

THE PRELIMINARY ASSESSMENT OF CHLORHEXIDINE AND LIDOCAINE RELEASE FROM PREPARATIONS OF ANIONIC POLYMER, EVALUATED BY THE CONDUCTIVITY MEASUREMENTS

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Summary

The aim of this work was the evaluation of conductivity assessments for the monitoring and controlling the release study process of chlorhexidine and lidocaine hydrochloride from the ionic polyacrylic gel, applying different temperatures. According to performed measurements of release, the chlorhexidine, characterized by very low water solubility, is observed in the acceptor compartment in the amount of 2,0-3,0% and its level depends of the temperature. The amount of well soluble lidocaine hydrochloride released in parallel conditions was between 60 and 70%.

Beyond, the assessments confirm the presence of a specific bond between the chlorhexidine imine groups and polyacrylic acid carboxylic groups. Presented

method may be applied in the prediction of release rates, before actual release analysis, and may assure better evaluation of the systems.

Key words: conductivity, release, polyacrylic acid, lidocaine hydrochloride, chlorhexidine

INTRODUCTION

In the wide spectrum of applied substances used in drug form technology, the important place have the ionic polymers. When they are used in a drug form, the active compound may be bonded according to the interaction between acidic group of a polymer and cationic group of the biologically active compound. Numerous innovative polymers are used in the technology have an interesting activity - they are sensible to the changes in the environmental temperature. The increase or decrease of the temperature in the specified range provokes the changes in the macromolecule shape. The changes may be gradual or very rapid, and they can influence the release rate of the active compound from the donor compartment.

These polymers are applied for the prolongation of the drug activity in the place of the application. They enable also the targeting of the drugs to specified tissues. In the case of thermosensitive additives, respective assessments must be performed with tension on the temperature maintaince during the study. The most used are actually N-isopropylacrylamide [1] derivatives, which were studied for

application in the medical devices for the controlled release of anticancers and products of advanced biotechnology [2].

The interest in known and good characterized polymers of acrylic acid is also expressed, as according to Irving et al., the polyacrylates may change the conformation with the increase or decrease of environmental temperature [3]. This changes are reflected by various resulting viscosity. For proper evaluation of the release kinetics advanced methods are applied, including complex interpretation. However the amount of substance released from donor compartment may be represented by the conductivity, resulting from the dissociation of the drug molecule [4]. The solubility is an important factor which enables the observation of the conductivity on the reasonable level. There are substances of very low water solubility - like chlorhexidine, or easy soluble e.g. lidocaine hydrochloride. Also the viscosity and molar mass must be evaluated in the measurements [5].

For the assessments two different substances were applied, with various solubility, and possible application in the medical preparations. Chlorhexidine is applied as an antiseptic for the stomatological and dermatological praxis. Its solubility is very low - only 0,008% [6]. Much higher solubility was measured for lidocaine hydrochloride, i.e. 0,68 g in 1,0 ml of water [7]. This compound has a history in anaesthetic formulations for the skin and mucosa (Fig. 1 and 2).

The aim of this work was the evaluation of conductivity assessments for the monitoring and controlling the release study process of chlorhexidine and lidocaine hydrochloride from the ionic polyacrylic gel, applying different temperatures. During this study numerous measurements were performed, both in donor and acceptor compartment, for the preparations containing chlorhexidine and lidocaine hydrochloride and modified polyacrylic acid.

MATERIAL AND METHODS

The chosen polymer and composition of the systems

Modified polyacrylic acid is widely applied in the practice of pharmaceutical technology, and its properties, both physical and chemical are good evaluated. There were two types of preparations - with 0,125% chlorhexidine or lidocaine hydrochloride and equal quantity of polyacrylic acid. The preparations with polyacrylic acid had increased viscosity, and in the case of lidocaine hydrochloride the gel was transparent. The composition was presented in table 1.

The release assessments

The release of the active substances was performed according to the European Pharmacopoeia. However the temperature was modified, as one of the topics of the study was to evaluate the influence of temperature on the drug release. In this study temperatures of 22°C, 32°C, oraz 42°C were maintained [9]. The first parameter was introduced to the study, as the shelf-conditions are specified in this temperature. The second temperature parameter is the standardized skin surface temperature, important for the patient, when applying the drug onto the skin. Both chlorhexidine and lidocaine hydrochloride are applied in this conditions. The 42°C temperature is a limit value - highest for the pathophysiological conditions [10]. The donor compartment, of 25 cm³ volume, was prepared from the dialysis membrane, closed

by lab clips, without air inside. In the acceptor compartment the deionized water was used, with conductivity not higher than 10 $\mu\text{S}/\text{cm}$.

The release vessels were tightly closed and the air was removed from the device, with the pressurized nitrogen. In the release the cumulated amounts of active substance after 6 h were evaluated - the topical dose interval was equal to four application daily of the drug on the skin. The chlorhexidine and lidocaine were assessed by the UV spectrophotometric method - TECAN Infinite 2000. The percentage extinction coefficient in 0.01 mol/L HCl solution was 223.41 by the $p > 0.999$, at 250 nm for the first mentioned compound. For the second one the percentage extinction coefficient was 203.16 ($p > 0.999$), at 254 nm. The method was linear in the response over concentrations range 1–20 $\mu\text{g}/\text{mL}$.

The conductivity assessments

The conductivity was assessed in donor compartment and acceptor compartment before release start, and after 6 h, at specified before temperatures. Also the conductivity of pure solutions of lidocaine hydrochloride and chlorhexidine was assessed in concentrations applied in the donor and acceptor compartment.

On the Scheme 1 the measurements rules were presented. We applied SevenMulti Metler Toledo, with conductivity segment TDS/SAL/resistivity with the conductivity sensor InLab 730, NTC, 0,001-1000 mS/cm, measurements range -5 $^{\circ}\text{C}$ – 100 $^{\circ}\text{C}$.

RESULTS

Release

The cumulated amounts of lidocaine hydrochloride and chlorhexidine in the acceptor compartment ,after specified time periods, were different, as it is presented on the Fig. 3 and 4. The lidocaine hydrochloride was released faster - the cumulated amount released to acceptor compartment after 6 h was 69,82; 64,08 and 57,98%, respectively for the temperatures 22, 32 and 45°C. For the comparison the cumulated amounts of chlorhexidine released from donor compartment were 2,82; 2,05 and 1,98%.

Conductivity

The conductivity of formulations of polyacrylic acid had various values - Tables 2 and 3. The values were in the range 128,98 $\mu\text{S}/\text{cm}$ - 3471,08 $\mu\text{S}/\text{cm}$. The total conductivity resulted from the conductivity of active compound, polymer and water. When the release process was developed, the drug amounts in donor compartment decreased, and in acceptor compartment decreased. Parallel the values of the conductivity decreased or increased.

After 6 h of process the conductivity assessed in the donor compartment was 104,77 - 804,91 $\mu\text{S}/\text{cm}$. The values were various according to the applied active compound and environmental temperature. In the chlorhexidine system, in donor compartment, the conductivity at the beginning was ca. 128,98 $\mu\text{S}/\text{cm}$, and after the process the conductivity increased to 804,91 $\mu\text{S}/\text{cm}$ at 22°C. The conductivity

assessed for the acceptor compartment after the termination of the process, was 6,64 $\mu\text{S}/\text{cm}$ for the chlorhexidine and 89,73 $\mu\text{S}/\text{cm}$ for the lidocaine hydrochloride at the temp. 22°C. The respective values of conductivity for the higher temperatures were gathered in the Table 2 for the donor compartment, and in the table 3 for the acceptor compartment.

DISCUSSION

As it is presented on the attached graphs, the release is much faster in the case of preparation with lidocaine hydrochloride, comparing to chlorhexidine preparation, even if the temperatures are the same. For the chlorhexidine preparations, when the temperature increased from 22°C to 32°C, the released amount decreased insignificantly. However, when the temperature increased more, up to the 42°C the decrease was much higher - Fig. 3. According to the solubility rules, with the increase of the thermodynamic activity of the chlorhexidine molecule, the amount of diffused chlorhexidine should be increased. However in this case also the thermodynamic activity of macromolecule increases - this may lead to the increased in binding of chlorhexidine by the polyacrylic acid. The dissociative activity of carboxylic groups of the polyacrylic acid, and as well the activity of imine groups of chlorhexidine increases, and the binding may be more effective, resulting in lower released amounts, with the increased temperature. The presented on the graph amount of released chlorhexidine is ca. 2,5% at 22%, whereas it does not exceed 1,8% in the temperatures 32 and 42°C.

The similar process was observed for the lidocaine hydrochloride released from the polyacrylic acid gel. The highest levels of lidocaine hydrochloride were

observed in the acceptor compartment at 22°C, and the increase in the temperature influenced the amount identified in the acceptor compartment - the differences were in the range of 5%. - graph on the Fig. 4. The analysis of the lidocaine hydrochloride binding is widely discussed, and the main proposed factor is ionic binding, depending of ion-pair presence [11].

The obtained data were plotted on common graphs to visualize the relations between the conductivity and the released amount, as some researchers proposed the conductivity measurements for the assessments of release kinetics [12]. Both in the donor compartment and in the acceptor compartment the differences were observed between the chlorhexidine and lidocaine hydrochloride preparations. In the case of chlorhexidine with the increase of temperature, the amount of released drug decreased - this may be assigned to increased availability of chlorhexidine for the carboxylic groups of the polyacrylic acid, as it is presented on the picture on Fig. 5.

There was no specific difference in the measurements of conductivity and released amounts for the lidocaine hydrochloride systems. This may be explained by high availability of lidocaine hydrochloride molecules both to the polymeric net and to the diffusion process - the observed values of conductivity and released amounts were presented on the graph - Fig. 6.

The various interactions with the anionic hydrogel in the case of soluble and insoluble molecules are confirmed by the macroscopic view recorded on the attached pictures - Fig. 7.

CONCLUSIONS

According to performed measurements of release, the chlorhexidine, characterized by very low water solubility, is observed in the acceptor compartment in the amount of 2,0-3,0% and its level depends of the temperature. The amount of well soluble lidocaine hydrochloride released in parallel conditions was between 60 and 70%.

The performed research confirms the possibility of the preliminary evaluation of gelling systems in the aspect of release kinetics using the conductivity assessments.

This may be applied in the case of soluble and insoluble substances embedded into an anionic gel. Beyond, the assessments confirm the presence of a specific bond between the chlorhexidine imine groups and polyacrylic acid carboxylic groups. The preliminary assessment of the release, applying the conductivity measurements, will be developed, to evaluate proper conditions of the assessments.

Presented method may be applied in the prediction of release rates, before actual release analysis, and may assure better evaluation of the systems.

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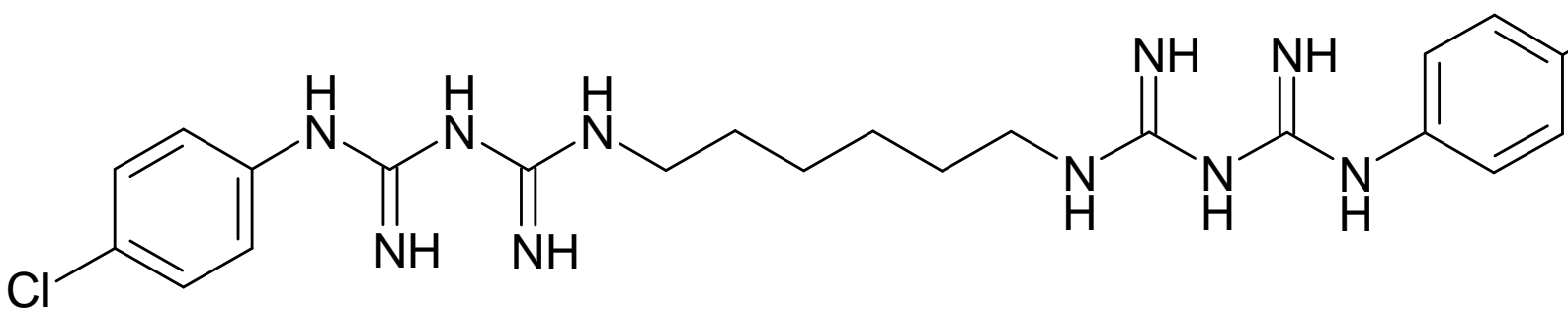
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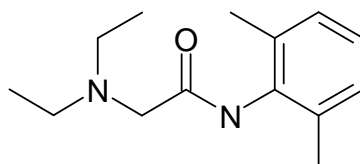
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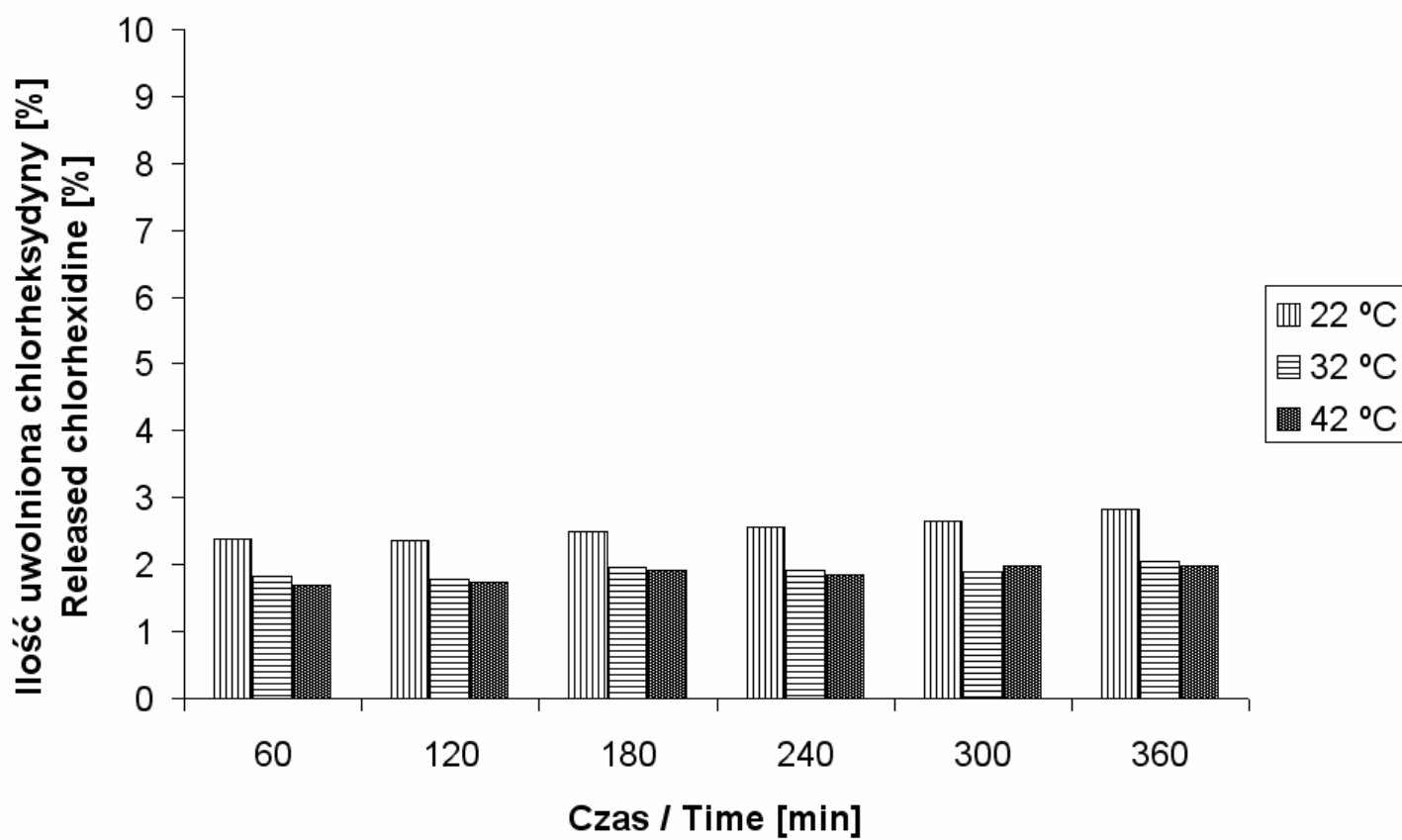
Ryc. 1. Struktura chlorheksydyny

Fig. 1. Structure of chlorhexidine



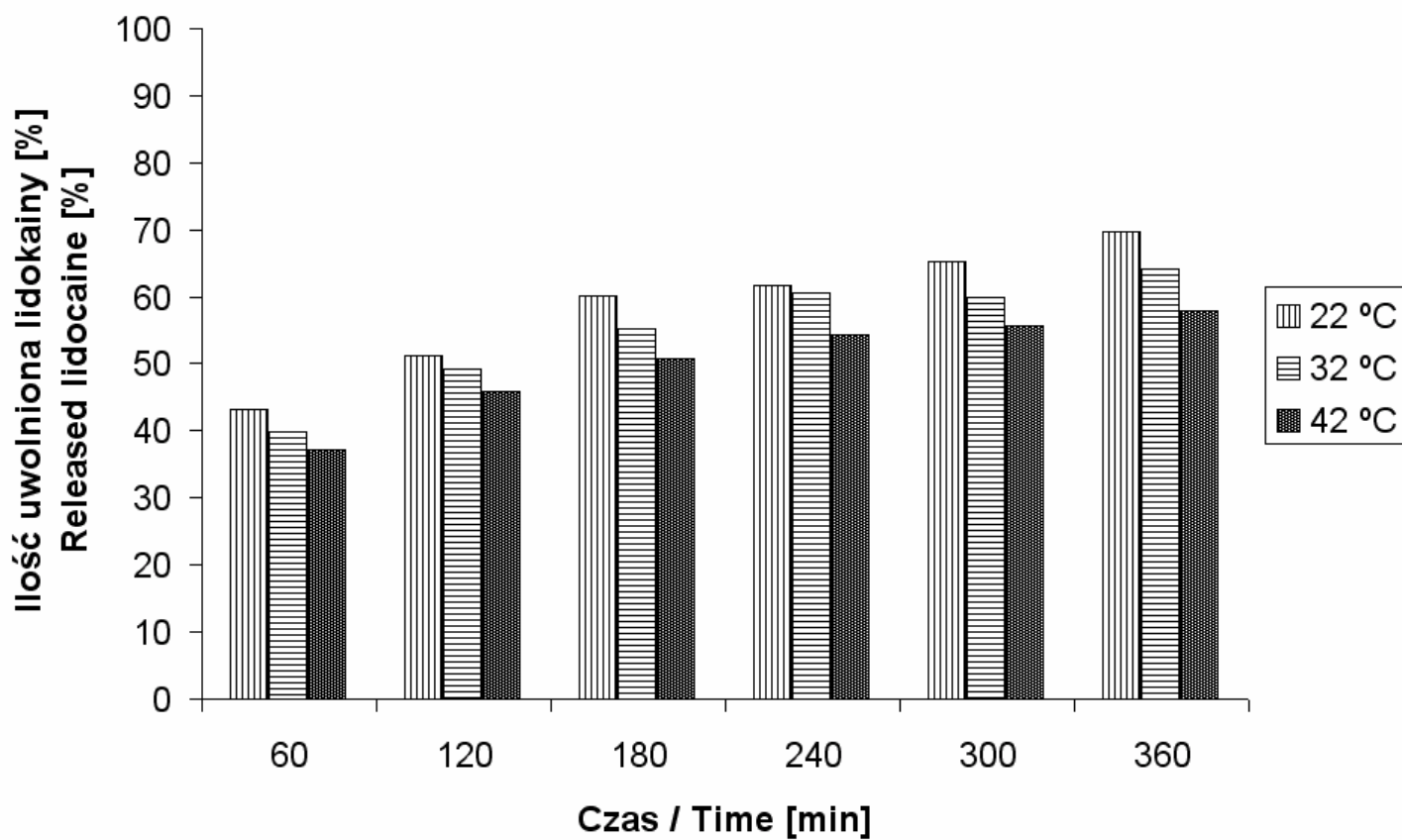
Ryc. 2. Struktura chlorowodorku lidokainy

Fig. 2. Structure of lidocaine hydrochloride



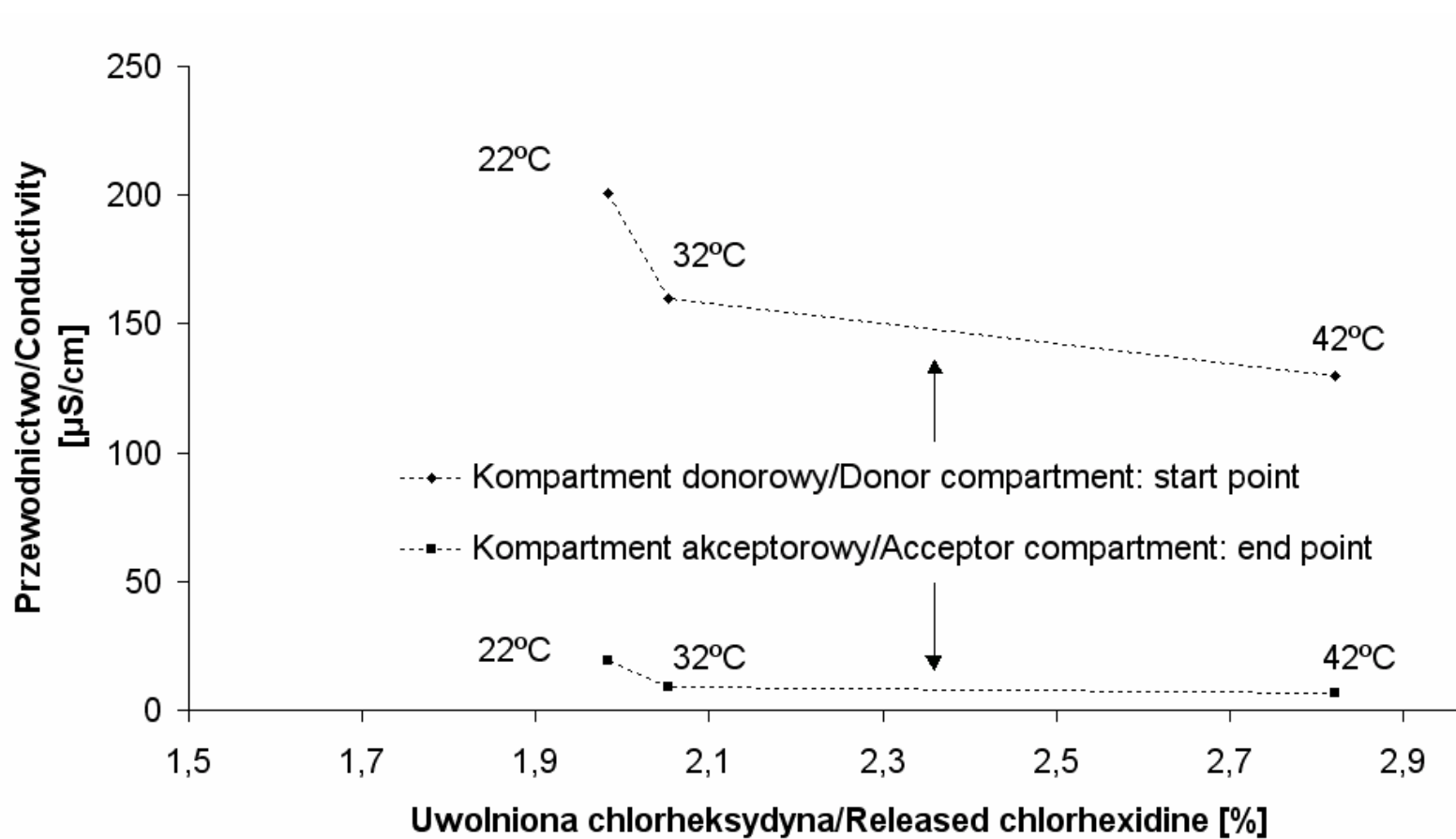
Ryc. 3. Stężenie uwolnionej chlorheksydyny po 1, 2, 3, 4, 5 i 6 godzinach procesu

Fig. 3. The percentage of released chlorhexidine after 1, 2, 3, 4, 5, and 6 hours



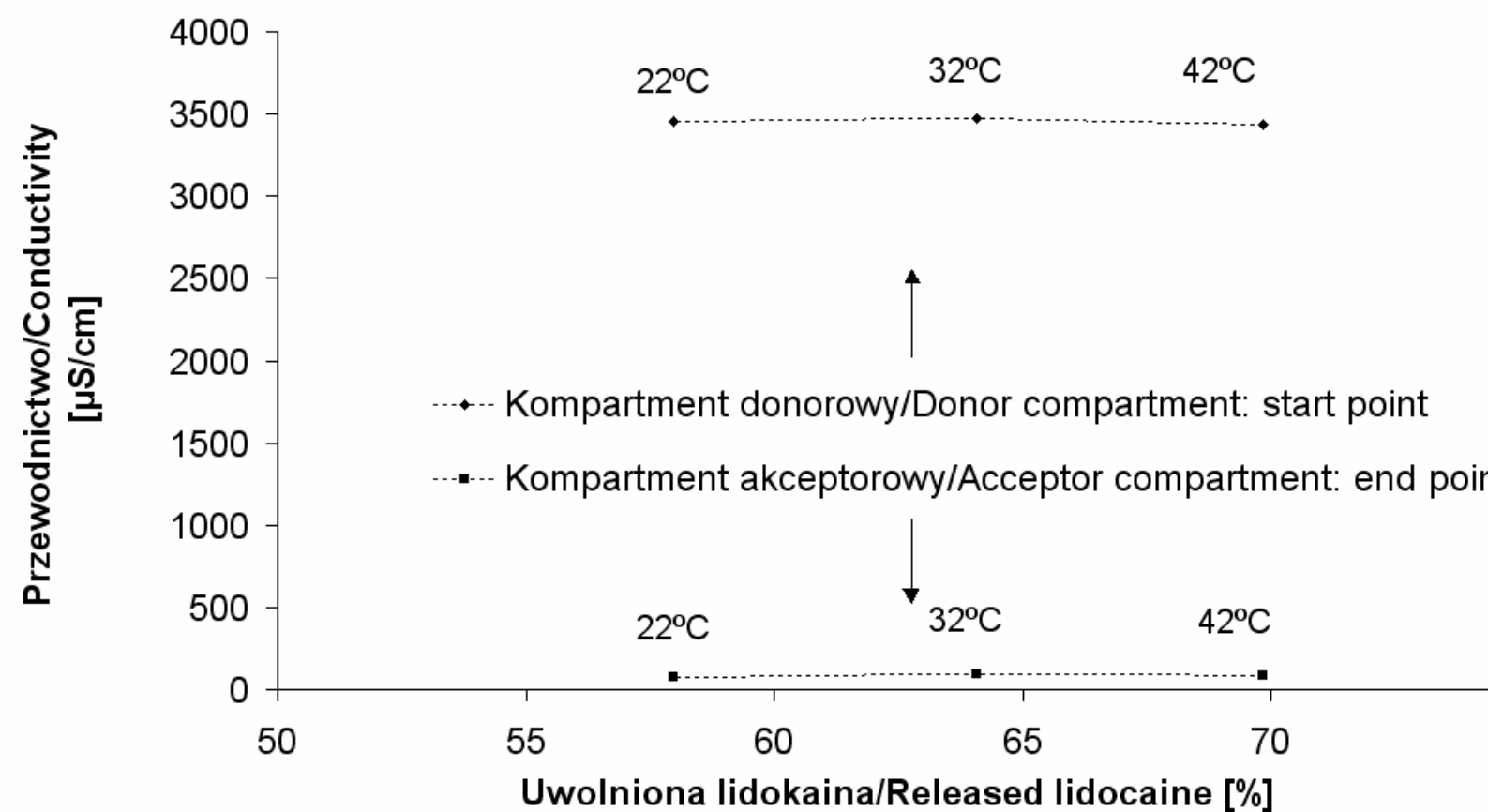
Ryc. 4. Stężenie uwolnionego chlorowodorku lidokainy po 1, 2, 3, 4, 5 i 6 godzinach procesu

Fig. 4. The percentage of released lidocaine hydrochloride after 1, 2, 3, 4, 5, and 6 hours



Ryc. 5. Przewodnictwo i ilości uwolnionej z łożyska polimerowego chlorheksydyny, odpowiednio w kompartmentcie donorowym i akceptorowym, zgodnie z oznaczeniami

Fig. 5. The conductivity and parallel released amounts of chlorhexidine, the respective values are presented both for the donor and acceptor compartment



Ryc. 6. Przewodnictwo i ilości uwolnionej z łożyska polimerowego lidokainy, odpowiednio w kompartmentcie donorowym i akceptorowym, zgodnie z oznaczeniami

Fig. 6. The conductivity and parallel released amounts of lidocaine, the respective values are presented both for the donor and acceptor compartment



Ryc. 7. Obrazy makroskopowe

Fig. 7. Visualized formulations of chlorhexidine (A) and lidocaine (B) with polyacrylic acid

Tabela 1. Skład badanych systemów

Table 1. Composition of assessed systems

Formulacja Formulation	PA	LID	CHX	Woda Water
PA-LID	0,125	0,125	-	25,750
PA-CHX	0,125	-	0,125	25,750

PA - zmodyfikowany kwas poliakrylowy/modified polyacrylic acid,

LID - chlorowodoreklidokainy/lidocaine hydrochloride,

CHX - chlorheksydyna/chlorhexidine,

PA-LIG, PA-CHX - odpowiednie formulacje/respective formulations

Tabela. 2. Wpływ temperatury na przewodnictwo połączeń kwasu poliakrylowego z chlorheksydyną w kompartmentie donorowym, na początku badania uwalniania oraz po zakończeniu tego procesu

Table 2. Temperature and conductivity in donor compartment

Typ preparatu Formulation	Temperatura Temperature [°C]	Przewodnictwo – początek procesu Conductivity - start point [μS/cm]	SD	Przewodnictwo – koniec procesu Conductivity - finish [μS/cm]	SD
PA-CHX	22	128,98	0,17	804,91	3,67
	32	161,19	0,82	104,77	0,58
	42	201,65	4,21	237,12	0,11
PA-LIG	22	3441,67	56,47	295,87	0,94
	32	3471,08	34,79	419,09	0,65
	42	3459,89	16,71	316,31	0,42

PA - zmodyfikowany kwas poliakrylowy/modified polyacrylic acid,
LID - chlorowodorek lidokainy/lidocaine hydrochloride,
CHX - chlorheksydyna/chlorhexidine, PA-LIG, PA-CHX - odpowiednie
formulacje/respective formulations, SD-standard deviation

Tabela 3. Wpływ temperatury na przewodnictwo połączeń kwasu poliakrylowego z chlorheksydyną w kompartmentie akceptorowym po zakończeniu tego procesu

Table 3. Temperature and conductivity in acceptor compartment

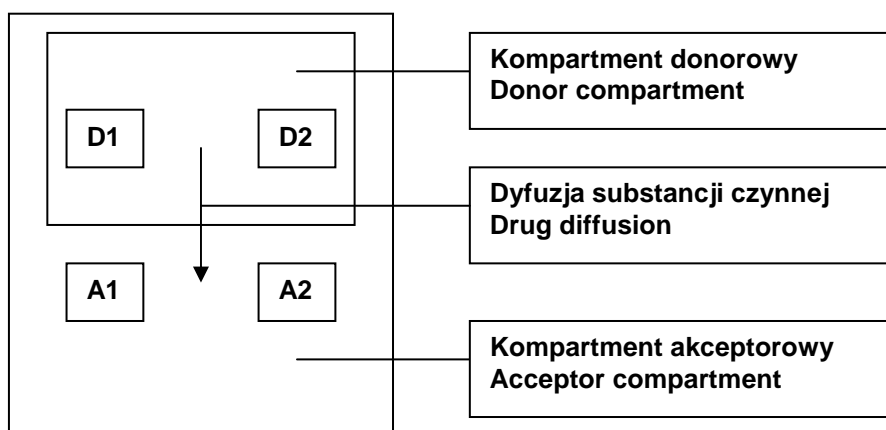
Typ preparatu Formulation	Temperatura Temperature [°C]	Przewodnictwo po zakończeniu procesu Conductivity after finish [μS/cm]	SD
PA-CHX	22	6,64	0,52
	32	9,11	0,71
	42	19,22	0,28
PA-LIG	22	89,73	2,91
	32	93,87	2,74
	42	76,12	1,61

PA - zmodyfikowany kwas poliakrylowy/modified polyacrylic acid,

LID - chlorowodorek lidokainy/lidocaine hydrochloride,

CHX - chlorheksydyna/chlorhexidine,

PA-LIG, PA-CHX - odpowiednie formulacje/respective formulations



Schemat. Sposób pomiaru przewodnictwa. D1 i D2 odpowiadają kompartmentowi donorowemu przed rozpoczęciem uwalniania i po jego zakończeniu. Analogicznie oznaczono kompartment akceptorowy jako A1 i A2

Scheme 1. Evaluated compartments. D1 - donor compartment at the starting point, D2 - donor compartment at the end point, A1 and A2 - respective assignments for the acceptor compartment