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Distribution and Resorption of Intravenously Administrated Polymer Microparticles in Tissues of Internal Organs of Laboratory Animals

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Resorbable polymer of hydroxybutyric acid labeled with ^{14}C was used to prepare microparticles (diameter smaller than 3.8 μm) that were then injected to laboratory animals (Wistar rats) via the tail vein, without causing any adverse effects on growth and development of the animals or altering the macroscopic and microscopic structure of the tissues of internal organs. Examination of the distribution of microparticles among the internal organs and the dynamics of accumulation of carbon-containing polymer degradation products in internal organs showed that the main targets for microparticles were tissues of the liver, kidneys, and spleen. The most rapid degradation of the polymer of microparticles occurred in the spleen and liver. The presence of high molecular weight polymer registered in internal organs suggested that the microparticles remained undecomposed and that the PHB microparticles could function in vivo for extended periods of time (up to 12 weeks).

Keywords: resorbable polyhydroxybutyrate; microparticles; intravenous administration; ^{14}C; tissues of internal organs

Introduction

Designing of controlled-release drug delivery systems is a promising and rapidly developing line of modern pharmacology (Amass et al., 1998). Drug delivery systems in the form of biodegradable microspheres and microcapsules can be injected subcutaneously, intramuscularly and into the bloodstream (Freiberg et al., 2004). Drug delivery systems intended for intravenous injection must be not only biocompatible but also hemocompatible, i.e. the materials used to construct them must not induce thromboses, thromboembolisms, antigenic response or destruction of blood constituents and plasma proteins; they must also retain their mechanical-physical properties (Yen et al., 2003; Kim et al., 2004).

Bioresorbable polyesters of microbiological origin – polyhydroxyalkanoates (PHAs) – are considered to be promising materials to be used as scaffold carriers for drug delivery (Amara et al., 2008). Polyhydroxybutyrate was used as a basis

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for production of polymer scaffold constructions in the form of films, tablets, and microparticles (Sevastianov et al., 2003; Shishatskaya et al., 2006); it was proved that PHB microparticles were highly biocompatible and could be injected intramuscularly (Shishatskaya et al., 2008a); experiments with PHB scaffolds loaded with rubomycin hydrochloride showed their suitability as carriers of anticancer drugs (Shishatskaya et al., 2008b). It should be mentioned that today the number of PHA studies devoted to the development of controlled-release systems is considerably less than the number of similar studies based on biodegradable polylactides and polyglycolides.

Today antibiotics, hormonal agents and anticancer drugs in the form of microparticles can be deposited into PHA matrices (Abe and Doi 1992; Kassab et al., 1997; Lionzo et al., 2007; Wang et al., 2007; Bazzo et al., 2008). PHA biocompatibility was proven *in vitro* using cells of different origins (Choi et al., 2005) and in *in vivo* experiments (Gogolewski et al., 1993; Qu et al., 2006).

However, despite the existing data about using PHAs for the microencapsulation of drugs, the problem of biocompatibility of polymer particles as carriers for drugs to be administered intravenously is not covered in the available literature. One of the earliest investigations devoted to the possible intravenous administration of PHA microparticles was performed by Bissery et al., 1984. Using the method of solvent evaporation from the ^{14}C-labeled PHB solution, microspheres were obtained with the diameter of 1-12 μm and injected intravenously to mice; after the injection the microspheres were localized mainly in lungs. However, introduction of these microspheres loaded with the anticancer agent, lomustine, to Levis' mice infected with carcinoma had minimal effect. In addition, the location of ^{14}C-labeled polyhydroxybutyrate granules was investigated with the intravenous injection (Saito et al., 1991).

E.T. Baran and co-authors (2002) studied the toxicity and half life of encapsulated L-asparaginase (ASNase) in poly (3-hydroxybutyrate-co-3-hydroxyvalerate) PHBV nanocapsules in mice. The PHBV nanocapsules with heparin conjugated on their surface had a longer presence in the circulation than unmodified PHBV nanocapsules. No adverse effects were observed upon injection of encapsulated ASNase-PHBV nanocapsules to mice i.v. through the tail vein.

The purpose of this study was to examine the distribution of PHB microparticles in the internal organs of laboratory animals; biocompatibility of PHB microparticles and their life-time in the organism after intravenous injection; distribution dynamics of microparticles and degradation products in the internal organs of laboratory animals.

Materials and methods

1. Preparation of ^{14}C-labeled PHB polymer

The tested material was the polyhydroxybutyrate (PHB) samples synthesized by the bacterium *Ralstonia eutropha* B5786 (Mw 340 000 Da, crystallinity 70-78 %). The strain is registered in the Russian Collection of Industrial Microorganisms. The 14C-labeled polymer was prepared by adding 1,2-^{14}C-acetate (6×10^4 cpm/ml; cpm- counts per minute) as substrate to the bacterial culture in the polymer synthesis phase. PHB is extractable from the bacterial biomass due to its ability to dissolve in organic solvents and to be then precipitated by alcohols. PHB was extracted from the bacterial biomass with chloroform and precipitated with ethanol. The procedure of re-dissolution and further precipitation of polymer was repeated several times to prepare specimens that would not contain organic impurities of protein, carbohydrate or lipid nature. We have previously shown that this

procedure can be used to prepare high-purity PHB specimens, which would not contain any organic impurities – components of bacterial biomass – and would exhibit excellent biocompatibility characteristics, allowing them to contact blood. The trademark of the material is Bioplastotan (Trademark «BIOPLASTOTANTM»). The radioactivity of the prepared PHB was 1.4×10^4 cpm per 1 mg of the polymer. The radioactivity of the samples was measured using the TRI-CARB 2100TR scintillation counter (Packard BioScience Company, USA).

The molecular weight data were obtained at 35°C by using the Waters 2414 GPC system and Waters refractive index detector with the PLgel Mixed C column (polymer Laboratories, Ltd.,UK). Chloroform was used as an eluent at a flow rate of 0.8 ml/min, and a sample concentration of 1.0 mg/ml was used. Polystyrene standards were used to construct a calibration curve.

For determination of the crystallinity degree, Cx, scan-step spectra were read off, with sensitivity 0.04°, and a 2-second optical exposure for determination of intensity at a certain point (the device functioning mode was 40 kW x 40 mkA). The IR-spectra of absorption of the PHA film samples were registered using the IR Fourier spectrometer INFALUM FT-02 (Lumex, Russia).

2. Preparation of microspheres

The ^{14}C-labeled microparticles were prepared by the solvent evaporation technique, using a triple emulsion. 600 mg of the polymer (PHB) and 200 mg of polyethylene glycol (PEG40, molecular mass 40 kDa) were dissolved in 10 ml of dichloromethane. Then, 1 ml of a 6 % gelatin solution (40°C) was added and the mixture was shaken vigorously. The resulting water/oil (W/O) double emulsion was allowed to cool to room temperature and then it was gradually poured into 150 ml of a 0.5 % PVA solution, which was stirred with a three-blade propeller (at 2000 rpm, for 20 min) (Heidolph, Germany), to obtain a triple (water/oil/water, W/O/W) emulsion. The emulsion was continuously mixed mechanically for 24 h, until the solvent was completely evaporated. Microspheres were collected by centrifuging (at 10000 rpm, for 5 min), rinsed 7-8 times in distilled water, and freeze-dried in the LS-500 lyophilizer (Prointex, Russia).

3. Microsphere characterization

The size of microspheres with a diameter bigger than 3 μm was determined using the Automatic Particle Counter + Analyser system (Casy TTC, Scharle System GmbH, Germany). The obtained size distribution was used to describe the particle size.

For intravenous injections a fraction of microspheres with a diameter smaller than 3.8 mkm was selected, using a treck filter. The size of particles was estimated using the Scan master program of the scanning multimicroscope CMM-2000 taking into account the parameters which determined the image size. The structure of microsphere surfaces was analyzed by electron microscopy, as was described previously (Shishatskaya et al., 2008a).

4. Animal model

Experiments were conducted on adult female Wistar rats (200-240 g each) in accordance with the international and Russian ethical rules for laboratory animals care. The rats were kept in an animal facility and fed a standard diet in accordance with the directive on maintaining animals and experimenting on them (Genin et al., 2001). A sterile suspension of microspheres (5 mg in 0.5 ml of physiological saline, 5×10^4 cpm/g) with a diameter not more than 3.8 μm was injected to rats through the tail vein, without any anesthesia. Intact animals were used as control.

Three hours after the injection, 24 hours after the injection, and then every week, three animals were sacrificed by using an overdose of a volatile anesthetic. Their internal organs were removed, examined macroscopically, weighed, dried and ground; then, radioactivity counts were performed. A 100 mg sample was placed into a plastic vial (PerkinElmer/Packard, USA) containing 15 ml of dioxane scintillation solution; 1 L dioxane contained 2,5-diphenyloxazole, 10 g; 1,3-di-2,5-phenyloxazolyl benzene, 0.25 g; naphthalene, 100 g. Radioactivity counts were performed in the TRI-CARB 2100TR scintillation counter (Packard BioScience Company, USA). Radiocarbon was measured in the heart, lungs, liver, kidneys, bone marrow, and blood, without taking into account the radioactivity of soft and hard tissues and excreted metabolic products. To study the resorption of the polymer scaffold and accumulation of ^{14}C-containing PHA degradation products, samples of the dried tissues were subjected to methanolysis, and fatty acid methyl esters were determined using the GCD plus chromatograph mass spectrometer (Hewlett Packard, USA). To determine high-molecular-weight (undecomposed) polymer in the organs, it was extracted from the tissues with chloroform and precipitated with hexane. Then the polymer was methylated and chromatographed as described above; the sensitivity was 10-11 g. The general tissue reaction to implanted microspheres was investigated using conventional histological techniques. The samples were fixed in 10 % formalin and embedded in paraffin; 5-10 μm thick microtome sections were stained with hematoxylin and eosin.

5. Statistics

The results were analyzed statistically using the standard software package of Microsoft Excel. Arithmetic means and standard deviations were found. Significant differences between average values in control and treatment groups were tested using Student's t-test (significance level: $p = 0.05$) by standard methods: using two sample equal variance, with two-tailed distribution. We used 3 samples (animals) per *in vivo* experiment.

Results

1. Microspheres characterization

The microspheres were of regular spherical shape and had a well-developed «wrinkled» surface; their diameters were significantly heterogeneous. Fig. 1 represents a typical appearance of microspheres with a regular spherical shape having no defects or inclusions. Microsphere size distribution varied within the range from 0.50±0.02 μm to 50.00±4.62 μm. The fraction of the microspheres with a diameter of 3-5 μm amounted to 21.1±1.8 %. Microspheres of this size are considered to be the best for injections. The fraction of the particles 5 to 10 μm in diameter constituted 30.4±1.1 %, and the fraction of the particles 10 to 20 μm – 34.4±2.3 %. The largest of the harvested particles were 35 μm in diameter, and their fraction did not exceed 3.5 %. The average diameter of microspheres was 10±0,23 μm. Particles taken for intravenous injection were 0.5-3.8 μm. The microparticles used in the experiment had an average diameter of 2.40 ±0.21 μm.

2. Distribution of PHB microparticles in internal organs

All animals that had been injected with a microspheres suspension were healthy and ate well throughout the experiment. Their body mass and masses of their internal organs were similar to those of the rats in the control group. Macroscopic examination of the rats' internal organs and histological studies of the tissue sections did not show any adverse changes in them throughout the observation period.

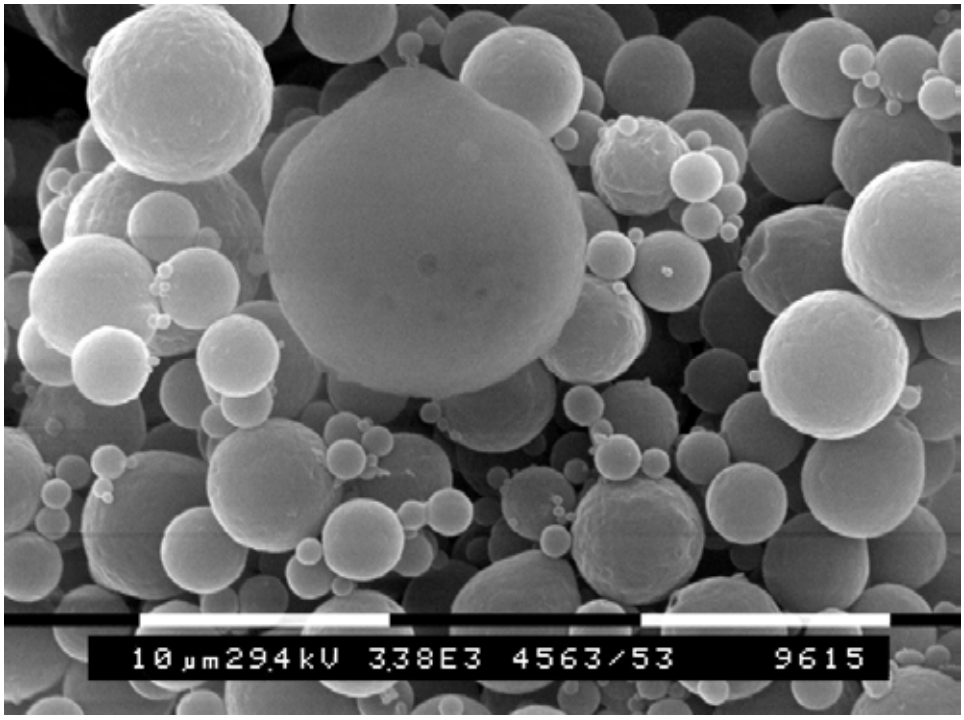

Fig. 1. Micrographs of the microspheres prepared from polyhydroxybutyrate

The dynamics of ^{14}C activity concentrations in tissues of internal organs in the course of the experiment is shown in Fig. 2. Three hours after the injection of the microparticles into the bloodstream of the animals, the largest ^{14}C activity concentration (14680±417 cpm×g) was registered in heart tissues. The second largest concentration of the label was determined in kidney tissues (7520±81 cpm×g) and the third – in lung tissues (5280±65cpm×g). Liver and spleen tissues contained similar ^{14}C activities – (4400±58cpm×g). The lowest radioactivity levels were registered in blood and bone marrow. One month later, ^{14}C activity concentration in the heart tissues was 4.5 times lower than its initial level amounting to 3240±57 cpm×g. Radioactivity of liver tissues dropped to 15120±90 cpm/g. In the tissues of kidneys and lungs decreased radioactivity levels were detected: from the initially detected, 4720±69 cpm/g and 940±97 cpm/g, correspondingly, to kidneys and lungs. At the same time, ^{14}C concentration in the spleen tissues somewhat rose, which may be accounted for by the accumulation of polymer resorption products in this organ, where, in addition to hydrolytic enzymes, there are active macrophage-type cells, which resorb cell elements. Macrophages are known to actively degrade polyhydroxybutyrate (Shishatskaya et al., 2008a).

The level of radioactivity in blood and bone marrow did not exceed 300 cpm/g.

Thus, the tissues of internal organs sorbed different amounts of intravenously injected microparticles. This is even more obvious from the analysis of the data in (Fig. 3), which shows in vivo accumulation of the label, taking into account the masses of the organs. Data on Fig. 2 correspond to Fig. 1, and allow us to make the following conclusion: the main target for microparticles was the liver tissue; the average level of accumulated ^{14}C in liver during the experiment was approximately 60 % of the injected dose.

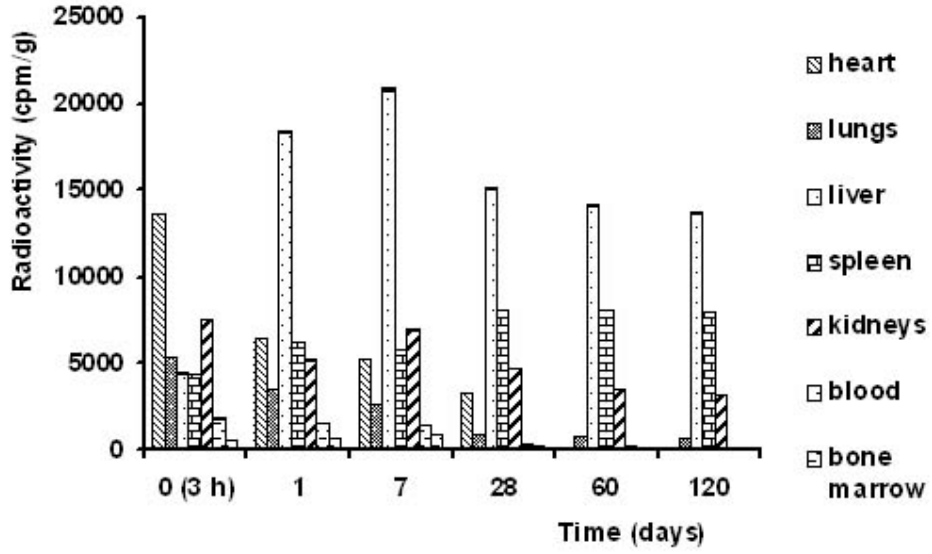

Fig. 2. Dynamics of radiocarbon concentration in tissues of internal organs of the animals intravenously injected with ^{14}C-labeled polymer microparticles

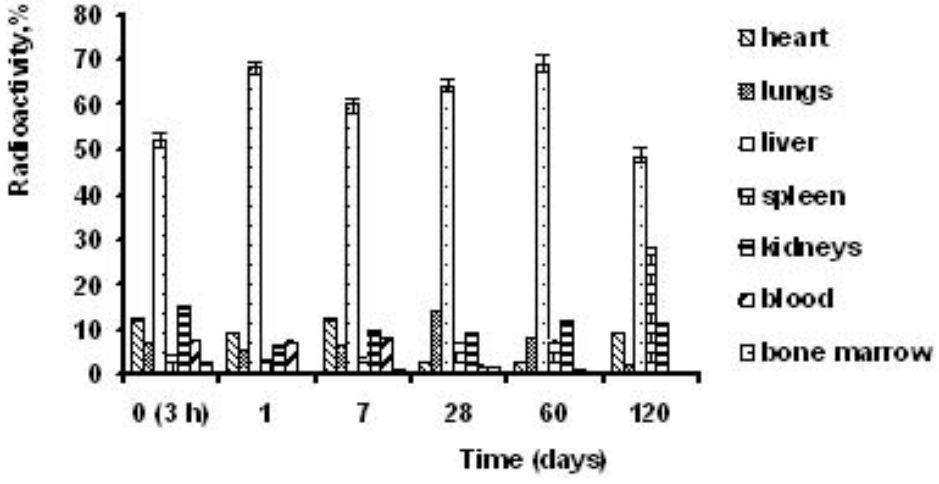

Fig. 3. Dynamics of radiocarbon accumulation in internal organs of the animals intravenously injected with ^{14}C-labeled polymer microparticles

During the period of microparticle circulation a reliable decrease in the organ radioactivity was detected, which we believe is due to the initiated process of polymer matrix biodegradation and excretion of the label part with carbon-containing PHB biodegradation products. Thus, three hours after the injection of microparticles to the animals, the total radioactivity of the organs was 38720 ± 2575 cpm/g, i.e. 80 % of the radioactivity of the injected dose (Fig. 4). 120 days after the intravenous injection the total radioactivity dropped to 28210 ± 2054 cpm/g, which can be attributed to polymer biodegradation.

3. PHB biodegradation in internal organs

We should note here that the registered amounts of radiocarbon in the rats' organs do not show the true accumulation of microparticles in the organs: PHAs are biodegradable polyesters and are bioresorbed in vivo by the enzymes

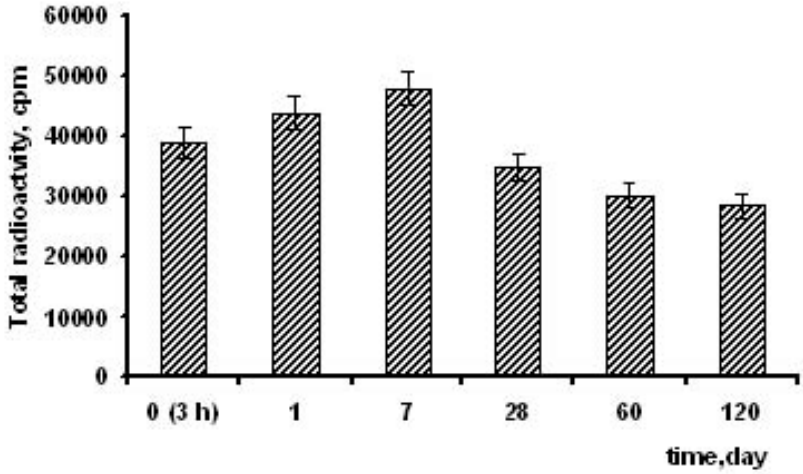

Fig. 4. Dynamics of total ^{14}C radioactivity in animal organism

and cell elements of blood and tissues, and the polymer degradation products are removed with metabolites (Jendrossek et al., 2001). The ^{14}C activities registered in the tissues comprise the radiocarbon of the high-molecular-weight polymer scaffold, i.e. undecomposed microparticles and the radiocarbon of polymer degradation products.

To compare the biodegradation rates of the polymer in different organs and to determine the «lifetime» of polymer microparticles, tissues were subjected to chromatographic analysis. During the experiment, the amounts of the polymer substance varied in every organ. At 8 weeks, polymer content in the heart and lungs dropped almost by a factor of ten compared to week 1. However, in our opinion, this cannot be accounted for by the degradation of polymer scaffold in these organs, but rather by the bloodstream washing out the initially introduced microparticles from the pulmonary circulation. Eight weeks later, polymer content in the liver and kidneys decreased insignificantly: 1.5 times in the kidneys and 1.2 times in the liver. A more significant, 2.5-fold, decrease was registered in the spleen. 12 weeks later, at the end of the experiment, polymer content decreased as compared to the values measured after an 8 week interval: almost twofold in the heart and lungs, threefold in the kidneys, 18-fold in the spleen, and 25-fold in the liver (Table 1).

Our results are indicative of different PHA biodegradation rates in animal tissues. They also show that at the end of the experiment the organs still contained high-molecular-weight polymer and, thus, some of the microparticles could have remained undecomposed. However, spectrometric methods used to detect high-molecular-weight PHAs are based on registering fatty acid methyl esters (i.e. polymer-forming monomers) – products of preliminary hydrolysis of the polymer to monomers and their subsequent methylation. Thus, the presented values can comprise both monomers of hydroxybutyric acid resulting from methanolysis of the high-molecular-weight polymer and monomer products of its natural biological degradation caused by enzymes and cells of the organs.

The high-molecular-weight (undecomposed) polymer was extracted from the samples and analyzed. That was done to determine the concentration of the high-molecular-weight undecomposed polymer in internal organs at different time points after the injection of microparticles (Table 2). One week after the injection, the polymer content registered in

Table 1. Results of chromatographic analysis of methyl esters of hydroxybutyrate monomers contained in tissues of rats' internal organs

Organ	PHB content (1×10^{-4} mg/organ)		
	1 week	8 weeks	12 weeks
heart	1527	132	75
lungs	1694	111	56
liver	5861	4889	197
spleen	606	251	14
kidneys	189	124	43

Table 2. Residual high-molecular-weight polymer in tissues of rats' internal organs

Organ	PHB content (1×10^{-4} mg/organ)		
	1 week	8 weeks	12 weeks
heart	420	30	5
lungs	600	5	6
liver	360	110	80
spleen	6	10	5
kidneys	16	20	7

the lungs, heart, and liver was larger than that registered in the spleen and kidneys. Eight weeks after the injection, the polymer content in the lungs and heart dropped dramatically (similarly to the data of Table 1), but that was rather due to particle washout than degradation processes. This conclusion was confirmed by the measurements of tissue radioactivity. It should be noted that the data at the end of a 12 week interval given in tables 1 and 2 differ significantly: chromatography of the tissues determined much higher amounts of the polymer substance (Table 1) than the amounts of the high-molecular-weight polymer recovered from the organs (Table 2). This leads to the conclusion that at the end of the experiment, the major portion of the ^{14}C-labeled polymer was present *in vivo* as monomers of hydroxybutyric acid and its low-molecular-weight degradation products.

The second important conclusion based on the data of Table 2 is that some polymer microparticles remained undecomposed in the animals' organs at different time points of the experiment. Finally, the fact that the examined organs, especially the liver and the spleen, contained relatively low amounts of the polymer, while radioactivity of the tissues was high, is indicative of the rapid degradation of the polymer scaffold in them.

Discussion

In this paper, we have presented the results of investigation into the distribution of intravenously injected ^{14}C-labeled polymer (PHB) microparticles in internal organs of laboratory animals and the localization of PHA biodegradation products.

There is substantial literature data on the *in vitro* and *in vivo* kinetics of drug release from polymer matrices, their medicinal effectiveness, and the possibilities of targeted delivery (Arulsudar et al., 2003; Petri et al., 2007; Bazzo et al., 2008). However, there are rather few studies that describe investigations of the in vivo distribution and dynamics of infused microparticles, especially PHA-based ones, although this aspect is obviously very important.

Distribution of microparticles and the rates of their elimination from the body depend on many factors, and the available literature data on mechanisms of biodistribution are contradictory. Most authors report that the main targets of intravenously injected particles are the organs of the reticuloendothelial system, namely the liver and the spleen (Owens et al., 2006). In one of the first published studies devoted to this subject it was reported that the distribution of ^{141}C-labeled polystyrene/divinylbenzene microparticles intravenously injected to dogs depended on the size of the particles and that particles of a larger diameter were taken up by the organs at a higher rate (Kanke et al., 1980). Microspheres of 7 μm and 12 μm in diameter were mostly retained in the lungs, and 3-5 μm ones – in the liver and spleen. Four weeks after the injection of microspheres, no phagocytosis of microparticles by lung macrophages was observed. Drug-loaded bovine serum albumin based microparticles with an average diameter of 2.58 μm were injected intravenously, into the tail vein of mice. The average distribution efficiency of the particles was found to be 11.74 % in the liver, 8.50 % in the kidneys, 7.69 % in the lungs, and 5.67 % in the spleen after 24 h (Dandagi et al., 2006). In another work, the authors studied the distribution of polylactide-based microparticles labeled $[^{99m}Tc(CO)_3]^+$ after the intravenous injection to mice during the period of six hours after the beginning of the experiment. It was found that the main target for the PLG microparticles with a diameter of 0.2-3 μm was the liver (55 % of the injected dose), the second largest, in terms of label inclusion, were the tissues of lungs and spleen (Saatchi et al., 2009).

Ballot and her co-authors studied the kinetic biodistribution of nanoparticles labeled with rhenium and technetium in rats. The particles were composed of a liquid lipidic core (triglycerides) surrounded by a surfactant shell (2-hydroxystearate of polyethylene glycol and lecithin); the mean size of the particles was 45 nm to 49 nm. Dynamic scintigraphic acquisitions revealed relatively long activity circulation in blood before location mainly in the liver and spleen. High activity in the cardiac area and low hepatic retention were observed within one hour after the injection. 30 minutes after the beginning of the experiment, nanoparticles were predominantly taken up by the liver and spleen. 24 hours after the injection the remaining activities in the liver and spleen were 5 % and 2.5 % of the initial value, respectively (Ballot et al., 2006). Different results were obtained in experiments with water-soluble poly(2-methyl-2-oxazoline) administered to mice by tail vein injection. The intravenously injected water-soluble polymer was not retained in the tissues but was quickly excreted by renal glomerular filtration. The lowest concentration of the polymer was found in the brain, indicating that poly(2-methyl-2-oxazoline) does not cross the blood-brain barrier. A slight increase of radioactivity was registered in the liver, spleen, and bone marrow within 24 hours (Graether et al., 2007).

One of the approaches to prolonging the time of nanoparticle circulation in the body is regulation of particle sizes and creation of hydrophilic surface on the nanomatrices. Shenoy and co-authors determined the distribution and localization of nanoparticles based on poly(ethylene oxide)-modified poly(β-amino ester) and poly(ethylene oxide)-modified poly(caprolactone). ^{11}In was chosen as the label for the nanoparticles mainly due to its short half-life and its availability in the lipophilic form for encapsulation in nanoparticles. Both types of nanoparticles showed higher tendency for accumulation in the liver, spleen and lungs during the initial phase and in the kidney at the later stages of biodistribution (Shenoy et al., 2005).

Poly(ethylene oxide)-modified nanoparticles had higher circulation times than particles without a PEO coating. Glen S. Kwon and co-authors studied biodistribution of 30 nm to 50 nm polymeric micelles based on block copolymers of polyethylene oxide and poly(aspartic) acid with covalently bound Adriamycin, which were labeled by ^{14}C-benzylamine. The micelles were studied as potential drug carriers. The authors registered prolonged circulation of micelles in blood (concentration of the radiolabel in blood gradually decreased from 50 % to 10 % of the injected dose within 24 h and then micelles accumulated in the liver and spleen) (Know et al., 1993).

Rather few in vivo investigations of the distribution of microparticles based on polyhydroxybutyrate or any other PHA have been reported in the available literature. Bissery and co-authors studied distribution of microspheres based on ^{14}C-labeled PHB, and 1-12 μm microspheres intravenously injected to mice were mostly found in the lungs (Bissery et al., 1984). Another distribution pattern was observed for smaller (0.3-0.5 μm) PHB particles injected to rats via the tail vein – at 2.5 h 86 % of radioactivity was registered in the liver, and the lungs and the spleen contained 2.5 % each (Saito et al., 1991).

Those results differed from Bissery's and Kanke's data. Saito et al. presumed that this could be accounted for by the difference in diameter of the particles and animal species used. We should note, however, that Saito et al. investigated native PHB granules recovered from *Zoogloea ramigera* cells grown on ^{14}C-labeled glucose rather than polymer-based microparticles. Hence, in addition to being very small, PHB granules also differed from Bissery's microparticles in their structure and chemical composition.

The pattern of the distribution of PHB particles under 3.8 μm in diameter in internal organs of laboratory animals that we obtained in our experiment is generally comparable with the data reported by other authors that used different polymers (Bissery et al., 1984; Ballot et al., 2006). The comparison of degradation of microparticle polymer scaffold in different organs showed that PHB is resorbed at the highest rate in the spleen and liver. In addition, at 12 weeks we observed undecomposed microparticles, which led us to the conclusion that PHB particles can be used as sustained drug delivery systems.

In conclusion, this study shows that polyhydroxybutyrate microparticles are suitable for intravenous administration; tissues of internal organs accumulate different concentrations of polymer microparticles, and polymer scaffold is degraded in them at different rates. The presence of high-molecular-weight polymer scaffold registered in internal organs, which is indicative of microparticles remaining undecomposed, suggests that polyhydroxybutyrate can be used to construct systems for sustained (up to 12 weeks) drug delivery to tissues of internal organs via intravenous administration.

Acknowledgments

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Распределение и резорбция полимерных микрочастиц в тканях внутренних органов лабораторных животных при внутривенном введении

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С применением резорбируемого полимера гидроксимасляной кислоты, меченого по ^{14}C, получены микрочастицы (диаметром менее 3,8 мкм), которые были введены лабораторным животным (крысы линии Вистар) в хвостовую вену без негативных последствий для роста и развития животных и без изменения макро- и микроскопической структуры тканей органов. Изучено распределение микрочастиц среди внутренних органов и динамика накопления углеродсодержащих продуктов разрушения полимера во внутренних органах. Показано, что основной мишенью для частиц являются ткани печени, а также почек и селезенки. Наиболее активное разрушение полимерного матрикса микрочастиц происходит в селезенке и печени. Выявленное наличие высокомолекулярного полимерного матрикса в органах, свидетельствует о целостности микрочастиц и возможности долговременного (до 12 недель) функционирования препарата в виде полимерных микрочастиц in vivo.

Ключевые слова: резорбируемый полигидроксибутират, микрочастицы, внутривенное введение, ^{14}C, ткани внутренних органов.