in theirs microspheres loaded by chlorhexidine modified, that is, acetylated and succinoylated inulin-obtained microspheres were characterized by prolonged release of CX.

Poly-N-isopropylacrylamides (pNIPAM) are among the group of most applied macromolecules, characterized by reversible volume-phase transition at ca. 31°C [11]. The
thermosensitive microgel particles may be applied in many medical devices, including drug forms for topical use [12, 13]. With the collapse and expansion of the macromolecule in the aqueous environment, the molecules of the biologically active substance may be released in a controlled manner [14, 15]. The deswelling process is controlled by diffusion, where the rate of the collapsing of the macromolecule is correlated to the dimensions of the pores in the polymeric matrix [16]. When the VPTT is crossed, the phase transition from one side enables the expelling of the drug from the polymeric environment, but on the other hand the aggregation may be expected, when the microspheres will adhere to the mucosa surface in the oral cavity.

In our previous studies, we investigated release of CX from ionic and nonionic polymer hydrogels, namely, from methylcellulose and modified polyacrylic acid [17]. Some approach was made to evaluate the amounts of CX released from modified poly-N-isopropylacrylamide by the conductometry method [18]. The aim of the present work is to evaluate the influence of three different microspheres batches on the release of CX in the conditions below and over the VPTT, applying pharmacopoeia release device.

The pNIPAM microgels, namely, pNIPAM-A, pNIPAM-B, and pNIPAM-C, with different terminal functional groups based on different initiators used in surfactant-free dispersion polymerization (SFDP), were synthesized in previous research [19]. For microgels pNIPAM-A and pNIPAM-C, potassium persulfate was used as an initiator in SFDP, while for pNIPAM-B, 2,2′-azo-bis(2-methylpropionamide)dihydrochloride was used. The microgel pNIPAM-C was synthesized with the addition of comonomer, N-tert-butyl acrylamide, to increase the hydrophobicity of the received particles due to the experiments performed by Lynch et al. [20] as well as Lindmann et al. [21]. The IR spectra of the particles due to the experiments performed by Lynch et al. 

2.1. Synthesis of the Microgels. The N-isopropylacrylamide derivative microgel particles were synthesized by SFDP in deionized water at 70°C, under an inert nitrogen atmosphere due to the procedure reported in former paper [18]. The pNIPAM-A was characterized as a polymer with terminal anionic function groups. The pNIPAM-B was synthesized in the presence of 2,2′-azo-bis(2-methylpropionamide)dihydrochloride, which resulted in cationic amide terminal functional groups. The pNIPAM-C was characterized as the polymer with anionic terminal functional groups, but with increased hydrophobicity according to the functional groups introduced during the synthesis. For better evaluation of the polymerization process, the IR spectra assessments were performed to exclude the presence of vinyl groups in the products of the reaction, as well as to confirm the implementation of respective comonomer [18]. Also the other basic data on the characteristics of the microspheres were presented in the previous study, as the VPTT and scanning electron microscopy images of entities obtained through the synthesis.

2.2. Preparations of Microspheres-CX Mixtures. The CX-loaded preparations were developed using the polymers pNIPAM-A, pNIPAM-B, and pNIPAM-C, and for comparison also MC and PA. The samples were allowed to swell in the 0.5% dispersions of CX for 48 h in a water bath at 298 K, under continuous stirring. After 48 h, when the incorporation procedure terminated, the samples were immediately frozen using liquid nitrogen and freeze-dried by MINI LYOTRAP LF/LYO/02/1 with vacuum pump model RV5, in high vacuum mode, at 50% power setting, with vacuum values in the range of 1 × 10⁻¹–1 × 100 mbar (i.e., 1 × 10⁻¹–1 × 10² Pa) for 24 h, and finally dispersed in water. The time for complete incorporation was demonstrated by previous consequent spectrophotometric assessments of the filtered samples, which came from the preparations loaded by chlorhexidine in various, increasing time periods. The exponential curve ranged the limit, and the amount of assessed drug did not decrease further after ca. 36 hrs. To receive the full load, the margin of 12 hrs was added. Composition of the obtained microgel preparations of CX is given in the attached Table 1.

2.3. Morphology of the Obtained Complexes of Polymer and CX. The surface and morphology of the freeze-dried samples were examined using light microscopy (LM). The morphology of the loaded samples was assessed by the optical microscope, Olympus BX51, with oculars 20 × 0.46 mm and 50 × 0.80 mm, and recorded using a digital camera, Olympus DP12, U-TVO.5XC-2, by applying direct day light. To obtain more data about the surface of the dry samples, the scanning electron microscope (SEM) was applied, using the FEI QUANTA 200 3D.

2.4. Release Rates. The in vitro release of CX from the solution in water and from the hydrogel preparations across artificial membrane was examined using United States Pharmacopoeia paddle method with the acceptor volume of
was assessed using the UV spectrophotometric method. The subsequently, every 1 h for up to 12 h, to achieve 20 mea-
for the first 100 min, then, every 30 min for the next 2 h, and,
adsorption on the glass. The samples were taken every 10 min
silanized using dichlorodimethyl silane to minimize CX
with fresh prethermostated acceptor phase. The vessels were
1 mL of receptor phase was taken as a sample and replaced
were conducted using these systems for a 24 h period. About
drug, was placed in the donor compartment. Six experiments
either of the solution of CX or a hydrogel containing the

3. Results and Discussion

The polymeric microgels obtained in the process of SFDP
were prepared using known method proposed and evaluated,
that is, by Pelton [23] as well as Saunders and Vincent
[24]. Consequent IR assessments confirmed the reduction of
the double bonds in the monomer molecule [25], demon-
strating that the polymer was obtained [26]. The VPTT
was observed in the turbidity measurements, and, hence, all
the synthesized products were considered as thermosensitive
[27]. In the present research, we confirmed the detailed
evaluations performed earlier—the VPTT for pNIPAM-A
and pNIPAM-B was around 34 ◦C, whereas, for pNIPAM-
C, it was observed at 32 ◦C. The conductivity measurements
revealed complete purification of obtained material from the
initiator or comonomer remains.
Both LM and SEM observations of freeze-dried mate-
rial revealed hydrogel-like structure in the case of CX-
pNIPAM-A compositions, whereas for CX-pNIPAM-B and
CX-pNIPAM-C compositions, we observed microspheres of
diameter between 0.5 and 5 µm (Figures 1 and 2). As it
evident from the LM microphotography, the spheres
tended to aggregate, however, in the observation field, there
were no particles actually aggregated. The SEM photograph,
panel A (Figure 1), gives impression of some artifacts or
deposited CX on the surface of the fiber-like structures.
On the panel B of Figure 2, the obtained microgels have
some observable empty areas, between planar surfaces of
poly-N-isopropylacrylamide, very characteristic for this kind
of material, possibly with some CX binded. This both
interesting issues, dealing with suspected specific CX depo-
sition on/in microgels, will be evaluated in next study. The
hydrophobized particles had rather smooth surface in the
SEM observations, with no observable artifacts, for example,
CX crystals.

The CX preparations, assessed in vitro at 22 ◦C, that
is, below the VPTT for the studied microgels, released an
initial burst of CX at different time periods between 120
and 240 min, followed by a period of ca. 24 h, in which
the rate of release was approximately constant, approaching
the zero-order kinetics as it is depicted in Figure 3. To
determine whether the release rate decreased exponentially,
the logarithms of the CX concentrations were plotted against
time, which produced straight lines, as shown in Figure 4.
The linear regression coefficients given in Table 2 were over
0.9584, indicating an extremely close fit of the values to
the line and supporting the premise that the release rate
decreased exponentially during the assay.

Depending on the preparations, the rates fell by approx-
mately up to 10 times in a period of 24 h. During that
period, the concentration of CX attained in each sample level
of >20 µg/mL, which is well above the minimal inhibitory
centration (MIC) for most of the microbes (Figure 3).
The release rate was the highest in the case of aqueous
suspension of the CX base. The release rates for the polymers
beads were as follows: pNIPAM-C>pNIPAM-B>pNIPAM-
A>MC>PA. Furthermore, the prolongation of CX release
was ca. 30–50 min. The release of CX in the presence of
pNIPAM can be divided into two stages (Table 3), and
the transition point for pNIPAM-A and pNIPAM-B was
observed at 90 min, whereas, for pNIPAM-C, the apparent
release rate decreased significantly after 130 min.

Additionally, the first-stage release rate for pNIPAM-
C was significantly higher than those for pNIPAM-A and

<table>
<thead>
<tr>
<th>Components preparation</th>
<th>CX (mg)</th>
<th>pNIPAM-A (mg)</th>
<th>pNIPAM-B (mg)</th>
<th>pNIPAM-C (mg)</th>
<th>MC (mg)</th>
<th>PA (mg)</th>
<th>Water (g)</th>
</tr>
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<tr>
<td>pNIPAM-A-CX</td>
<td>45</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>pNIPAM-B-CX</td>
<td>45</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>pNIPAM-C-CX</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>20</td>
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<tr>
<td>MC-CX</td>
<td>45</td>
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<td>—</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>20</td>
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<tr>
<td>PA-CX</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>H2O-CX</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
</tr>
</tbody>
</table>


900 mL and a defined diffusional area of 64 cm². Water was
used as the acceptor phase, and it was adjusted to a pH of 5.5
by the addition of small quantities of 0.1 M HCl, to maintain
the pH close to the physiological pH of the skin surface.
After preparation, all the samples, that is, CX dispersion
and loaded hydrogels, were placed in a thermostated water
bath, at 22 and 37 ◦C for 24 h. About 20 mL of the sample,
either of the solution of CX or a hydrogel containing the
drug, was placed in the donor compartment. Six experiments
were conducted using these systems for a 24 h period. About
1 mL of receptor phase was taken as a sample and replaced
with fresh prethermostated acceptor phase. The vessels were
silanized using dichlorodimethyl silane to minimize CX
adsorption on the glass. The samples were taken every 10 min
for the first 100 min, then, every 30 min for the next 2 h, and,
subsequently, every 1 h for up to 12 h, to achieve 20 mea-
asurement points for this time period. The CX in the eluent
was assessed using the UV spectrophotometric method. The
percentage extinction coefficient (a1%,1 cm) in 0.01 mol/L
HCl solution was 224.12 (P > 0.999) at 250 nm, and the
method gave a linear response over a concentration range
of 1–20 µg/mL [22]. The UV spectrophotometer, TECAN
Infinite 200, with 96 wells plates, Greiner 96 flat-bottom
transparent polystyrol plates, was used for the determination
of CX concentrations in the studied samples.

<table>
<thead>
<tr>
<th>Components preparation</th>
<th>CX (mg)</th>
<th>pNIPAM-A (mg)</th>
<th>pNIPAM-B (mg)</th>
<th>pNIPAM-C (mg)</th>
<th>MC (mg)</th>
<th>PA (mg)</th>
<th>Water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNIPAM-A-CX</td>
<td>45</td>
<td>90</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>pNIPAM-B-CX</td>
<td>45</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>pNIPAM-C-CX</td>
<td>45</td>
<td>—</td>
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<td>90</td>
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<td>—</td>
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<tr>
<td>MC-CX</td>
<td>45</td>
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<td>—</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>PA-CX</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>H2O-CX</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
</tr>
</tbody>
</table>

Figure 1: Morphology of obtained polymers; the light microscopy images: (a) pNIPAM-A, (b) pNIPAM-B, (c) pNIPAM-C.

Figure 2: Morphology of obtained polymers; the scanning electron microscopy images: (a) pNIPAM-A, (b) pNIPAM-B, (c) pNIPAM-C.

Figure 3: Influence of the type of polymer in the donor compartment on the CX concentration in the acceptor medium at 22°C. The release from respective preparations was depicted: pNIPAM-A-CX (♦), pNIPAM-B-CX (▲), pNIPAM-C-CX (■), MC-CX (○), PA-CX (×), and aqueous dispersion of CX (+), data from repeated six experiments. The dashed straight line, parallel to the x-axis, represents the MIC of CX for Staphylococcus mutans.

Figure 4: Influence of the type of polymer on the release kinetics of CX from the polymeric bead at 22°C. The release from respective preparations was depicted as follows: pNIPAM-A-CX for first stage (♦) and second stage (●), pNIPAM-B-CX for first stage (▲) and second stage (△), pNIPAM-C-CX for first stage (■) and second stage (□), MC-CX (○), PA-CX (×), and aqueous dispersion of CX (+), data from repeated six experiments.

pNIPAM-B. Also, the release curves for pNIPAM-A and pNIPAM-B did not show much difference in group. For comparison, the respective data of the release rates for MC and PA are presented in Table 3, although the VPTT was not assessed for these polymers. For a specific time period, the release of CX at temperature over VPTT was different than that at temperature below VPTT (Figure 5).
to a buffer

...in which the samples of CX with polymer were exposed

...influence the release kinetics of CX, an in vitro model was

...and the concentrations observed in the acceptor fluid to

...proper for the comparison of semisolid-drug forms applied

...Pharmacopoeia and the United States Pharmacopoeia as

...determined (µg/mL). Furthermore, the logarithms

...of these parameters can be

...within a matrix system, when the drug is present in the core

...release in numerous cases is considered to be the ideal system

...the drug in the polymeric matrix. However, the zero-order

...kinetics, in which the rate of release diminishes exponentially

...matrix systems. They usually exhibit first-order release

...for drug administration. That case is considered to occur

...with regard to the differences in the location of the
dermis, exposure to surface lipids, washing, and other effects

...observed on the skin surface. Nevertheless, the model system

...expected with regard to the differences in the location of the
dermis, exposure to surface lipids, washing, and other effects

...that might be absorbed over an 8 h period by a patient

...employed for the evaluation of the maximum dose of CX

...that might be absorbed over an 8 h period by a patient

...receiving a topical treatment. The received concentration in

...in the acceptor fluid was up to 13 mg/mL in the first hour,
equivalent to a release of an estimated 1300 mg of the drug

...for the same period at a temperature over the VPTT, under

...on the skin surface. This is far below the daily dose of 2000 mg

...that humans are capable of ingesting without producing

...any adverse effects [29]. However, at temperature below

...VPTT, the values were not higher than 10 mg for pNIPAM-

...B and pNIPAM-C and reached almost 20 mg for pNIPAM-

...in this study, in which a drug is dissolved or dispersed in a polymer vehicle, can be classified as diffusional matrix systems. They usually exhibit first-order release kinetics, in which the rate of release diminishes exponentially with time, in response to the decreasing concentrations of the drug in the polymeric matrix. However, the zero-order release in numerous cases is considered to be the ideal system for drug administration. That case is considered to occur within a matrix system, when the drug is present in the core of the matrix in a highly saturated state. Consequently, the diffusion of the drug from the matrix is rate limiting [28].

...employing the European Pharmacopoeia and the United States Pharmacopoeia as proper for the comparison of semisolid-drug forms applied topically. It would be unlikely for the release rates of CX and the concentrations observed in the acceptor fluid to

...be in exact agreement with those on the skin surface, where considerable variation in these parameters can be expected with regard to the differences in the location of the dermis, exposure to surface lipids, washing, and other effects observed on the skin surface. Nevertheless, the model system demonstrated that the characteristics of the kinetics of release differ among the applied polymers. Release systems, like those described in this study, in which a drug is dissolved or dispersed in a polymer vehicle, can be classified as diffusional matrix systems. They usually exhibit first-order release kinetics, in which the rate of release diminishes exponentially with time, in response to the decreasing concentrations of the drug in the polymeric matrix. However, the zero-order release in numerous cases is considered to be the ideal system for drug administration. That case is considered to occur within a matrix system, when the drug is present in the core of the matrix in a highly saturated state. Consequently, the diffusion of the drug from the matrix is rate limiting [28].

...employmen...
of the CX from the polymeric preparations is observed to µ0.25–64 µg/mL, that is, 0.25–64 mg/L [30–32]. The proposed
microlgel, the effective time, that is, the duration since the start of the release to the moment when the MIC is
temperature below the VPTT, increased from 60 to 90 min. The pNIPAM-C polymer was characterized as a hydrophobized macromolecule, with butyl acrylate functional group—thus, the release prolongation could be attributed to some interactions between the insoluble CX molecule and the hydrophobic functional groups of the polymer. The assessed effective times are presented in Table 4.

The MIC of CX for Streptococcus specia, one of the main pathogens in the respiratory tract, is in the range of 0.25–64 µg/mL, that is, 0.25–64 mg/L [30–32]. The proposed polymer systems for the release of active substance enable the achievement of direct bactericidal and bacteriostatic levels of CX in the application area after ca. 60–130 min, in the case of pNIPAM polymers at temperature below the VPTT. However, when the temperature is over the VPTT value for the assessed synthesized polymers, the antibacterial effect is observed at 80–90 min. The release of the CX from the polymeric preparations is observed to intensify simultaneously with the increase in the temperature during the release process. However, the only exception was pNIPAM-C. In the presence of this polymer, the effective time, that is, time needed to observe the MIC in the acceptor compartment, increased at the temperature over the VPTT. This can be owing to the effective embedding of the CX in the microsphere structure—one of the factors may be the lipophilic interaction of the polymer tertiary-butyl chains with the CX molecules. The future development of the N-isopropyl acrylamide microgels as drug carriers is supported by reported cytocompatibility of the pNIPAM nanoparticles [33]. The obtained data may be valuable for the development of new drug forms for controlled delivery of active substances onto the skin at different environmental temperatures, where the skin surface temperature could vary in the range from 14°C up to 42°C. Therefore, the therapeutic activity of the locally applied drug depends on both the thermodynamic activity of the active molecule compound and the pharmaceutical system, which enables the release of the molecule, as well as on the vasoconstrictive activity of the skin blood vessels. However, the release of the drug might be different when a patient is suffering from fever, when compared with the healthy subject. Furthermore, cryotherapy might also influence the release of the drug applied onto the skin.

4. Conclusions

The preparations evaluated in this study could be employed as CX carriers to achieve effective drug concentrations at

Table 3: Release rates of CX from polymeric preparations.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Release rates assessed at 22°C (min⁻¹)</th>
<th>Release rates assessed at 37°C (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st stage SD</td>
<td>2nd stage SD</td>
</tr>
<tr>
<td>pNIPAM-A-CX</td>
<td>2.85 × 10⁻³</td>
<td>0.01 × 10⁻³</td>
</tr>
<tr>
<td>pNIPAM-B-CX</td>
<td>2.62 × 10⁻³</td>
<td>0.02 × 10⁻³</td>
</tr>
<tr>
<td>pNIPAM-C-CX</td>
<td>7.43 × 10⁻³</td>
<td>0.04 × 10⁻³</td>
</tr>
<tr>
<td>MC-CX</td>
<td>1.66 × 10⁻³</td>
<td>0.03 × 10⁻³</td>
</tr>
<tr>
<td>PA-CX</td>
<td>3.60 × 10⁻³</td>
<td>0.04 × 10⁻³</td>
</tr>
<tr>
<td>H₂O-CX</td>
<td>3.29 × 10⁻⁴</td>
<td>0.07 × 10⁻³</td>
</tr>
</tbody>
</table>


Table 4: Assessed effective times*.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Effective time at the temperature of 22°C (min)</th>
<th>Effective time at the temperature of 37°C (min)</th>
<th>The decrease of time at which the MIC is acquired with the increase in the temperature in the range of 15°C (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNIPAM-A-CX</td>
<td>130</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>pNIPAM-B-CX</td>
<td>145</td>
<td>80</td>
<td>65</td>
</tr>
<tr>
<td>pNIPAM-C-CX</td>
<td>60</td>
<td>90</td>
<td>−30</td>
</tr>
<tr>
<td>MC</td>
<td>210</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>CX</td>
<td>110</td>
<td>50</td>
<td>60</td>
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<tr>
<td>PA</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* Effective time was recognized as the period from the start of the release to the moment when MIC for CX was observed, n/a: not assessed.
different skin surface temperatures. The proposed polymer systems for the release of active substance enable the achievement of direct bactericidal and bacteriostatic levels of CX in the application area after ca. 60–130 min, in the case of pNIPAM polymers at temperature below the VPTT. The antibacterial effect is observed at 80–90 min when the temperature is over the VPTT value. Also, the data obtained for the in vitro preliminary selection of the thermosensitive polymers could be used for the further in vivo assays. This class of thermosensitive polymers can be further developed to achieve controlled release of the drug at different thermal conditions of the body.

Acknowledgments

This research was cofinanced by a Marie Curie Transfer of Knowledge Fellowship of the European Community 6th Frame Program under Contract no. MTKD-CT-2005-029540-POLYSURF, at the University of Maribor. Authors are grateful to Professor Brian Vincent from the University of Bristol for the valuable comments and to Mr. Tonica Boncina from the University of Maribor for the assistance in SEM measurements.

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