ORIGINAL ARTICLE

Polymeric Material With Controlled Release of Antimicrobial Agents for Medical Application

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ABSTRACT

Introduction: Nowadays the use of synthetic polymers has become an integral part of modern medicine. Poly(2-hydroxyethyl methacrylate) has attracted special attention for therapeutic use. The objective of this study was to develop novel polymeric material based on poly(2-hydroxyethyl methacrylate) by addition of water as pore-forming agent and antimicrobial components, which would differ from similar materials by controlled release of active substances. **Methods:** The antimicrobial release kinetics study materials were immersed into distilled water followed by sampling and measuring their concentration. Concentration of chlorhexidine bigluconate and metronidazole was determined using spectrophotometric method and decamethoxine by photocolorimetric method based on reaction with eosin. The swelling rate was determined by gravimetric method. **Results:** Conventional dressing materials, after being soaked with antiseptic solutions, have demonstrated limited abilities in releasing active substances. Gauze pads were found to release antimicrobials during a short period of time reaching 50–80 % for decamethoxine containing samples and almost 100 % for those with metronidazole and chlorhexidine bigluconate at 2 h of observation. No study active substances were released from activated charcoal dressings. Similar results were obtained with porcine xenografts. Unlike the above mentioned dressing materials, modified polymer matrix based on poly(2-hydroxyethyl methacrylate) showed the controlled release of antimicrobial substances into water medium. Study material containing 3.0 % of decamethoxine and 76.3 % of water demonstrated optimal efficiency in the rate and duration of release, exerting high physical and mechanical properties. **Conclusion:** The synthesized polymers are similar to conventional dressings in antimicrobial release kinetics, but in some characteristics they are better for practical application.

Keywords: Wound infection, Poly(2-hydroxyethyl methacrylate), Controlled release, Local antimicrobial agents, Bandages

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INTRODUCTION

Active development of new and improvement of existing polymeric materials for medical purposes have allowed to expand the scope of their use (1). Many studies have been devoted to searching for effective wound dressings that could influence certain phases in wound healing process (2-4). More than 300 wound dressings are known today; being at different stages of development they differ fundamentally only by their origin - biological or synthetic ones (5-7). Despite of numerous advantages of biological coatings, materials of synthetic origin remain as the "gold standard" for temporary closure of wound surfaces (8). Poly(2-hydroxyethyl methacrylate) (PHEMA), biocompatible hydrophilic methacrylate polymer, has attracted special attention for therapeutic use in recent years. The advantages of this material include its hydrolytic and biochemical stability, high permeability, biocompatibility, absence of local and general toxic effects on the body (9-11). Having hydrophilic (due to hydroxyl and carbonyl groups in each segment) and hydrophobic (due to alpha-methyl groups and carbon chain) groups in its structure, the material is characterized by physical and mechanical resistance to hydrolysis in particular.

PHEMA materials, first used in treatment of burn patients in the middle of the XXth century, proved their

effectiveness in numerous experimental and clinical studies (12-13). But since that time great advances have been achieved in understanding of both the pathogenesis of wound process and the principles of its correction. Besides, wound infection remains one of the greatest challenges in wound care management because of the development of aggressive, multidrug-resistant pathogens, their associations and bacterial biofilm formation. Hence, the development of topical drugs with sufficient antimicrobial activity is urgently required for treatment of wounds with various etiologies.

Conventional topical antimicrobial drugs are not quite effective in wound care therapy, as sometimes they inhibit biosynthetic processes in formation of new cellular elements leading to delayed healing (14). Thus, improvement of physical, chemical and therapeutic properties of PHEMA polymer matrix by its modification and addition of modern effective antimicrobial components, as well as the possibility of their long-term controlled release into the wound seems to be warranted.

The aim of this study was to develop novel polymeric material based on poly(2-hydroxyethyl methacrylate) by addition of water as pore-forming agent and antimicrobial components, which would differ from similar materials by controlled release of active substances, as well as to demonstrate its potential in clinical use.

MATERIALS AND METHODS

Samples of study material were synthesized by free radical thermal polymerization in polypropylene-polyethylene cylindrical container at the temperature range of 70–90 °C. The polymerization mixture consisted of liquid monomer 2-hydroxyethyl methacrylate (Sigma-Aldrich, Munich, Germany), a cross-linking agent triethylene glycol dimethacrylate (Sigma-Aldrich, Munich, Germany) (1% of monomer weight), polymerization initiator azobisisobutyronitrile (Sigma-Aldrich, Munich, Germany). In addition to distilled water used as pore-forming agent, the following antimicrobial substances were added: decamethoxine (Pharmhim, Shostka, Ukraine), metronidazole (Hubei Hongyuan Pharm. Co., Fengshan, Hubei, China), chlorhexidine bigluconate (Viola, Zaporizhzhia, Ukraine). Materials with an extended-release effect require the administration of several single doses of active substances. The applied concentration of antimicrobials and water, in previous studies, has been selected empirically based on the most optimal release curves (15). Three types of polymer matrix were formed. The volume of distilled water added as porogen exceeded that of the monomer two, four and eight times, respectively. In terms of sample weight, the concentration of water was 63.0 wt% (1:2), 75.4-78.7 wt% (1:4) and 85.4 wt% (1:8) in the first, second and third matrix, respectively (Table I). Polymer with content of water less than 63.0 wt% was rigid with very narrow low available pores, and polymer with content of water more than 85.4 wt% was formless and lost its integrity.

Table I: Content of antimicrobial substances and pore-forming agent in study samples

No of sample	Antimicrobial agent	Content of antimicrobial agent, %	Content of water as pore-forming agent, wt%
1	Decamethoxine, substance	3.0	63.0
2			76.3
3			85.4
4	Metronidazole, substance	4.1	75.4
5	Chlorhexidine bigluconate, 0.5% solution	0.1	78.7

For comparison, wound dressings commonly used in clinical practice today were chosen. They included both synthetic wound dressings (gauze pads, "Fuhrmann GmbH", Much, Germany; activated carbon material, "Dnipro", Kyiv, Ukraine) and biological ones (lyophilized porcine xenograft, LLC "Institute of Biomedical Technologies", Ternopil, Ukraine). Because the materials mentioned require prior immersion in antiseptic solution before application, the samples were dried after their immersion into one of the following solutions for 30 minutes: 0.02 %, 0.1 % or 1 % solution of decamethoxine; 1 % solution of metronidazole or 0.1 % solution of chlorhexidine.

To investigate the antimicrobial release kinetics, study materials were immersed into 100 ml of distilled water, followed by sampling and measuring their concentration at 2, 6, 12, 24, 48, 120 h of observation. Concentration of chlorhexidine bigluconate and metronidazole was determined using spectrophotometric method with UV-Vis spectrophotometer Agilent Cary 60 (Santa Clara, CA, USA) by optical density at maximum absorption and wavelength of 253 ± 2 and 318 ± 2 nm, respectively (16, 17). Decamethoxine concentration was measured by photocolorimetric method based on reaction with eosin (18) with photoelectric colorimeter KFK-2, (Sergiev Posad, Russia). The swelling rate was determined by gravimetric method.

RESULTS

Changing the content of pore-forming agent and antimicrobial component, samples with different properties and release rate of active substances into water medium were synthesized. The results are given in table II.

So, decamethoxine release rate from the material synthesized using 63 wt% water (sample No 1) was 18.1% (20.8 μg/ml) at 6 h of observation with further regular increase of concentration up to 45.2% (52.0 μg/ml) at 120 h, not reaching the plateau.

As to the material obtained by addition of 76.3 wt%

Table II:Release rate (%) of decamethoxine and metronidazole from study samples and their concentration (μg/ml) in water medium

	Study material	Time of observation, h											
		2		6		12		24		48		120	
		%	μg/ml	%	μg/ml	%	μg/ml	%	μg/ml	%	μg/ml	%	μg/ml
Poly(2-hydroxyethyl methacrylate)	No 1, decamethoxine	9.9	11.4	18.1	20.8	20.6	23.7	24.7	28.4	30.9	35.5	45.2	52.0
	No 2, decamethoxine	23.3	30.7	33.7	44.5	39.4	52.0	53.8	71.1	53.9	71.0	55.5	73.3
	No 3, decamethoxine	27.8	37.8	59.1	80.4	69.6	94.6	66.1	89.9	66.2	90.2	73.1	99.3
	No 4, metronidazole	57.2	85.8	100.0	150.0	-	-	-	-	-		-	-
	No 5, chlorhexidine bigluconate	-	-	-	-	-	-	-	-	-	-	-	-
Gauze pads	decamethoxine 0.02%	50.1	22.1	53.7	29.6	54.7	23.7	67.9	27.2	69.5	29.6	-	-
	decamethoxine 0.1%	82.0	128.3	82.2	137.2	80.4	132.4	87.4	146.6	92.1	151.4	-	-
	decamethoxine 1%	63.6	1702.9	67.5	1844.8	70.0	1750.2	68.6	1702.9	78.4	2554.3	-	-
	metronidazole	100.0	365.0	-	-	-	-	-	-	-	-	-	-
	chlorhexidine bigluconate	100.0	29.2	-	-	-	-	-	-	-	-	-	-
Activeted carbon material		does not release any of the studied drugs											
Porcine xenograft	decamethoxine 0.02%	8.5	0.07	11.9	0.1	12.1	0.1	-	-	-	-	-	-
	decamethoxine 0.1%	9.5	0.24	11.6	0.3	13.5	0.35	-	-	-	-	-	-
	decamethoxine 1%	11.4	3.4	12.1	3.8	15.6	4.7	-	-	-	-	-	-
	metronidazole	73.2	190.2	76.0	197.6	-	-	-	-	-	-	-	-
	chlorhexidine bigluconate	-	-	-	-	-	-	-	-	-	-	82.1	14.8

water (sample No 2), the equilibrium release rate of decamethoxine was reached at 24 h of observation being 53.8% (71.1 μg/ml) with subsequent gradual increase in concentration to 73.3 μg/ml (55.5%) by 120 h.

The material synthesized by addition of 85.4 wt% water (sample No 3) showed the best release of decamethoxine - 69.6% (94.6 μg/ml) at 12 h and 73.1% (99.3 μg/ml) at 120 h of observation. However, this sample was characterized by low mechanical strength and structural disintegration. The addition of 85.4 wt % of porogen to the polymerization mixture prevents the process of crosslink-formation between the polymer units, which degrade the mechanical properties of the sample. In general, concentration of decamethoxine released from study materials was sufficient to exert bactericidal effect on sensitive flora (19).

Metronidazole sample synthesized by addition of 75.4 wt% water (sample No 4) demonstrated complete release of antimicrobial drug at 6 h of observation (150 μg/ml), and its major part (57.2%, 85.8 μg/ml) was determined in solution already within the first 2 h (Fig. 1).

Polymeric material chlorhexidine bigluconate synthesized in the presence of 78.7 wt% water (sample No 5) released no antimicrobial substance at all. The principal reason is the specific form of interaction between cations of chlorhexidine bigluconate and carboxyl groups of methacrylic acid impurities in PHEMA. A team of authors led by Plaut B.S., describes a deceleration of desorption of the named antimicrobial agent from the suggested polymeric material (20). Another reason is suggested to be in the role of the spatial bigluconate anions that, in contrast to the chloride anions, do not dissociate and interrupt the passage of chlorhexidine bigluconate molecules through the polymer.

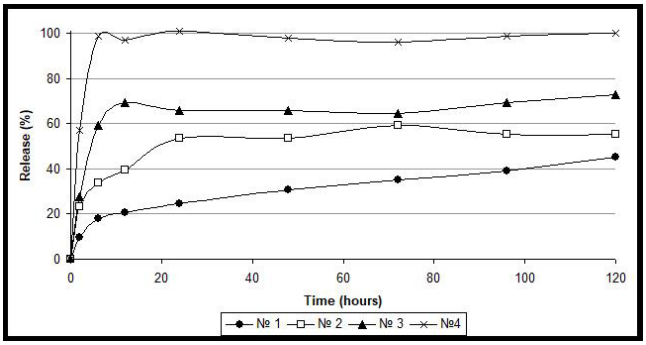

Figure 1: Kinetics of decamethoxine release from materials No 1-3 and metronidazole from material No 4 into water medium

The analysis of polymer swelling degree found the samples No1-5 to have gradual decrease in weight as compared to baseline values, samples No 2 and No 3 having more than twofold decrease. It can be assumed that polymer units are stabilized during immersion of the sample in water and pores slightly shrink over time. However, the sample containing chlorhexidine bigluconate was considered an exception as no changes in its weight were observed during the whole study period (Fig. 2).

Investigation of conventional synthetic wound dressings chosen for comparison found activated charcoal dressings to release none of study active substances, probably due to irreversible adsorption in coal pores.

Gauze pads, on the contrary, were found to release antimicrobials rather quickly. Those soaked with decamethoxine released a significant portion of the drug in 2 h after exposure: 50.1% (22.1 μg/ml) for samples immersed in 0.02% decamethoxine solution; 82.0% (128.3 μg/ml) for samples immersed in 0.1% solution

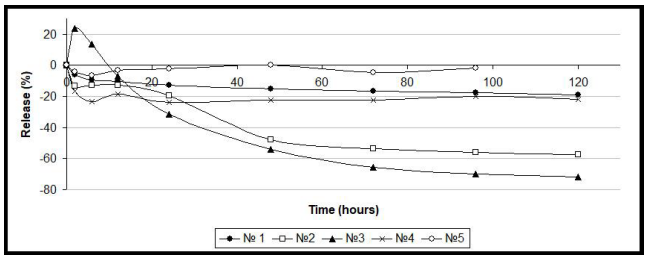

Figure 2: Degree of swelling of polymer samples containing decamethoxine (No 1-3), metronidazole (No 4) and chlorhexidine bigluconate (No 5) in water medium

and 63.6% (1702.9 μg/ml) for those immersed in 1% solution (Fig. 4). Subsequently, within 2-48 h there was a tendency to moderate increase in concentration of decamethoxine in release medium reaching the highest values at 48 h - 69.5% (29.6 μg/ml), 92.1% (151.4 μg/ml) and 78.4% (2554.3 μg/ml), respectively (Fig. 3).

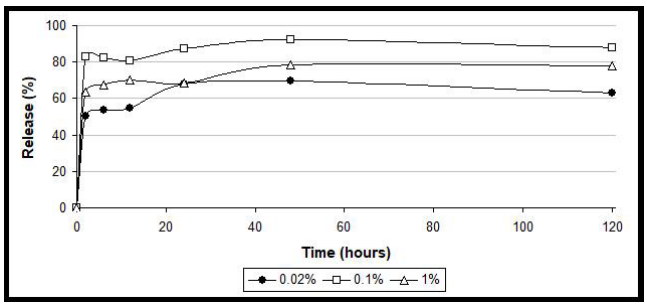

Figure 3: Kinetics of decamethoxine release (concentrations of baseline solutions for immersion – 0.02%, 0.1%, 1%) from gauze pads in water medium

In 2 h gauze pads soaked with metronidazole and chlorhexidine bigluconate showed 100% release of active substances with their optical density in maximum absorption 0.495 at wavelength of 320 nm, and 0.874 at wavelength of 254 nm, respectively.

Porcine xenografts previously immersed in decamethoxine demonstrated maximum release rate of antiseptic at 12 h - it was 12.1% (0.095 μg/ml), 13.5% (0.35 μg/ml) and 15.6% (4.73 μg/ml) for samples with decamethoxine concentration 0.02 %, 0.1 % and 1 %, respectively. No further increase in concentration of that antiseptic in release medium was detected.

Almost complete release of metronidazole from xenoskin samples was established at 2 h - 73.2% (190.19 μg/ml) reaching its maximum release rate in 6 h - 76.0% (197.57 μg/ml) with no further changes throughout the study period (Fig.4).

According to the results of spectrophotometric studies, the presence of chlorhexidine bigluconate in water medium (in concentration of 14.77 μg/ml) was established only at 120 h of observation, optical density at maximum absorption and wavelength of 254 nm being 0.468. No explanation for this phenomenon could be found in available literature suggesting probable

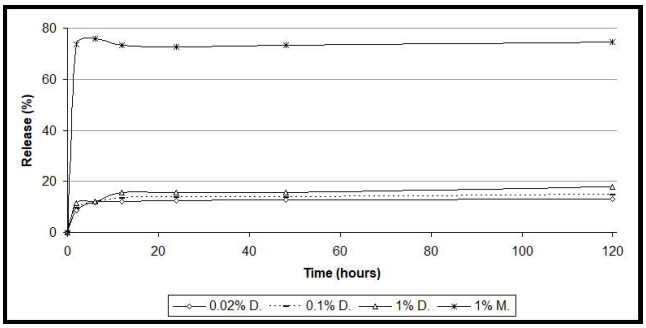

Figure 4: Release kinetics of decamethoxine (D.) (concentrations of baseline solutions for immersion - 0.02 %, 0.1 %, 1 %) and metronidazole (M.) from porcine xenografts in water medium

influence of structural features and chemical properties of study materials taken alone and in their interaction.

DISCUSSION

The study has found limited abilities of commonly used dressing materials to release active substances after their prior saturation with antiseptic solutions. The release of antimicrobial substances from gauze pad occurred during a short period of time reaching 50-80 % in the samples containing decamethoxine and almost 100% in those with metronidazole and chlorhexidine bigluconate already at 2 h of observation. However, no drug release from activated carbon based material was registered. This can be explained by the characteristics of activated carbon, which is an effective adsorbent for organic molecules, including drugs that are absorbed and binded in its pores.

Similar results were obtained with porcine xenografts providing sufficient release of only metronidazole at the level of 80 %. At the same time, the release of decamethoxine of different concentrations did not exceed 20 %, and the presence of chlorhexidine bigluconate was first determined only at 120 h of observation.

The results obtained in the study are indicative of great potential of PHEMA based polymeric materials with gradual long-term release of antiseptic compounds, one of them being decamethoxine - modern, reliable antimicrobial agent highly effective against various pathogens. Those data are consistent with earlier studies dealing with development and comprehensive investigation of polymeric materials with long-term release of active substances on the bases of PHEMA matrix modified by addition of porogen, as well as by synthesis of interpenetrating polymer networks (IPN) of PHEMA and polyurethane (PU) (21-23). In those studies, biologically active substances were introduced into polymer matrix being immobilized on the surface of highly dispersed silica by gas-phase mechano-sorption modification. Due to this method the compounds were transformed into highly dispersed state, and mono- and polymolecular layers were formed on the surface

of nanoparticles creating conditions for deposition. The filler obtained was dispersed in the matrix before polymerization.

The analysis of study results found the release rate of nanocomposites, metronidazole in particular (content in nanocomposite 3.9-4.1 %) to increase gradually and reach the plateau with the following values: for the sample of PHEMA-porogen - 41% at 168 h, and for the sample of IPN PU/PHEMA - 31% at 48 h of observation. As to nanocomposites with decamethoxine (content is 3%) synthesized on the basis of PHEMA-porogen matrix, kinetic curves are far from reaching the plateau even after 600 h of observation: for example, at 168 h the release rate is 22%, and at 672 h it is about 40 %.

Release of active substances from the samples based on IPN PU/PHEMA matrix began after a certain "latent" period lasting for about 72 h, maximum release rate being 10% or less. Such low concentrations can be explained by large size of decamethoxine molecule as compared to metronidazole, and because of that it is kept in nanocomposite not only by adsorption forces but also by polymer chains due to steric factor.

Due to long-duration release profile of active substances, materials based on IPN PU/PHEMA matrix and modified with highly dispersed filler can be used in creation of such medical devices which could be placed in tissues and cavities of the human body for a long period of time - stents, drainages, catheters, etc. (24, 25). However, treatment of patients with wounds of various origins, including burns, require antimicrobial coatings with steeply sloping kinetic curves to maintain maximum therapeutic concentrations with high release rate of active substances within 24-48 h to control pathogens, prevent the development of resistance and formation of biofilms. For this reason, in order to accelerate the release of antimicrobial substances, an alternative method of polymer synthesis was used in the study - addition of pore-forming agent, but not silica filler which is considered to be release prolongator. Addition of water as porogen during synthesis leads to formation of system of pores due to lengthening of poly(2-hydroxyethyl methacrylate) chains and reduction of the number of crosslinks between the chains, which probably improves the diffusion of incorporated substances and increases material elasticity (26). However, an excessive amount of water was associated with structural disintegration and low mechanical strength of study material. Because of that, PHEMA matrix which would contain four times as much the volume of porogen as that of monomer is suggested by the authors for further research.

CONCLUSION

The results obtained in the study demonstrate the controlled release of antimicrobial substances into water medium from polymer matrix based on poly(2-hydroxyethyl methacrylate) modified with pore-forming agent. At the same time, study material containing 3.0 % of decamethoxine and 76.3 % of water demonstrated optimal efficiency in the rate and duration of release, exerting high physical and mechanical properties. In general, the synthesized polymers are similar to commonly used dressings in antimicrobial release kinetics, but in some characteristics they are better for practical application.

Therefore, further research dealing with technology for obtaining the proposed polymeric materials and their comprehensive study using additional experimental methods and covering a wider range of antimicrobial drugs are suggested to be carried out.

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