

The influence of lidocaine hydrochloride on environmental pH changes of diluted dispersions of poly(N-isopropylacrylamide) below and over the LCST

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Summary

In this study we assessed the influence of lidocaine hydrochloride on the pH of diluted aqueous dispersions of modified poly(N-isopropylacrylamide), at temperature assigned as normalized skin surface temperature, and below and over the lower critical solution temperature value. Three different N-isopropylacrylamide polymer derivatives were synthesized by surfactant free emulsion polymerization, and assessed in the terms of pH in the aqueous dispersions in the presence and absence of lidocaine hydrochloride.

The tendency in observed system was similar at three different temperatures, when lidocaine was applied. The pH value increased from the range between 5,39 - 5,90 up to the range 6,22 - 6,55. However, the step of pH between the temperature of 25°C and 32°C was more radical, comparing to 32°C and 45°C.

The lidocaine hydrochloride influences the pH patterns observed at various temperature in polymeric systems: measurements of preparations applied on the skin or mucosa should be evaluated in respective temperature range.

Key words: lidocaine hydrochloride, microgels, N-isopropylacrylamide, thermosensitivity

INTRODUCTION

Poly(N-isopropylacrylamide) microgel is a known and researched in many fields polymer that undergoes a volume phase transition at the lower critical solution temperature (LCST), at 32°C in water solutions [1-3]. The microgels are stable polymeric networks, characterized by dimensions between nanometers and micrometers. The process of deswelling in this group of polymers is controlled by diffusion, and the rate of the collapsing of the macroparticle is correlated to the dimensions of pores in the polymeric net [4].

Thermosensitive polymers in the medical research have been applied as factors responding to environmental changes at the temperature in the range of 32-36 °C. The medicinal agents may be delivered in the controlled manner to the specified place of activity [5]. The controlled delivery of actives to the skin can provide therapeutic levels where required and minimize systemic uptake.

Binding of small bioactive molecules with the use of that kind of polymers was studied i.a. for benzoate, diltiazem, cyanocobalamin, dextrans [6]. The chemical modifications in that group of polymers may enhance the release prolongation, or enable the specified targeted drug delivery.

However, this potential drug carriers may influence the natural environment of the skin surface, and change the natural pH to undesirable values. In complicated aqueous systems, with thermosensitive polymer and medicinal agent, the pH should be determined at various temperatures, to demonstrate the respective properties of preparation in the place of application. One of the local anesthetics commonly applied on the skin is lidocaine hydrochloride. This bioactive was evaluated in the terms of release from polymeric vehicles [7, 8].

In this study we assessed the influence of lidocaine hydrochloride on the pH of diluted aqueous dispersions of modified poly(N-isopropylacrylamide), at temperature assigned as normalized skin surface temperature, and below and over the LCST value.

MATERIAL AND METHODS

Materials

Lidocaine hydrochloride was supplied by Sigma-Aldrich. Deionized water from the TKA DI 6000 system (Germany) was used for all the dispersions, and respective operations during the measurements. N-isopropylacrylamide 97%, respective initiators and co-monomer were obtained from commercial suppliers and used without further purification. The monopotassium phosphate, and the disodium phosphate used in the buffer solutions were of pharmacopoeial purity.

Applied polymers

pNIPAM microgels particles derived from former experiments in the field of polymer chemistry. They were synthesized by surfactant free emulsion polymerization (SFEP) in deionised water at 343 K, under an inert nitrogen atmosphere, according to the procedure evaluated by Pelton [9] and developed i.a. by Vincent [10] D'Emanuele and Dinarvand [11]. PNM-I was characterized as a polymer with terminal anionic functional groups, according to the applied initiator. The PNM-II was synthesized in the presence of initiator with cationic groups, resulting in cationic amidine terminal functional groups. The PNM-III was assumed to have increased hydrophobicity according to the functional groups introduced during the synthesis.

Composition of assessed systems

The composition of evaluated systems was presented in the Table 1. The respective mass of lidocaine hydrochloride was mixed with the dispersion of synthesized polymer. The mixing period was maintained for 24 h, at the room temperature.

pH measurements

The pH of the prepared systems was measured using the SevenMulti Metler Toledo device with attached ION segment, pH/mV/ORP. The pH electrode InLab 413, NTC, pH 0–14, 0–80°C, was used for the measurements, and five repetitions for every measurement were carried out, using deionized water.

Applied buffer solutions

For comparison of pH at different temperature, standard buffer solutions were prepared [12]. Buffer of pH 6,87 and buffer solution of pH 7,41 were assigned as best fitted to the pH range measured in present research. Composition of applied buffers is presented in the Table 2.

Turbidity and LCST

Turbidity measurements of the microgel dispersions were performed over the temperature range 18–50°C. That range of temperatures covered the LCST range for the synthesized polymers.

RESULTS

The evaluated LCST of the assessed systems was over 32 °C and is presented in the Table 3. The observed tendency suggests that the phase transition point temperatures may be presented as follows PNM-I<PNM-II<PNM-III.

The pH of assessed polymeric dispersions changed with the increase of the temperature. pH of PNM-I increased from ca. 6,21 at 25°C to ca. 6,66 maximum at 32°C. After following increase of temperature up to 45°C the pH decreased to 6,38. Opposite sequence was observed in the dispersion of PNM-II. The relatively high pH of 6,87 at 25°C decreased to minimum of 6,14 at 32°C, and then increased to 6,54. Similar scheme was observed in the case of PNM-III, however the absolute differences were very small. For comparison, measurements of normalized buffer

solution of pH 6,87 at three different temperatures are presented on the common graph - Figure 1.

With the addition of lidocaine hydrochloride, the pH of the system changed. The tendency in observed system was similar at three different temperatures. The pH value increased from the range between 5,39 - 5,90 up to the range 6,22 - 6,55. However the step of pH between the temperature of 25°C and 32°C was more radical, than that between 32°C and 45°C. For the PNM-III, the change observed was low - from 6,13 to 6,22, respectively from 32°C to 45°C.

The buffer solutions of pH 6,87 and 7,41 were measured at the same temperature and are depicted commonly on the graph on the Figure 2. The lines, representing buffers pH are rather straight, without specific maxims or minims.

DISCUSSION

The temperature of a medium, measured at different temperature may vary. According to the Equation 1 the potential is changing with the increase of the temperature.

$$E = E^0 - 2,3 (RT/nF) \log a_{H^+} \quad (1)$$

where: E - total potential (in mV) developed between the sensing and reference electrode, E^0 - standard potential of the electrode at $a_{H^+} = 1 \text{ mol/l}$, R - gas constant, T - temperature, n - valency of ion

The activity of hydrogen ions is changing, as well as the characteristics of the electrode sensor, so with the increase of the temperature, the slight decrease of pH is usually observed when alkali buffers are applied. Adversely, in some cases the increase of pH value is observed, when the acidic buffers are heated. According to the sequential measurements of polymer dispersions, and respective dispersions of polymer and lidocaine hydrochloride, some minims and maxims were observed during the preliminary measurements. The differences are statistically significant, and confirmed in several repetitions.

The proposed mechanism of observed pH changes is the thermosensible characteristics of the polymers applied in the research. Below the so called LCST the particles of polymer are almost totally swollen. Some of the remaining initiator

molecules, still attached to the polymer backbone may express ionic activity parallel to the acidic or alkali character of the initiator. This was confirmed in our research, as the initial pH is in the range of 6,21 for the polymer synthesized with the use of acidic initiator. For the polymer synthesized using the alkali initiator, the higher initial pH was observed - ca.6,87. With the increase of temperature up to the point of phase transition, actually the LCST, the polymer branches collapsed, and the remained initiator was closed in mesophormic area.

The presence of mesostructures was studied in dispersed macromolecules of proteins [13], and synthetic polymers [14,15] including microgels, where the space spanning networks were formed [16].

The next step - radical heating over the LCST value results in damage of mesophorms through the division, and consecutive collapsing of the polymeric microspheres. The observed pH may be assigned to the expelled remains of the initiator. However part of the functional groups of initiator are hidden in the polymeric matrix, so the pH is still different, comparing to that initial measured pH value. The respective scheme is presented on the graph on Figure 3.

When the lidocaine hydrochloride is implemented into the polymeric dispersion, the pH values are increasing with the increase of the temperature. There is no minimal or maximal pH between 25°C and 45°C, but sequential increase, more evident between 25°C and 45°C. The PNM-III does not change the pH between 32°C and 45°C. This may be elucidated by early finishing of the process of expelling the water solution of lidocaine hydrochloride from the polymer matrix. The PNM-III is a polymer with increased hydrophobicity. The dependency between the equilibrium rates, according to the Figure 4, may be expressed like: $KI < KII < KIII$, however the $\Delta KII-KI$, is higher than $\Delta KIII-KII$.

CONCLUSIONS

1. According to the presented data, the N-isopropylacrylamide polymers exhibit interesting behavior, in the terms of pH at different temperatures.
2. The presence of lidocaine hydrochloride influences the pH patterns observed at various temperatures.

3. In the case of assessed systems the pH was in the range of 5,39 - 6,55. Comparing these values to the pH of skin surface, we can conclude the good adherence of the systems to dermal physiological pH conditions.

4. However the temperature has high impact on the pH values of the dispersions, and pH measurements of preparations applied on the skin or mucosa should be evaluated in respective temperature range.

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Tabela 1. Skład badanych układów

Table 1. The composition of evaluated dispersions

Skład Compositio n	PNM- I [mg]	PNM- II [mg]	PNM- III [mg]	LD [mg]	Woda Water [g]
PNM-I-LD	2,5	-	-	2,5	30,00
PNM-II-LD	-	2,5	-	2,5	30,00
PNM-III-LD	-	-	2,5	2,5	30,00
LD	-	-	-	2,5	30,00

PNM-I, PNM-II, PNM-III - polimery/polymers,
LD - chlorowoderek lidokainy/lidocaine hydrochloride

Tabela 2. Skład porównawczych roztworów buforowych

Table 2. Composition of buffer solutions

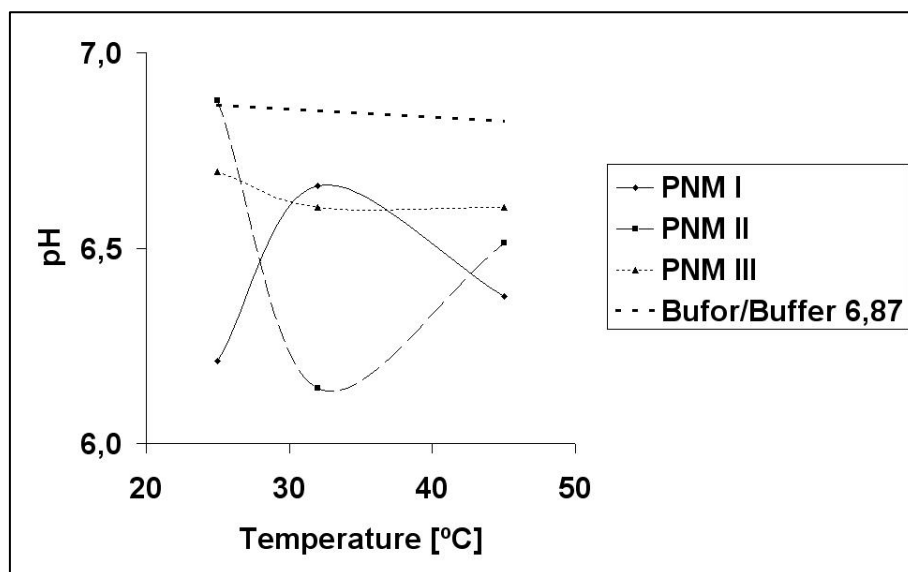
Składniki Components	Roztwór buforowy Buffer solution pH 6,87	Roztwór buforowy Buffer solution pH 7,41
Diwodorofosforan potasu Monopotassium phosphate [M]	0,0125	0,00435
Wodorofosforan sodu Disodium phosphate [M]	0,0125	0,01515
Objętość roztworu wodnego Aqueous solution volume [ml]	1000,0	1000,0

Tabela 3. LCST badanych systemów

Table 3. The LCST of assessed systems

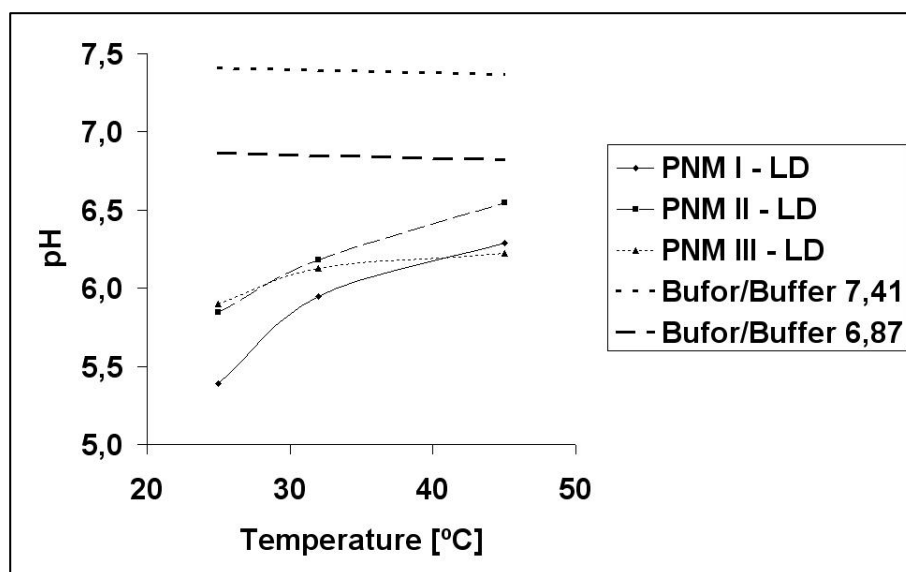
Polimer	LCST [°C]
PNM-I	32
PNM-II	34
PNM-III	35

LCST - temperatura w punkcie przemiany fazowej
/lower critical solution temperature



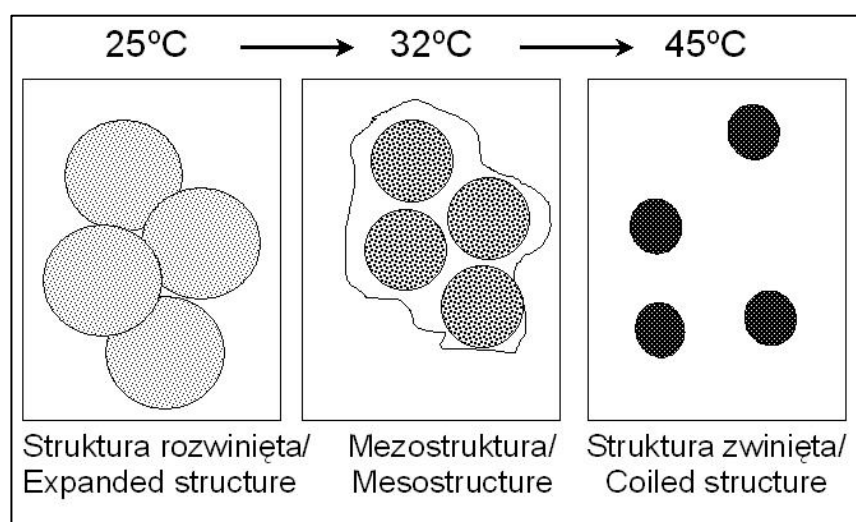
Ryc.1. Wpływ temperatury na odczyn badanych polimerów
N-izopropylakryloamidu

Fig.1. The environmental pH of synthesized polymers at different
temperatures



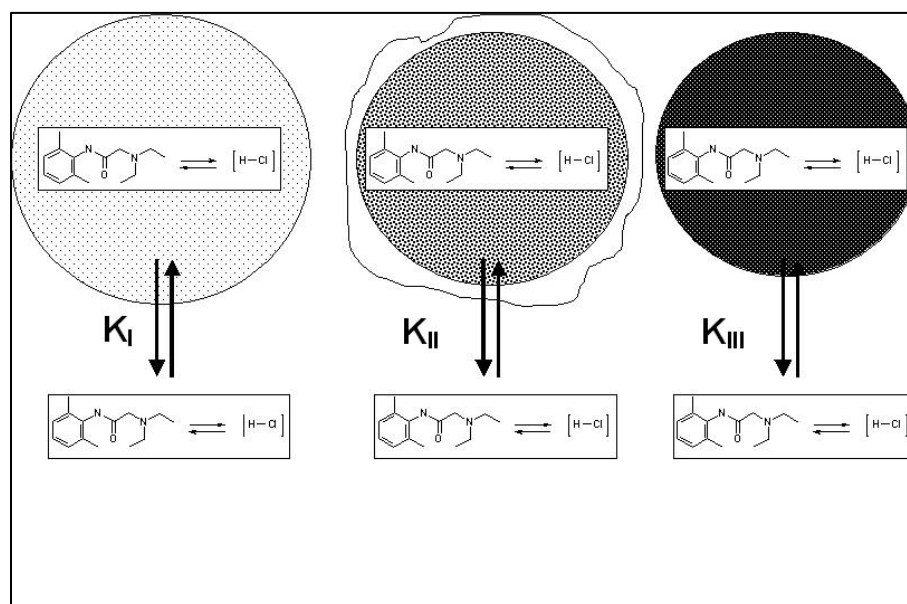
Ryc.2. Odczyn rozcieńczonych układów lidokaina–polimer

Fig. 2. The influence of lidocaine hydrochloride on the pH of diluted dispersions of synthesized polymers



Ryc.3. Schematyczne przedstawienie zmian średnicy i morfologii zsyntetyzowanych polimerów

Fig. 3. Schematic representation of changes in the diameter and morphology of synthesized thermosensitive polymers



Ryc. 4. Zobrazowana równowaga dynamiczna pomiędzy cząsteczkami lidokainy pozostającymi w obrębie nośnika polimerowego, oraz w otaczającym go środowisku wodnym

Fig. 4. Depicted dynamic equilibrium between lidocaine hydrochloride attached to the polymeric carrier and present in the aqueous environment

