A novel electrochemically synthesized biodegradable thin film of polypyrrole–polyethyleneglycol–polylactic acid nanoparticles

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Nanoparticles having reactive pyrrole residues were prepared from poly(1-ethoxyethylglycidyl ether)-*block*-poly(L,L-lactide) block copolymer. The nanoparticles were electropolymerized in aqueous media through the oxidation of the pyrrole residue and in the presence of pyrrole to form a nanocomposite thin film. The novel synthesis of these pyrrole-functionalized nanoparticles is described and the electrochemical deposition of the corresponding coating is characterized using electrochemistry, SEM and EDX.

Introduction

Electrically conducting polymers have attracted much interest in the last twenty years because they combine the physical and chemical properties of organic polymers with the electric characteristics of metals. Among the known conducting polymers, polypyrrole has probably been the most investigated and applied, because of its simple method of preparation, high conductivity and durability.[1,2] Polypyrrole has been frequently utilized in biochemistry and medicine as a matrix for assembling biosensors.[3–10] Moreover, the reversible doping–undoping mechanism of polypyrrole has been the driving force for the delivery of charged biological substances to and from the polymer matrix.[11–15] For example, Miller and Zhou showed that a copolymer film was doped with dopamine upon its reduction.[12] The entrapped dopamine was released by stepping the polymer to a positive potential.

The chemical and physical properties of conducting polymers, such as redox activity, morphology and conductivity, can be tuned by incorporating nanoparticles into the polymeric matrix.[5,16–34] For example, the conductivity of polyaniline and polypyrrole was markedly improved upon embedding gold and silver nanoparticles.[17,33] Lee and Liu reported that pyrrole, which was catalytically electrooxidized upon incorporating silver nanoparticles into the polypyrrole matrix, showed superior conductivity.[16] Nanoparticle-doped conducting polymers can also be used as electrochemical sensors[5,34] as has been demonstrated by Xian and coworkers, who described a glucose biosensor based on gold nanoparticles embedded in polyaniline nanofibers.[5]

To date, several different approaches have been employed for the preparation of *metal* or *inorganic* nanoparticle-conducting polymer nanocomposites, such as chemical polymerization, physical mixing,[35] layer-by-layer assembly[17] and sol–gel deposition.[36] Only a few studies have focused on the incorporation of *organic* nanoparticles into conducting polymers.[37–39] Shi and coworkers synthesized a conductive polypyrrole nanoparticle–poly(D,L-lactide) composite on which the growth of fibroblasts was regulated by direct electron current.[37]

In spite of the fact that organic nanoparticles can be formulated from a wide variety of synthetic and natural polymers, biodegradable polymers are especially appealing due to their biodegradability and biocompatibility with cells and tissues.[40] Nanoparticles of biodegradable polymers, such as polylactic acid (PLA) and polyethyleneglycol (PEG)-modified PLA, have recently been used for sustained and localized administration of different therapeutic agents.[41–44]

In this study we report the formation and characterization of a thin polypyrrole matrix to which PLA nanoparticles are covalently attached *via electropolymerization* in a single step. Firstly, PLA nanoparticles having reactive pyrrole residues were synthesized from poly(1-ethoxyethylglycidyl ether)-*block*-poly(L,L-lactide) block copolymer. In a subsequent step, the modified PLA nanoparticles were electropolymerized on 316L stainless steel and evaporated gold electrodes in the presence of pyrrole. Such a thin polypyrrole film containing biodegradable nanoparticles can be used for coating implantable medical devices usually made of 316L stainless steel. The advantages of the approach described here include highly biocompatible organic material, large drug loading (compared to polymer swelling for example) and good control of drug release. These features can be tailored by controlling the size, shape, and functions of the nanoparticle building blocks.

Materials and methods

Materials

Pyrrole (98%) was purchased from Sigma-Aldrich and was freshly purified by alumina column chromatography before

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use. Alumina for column chromatography was purchased from ICN Biomedicals, Germany (activity grade I). NaF (99%) was obtained from BDH Chemicals and used as received. Deionized water (Barnstead Easypure UV system) was used for preparing the different solutions. Acetonitrile (ACN, >99.8%) was obtained from J. T. Baker while acetone and dichloromethane HPLC grade were from BioLab (Jerusalem, Israel).

L,L-Lactide (Boehringer, Germany) was purified by crystallization from 2-propanol and subsequent sublimation. Purified monomer was protected from contact with air by being stored in an evacuated ampoule. 1-Ethoxyethylglycidyl ether was synthesized by reaction of glycidol (Aldrich) and ethyl vinyl ether (Fluka) according to the known procedure.[45] The initiator potassium *tert*-butoxide (Aldrich) was used as received. Tetrahydrofuran (THF, POCh, Poland) was distilled and dried over Na wires. Thereafter, these solvents were dried over a Na–K alloy in ampoules equipped with Teflon® stopcocks and stored under vacuum. The required amounts of THF were distilled using a vacuum line to polymerization vessels. 1,4-Dioxane (POCh, Poland) was purified by distillation. The fraction boiling in a range of 100–102 °C was collected. Methylene chloride (POCh, Poland) was purified according to the following procedure. First, solvent was stirred with concentrated sulfuric acid (10% v/v with respect to the solvent). Thereafter, methylene chloride was isolated using a separating funnel and washed with several portions of distilled water. Then it was preliminarily dried with $CaCl_2$, distilled (the fraction boiling at 40 °C was collected) and dried in an evacuated ampoule over P_2O_5. The necessary amount of methylene chloride was distilled prior to use.

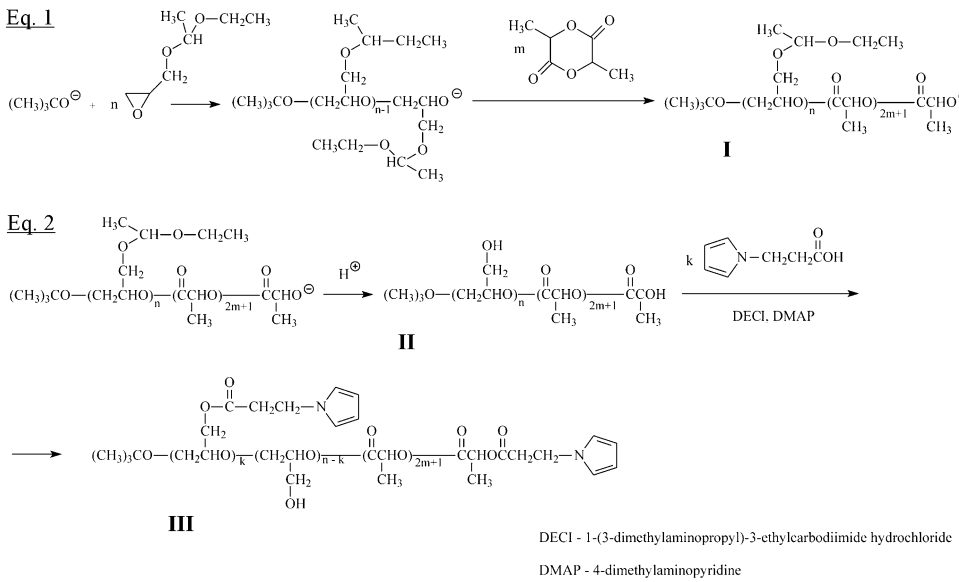
Syntheses

Synthesis of polyglycidol–*block*-poly(L,L-lactide) (Scheme 1, II). Poly(1-ethoxyethylglicydyl ether) block polymer (Scheme 1, **I**) was synthesized by polymerization of 1-ethoxyethylglicydyl ether initiated with *t*-BuOk and carried out in THF. Briefly, *t*-BuOK (0.186 g, 1.66 mmol) was placed into an ampoule equipped with a Teflon® stopcock. The content was evacuated using a vacuum line and THF (100 mL) and 1-ethoxyethylglicydyl ether (6.95 g, 47 mmol) were distilled into the ampoule, which was kept in liquid nitrogen. The temperature of the ampoule content was increased quickly to 45 °C and polymerization was allowed to continued for 96 h. Thereafter, the polymerizing mixture was transferred to an evacuated ampoule containing L,L-lactide (6.7 g, 46 mmol) and polymerization was continued at 45 °C for 24 h. After completion of poly(L,L-lactide) block polymerization, active centers were eliminated by addition of acetic acid (tenfold molar excess with respect to the initiator) and THF was removed under vacuum.

Signals in the ^{1}H NMR spectrum of **I** were assigned as follows: 1.0–1.3 (overlapping s and d, $(CH_3)_3C$– end-group from initiator and $CH_3CH<$, polyEEGly); 1.55 (t, –CO(CH-CH_3)O–, PLLA); 3.20–3.85 (m, –OCH_2–, –O$CH<$; polyEEGly); 4.64 (q, –OCH(CH_3)O–, polyEEGly); 5.05–5.25 (m,–COCH(CH_3)O–, PLLA).

The hydroxyl groups were deprotected by dissolving **I** in 1,4-dioxane : water 8 : 2 (v/v) mixture (*ca.* 150 mL) to which 20 mL of concentrated formic acid was added. The mixture was stirred for 4 days. Then it was frozen and lyophilized to give polyglycidol–*block*-poly(L,L-lactide) (**II**).

Functionalization of polyglycidol-*block*-poly(L,L-lactide) with 3-(pyrrol-1-yl)-propanoic acid (Scheme 1, III). Polyglycidol-*block*-poly(L,L-lactide) (**II**) was labeled with 3-(pyrrole-1-yl)-propanoic acid according to the general procedure developed by Le Gall *et al.*[46] 3-(Pyrrol-1-yl)-propanoic acid was synthesized by basic hydrolysis of 1-pyrrolepropionitrile (Sigma, Israel). The copolymer (8.0 g), 3-(pyrrole-1-yl)-propanoic acid (5.0 g, 40 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DECI) (7.5 g, 40 mmol) and 4-dimethylaminopyridine (DMAP) (0.5 g, 4.1 mmol) were dissolved in methylene chloride (100 mL). The mixture was stirred for 24 h Thereafter, the liquid components of the mixture were



Scheme 1

evaporated using a rotary evaporator. The remaining copolymer was dissolved in 15 mL of 1,4-dioxane and dialyzed (using a Serva SpectraPor dialysis tube) against water. The dialysis was continued for 96 h and the product was lyophilized.

Signals in the ^{1}H NMR spectrum of **III** were assigned as follows: 1.15 (s, $(CH_3)_3C$– end-group from initiator; 1.56 (d, overlapping doublets of –C(O)CH(CH_3)O– groups along the chain and end groups of PLLA blocks), 2.65–2.90 (t, –CH_2CH_2C(O)–, labeled polyGly); 3.30–3.65 (m, –OCH_2–, –OCH<, polyGly labeled and not labeled, >$CHCH_2OH$, polyGly); 3.9–4.4 (m, >$CHCH_2O$– and >NCH_2CH_2–, labeled polyGly); 5.25 (q, –C(O)CH(CH_3)O–, PLLA); 6.05 (d, –CH=CHN–, pyrrole); 7.23 (d, –CH=CHN–, pyrrole). Integration of signals in the spectrum was in agreement with the number average degree of polymerization of the PLLA block ($2m$ + 1) being equal to 42 (M_n = 3000), of the labeled polyGly block (k) equal to 24 (M_n = 4700) and of the unlabeled polyGly segment (n + k) being equal to two. Thus, the efficiency of labeling was *ca.* 92%.

Synthesis of monomers and nanoparticle preparation. The so called pyrrole–PEG–PLA nanoparticles were prepared as follows: 50 mg of **III** was dissolved in an organic mixture consisting of 15 mL acetone and 0.5 mL dichloromethane. This organic solution was poured under moderate stirring on a magnetic plate into 40 mL double distilled water. The volume of the resulting dispersion was adjusted to 10 mL using rotary evaporation. The nanoparticle size distribution was determined by ALV-NIBS/HPPS (high performance particle sizer, ALV-Laser Vertriebsgesellschaft, Germany) of the nanoparticle suspension diluted with double distilled water at 22 °C.

Characterization

The surface morphology of the modified electrodes was examined by HR-SEM using a Sirion scanning electron microscope (SEM, FEI Company, the Netherlands) equipped with Shottky type field emission source at 10 kV accelerating voltage. For this purpose, the samples were washed with water, dried at room temperature and sputter-coated with a Au–Pd thin film prior to HR-SEM analysis. An EDX detector was utilized to analyze film composition.

The molecular weight of **I** was estimated using a GPC system equipped with a LKB 2150 pump, a Wyat Optilab 903 refractive index (RI) detector and a Rheodyne (Coatati, CA) injection valve with 20 μL loop (Waters Ma). Samples were eluted with THF through a set of PSS SDV Gels 100 Å and 10 000 Å columns (TOS OH Bioscience) at a flow rate of 0.8 mL min^{-1}. The molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA) with a molecular weight range of 500–10 000. The molecular weight of **III** was determined using a similar set as that described above but equipped additionally with light scattering (Wyat Dawn DSP) and UV (LKB 2238 UVICORD) detectors.

^{1}H-NMR spectra ($CDCl_3$) were obtained by a Bruker AC 200 spectrometer in tubes with a 5 mm od. $CDCl_3$ containing tetramethylsilane served as a solvent and shift reference, respectively.

Electrochemical measurements were conducted with an AUTOLAB PGSTAT10 potentiostat (EcoChemie, Utrecht, The Netherlands) using a single compartment three-electrode glass cell. The working electrodes were either evaporated Au on glass or polished (1200 grit emery paper) 316L stainless steel plates. The reference electrode was a saturated $Hg|Hg_2SO_4|K_2SO_{4(sat)}$ electrode and a graphite rod was used as an auxiliary electrode.

Polymeric films were prepared by cyclic voltammetry (CV). The working electrode was immersed into a deaerated aqueous solution containing 0.1–0.01 M distilled pyrrole monomer and 0.45 mg mL^{-1} polypyrrole–PLA nanoparticle emulsion and 0.1 M NaF (used as an electrolyte to facilitate anion incorporation in the course of polymerization) at room temperature. A potential sweep between −0.8 and 1.0 V of 10 cycles and 100 mV s^{-1} scan rate were typically applied (unless otherwise mentioned). Then, the electropolymerized electrodes were rinsed with pure water and dried with a gentle stream of nitrogen at room temperature.

Results and discussion

Synthesis of polyglycidol-*block*-poly(L,L-lactide) labeled with pyrrole (III) and preparation of nanoparticles

Polyglycidol-*block*-poly(L,L-lactide) labeled with pyrrole (**III**) was synthesized by anionic copolymerization of blocked glycidol (1-ethoxyethylglycidyl ether) and L,L-lactide (Scheme 1, eqn (1)) with subsequent deblocking of hydroxyl groups in the polyglycidol block and attachment of pyrrole moieties in reaction with 3-(pyrrol-1-yl)-propanoic acid (Scheme 1, eqn (2)). The synthesis of polyglycidol-*block*-poly(L,L-lactide) copolymer (**II**) was described earlier for synthesis of poly(ethylene oxide)-*block*-polyglycidol–*block*-poly(L,L-lactide).[47] The obtained poly(1-ethoxyethylglycidyl ether)-*block*-poly(L,L-lactide) copolymer (polyEEGly-*block*-PLLA, **I**) was characterized by GPC (see Fig. 1) and ^{1}H NMR (see Fig. 2). The number average molecular weight (M_n) and molecular weight polydispersity (M_w/M_n) were 5700 and 1.25, respectively (relative values based on polystyrene standards calibration). Integration of these signals revealed that the number average degree of polymerization of polyEEGly and PLLA blocks was 26 and 42, respectively (see Fig. 2). Thus, the M_n of polyEEGly was 3800 and the M_n of PLLA was 3000.

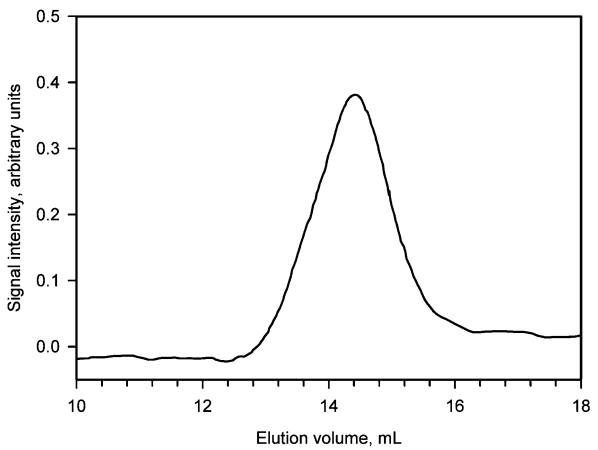


Fig. 1 GPC trace of **I**.

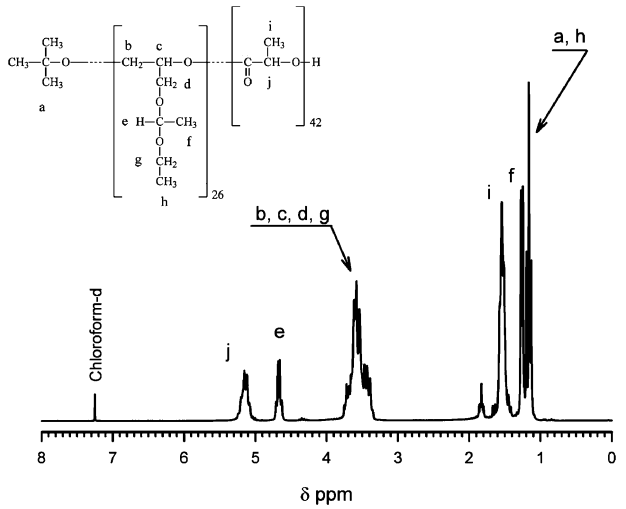


Fig. 2 ^{1}H NMR spectrum of **I**.

II was functionalized with 3-(pyrrole-1-yl)-propanoic acid and prepared according to a general procedure developed by Le Gall *et al.*[46] The copolymer was characterized by GPC and ^{1}H NMR (Fig. 3 and 4). GPC traces of eluted polymer were registered using three detectors (detector of laser light scattered at 90° (LS90), refractive index (RI) and ultraviolet light detectors). All three detectors gave a similar molecular weight distribution. A shoulder noticed at the high molecular weight side registered by the LS90 detector was probably due to the presence of some aggregates (aggregates scatter light strongly even if they are present in small number). The number average molecular weight of the copolymer determined from these GPC traces was *ca.* 7900.

Nanoparticles of this copolymer, pyrrole–PEG–PLA, were prepared using a spontaneous emulsification–solvent displacement procedure. The mean diameter particle size obtained by ALV-NIBS/HPPS was 180 nm, with particle size distribution in the range of 100–350 nm. This size range was in good correlation with a size assessment using a HR-SEM high magnification picture (×40 000).

Preparation of polypyrrole–PEG–PLA nanoparticle thin film

Fig. 5 shows the cyclic voltammetry (CV) of a 0.01 M pyrrole and 0.45 mg mL^{-1} suspension of pyrrole–PEG–PLA nanoparticles in an aqueous solution of 0.1 M NaF using a 316L stainless steel electrode. It should be mentioned that a similar CV was obtained using an evaporated gold electrode.

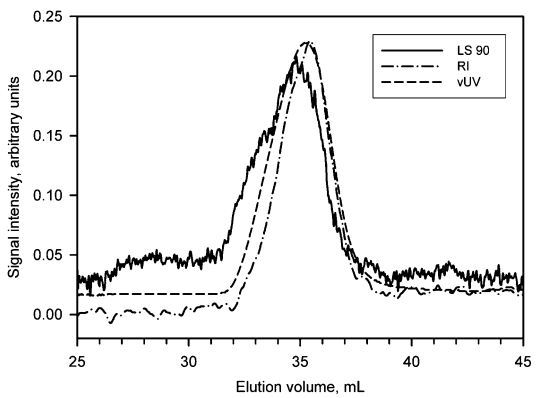


Fig. 3 GPC trace of **III**.

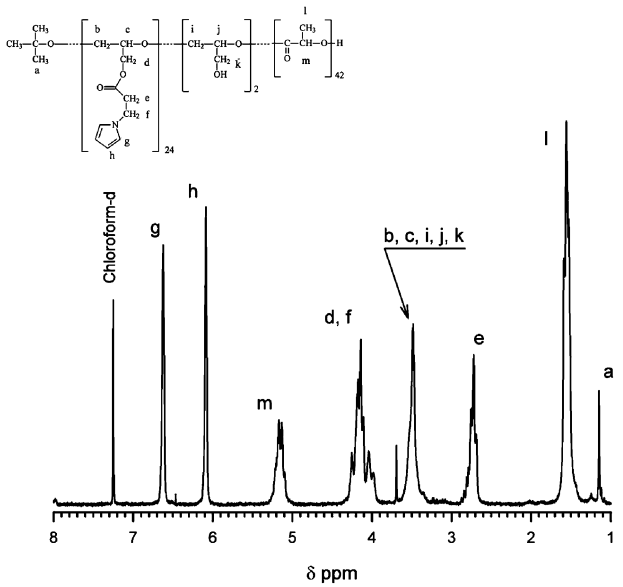


Fig. 4 ^{1}H NMR spectrum of **III**.

Upon sweeping the potential to the positive direction in the first scan, the anodic current increased, indicating the oxidation of pyrrole monomer ($E_{p,a}$ = ~0.75 V *vs.* Hg|Hg_2SO_4|$K_2SO_{4(sat)}$). This anodic wave could not be detected in the absence of pyrrole, implying that the pyrrole–PEG–PLA nanoparticles do not undergo independent electrochemical polymerization and the presence of pyrrole in the solution is essential. The oxidation of the monomer occurs at more positive potentials in the successive potential scans. This shift can be attributed to the more sluggish kinetics of the monomer oxidation on the film relative to that on a bare 316L stainless steel or gold surface. During the sweep back, a small cathodic peak is observed ($E_{p,c}$ = −0.45 V) which is coupled with an anodic wave ($E_{p,a}$ = ~0.0 V). The latter waves are attributed to the doping/undoping process, in which anions generally

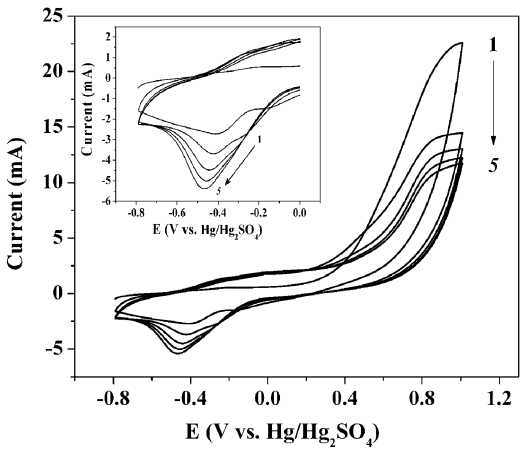


Fig. 5 Cyclic voltammetry of a 316L stainless steel electrode in an aqueous solution containing 0.1 M NaF, 0.01 M pyrrole and 0.45 mg mL^{-1} pyrrole–PEG–PLA nanoparticle emulsion. Scan rate equals 100 mV s^{-1}.

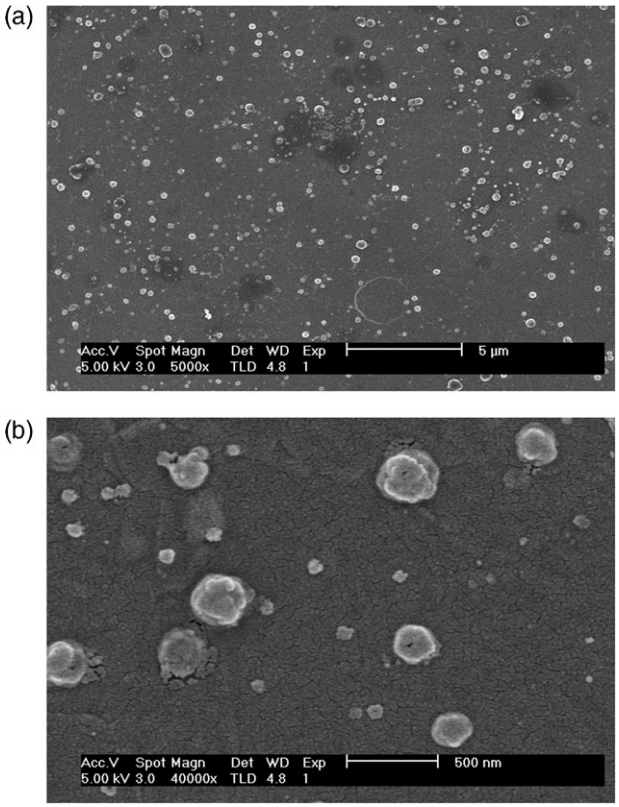


Fig. 6 SEM images of the film synthesized in the same conditions as in Fig. 5, but on an evaporated gold electrode. Magnifications: (a) ×5000, marker equals 5 µm, (b) ×40 000, marker equals 500 nm.

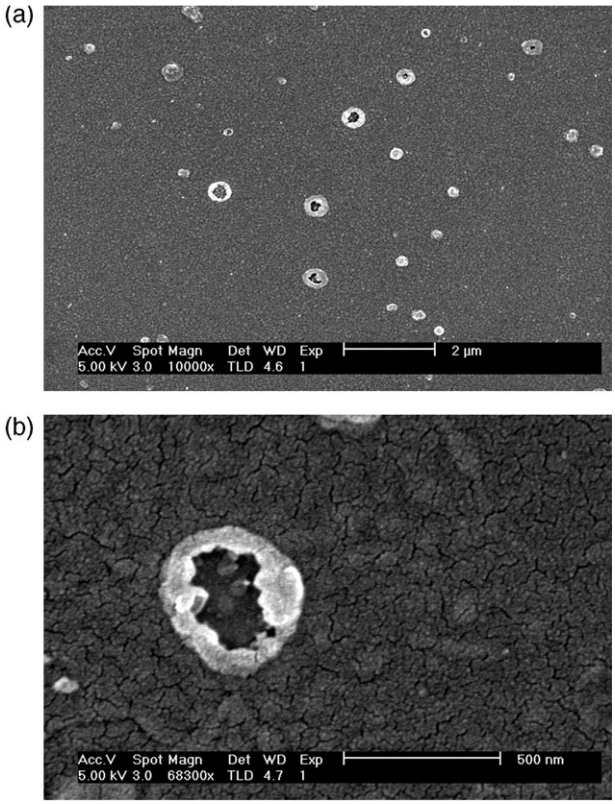


Fig. 7 SEM images of the film shown in Fig. 6 after immersion in ACN for one hour. Magnifications: (a) ×10 000, marker equals 2 µm, (b) ×68 300, marker equals 500 nm.

ingress and egress the film as a result of its oxidation and reduction, respectively.[48–50] Since the doping/undoping wave currents depend on the thickness of the conducting polymer, they increase with each cycle provided that the film is conducting. It can be seen (Fig. 5, inset) that, indeed, the anodic currents increase during subsequent scans employing a stainless steel electrode. Yet, it should be noted that this behaviour is reversed on an evaporated gold electrode (results not shown). This different behaviour must be due to differences in the kinetics of polymerization between stainless steel and gold. The doping/undoping currents are also sensitive to the presence of water.[37,39] Water is usually replaced by aprotic solvents[48] or ionic liquids[51] in order to enhance the electrical stability of polypyrrole. In biomedical applications, however, the presence and absorbance of water is normally unavoidable. As a matter of fact, water swelling into the polypyrrole–PEG–PLA film is necessary in order that the PLA will be able to hydrolyze and eventually biodegrade and release a drug. This will affect film conductivity. In fact, film conductivity is not an important feature for biocompatible coatings. The advantages in using a polypyrrole matrix stem mainly from its facile and cost-effective preparation and from the need to control film thickness and uniformity.

Characterization of the polypyrrole–PEG–PLA coating

Fig. 6 shows SEM images of a thin film of polylpyrrole–PEG–PLA electrodeposited on an evaporated gold electrode. After electropolymerization, the electrode was washed with water several times before conducting electron microscopy measurements. The SEM measurements reveal PEG–PLA nanoparticles embedded in the electropolymerized polypyrrole matrix (Fig. 6(a) and (b)). The images show a relatively smooth matrix in which nanoparticles are uniformly grafted without aggregation. The mean diameter particle size measured by ALV-NIBS/HPPS was *ca.* 180 nm, with a particle size distribution in the range of 100–350 nm, which is in agreement with the HR-SEM picture. It should be mentioned that no nanoparticles were observed either when electropolymerization was conducted in a pyrrole–PEG–PLA-free solution or in the absence of pyrrole (not shown). The latter inspection strengthens the electrochemical observation described before, that no electropolymerization takes place when pyrrole monomer is absent.

Fig. 7 presents the morphological changes inside the polypyrrole–PEG–PLA nanocomposite film caused by immersion in pure acetonitrile (ACN) solution. Small voids in the PEG–PLA nanoparticles, which could not be found in the non-immersed film, were detected after one hour of immersion. These voids are caused by the dissolution of PLA by ACN. It is well-known that PLA particles are susceptible to hydrolysis. Elemental analysis of the polypyrrole–PEG–PLA matrix was also used to confirm the presence of PEG–PLA nanoparticles and showed that the oxygen to carbon weight ratio in the particles (21.22) is larger than in the polypyrrole matrix (16.00). This is expected, owing to the oxygen that constitutes the PEG–PLA building blocks and is absent in the

conductive matrix. This result is in line with the solubility of the nanoparticles in ACN. In the case of the polypyrrole matrix, fluoride was also detected due to the ingress of fluoride in the course of the electropolymerization.

Conclusions

Polypyrrole–PEG–PLA nanocomposite film was deposited on gold and stainless steel surfaces by electropolymerization of pyrrole and pyrrole-functionalized PEG–PLA nanoparticles. This novel approach comprises the advantages of electropolymerization, which allows the fine control of an organic coating, and the nanoparticulate nature of PLA, which leads to the electrodeposition of nanoparticles. Taking into account the biodegradable nature of the PLA nanoparticles and the polymer matrix, this polypyrrole–PEG–PLA film could therefore be considered as a feasible partially biodegradable electrodeposited nanocomposite coating for metal implants. The biocompatibility of this novel coating is currently under examination.

Acknowledgements

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