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POLYURETHANE COMPOSITES AS DRUG CARRIERS: RELEASE PATTERNS

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Biodegradable polyurethanes attract interest of those developing composite materials for biomedical applications. One of their features is their ability to serve as carriers, or matrixes, for medicines and other bioactive compounds to produce a therapeutic effect in body through targeted and/or prolonged delivery of these compounds in the process of their controlled release from matrix.

The review presents polyurethane composites as matrices for a number of drugs. The relation between structure of the composites and their degradability both *in vitro* and *in vivo* and the dependence of drug release kinetics on physicochemical properties of polyurethane matrix are highlighted. The release of drugs (cefazolin, naltrexone and piroxicam) from the composites based on cross-linked polyurethanes (synthesized from laprols, Mw between 1,500 and 2,000 Da and toluylene diisocyanate) demonstrated more or less the same pattern (about 10 days *in vitro* and three to five days *in vivo*). In contrast, the composites with dioxydine based on a linear polyurethanes (synthesized from oligotetramethilene glycol, Mw 1,000 Da, diphenylmethane-4,4'-diisocyanate and 1,4-butanediol) retained their antimicrobial activity at least 30 days. They also showed a significantly higher breaking strength as compared to that of the composites based on cross-linked polyurethanes.

Key words: polyurethane composites, drug carriers, release characteristics.

The biocompatibility and physicochemical properties of polyurethanes (PUs) have long been drawing attention of developers of composite materials. The variety of diisocyanates and glycols, which are the stock in synthesis of PUs, and their reactivity make it possible to develop composites widely applicable in medicine, *e. g.*, in implants, glues and coatings [1–5].

PUs have also performed well as drug carriers, especially where the goal is to ensure continuous, long-lasting supply of a drug to the body. Such extended-release, or depot, forms are essentially a polymeric base (matrix) with embedded low-molecular bioactive substances. In addition to their extended drug delivery feature, advantages of the depot forms also include reduced side effects.

PUs (either linear or network) are a good basis for developing polymeric composites — in fact macromolecular therapeutic systems — with controlled physicochemical properties, allowing a developer to vary the drug immobilization level. Such systems, ensuring a locally effective concentration, may be used in a form of films or foams in surgery, gynecology, urology, etc.

Due to the higher structural heterogeneity and contact area of drug-filled PU composites vs. non-filled ones, the former are known to degrade much faster both *in vitro* and *in vivo* [6–8]. An increase in the wetting ability of a PU matrix, resulting from its modification with drug, also has a significant effect on the polymeric destruction progress and the pattern of drug release from a PU depot form [9, 10].

In a drug depot form, used for the controlled drug delivery to a target organ, the synthetic polymeric matrix seems to perform a «minor» function, because the major effect belongs to the drug as a biologically active substance. Nonetheless, there are very severe requirements set for matrices, which often are difficult to meet.

What needs to be done to develop such polymeric materials? According to [11], the stage of design and experimental evaluation *in vitro* (for shape-memory polymers) comprises four steps: (i) impact of aqueous environment on thermomechanical and shape-memory properties; (ii) determination of the maximum drug loading; (iii) effect of drug incorporation on the thermomechanical properties of dry and

wet material as obtained from preparation; and (iv) drug release pattern and degradation behavior including mechanical properties and the influence of a cycle consisting of programming and recovery on drug release.

The present review focuses on step four of the above for a few depot systems based on different PU composites, highlighting the relation between drug release types and PU matrix degradation behavior, the effect of the matrix mechanical properties, and the dependence of drug release kinetics on the matrix structure and properties as well as the nature of drug immobilization.

Dioxydine/Polyurethane Composite

A composite with dioxydine, an antimicrobial, was synthesized from oligotetramethilene glycol, Mw 1,000, diphenylmethane-4,4'-diisocyanate and 1,4-butanediol. Dioxydine was added at 3 percent of the PU weight. The composite can be characterized as being rather stable in body fluids and having a steady antimicrobial activity. The synthesis procedure and dioxydine release determination are described in [12].

Studied for their mechanical properties, the PU samples demonstrated quite high breaking strength (12.5 MPa), elongation (3.780 percent) and modulus of elasticity (2.46 MPa) [12].

The dioxydine composite samples were placed in a model medium (physiological solution), and release of the drug into the medium was studied for one month. By the end of the observation period, about 23 percent of the initial dioxydine had been released, and its concentration in the medium reached 0.66 mg/mL (Fig. 1).

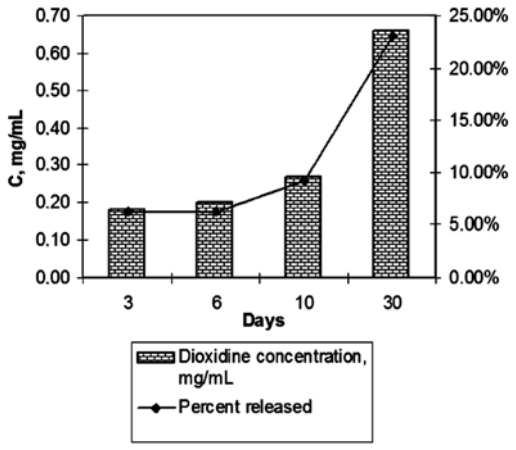

Fig. 1. **The dynamics of dioxydine release from polymeric matrix into model medium:** *(M±m, n = 3)*

In vivo, polymeric samples with dioxydine were implanted subcutaneously in rats. In 3, 6, 10 and 30 days they were removed and their antimicrobial activity measured for four bacterial species: a *Klebsiella* sp., *E. coli*, a *Proteus* sp., and a *Pseudomonas* sp. The PU/dioxydine composite retained relatively high antibacterial activity after the implantation at all of the intervals, even as long as one month.

Cefazolin/Polyurethane Composite

A PU matrix for cefazolin, an antibiotic, was synthesized from Laprol-1600 (a mixture of polyoxyethylene and polyoxypropylene glycols, Mw 1,600) and toluylene diisocyanate T65/35 (TDI, a mixture of 2,4 and 2,6 isomers at a mass percentage ratio of 65 to 35), either in presence or in absence of a catalyst, iron tris-acetylacetonate [$Fe(acac)_3$]. The synthesis procedure and cefazolin release determination technique are described in [9].

Like it had been reported earlier [13], glycols were found to affect the durability, elasticity and sorption properties of PUs and their compatibility with living tissues. Similarly, it was also shown that an increase in Laprols' molecular weight was accompanied by an increase in the hydrophilicity and a decrease in the mechanical strength of the polymer. Laprol-4500-based polymeric films turned out to be fragile and too porous, whereas compositions based on Laprol-1600 were elastic and smooth, and had satisfactory mechanical properties (Table 1). That was the reason for choosing Laprol-1600 to synthesize the PU matrix for cefazolin in the study.

Table 1. **Mechanical properties of polyurethanes depending on their composition**

Polyurethane composition (Samples)	Breaking strength σ, MPa	Elongation L×100%	Modulus of elasticity E, MPa
1. Laprol-1600 + 2 TDI	2.6	1.134	2.297
2. Laprol-1600 + 2TDI + + 0,02% cat.	1.64	1.145	0.147
3. Laprol-1600 + 2TDI + + Cefazolin	0.73	1.250	0.058
4. Laprol-1600 + 2TDI + + 0,01% cat. + Cefazolin	0.67	1.254	0.053
5. Laprol-1600 + 2TDI + + 0,02% cat. +Cefazolin	0.77	1.111	0.069

Note: MPa — megapascal.

The addition of 0.02 percent of the catalyst to the polymer decreased the breaking strength and the elasticity modulus from 2.6 MPa and 2.3 MPa for the catalyst-free sample (Sample 1 in Table 1) to 1.64 MPa and 0.15 MPa, respectively (Sample 2). The catalyst is known to increase the extent of cross-linkage lacing, which results in lesser chain orientation and intermolecular interaction effectiveness. In turn, polymer Samples 3 (catalyst-free), 4 (0.01% cat.) and 5 (0.02% cat.) with cefazolin as a filler had significantly poorer mechanical properties compared to the non-filled polymer (Sample 2): the three cefazolin-containing samples showed a breaking strength at 0.73, 0.67 and 0.77 MPa and an elasticity modulus at 0.058, 0.053 and 0.069 MPa, respectively. These mechanical characteristics were quite acceptable for the purpose of serving as a drug carrier. Moreover, the study focused on the optimization of polymerization process. The use of $Fe(acac)_3$ (optimal concentration was 0.01 to 0.02 percent by mass) made this process considerably faster — 5 to 6 h as compared with 1 to 2 days without catalyst.

In earlier studies [8, 13], polyurethanes of similar composition had been found to swell well, suggesting that the cefazolin diffusion must have gone from both the surface and the inside of polymeric films.

To investigate the kinetics of cefazolin release from the polymeric matrix into the model medium, and to find out if the presence of catalyst in the composites had an impact on the process, three samples were studied: Sample 3 (without catalyst, Table 1), Sample 4 (0.01% mass of the catalyst $Fe(acac)_3$, and Sample 5 (0.02% mass of the catalyst). The cefazolin concentration was measured at 1, 3, 5 and 7 days. Fig. 2 shows the cefazolin release kinetics over this period.

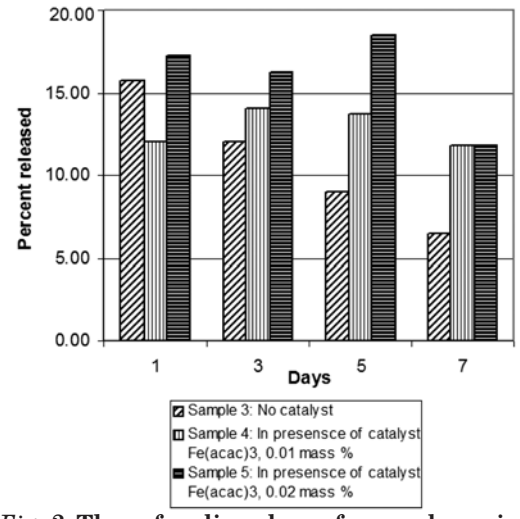

Fig. 2. **The cefazolin release from polymeric matrix into model medium (HPLC determination)**

For ease of description, the release process was schematically divided into two stages. In the first («fast») stage, the cefazolin concentration was measured at 0.5, 1.0, 2.0, 3.0 and 4.0 hours, and in the second («slow») stage, at 1, 3, 5 and 7 days. Within first four hours, the cefazolin concentration dependence on time was linear. The release rate constants (k) for Sample 1 was 4.4×10^{-3} s^{-1}; for Sample 2, 3.4×10^{-3} s^{-1}; and Sample 3, 4.1×10^{-3} s^{-1}. In the first stage, when cefazolin was released primarily from polymeric film surface, the catalyst-free sample had the highest k value. However, in view of possible use of a PU-cefazolin system as a prolonged-dosage form, the second stage — slow and more protracted — is of more interest.

In the second (slow) stage (Fig. 2), when the polymeric film was swollen and cefazolin was delivered predominantly from the inside of the film, the dynamics of cefazolin release from the films significantly differed between the samples with catalyst and the sample without catalyst. In the latter case, the cefazolin concentration in the physiological solution was steadily decreased after the first day. Samples 2 and 3 showed a small increase in the drug concentration during 1–5 days. It was only after 7 days that the concentration of cefazolin released from these samples into the model medium dropped below the first day value. Importantly, drug release from Samples 2 and 3 on the seventh day was double that for Sample 1. The release rate constants for Samples 1, 2 and 3 in this stage equaled 0.84×10^{-5} s^{-1}, 1.16×10^{-5} s^{-1} and 1.12×10^{-5} s^{-1}, respectively.

As demonstrated by these findings, the addition of $Fe(acac)_3$ as a catalyst to the cefazolin-PU system not only enhanced the polymerization process but also ensured stable release of cefazolin from the polymeric matrix into the model medium. The presence of active isocyanate groups gave an opportunity for the immobilization of biologically active compounds in the polymer.

Similar two-stage kinetics was described [14] for *in vitro* release of ciprofloxacin (an antibiotic) from monolithic nonporous PU into water. During the first stage (fast), the release rate was almost invariant and depended on diffusion through the steady diffusion layer. In this first stage, the influence of the initial internal transport was weak because it took place at a negligibly small distance from the interface. After the decrease in antibiotic concentration extended onto a much broader layer of the matrix near the interface, internal

transport became important. This was a manifestation of the beginning of the second stage in the measured kinetics of release curves, which featured a gradual decrease in the rate. The fast release stage lasted for 6 days.

Naltrexone/Polyurethane Composite

Biocompatible oligoetherurethane diisocyanate based on a mixture of oligoglycols (Laprol), Mw 1,002 and 2,002 Da at a mass proportion of 1:1, and TDI T80/20 (a mixture of 2,4 and 2,6 isomers at a mass percentage ratio of 80 to 20) was used as a polymeric matrix for naltrexone, an antagonist, in a study that included both *in vitro* and *in vivo* experiments. Hydrophilic composites were made by adding poly-N-vinylpyrrolidone (PVP), Mw 12,600±2,700, and the antagonist (at 10 percent and 1 percent, respectively, of the prepolymer mass) to the polymeric matrix [15].

The samples thus produced were immersed in simulated body fluids (0.9% physiological solution) for 24 h at 37 °C, during which time the polymer attained equilibrium swelling. The degree of swelling was calculated as describe in [16].

As can bee seen in Table 2, all the samples with PVP showed a greater degree of swelling, which was probably due to the hydration characteristics of PVP.

The naltrexone release from the PVP-modified matrix was studied *in vitro* using HPLC in comparison with non-modified matrices.

During the first three days, naltrexone was released from the polymeric samples with PVP at a higher rate than from the samples without PVP. Over 50 percent of the antagonist originally incorporated in the PVP-containing samples escaped into the model medium over this period. The release from these samples then

Table 2. **Water absorption by PU samples (%)**

Sample	Composition	Degree of swelling, % ($M+m$)
1	Matrix	14.95±0.71
2	Matrix + 10% PVP	22.03±1.46
3	Matrix + 10% PVP + 1% Naltrexone	28.93±2.70
4	Matrix + 15% PVP + 1% Naltrexone	31.44±2.54
5	Matrix + 20% PVP + 1% Naltrexone	33.47±1.83

Note: $n = 3$.

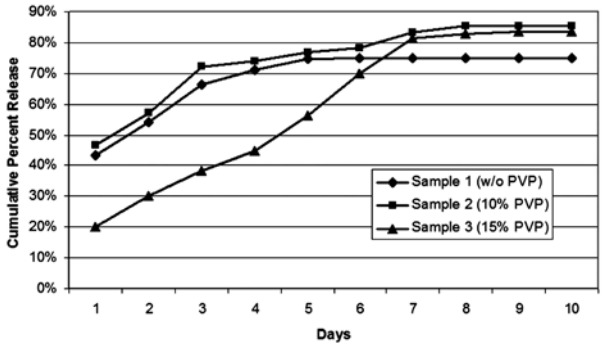

Fig. 3. **The naltrexone release from PU samples into model medium**

continued steadily for 10 days, totaling in 85 percent to 90 percent of initial naltrexone. In contrast, the release from the PVP-free samples was gradually declining, and a significant proportion of the antagonist originally incorporated was retained.

The *in vivo* part of the study — the effect of PU implants with naltrexone on the level of L-3,4-dihydroxyphenylalanine (L-DOPA) in blood of alcohol-intoxicated rats — showed reduced L-DOPA levels in animals with naltrexone-containing implants for the first three days (Fig. 4).

The following conclusion can be made: introduction of PVP into the composites resulted in an increase in water absorption. This was most likely due to the hydration properties of PVP. The fact that the PVP-modified PU samples released naltrexone longer than the samples without PVP did (up to 10 days vs. five, respectively) also could be attributed to these hydration properties. However, a change in the sample structure resulting from the PVP introduction (the samples became less porous) seems to play as important role.

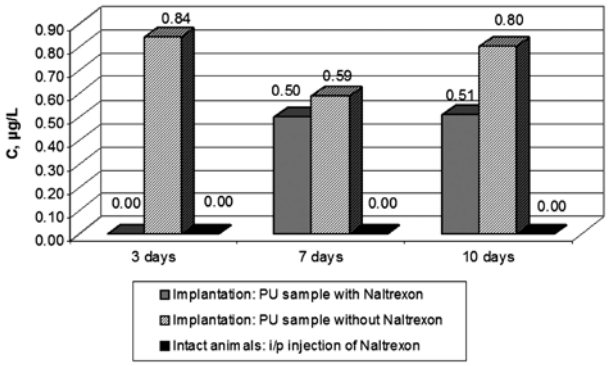

Fig. 4. **L-DOPA levels in murine blood after implantation of PU-samples**

Thus, by varying proportions of the diisocyanate and glycol components in PU synthesis one can get polymeric matrices of different structures, and in this way control their hydrophilicity. This, in turn, makes it possible to achieve different levels of drug immobilization on the carriers for the development of effective macromolecular therapeutic systems.

Piroxicam/Polyurethane Composite

Polyester urethane was synthesized through reaction of oligoglycol (Mw 2,002) with toluylene diisocyanate (TDI, a mixture of 2,4 and 2,6 isomers, 80:20) as described in [17]. Sponge-like composites of PU with piroxicam (Px) were produced by adding the non-steroidal anti-inflammatory drug, at 3 percent by weight, 2,4,6-tris(dimethylamino)methane as catalyst and distilled water to the prepolymer.

The abovementioned earlier studies with cefazolin and naltrexone as drug fillers had shown that the drug immobilization on a polymeric matrix did not change the polymer's chemical structure but led to formation of hydrogen bonds between functional groups of the drug and reactive groups of the polymer. It had been also shown that this physical polymer modification was the main factor of drug retention within a PU/drug system; the drugs were released into body through diffusion and polymer surface hydrolysis. It is safe to assume that the same was the case with Px, too.

The Px case is interesting because this drug is hydrophobic, which forbids studying it *in vitro* in an aqueous medium. So the PU/Px implants were imbedded in rats with an acute inflammatory model.

The anti-inflammatory effect of the PU/Px composites was studied by comparing it with that of the drug's conventional dosage form by determining t-methylimidazole acetic acid (t-MeImAA), which is the final histamine metabolite, in murine urine using reversed-phase HPLC. The change in the t-MeImAA level in urine was measured in five days after implantation (Fig. 5). This time span was chosen taking into account the findings of the earlier study on similar PU depot forms with naltrexone [8, 13], which had shown that the drug was actively released for five days with a sharp slowdown in the process thereafter.

As can be seen on Fig. 5, the t-MeImAA level in the animals with PU/Px implants declined to 0.004±0.001 mg/mL (n=3), and in the animals that received the drug through feeding tube, to 0.01±0.002 mg/mL (n=3). This is by 90 percent and 75 percent, respectively, lower then the t-MeImAA level detected in five days in the rats with inflammation that had not been treated with Px in any form. It can be presumed that the administration of Px suppressed manifestations of the inflammation process (redness, edema, dysfunction of injured organ, etc.) through painkilling, resulting in reduced levels of histamine and, accordingly, its final metabolite — t-MeImAA.

The above examples illustrate how PU properties, especially those relevant to the polymer's drug carrier function, can be influenced by playing with its components. Polyurethanes are known to basically consist of two components: an isocyanate and polyol [18]. Typically, the polyol (soft segment) is an oligomer comprising a chain having a low glass transition temperature and terminated by hydroxyl groups [19]. Generally, the chain extender is a small molecule with either hydroxyl or amine end groups. The diisocyanate is a low molecular weight compound that can react with either the polyol or the chain extender. The combination of these components is referred to as a hard segment of polymer [20, 21].

Both segments not only determine the polymer structure and properties [22–24], including biodegradation [25, 26], but also influence the drug release patterns, when PUs are used as matrices [1, 27, 28]. However, as much as PU biodegradation is concerned, the role of the soft segment is greater. Literature has reported about a variety of soft segments [19] including polylactide, polyglycolic acid [29, 30], polycaprolactone [10, 31], polyethylene oxide [32], and polyethylene glycol (PEG) [22, 33, 35]. The presence of PEG as the soft segment in biodegradable PUs can increase their degradation rate as well as that of drug release.

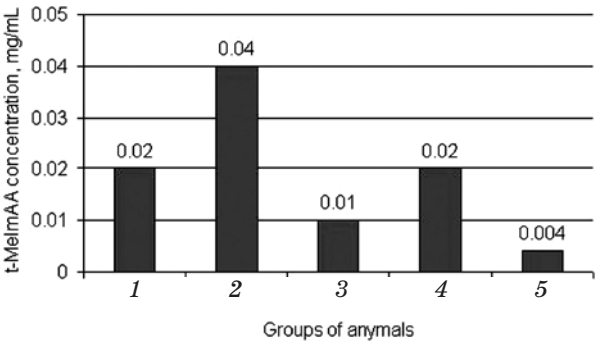

Fig. 5. ***t*-MeImAA concentration in different groups of animals:**
intact animals (control) (*1*); animals with inflammation (*2*); animals with inflammation + Px (therapeutic dose through tube) (*3*); animals with inflammation + PU matrix without Px (*4*); and animals with inflammation + PU matrix with Px (*5*)

An aromatic diisocyanate was employed for applications where degradation was not desired, such as covering, catheters and wound dressings [34, 35]. Degradable PUs are more frequently made from diisoceanates such as lysine-diisocyanate [36–38]; 1,4-diisocyanatobutane [39]; 1,6-diisocyanatohexane [25], hexamethylene diisocyanate [27] and 2,4-toluene diisocyanate [9, 13, 17, 29].

The PU composites with cefazolin, naltrexone and piroxicam, all based on Laprols between 1,500 and 2,000 Da and TDI, demonstrated more or less the same pattern of drug release, which lasted for about 10 days *in vitro* and three to five days *in vivo*, although their preparation procedures, swelling degrees and mechanical properties differed. In contrast, the composites with dioxydine (based on oligotetramethilene glycol, Mw 1,000 Da, diphenylmethane-4,4′-diisocyanate and 1,4-butanediol) performed much better both *in vitro* and *in vivo*, releasing dioxydine into the model medium for about a month and retaining their antimicrobial activity after 30 days of implantation, respectively. The dioxydine/PU composites also showed quite a high breaking strength — 12.5 MPa — which was about 20 times higher than that of the Laprols-based composites.

Thus, by varying the combination of hard and soft segments, one can design the PU matrix structure to meet specific therapeutic application needs and program drug release pattern.

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ПОЛІУРЕТАНОВІ КОМПОЗИТИ ЯК НОСІЇ ЛІКІВ: ХАРАКТЕРИСТИКИ ВИВІЛЬНЕННЯ

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Поліуретани, що біодеградують, становлять значний інтерес для розробників композиційних матеріалів з метою біомедичного застосування. Однією з характеристик цих полімерів є здатність бути носіями ліків та інших біологічно активних сполук, що виявляють терапевтичний ефект в організмі за рахунок спрямованого та/або тривалого доставлення у процесі контрольованого вивільнення з носія.

В огляді розглянуто поліуретанові композити як носії низки ліків. Показано взаємозв'язок між структурою цих композитів та їхньою здатністю до деградації *in vitro* й *in vivo*, а також вплив фізико-хімічних властивостей поліуретанового носія на кінетику вивільнення іммобілізованих ліків. Характер вивільнення ліків (цефазоліну, налтрексону, піроксикаму) із композитів на основі зшитих поліуретанів (синтезованих з лапролів із Мм 1500–2000 Да і толуїлендіізоціанатів) був подібним (приблизно 10 днів *in vitro* та 3–5 днів *in vivo*). На противагу цьому композити з діоксидином на основі лінійного поліуретану (синтезованого з оліготетраметиленгліколю з Мм 1000 Да, дифеніл-4,4′-діізоціанату та 1,4-бутандіолу) зберігали антимікробну активність щонайменше 30 днів. Їхні міцнісні характеристики були також значно вищими, ніж у систем на основі зшитих поліуретанів.

Ключові слова: поліуретанові композити, носії ліків, характеристики вивільнення.

ПОЛИУРЕТАНОВЫЕ КОМПОЗИТЫ КАК НОСИТЕЛИ ЛЕКАРСТВ: ХАРАКТЕРИСТИКИ ВЫСВОБОЖДЕНИЯ

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Биодеградируемые полиуретаны представляют значительный интерес для разработчиков композиционных материалов с целью биомедицинского применения. Одной из характеристик этих полимеров является их способность быть носителями лекарств и других биологически активных соединений, обладающих терапевтическим эффектом в организме за счет их направленной и/или длительной доставки в процессе контролируемого высвобождения из носителя.

В обзоре представлены полиуретановые композиты как носители ряда лекарств. Показана взаимосвязь между структурой этих композитов и их способностью к деградации *in vitro* и *in vivo*, а также влияние физико-химических свойств полиуретанового носителя на кинетику высвобождения иммобилизованных лекарств. Характер высвобождения лекарств (цефазолина, налтрексона, пироксикама) из композитов на основе сшитых полиуретанов (синтезированных из лапролов с Мм 1500–2000 Да и толуилендиизоцианата) был подобным (приблизительно 10 дней *in vitro* и 3–5 *in vivo*). В противоположность этому композиты с диоксидином на основе линейного полиуретана (синтезированного из олиготетраметиленгликоля с Мм 1000 Да, дифенил-4,4′-диизоцианата и 1,4-бутандиола) сохраняли антимикробную активность как минимум в течение 30 дней. Их прочностные характеристики были также значительно выше, чем у систем на основе сшитых полуретанов.

Ключевые слова: полиуретановые композиты, носители лекарств, характеристики высвобождения.