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P O L I M E R Y

MIESIĘCZNIK POŚWIĘCONY CHEMII, TECHNOLOGII i PRZETWÓRSTWU POLIMERÓW

Od redakcji

Niniejszy zeszyt „Polimerów" zawiera treść wybranych wystąpień (w języku angielskim) wygłoszonych w ramach sympozjum „Hybrid Polymer Systems of Industrial Importance". Sympozjum zostało zorganizowane w dniach 5—7 września 2005 r. na terenie Politechniki Warszawskiej przez Centrum Kompetencji Nowoczesnych Materiałów Polimerowych o Znaczeniu Przemysłowym Polmatin działające w Instytucie Chemii Przemysłowej.

Za cenną pomoc w opracowaniu artykułów zamieszczonych w tym zeszycie zespół redakcyjny serdecznie dziękuje współorganizatorce sympozjum pani dr Marii Zieleckiej.

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Hybrid polymeric materials for medical applications

Summary — Paper presents recent achievements related to polymer containing organic-inorganic hybrids used for various medical applications. In particular, there are described syntheses of polymers on inorganic supports, syntheses of hybrid nano- and microparticles, self-assembly of nano- and microparticles into hybrid structures, and also hybrid materials obtained in sol-gel processes. Moreover, presented are selected applications of these materials for medical diagnostic, fabrication of temporary bone-growth inducing implants, and examples of drug delivery systems from implantable devices, like scaffolds for tissue engineering and stents for coronary angioplasty.
Key words: polymer hybrid materials, medical applications, nano- and microparticles, biodegradable polymers, biosensors, polymeric scaffolds, drug delivery.

HYBRYDOWE MATERIAŁY POLIMEROWE DO ZASTOSOWAŃ MEDYCZNYCH

Streszczenie — Przedstawiono wyniki najnowszych badań dotyczących polimerowych układów organiczno-nieorganicznych przydatnych do zastosowań medycznych. W szczególności opisano syntezy polimerów na podłożach nieorganicznych, sposoby otrzymywania hybrydowych nano- i mikrocząstek, procesy wytwarzania układów hybrydowych z nano- i mikrosfer, a także uzyskiwanie materiałów hybrydowych metodą zol-żel. Opisano również zastosowania otrzymywanych materiałów w diagnostyce medycznej do wytwarzania implantów indukujących wzrost tkanki kostnej oraz wybrane przypadki układów umożliwiających uwalnianie leków z rusztowań stosowanych w inżynierii tkankowej i ze stentów stosowanych w angioplastyce naczyń wieńcowych.
Słowa kluczowe: polimerowe materiały hybrydowe, zastosowania medyczne, nano- i mikrocząstki, polimery biodegradowalne, biosensory, rusztowania polimerowe, transport leków.

Materials used for medicine often should have a set of properties that are difficult to obtain for polymers, metals or ceramics alone. Some of the properties are related to interactions of materials with particular organs, tissues, cells, or natural macro- or small molecules (*e.g.* proteins, nucleic acids, polysaccharides, urea, glucose, *etc.*). Moreover these materials should have the required mechanical strength, toughness, electric conductivity, transparency, hydrolytic and enzymatic activity, morphology of interfacial layer, and many other properties, related to specific applications. In many instances these properties could be achieved by combining materials belonging to particular classes into polymer-polymer blends or other polymer-metal and polymer-ceramic hybrid constructs. Structure of materials in the range of nano- and micrometers is often also very important.

In this short review we will report on synthesis and on other means of formation of hybrid polymer containing materials useful for medical applications. There will be presented methods used for *in-situ* formation of polymeric materials on inorganic supports, for synthesis of hybrid nano- and microparticles, self-assembly of nano- and microparticles into hybrid structures, and for formation of hybrid materials by sol-gel processes. There will be discussed also examples of application of hybrid materials for particular medical purposes. In addition to results of our research in area of hybrid materials selected achievements of other researchers will be also discussed.

SYNTHESIS OF POLYMERS ON INORGANIC SUPPORTS

A direct method for production of inorganic-organic hybrid materials composed from inorganic support coated with a polymer consists of grafting polymer from the surface during any of the polymerization processes, with initiation leading to formation of propagation active centers at the surface. Polymers may be formed either by electropolymerization or in course of radical, ionic or pseudoionic polymerizations initiated with initiators bound to the surface.

A typical example is electropolymerization of pyrrole on conducting substrates. Simplified scheme of reactions involved in electropolymerization of pyrrole is shown in Scheme A.

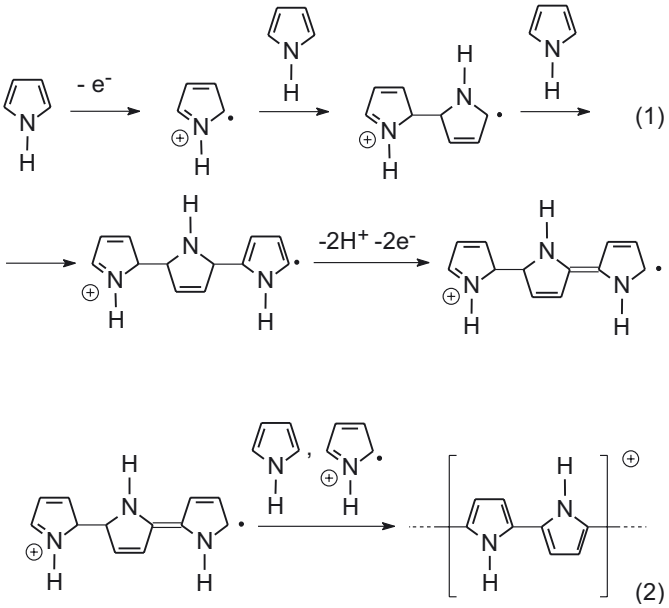
Short recipe for electropolymerization process based on description in Ref. [1, 2] is given below. Platinum-coated 12×12 mm glass slides were placed in a one compartment cell filled with solution containing pyrrole at concentration 0.1 mol/l and supporting electrolyte solution containing salts (sodium chloride, sodium dodecylsulfate and sodium tosylate) at concentration 0.1 mol/l. Polypyrrole film was deposited onto the slides galvanostatically, at current density 0.4 mA/cm^2 for 4 min. Obtained film was *ca.* 100 nm thick with average roughness less than 5 nm.

Electrodeposition from monomer mixture that in addition to pyrrole did contain pyrrole derivatives with functional groups (see Scheme B) or bioactive molecules, for example enzymes, yielded materials containing required reactive moieties [3—6].

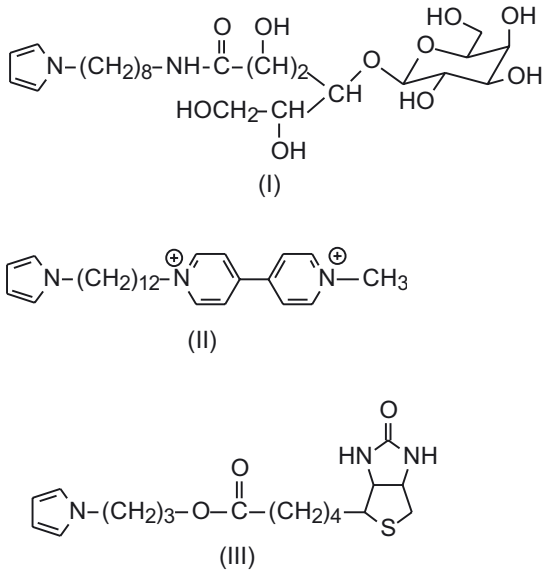
Hybrid materials based on polyaniline [6—8] and thiophene [8, 9] were prepared in the similar manner.

Polymers produced electrochemically often are not immobilized covalently onto inorganic supports but are attached so strong by Van der Waals and ionic interactions that the adsorption is usually irreversible.

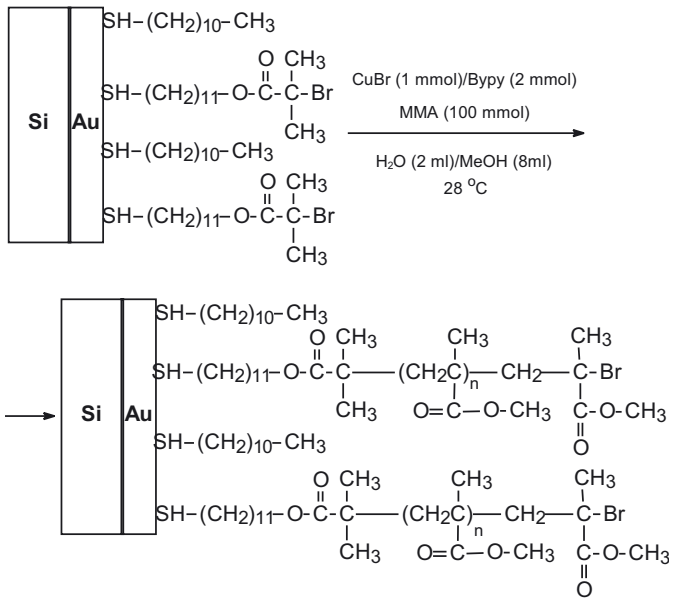
Development of controlled radical polymerization did open a way to synthesis of macromolecular mono-



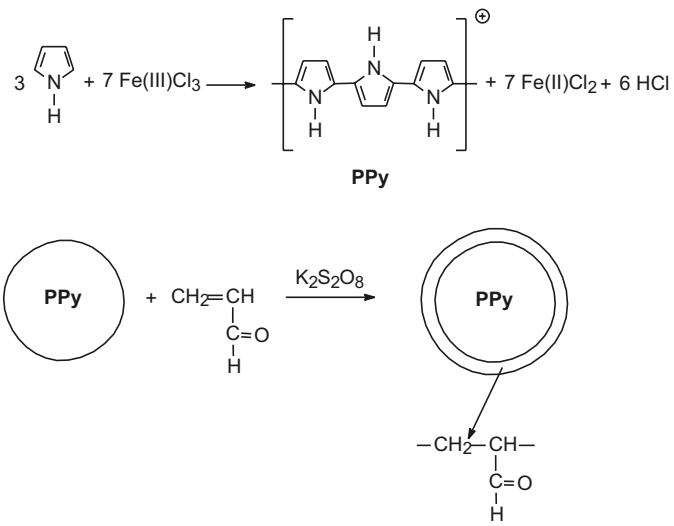
Scheme A. Reactions involved in electropolymerization of pyrrole



Scheme B. Structures of electropolymerizable pyrrole derivatives with sugar (I), redox (II) and biotin (III) moieties (based on data from Ref. [5])



Scheme C. Synthesis of poly(methyl methacrylate) brushes from the surface of silica covered with gold. Bypy denotes bipyridine. Polymerization conditions after Ref. [12]



Scheme D. Synthesis of (polypyrrole core)-(polyacrolein shell) nanoparticles

layer on solid support equipped with appropriate initiating groups [10—12]. Scheme C illustrates synthesis of poly(methyl methacrylate) brushes from gold surface by atom transfer radical polymerization (ATRP). Surface of silica covered with gold was modified in a manner allowing for control of density of initiating $-OC(O)C(CH_3)_2Br$ groups.

Thickness of polymer layer formed by ATRP on inorganic substrate could be easily controlled in the range from 6.6 to 70 nm by controlling molecular weight of tethered macromolecules [13]. The latter depends on time of polymerization.

SYNTHESIS OF HYBRID NANO- AND MICROPARTICLES

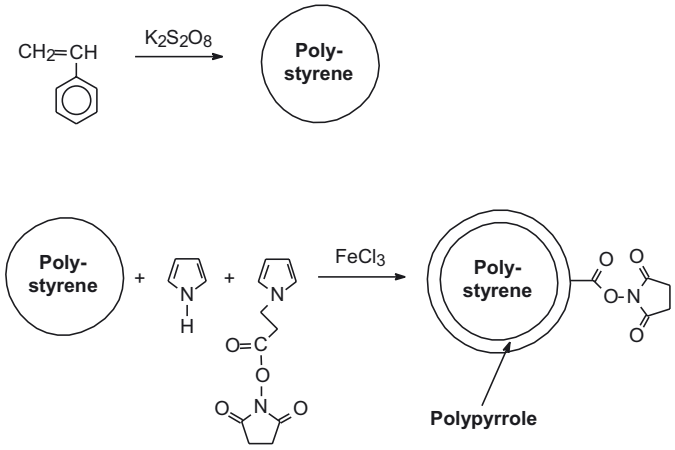
Polymer containing hybrid objects, in form of nano- and microparticles with cores composed of one type of material and shells made of another one, are needed for several diagnostic applications. Often one of these materials should allow for controlled immobilization of biomolecules (*e.g.* immunoglobulins or enzymes) whereas the second one provides the needed mechanical, electrical or optical properties.

Particles with the mentioned above morphology were obtained by seeded heterogeneous polymerization. Below there are given examples of synthesis of (polypyrrole core)-(polyacrolein shell) and (polystyrene core)-(polypyrrole shell) microparticles, as well as composite magnetic microparticles with raspberry-type morphology composed of silica-coated magnetite and polypyrrole nanoparticles.

(Polypyrrole core)-(polyacrolein shell) nanoparticles were obtained by sequential redox polymerization of pyrrole followed by polymerization of acrolein carried on in the presence of polypyrrole seeds [14]. Formation of particles is illustrated in Scheme D.

In a typical synthesis 0.2 g of acrolein was polymerized in presence of 0.6 g of polypyrrole particles with average diameter equal 121 nm. Polymerization initiated with 0.022 g of $K_2S_2O_8$ was carried on at 65 °C in 50 ml of water with stirring at 60 rpm for 30 hours. Obtained black particles with polypyrrole core and polyacrolein shell had average diameter equal 148 nm. Surface concentration of aldehyde groups on these particles was equal $7.47 \cdot 10^{-6}$ mol per 1 g of particles.

(Polystyrene core)-(polypyrrole shell) nanoparticles were synthesized in a two-step process [15]. In the first step the polystyrene-core particles were synthesized during the emulsifier-free emulsion polymerization. For example, polymerization of 20 g of styrene, initiated with 0.65 g of $K_2S_2O_8$ in 200 g of distilled water (oxygen was removed from the mixture by purging nitrogen), carried on with stirring at 75 °C for 28 hours yielded nanoparticles with average diameter 450 nm. The second step consisted on redox copolymerization of pyrrole and N-hydroxysuccinimide ester of 1-(2-carboxyethyl)pyrrole. The latter comonomer with N-hydroxysuccinimide ester function was used with purpose to provide groups suitable for convenient immobilization of proteins. Typically, 0.3 g of freshly distilled pyrrole, 1.07 g of N-hydroxysuccinimide ester of 1-(2-carboxyethyl)pyrrole, 1.8 g of $FeCl_3$, and 0.2 g of poly(N-vinylpyrrolidone) (colloid stabilizer with nominal molecular weight 360 000) were added to suspension containing 1 g of polystyrene nanospheres [15, 16]. Reaction mixture was stirred at 75 °C for 24 hours. Obtained particles were isolated by centrifugation and redispersion in pure water. Scheme E illustrates the described above synthesis.

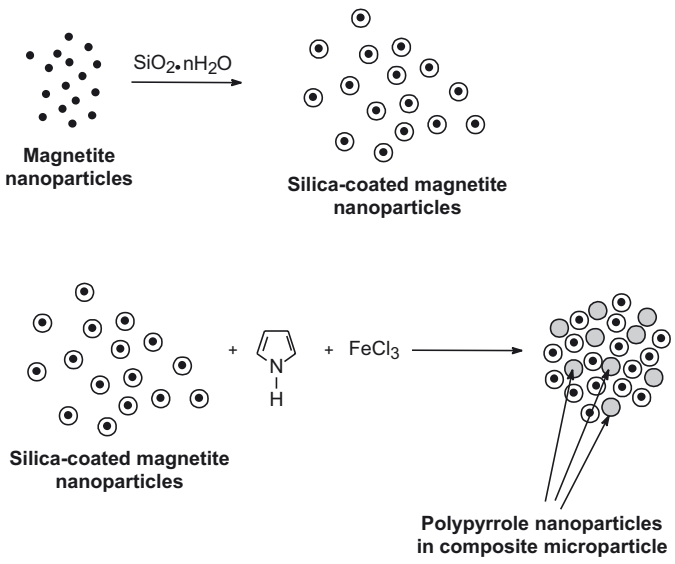


Scheme E. Synthesis of (polystyrene core)-(polypyrrole shell) nanoparticles with succinimide functions

Diameter of microspheres increased from 450 nm to 460 nm after polypyrrole coating. It is worth noting that ζ-potential of the polystyrene seed particles equal -67 mV did change to a positive value +1.4 mV after attachment of polypyrrole forming the positively charged shell.

Composite polypyrrole-magnetite-silica microparticles were obtained by synthesis of silica-coated magnetite nanoparticles that later were added to a mixture in which the red-ox polymerization of pyrrole was carried on [17]. Synthesis of these particles is shown in Scheme F.

A short description (based on data in Ref. [17]) of the synthesis is given below. Sodium silicate (60 g, containing *ca* 27 % wt/v of soluble silica) in 1600 ml of H_2O was passed through the ion-exchange resin in a process generating the silicic acid. The eluent was combined with 1200 ml of the magnetite sol. The stirred mixture was titrated with HCl to pH = 10. Thereafter the sol was purified by dialysis against $N(CH_2CH_3)_4OH$ at pH equal 10, 9.5, 8, and eventually against distilled water. Diameters of obtained silica-coated magnetite nanoparticles were in the range from 5 to 20 nm. Pyrrole and $FeCl_3 \cdot 6H_2O$ (oxidant) were added to suspension of silica-coated magnetic nanoparticles. Concentrations of the reagents were 8.28, 0.91 and 1.77 % wt/v for oxidant, pyrrole and silica-coated magnetic nanoparticles appropriately. Polymerization was carried on for 3 hours yielded composite nanoparticles containing polypyrrole. Number average diameters of these nanoparticles estimated from transmission electron microscopy pictures were ca 150 nm (diameter distribution was very broad), their conductivity was 10^{-1} S · cm^{-1}.



Scheme F. Synthesis of composite polypyrrole-magnetite-silica microparticles

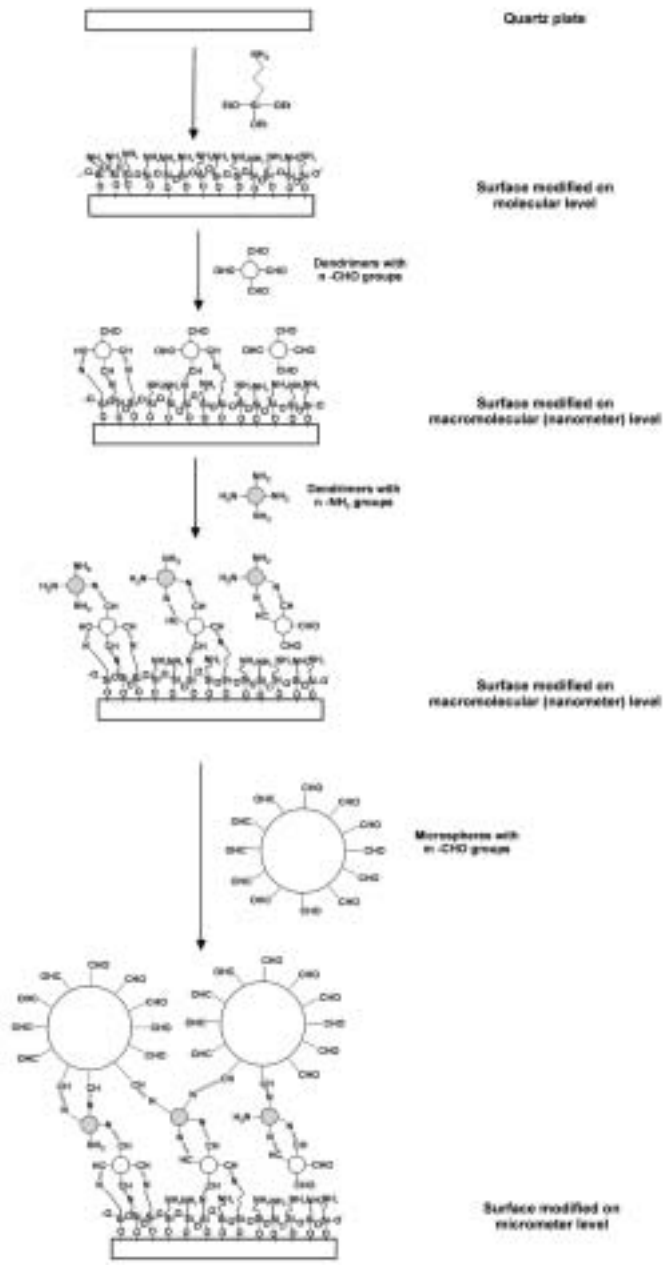
SELF-ASSEMBLY OF NANO- AND MICROPARTICLES INTO HYBRID STRUCTURES

Materials with controlled surface roughness on nano- and micrometer level

Construction of various types of biosensors requires materials formed to appropriate shape (*e.g.*, disks or rectangular plates), materials being not only suitable for controlled covalent immobilization of proteins or other biomolecules but having also roughness controlled on molecular, macromolecular (*i.e.*, nano-) and micrometer level. There are hundreds of papers on modification of quartz or metal (*e.g.*, gold) surfaces by attachment of small molecules (*e.g.*, organosilanes or thiols attached onto quartz and glass or gold, respectively). There are also many papers on adsorption of nano- and microparticles onto solid substrates. In our studies we developed methods allowing for a layer-by-layer deposition of low molecular weight silanes, dendrimers and polymer microspheres equipped with amino (silanes, dendrimers) and aldehyde (dendrimers and microspheres) groups [18, 19]. Scheme G shows arrangements of molecular, macromolecular and particulate building blocks in hybrid materials obtained according to the described above strategy.

Quartz plates were coated with γ-aminopropyltriethoxysilane by incubation of cleaned (with 5 mol/l KOH solution and then washed several times with fresh water to neutral pH) plates with γ-aminopropyltriethoxysilane in toluene (8 % v/v) for 20 hours. Then, the slides were washed several times with water, thereafter with ethanol and dried at room temperature. Absence of nitrogen (N1s) signal in XPS spectra of clean quartz plates and presence of strong signal in spectra of plates incubated with γ-aminopropyltriethoxysilane (Quartz--APTS plates) revealed that surface of plates was effectively coated with an amino functionalized siloxane layer [20].

Plates covered with silane layer were immersed for 3 hours in CH_2Cl_2 solution of dendrimers containing alde-



Scheme G. Modification of quartz surface by sequential deposition of γ-aminopropyltriethoxysilane, dendrimers with aldehyde, dendrimers with amine groups, and microspheres with aldehyde groups (see text)

hyde groups (dendrimers of generation 5, with molecular weight 31 300 synthesized according to description in Ref. [21]). Concentration of dendrimers was equal $4.5 \cdot 10^{-1}$ g/l. Deposition of dendrimers onto surface of Quartz-APTS plates was carried on for 3 hours. XPS measurements revealed that the average thickness of dendrimer ad-layer was equal 3.7 nm and was close to the diameter of G5 dendrimers [19]. AFM observations proved that the surface of Quartz-APTS-G5 plates was smooth with uniformly distributed dendrimers. Thus, it was possible to conclude that the plates were covered with monolayer of G5 dendrimers.

Subsequent incubation of Quartz-APTS-G5 plates with methanol:ethanol (1:10) solution of PAMAM generation 4 dendrimers (polyamidoamine type) ([-$CH_2N[CH_2CH_2CONHCH_2CH_2N[CH_2CH_2CONHCH_2CH_2N[CH_2CH_2CONHCH_2CH_2$-N-$[CH_2CH_2CONHCH_2CH_2N(CH_2CH_2CONHCH_2CH_2NH_2)_2]_2]_2]_2]_2$, concentration 10 g/l) for 38 hours yielded plates with thickness (determined by XPS) increased by 3.2 nm [21]. It is worth noting that diameter of PAMAM dendrimers used in these studies was *ca* 3 nm. This means that in Quartz--APTS-G5-PAMAM plates PAMAM dendrimers formed an external monolayer.

Incubation of Quartz-APTS-G5-PAMAM plates with suspension of poly(styrene-*co*-divinylbenzene-*co*-acrolein) (PSDA) microspheres in water (microspheres with diameters 310 nm and concentration of aldehyde groups equal $4.04 \cdot 10^{-6}$ mol/m^2 were used; concentration of microspheres was equal 1.5 % wt/v) was carried on for 24 hours. XPS technique was used for determination of the degree of surface coverage with microspheres. Measurements of attenuation of N1s, P2p and S2p signals (the latter two due to G5 dendrimers) gave values of the degree of surface coverage equal 0.60, 0.61 and 0.65 calculated on the basis of nitrogen, phosphorus and sulfur signals, respectively [21]. It is worth noting that maximal surface coverage by irreversibly attached particles is close to 0.64 [22].

Amine and aldehyde groups on surface of quartz--polymer hybrid materials described above are suitable for efficient covalent immobilization of proteins [20]. Thus, the Quartz-APTS, Quartz-APTS-G5, Quartz--APTS-G5-PAMAM, and Quartz-APTS-G5-PAMAM--PSDA plates can be considered as good candidates for construction of biosensors in which detection is based on protein-analyte interactions.

Biodegradable materials with controlled porosity

In medicine there is a great need for materials that inoculated with bone-forming cells and implanted into a living organism could be gradually converted into hard tissue replacing various kinds of bones. Materials used for making scaffolds for bone-forming cells should be biocompatible, biodegradable, with proper mechanical strength, porosity allowing ingrowth of cells, diffusion in of nutrients and diffusion out of degradation products and unwanted cell metabolites. Due to biocompatibility and biodegradability requirements scaffolds for tissue engineering are often made from such polymers as polylactides, polyglycolide, poly(ε-caprolactone), polyhydroxybutyrate, various polycarbonates and their copolymers [23]. In many instances, needed properties have hybrids of synthetic and natural polymers, often containing additionally calcium salt particles added with purpose to improve mechanical strength of scaffolds.

Foaming of polymer mixtures or preparation of mixtures of polymers with large portion of NaCl or sugar

particles of required size, followed by washing out these low molecular weight compounds, ensures porosity of scaffolds for tissue engineering [24—26]. Recently there were developed also methods suitable for formation of porous polyester scaffolds by sintering polyester microspheres [27, 28]. Microspheres were produced from poly(L,L-lactide-*co*-glycolide) (PLAGA) (polylactide: polyglycolide 85:15, molecular weight 420 000) by solvent evaporation method. For this purpose a sample of PLAGA was dissolved in CH_2Cl_2 (polymer concentration 6.7 % wt/v). Polymer solution in CH_2Cl_2 was added dropwise, during 10 hours, to stirred poly(vinyl alcohol) solution in water (1 % wt/v). Formed particles were isolated by vacuum filtration and divided, using micron sieves, into fractions with various diameters in a range from *ca* 200 to 700 mm [28]. Particles were placed into molds and heated at 160 °C for required time in the range from 2 to 4 hours. After slow cooling the highly porous (pores ranging from *ca* 50 to 250 μm, depending on particle diameters) were obtained.

Recently, we developed a new method for preparation of polyester scaffolds with small (*ca* 1 μm) and large (from 100 to 400 μm) pores [29, 30]. Scaffolds were formed from microparticles obtained by dialysis of poly(L,L-lactide) solutions in acetonitrile. Microparticles composed of poly(L,L-lactide) lamella and crystallites were irregular in shape. Their dimensions were from a few to *ca* 25 μm. Poly(L,L-lactide) microparticles were mixed with NaCl crystals with diameter ranging from 80 to 350 μm. NaCl content in the mixture was varied from 80 to 94 wt. %. The mixture was placed in a mold and pressed under pressure 10 MPa for 24 hours at 70 °C. Scaffolds, in form of pellets with 6 mm diameter, were obtained. Total porosity of the scaffolds was *ca* 80 %.

HYBRID MATERIALS OBTAINED IN SOL-GEL PROCESSES

Bioactive compounds are usually attached to solid supports either by simple physical adsorption or by covalent immobilization. Recently M. A. Brook and coworkers elaborated a method allowing for one step synthesis of highly porous gels containing entrapped biomacromolecules [31, 32]. According to this method a portion of the solution of hydrolyzed tetraethoxysilane (*e.g.*, 4.5 ml of tetraethoxysilane, 14 ml of water and 0.1 ml of 0.1 N HCl sonicated for 1 hour to give a homogeneous solution) was mixed with an equal portion of buffered solution of the enzyme (*e.g.*, Factor Xa, γ-glutamyl transpeptidase, dihydrofolate reductase, or cyclooxygenase-II) were mixed and allowed to gel for time ranging from 5 to 20 min [31].

Gels with entrapped enzymes were obtained also in processes based on gelation of diglycidylsilane — enzyme mixtures. The mentioned above enzymes were entrapped effectively and retained their biological activity.

EXAMPLES OF APPLICATION OF HYBRID MATERIALS FOR MEDICAL PURPOSES

Polymeric hybrid materials were used very often in construction of biosensors for medical diagnostics, usually for biosensors with amperometric or potentiometric detection. Many sensors were constructed using conducting supports (metals or glass coated with metallic ad-layer) covered with polymer films containing entrapped bioactive compounds. For example, Adeloju *et al.* described fabrication of platinum electrode covered with ultra-thin (*ca* 55 nm) polypyrrole film with immobilized glucose oxidase [33]. This electrode was used as an element of biosensor for potentiometric determination of glucose. There was described also a design of biosensor for amperometric detection of glucose, galactose and cholesterol containing platinum foil electrode covered with polypyrrole hydrogel composite [made of polypyrrole and poly(hydroxyethyl methacrylate)] with entrapped glucose oxidase, galactose oxidase and cholesterol oxidase [34]. Polymer hydrogel films with thickness from 100 to 800 μm were efficiently penetrated by analytes. Combination of galvanometric metal deposition and vacuum evaporation/deposition as well as electropolymerization of pyrrole [in presence of glucose oxidase, catalase, lactate oxidase, and glutamin(asparagin)ase] on patterned surfaces of thin glass wafers allowed production of microbiosensor arrays [35]. The microbiosensors, suitable for parallel determination of glucose, glutamine, lactate, and glutamate, could be used for *in-vivo* and *ex-vivo* analysis of the whole blood.

Recently, Kim *et al.* described an immuno-sensor composed of glass fiber membrane, nitrocellulose membrane and cellulose membrane connected sequentially into one strip [36]. Glass fiber membrane contains nanoparticles of gold with immobilized antibodies against antigen to be detected. Antibodies of the same kind are immobilized in the nitrocellulose membrane on which silver electrodes were deposited. Application of a drop of liquid containing appropriate antigen leads to formation of gold nanoparticle-antibody-antigen conjugates transported (like in thin layer chromatography) to the nitrocellulose membrane. Antigen antibody interaction in the nitrocellulose membrane results in formation of the gold nanoparticle-antibody-antigen-antibody-nitrocellulose membrane structures, presence of which is detected by increased conductivity between deposited electrodes (bridging effect of nanogold particles).

The most common deficiency of sensors containing biomolecules entrapped in polymer films consists on leaking of biomolecules during prolonged storage. Recently, we developed a method in which polymer film was formed by electrocopolymerization of pyrrole and vinyl sulphonate on surface of indium-tin oxide covered plates. Electropolymerization was carried on in presence of polypyrrole nanoparticles with covalently immobilized urease [5]. The obtained film did contain entrapped

polypyrrole nanoparticles with covalently immobilized urease. Nanoparticles much larger than enzyme molecules did not leach from the film. In effect, the electrodes could be stored at temperatures up to 50 °C for 40 days.

Kros *et al.* developed a system consisting of conducting ink and polypyrrole-coated polystyrene microspheres with immobilized glucose oxidase [37]. This mixture was used for printing electrodes for biosensors for determination of glucose.

Polymeric hybrid materials are indispensable for production of bone cements [38] and various temporary biodegradable implants that after implantation are slowly decomposed and gradually replaced by tissue formed by the host organism. There are reports on using porous β-tricalcium phosphate loaded with poly(L,L-lactide-*co*--glycolide) and recombinant bone morphogenetic proteins as temporary bone-inducing implants [39]. Implantation of this material into 1.5 cm femur bone defect resulted in complete healing after 24 weeks. Blends of poly(L,L-lactide-*co*-D,L-lactide) with β-tricalcium phosphate were used for fabrication of pins for bone fixation [40, 41].

Composite materials made from poly(ε-caprolactone) films irradiated with Ar^+ ions and then modified by adsorption of Arg-Gly-Asp tripeptide were found to be good substrates for growing osteoblasts accompanied with bone deposition [42].

Shikinami reported on the fate of cylinders made of forged composites of hydroxyapatite (particles with diameters ranging from 0.2 to 20 μm) and poly(L,L-lactide) (molecular weight from 180 000 to 220 000) after implantation into distal femoral condyle of rabbits [43]. It was found that 2.5 years after implantation hydroxyapatite particles were released from the implants. The poly(L,L--lactide) matrix was completely degraded and replaced with the new bone after period from 4.5 to 5 years. Thus, in animal test the material was proven to be suitable for regeneration of large bone defects.

Since many years natural and synthetic polymers are used in various drug formulations, like tablets, capsules, sponges, liposomes and others [23, 44]. Recently there is a growing interest in polymeric nano- and microsphere drug carriers [45, 46]. In this paper, however, we will concentrate our attention only on drug delivery from hybrid materials that mainly have to fulfill other functions in implantable devices.

There are two important needs of local drug delivery accompanying implantation of prosthetic devices. In the case of biodegradable temporary implants there is useful a local delivery of drugs facilitating growth of required tissue. Thus, many biodegradable temporary bone replacing implants are loaded with bone morphogenetic proteins that are slowly released on site [39, 47—50].

Implantation of nondegradable devices is often accompanied with unwanted side effects. One of them is inflammation that in the case angioplasty used for treatment of coronary narrowings by implantation of metal stents is followed in many cases by unwanted restenosis. Extensive investigations [51—55] resulted in development of stents coated with various oligo- and polymers [phosphorylcholine and phosphorylcholine based polymers, gelatin and crosslinkable gelatin derivatives, polysiloxane, poly(lactide-*co*-glycolide), poly(ε-caprolactone), poly(hydroxybutyrate-*co*-hydroxyvalerate), polyorthoesters, poly(ethylene oxide)-poly(butylene terephthalate)]. Coatings of these stents are loaded with various drugs (*e.g.*, paclitaxel, sirolimus, tacrolimus, methylprednisolone, and dexamethason). Their release during first days after stent implantation leads to significant decrease of inflammatory response and in long term to reduction of restenosis.

ACKNOWLEDGMENT

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REFERENCES

[1] Azioune A., Chehimi M. M., Miksa B., Basinska T., Slomkowski S.: *Langmuir* 2002, **18**, 1150. [2] Azioune A., Siroti F., Tanguy J., Jouini M., Chehimi M. M., Miksa B., Slomkowski S.: *Electrochim. Acta* 2005, **50**, 1661. [3] Adeloju S. B., Moline A. N.: *Biosens. Bioelectron.* 2001, **16**, 133. [4] Brahim S., Narinesingh D., Guiseppi-Elie A.: *Biosens. Bioelectron.* 2002, **17**, 53. [5] Gambhir A., Kumar A., Malhotra B. D., Miksa B., Slomkowski S.: *e-Polymers* 2002, **052**, 1. [6] Cosnier S.: *Biosens. Bioelectron.* 1999, **14**, 443. [7] Iwuoha E. I., de Villaverde D. S., Garcia N. P., Smyth M. R., Pingarron J. M.: *Biosens. Bioelectron.* 1997, **12**, 749. [8] Saxena V., Malhotra B. D.: *Curr. Appl. Phys.* 2003, **3**, 293. [9] Ryder K. S., Morris D. G., Cooper J. M.: *Biosens. Bioelectron.* 1997, **12**, 721. [10] Rademacher J. T., Baum R., Pallack M. E., Brittain W. J., Simonsick W. J.: *Macromolecules* 2000, **33**, 284.

[11] Matyjaszewski K., Xia J.: *Chem. Rev.* 2001, **101**, 2921. [12] Jones D. M., Brown A. A., Huck W. T. S.: *Langmuir* 2002, **18**, 1265. [13] Zhao B., Brittian W. J.: *J. Am. Chem. Soc.* 1999, **121**, 3557. [14] Miksa B., Slomkowski S.: *Colloid Polym. Sci.* 1995, **273**, 47. [15] Boussalem S., Yassar A., Basinska T., Miksa B., Slomkowski S., Azioune A., Chehimi M. M.: *Polym. Adv. Technol.* 2003, **14**, 820. [16] Bousalem S., Mangeney C., Alcote Y., Chehimi M. M., Basinska T., Slomkowski S.: *Colloids Surf. A* 2004, **249**, 91. [17] Butterworth M. D., Bell S. A., Armes S. P., Simpson A. W.: *J. Colloid Interface Sci.* 1996, **183**, 91. [18] Miksa B., Slomkowski S., Chehimi M. M., Delamar M., Majoral J.-P., Caminade A.-M.: *Colloid Polym. Sci.* 1999, **277**, 58. [19] Slomkowski S., Miksa B., Chehimi M. M., Delamar M., Cabet-Deliry E., Majoral J.-P., Caminade A.-M.: *React. Funct. Polym.* 1999, **41**, 45. [20] Kowalczyk D., Slomkowski S., Chehimi M. M., Delamar M.: *Int. J. Adhesion Adhesives* 1996, **16**, 227.

[21] Galliot C., Prévoté D., Caminade A.-M., Majoral J.-P.: *J. Am. Chem. Soc.* 1995, **117**, 540. [22]

Trznadel M., Slomkowski S.: *Colloid Polym. Sci.* 1996, **274**, 1109. [23] Jagur-Grodzinski J.: *e-Polymers*, http://www.e-polymers.org, 2003, No 012. [24] Yoon J. J., Kim J. H., Park T. G.: *Biomaterials* 2003, **24**, 2323. [25] Gross K. A., Rodríguez-Lorenzo L. M.: *Biomaterials* 2004, **25**, 4955. [26] Zhang J., Wu L., Jing D., Ding J.: *Polymer* 2005, **46**, 4979. [27] Borden M., Attawia M., Khan Y., Laurencin C. T.: *Biomaterials* 2002, **23**, 551. [28] Borden M., El-Amin S. F., Attawia M., Laurencin C. T.: *Biomaterials* 2003, **24**, 597. [29] Gadzinowski M., Sosnowski S., Slomkowski S.: *Eng. Biomater.* 2003, **6**, 75. [30] Gadzinowski M., Sosnowski S., Slomkowski S.: *Eng. Biomater.* 2004, **7**, 118.

[31] Besanger T. R., Chen Y., Deisingh A. K., Hodgson R., Jin W., Mayer S., Brook M. A., Brennan J. D.: *Anal. Chem.* 2003, **75**, 2382. [32] Cruz-Aguado J. A., Chen Y., Zhang Z., Elowe N. H., Brook M. A., Brennan J. D.: *J. Am. Chem. Soc.* 2004, **126**, 6878. [33] Adeloju S. B., Moline A. N.: *Biosens. Bioelectron.* 2001, **16**, 133. [34] Brahim S., Narinesingh D., Guiseppi-Elie A.: *Biosens. Bioelectron.* 2002, **17**, 53. [35] Moser I., Jobst G., Urban G. A.: *Biosens. Bioelectron.* 2002, **17**, 297. [36] Kim J.-H., Cho J.-H., Cha G. S., Lee Ch.-W., Kim H.-B., Paek S.-H.: *Biosens. Bioelectron.* 2000, **4**, 907. [37] Kros A., van Hövel S. W. F. M., Nolte R. J. M., Sommerdijk N. A. J. M.: *Sensors Actuators B* 2001, **80**, 229. [38] Łukaszczyk J.: *Polimery* 2004, **49**, 79. [39] Yoneda M., Terai H., Imai Y., Okada T., Nozaki K., Inoue H., Miyamoto S., Takaoka K.: *Biomaterials* 2005, **26**, 5145. [40] Claes L., Ignatius A., Rehm K. E., Scholz C.: *Biomaterials* 1996, **17**,1621.

[41] Prokop A., Jubel A., Helling H. J., Eibach T., Peters C., Baldus S. E., Rehm K. E.: *Biomaterials* 2004, **25**, 259. [42] Marletta G., Ciapetti G., Satriano C., Paganib S., Baldini N.: *Biomaterials* 2005, **26**, 4793. [43] Shikinami Y., Matsusue Y., Nakamura T.: *Biomaterials* 2005, **26**, 5542. [44] Ravi Kumar M. N. V., Kumar N., Domb A. J., Arora M.: *Adv. Polym. Sci.* 2002, **160**, 45. [45] Edlund, Albertsson A.-C.: *Adv. Polym. Sci.* 2002, **157**, 67. [46] Slomkowski S., Gadzinowski M., Sosnowski S., Radomska-Galant I.: *Polimery* 2005, **50**, 546. [47] Yamamoto M., Takahashi Y., Tabata Y.: *Biomaterials* 2003, **24**, 4375. [48] Rai B., Teoh S. H., Ho K. H., Hutmacher D. W., Cao T., Chen F., Yacob K.: *Biomaterials* 2004, **25**, 5499. [49] Kaito T., Myoui A., Takaoka K., Saito N., Nishikawa M., Tamai N., Ohgushi H., Yoshikawa H.: *Biomaterials* 2005, **26**, 73. [50] Rai B., Teoh S. H., Hutmacher D. W., Cao T., Ho K. H.: *Biomaterials* 2005, **26**, 3739.

[51] Lewis A. L., Tolhurst L. A., Stratford P. W.: *Biomaterials* 2002, **23**, 1697. [52] Nakayama Y., Nishi S., Ueda-Ishibashi H., Matsuda T.: *J. Biomed. Mater. Res.* 2003, **64A**, 52. [53] Nakayama Y., Ji-Youn K., Nishi S., Ueno H., Matsuda T.: *J. Biomed. Mater. Res.* 2001, **57**, 559. [54] Fontaine A. B., Borsa J. J., Hoffer E., Bloch R., So C.: *Cardiovasc. Intervent. Radiol.* 2001, 24, 324. [55] Wieneke H., Sawitowski T., Wnendt S., Fischer A., Dirsch O., Karoussos I. A., Erbel R.: *Herz* 2002, **27**, 518.