Fabrication methods of smart composite coatings – review

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Abstract

Postoperative bacterial infections are one of the main reasons for unsuccessful implantation of long-term implants. The development of bacterial infection requires antibiotic therapy, in extreme cases a reimplantation procedure is necessary. In order to provide materials for implants with antibacterial properties, they are subjected to modifications to create a coating that will release the drug substance, when the inflammation occurs. Significant interest is now gained by the so-called smart polymers, that react to the stimuli from the external environment such as pH change, temperature change, the influence of UV-VIS radiation or interaction of electric and magnetic fields. When designing drug delivery systems, the characteristics of the inflamed tissue may be taken into account, because they are characterized by increased temperature and reduced pH. It would, therefore, be reasonable to create biopolymer coatings that under these conditions degrade and release the drug substance. However, the problem is the controlled release of the drug substance trapped in the biopolymer matrix. This review paper presents most often used methods of smart biopolymer coatings production, which release the drug substance in a controlled manner. Methods such as electrophoretic deposition, dip-coating, spin-coating, and layer-by-layer are discussed, including process parameters, steps of the coating production, possible post-processing and examples of smart coatings produced using these methods. Each of these methods offers a wide range of process parameters, by changing these parameters it is possible to fine-tune the properties of the coatings produced to the desired values. Extensive research is needed to determine the optimal process parameters that will allow the production of coatings with the desired properties.

Key words:

smart coatings, electrophoretic deposition, dip-coating, spin-coating, layer-by-layer

Introduction

The body's biological response to implant placement depends mainly on its chemical composition and surface morphology. The surface properties of metallic biomaterials are modified, among others, by the production of nanotubular oxide layers, laser treatment or the deposition of bioceramic and biopolymer coatings improving the biocompatibility and bioactivity of the implant. In addition, obtained through modification coatings and layers, they can act as a barrier separating the implant from the body fluid environment, providing protection against corrosion [1]. These surfaces can also act as a local drug delivery system. Because bacterial infections and biofilm formation on the surface of implants are one of the main reasons for unsuccessful implantation, hence numerous research works are carried out on the design of systems that release the drug substance in a controlled manner [2]. At present, so-called intelligent coatings gain a lot of interest. They show a reaction to the influence of the external environment like pH change, temperature changes, UV-VIS radiation, electric field or magnetic field and can release the drug substance in a controlled way. They are usually biopolymer materials [3]. In designing this type of coatings, it may be considered the characteristics of inflamed tissues such as elevated temperature and reduced pH value [4].

There are many methods for making coatings that are used to cover implants and provide them antibacterial properties. The most commonly used are electrophoretic deposition, electrochemical anodization, dip-coating, spin-coating, layer-by-layer method, thermal spraying, sol-gel and biomimetic deposition [1]. Some of them are discussed in more detail in this manuscript.

Electrophoretic deposition

Electrophoretic deposition (EPD) is a procedure that allows the manipulation of charged particles or molecules forming a suspension and their deposition on a given electrode in the form of a coating. The deposition process takes place in two stages. In the first stage, charged particles or molecules are moved into an oppositely charged electrode under the influence of an external electric field. The second step is the deposition and consolidation of the particles that form the coating on a particular electrode [5]. The instrumentation needed to carry out the EPD process consists of a power source, an electrode and a beaker with homogeneously dispersed particles or molecules. Depending on which electrode the coating is formed on, cathode and anodephoresis are distinguished. Particles charged positively under the influence of the external electric field will be deposited on the cathode, while the particles charged negatively - on the anode [5,6]. The EPD process is characterized by a significant number of parameters determining the quality of the produced coatings. There are parameters related directly to the suspension and parameters related to the technical aspects of the process. Regarding the suspension, the following parameters should be taken into account: particle size, surface properties of the powder particles and degree of dispersion, pH and viscosity of the suspension, and concentration of additives (mainly dispersants). The technical parameters of the EPD process include setting time, applied voltage, temperature and type of substrate. A common approach is to set fixed parameters relating to the suspension and fine-tune the quality of the coatings created by changing parameters related to the technical aspects of the EPD process [5]. Compared to other techniques, EPD is a simple and inexpensive method allowing the creation of a variety of coatings on a wide range of substrates. It is possible to uniformly cover irregularly shaped materials, which may be important in the case of, for example, dental implants. In addition, this technique allows the simultaneous deposition of several components and the creation of composite coatings or laminates. One of the main disadvantages of the EPD method (when the particles are dispersed in water) is the electrolysis of water leading to the formation of cracks in the coating. The formation of bubbles on the electrode can be overcome by using an organic liquid medium to prepare the suspension [7]. EPD is a promising coating method for biomedical applications. Performing the deposition process at room temperature allows the introduction of biological agents into the coating

to accelerate osseointegration or provide protection against bacteria. Electrophoretic deposition is most often used to produce bioceramic coatings for orthopedic implants (from hydroxyapatite or bioactive glasses), composite coatings (biopolymer-ceramics), coatings from carbon nanotubes, scaffolds for tissue engineering and deposition of peptides, proteins and other biological compounds to create biosensors [8]. Ma et al. [9] fabricated Ag-containing nanocomposite coatings on pure titanium (grade 2) via EPD process. Authors proposed coatings of Ag_2O/AgCl mixed with chitosan/gelatin polymers. Gelatin was used for the improvement of the biocompatibility and bond strength of the chitosan coating. The coatings were characterized by an initial burst release of Ag ions, followed by a decrease in the release rate. Qi et al. [10] prepared dexamethasone-loaded gelatin nanospheres/chitosan coatings also using this method. This type of structure showed a two-stage release profile. For the first two days, the burst release phenomenon dominated, then the drug was released in a sustained manner for 28 days. Song et al. [11] also produced coatings made of gelatin nanospheres filled with a medicinal substance – vancomycin, and moxifloxacin – dispersed in a chitosan matrix on a 316L stainless steel substrate using the EPD method. In this case, vancomycin was released in a sustained manner for two weeks, however, moxifloxacin was released in a burst-type manner, which may be due to the poor interaction of this substance with gelatin nanospheres.

Dip-coating

Dip-coating is a simple and relatively cheap method of thin coatings production on different substrates with irregular shapes. The deposition procedure consists of the following steps: cleaning the substrate, immersion at a certain speed of the coated material in the coating solution, leaving the substrate in a solution for some time, removing the substrate from the solution and leaving it for solvent evaporation [12]. The thickness of the deposited coating depends on the speed of removing the sample from the solution and the number of immersion cycles carried out. Dip-coating technique does not require sophisticated equipment. One of the disadvantages may be the poor quality of coatings [13]. This method is used for preparing a broad spectrum of biopolymer coatings applied in implantology, including those sensitive to lower pH. Li et al. [14] created enoxacin-loaded poly(lactic-co-glycolic acid) (PLGA) coating on porous magnesium scaffold, which may be used for bone and cardiovascular application. Application of PLGA coating allowed a ten-fold increase in the amount of drug introduced into the scaffold and ensured sustained drug release for more than 14 days. Prepared structures inhibited a bacteria adhesion and biofilm formation. The addition of PLGA improved the biocompatibility of magnesium scaffold. This type of modified scaffold would be suitable for the prevention and treating orthopedic peri-implant infections. Kumeria et al. [15] filled titania nanotubes with gentamicin and covered it chitosan or PLGA coating via the dip-coating method. The addition of biopolymer coating extended the release of drug for up to 22 (chitosan) and to 26 (PLGA) days in comparison to structure without polymer coating (7 days). To improve drug release kinetics, gentamicin can be incorporated into micelles, which are then filled into nanotubes. The thickness of the deposited coating has an impact on the release profile. The longer release period is observed for a structure with a thicker coating [15]. A similar drug delivery system has been created by Wang et al. [16].

Spin-coating

The spin-coating method is used for fabrication of polymeric coatings on flat substrates. The coating material is applied in solution form by drops on a substrate in rotary motion. The solvent used for solution preparation is usually volatile. The coating is produced according to the following steps: deposition of coatings material solution on the spinning substrate, spreading the polymer solution on the surface thanks to the centrifugal force, centrifuging the substrate for a given time to obtain the desired coating thickness and evaporation of solvent until the

coating dried [17]. Parameters that affect the quality (especially the thickness) of the coating are the composition of the coating, its viscosity, coefficient of solvent diffusion and rotation speed. The coatings produced by this method are characterized by higher density and homogeneity in comparison to the dip-coating method. The spin coating method is rather suitable for flat substrates [13,18]. Chen et al. [19] created a chitosan coating using a spin coating method on titania nanotubes filled with selenium. Such modified titania nanotubes ensure the proliferation of healthy osteoblasts and reduce the growth of cancerous osteoblasts. This composite coating has the ability to sustained release of selenium for 21 days and has long term antibacterial capacity. Huang et al. [20] proposed polycaprolactone based antibacterial bilayer wound dressing made by two-step spin-coating technique. The polymer of [(2-methacryloyloxy) ethyl] trimethylammonium chloride (PMTA)/PCL top layer displayed biocidal activity against *E. coli* and *S. aureus*. Maver et al. [21] also used the spin-coating technique to create a system, that could release the drug substance. The biopolymer matrix was cellulose, while the drug substance – diclofenac (DCF) – was used to relieve pain. The release of DCF from cellulose films may be controlled by the number of deposited layers of biopolymer.

Layer-by-layer-method

Layer-by-layer (LBL) method is used for multilayered coatings production from ionic polymers. This technique is based on the phenomenon of attracting polyanionic and polycationic layers and formation of self-assembled multilayered coatings. The pre-treated coated material is immersed alternately in polyanionic and polycationic solutions to form multilayered structures. Pre-treatment of the substrate by functionalization is used to provide a surface charge. The layer thickness can be tuned by changing the number of deposition cycles. This method can be applied to a variety of substrates. The LBL method can be described as a more complex immersion coating, however, in this case, the coatings produced have a higher packing density due to electrostatic interactions [22]. Except for electrostatic interaction, each layer can be linked by covalent bonding, hydrogen bonding or biological affinity. Multilayers can be created from biopolymers, synthetic polymers, inorganic particles or carbon nanotubes. Drug substances can be incorporated into these multilayered structures and create a stimuli-responsive drug delivery system [23]. The LBL method is often used for the preparation of multilayered microcapsules filled with the drug. In this type of structures, drug molecules can be entrapped in the microcapsule shell or in its cavity. The drug substance encapsulated in the microcapsule may be released by external stimuli detected by receptors created on the microcapsule shell [24].

Drug substances dispersed in LBL coatings can be released under the influence of acidic environment by enhanced permeability, which allows faster diffusion of the drug outside the coating. Another mechanism of drug release is a decomposition of the multilayered coating. However, it may cause a burst release phenomenon which is unfavorable [25].

Zhong et al. [26] prepared biocompatible, pH-sensitive coatings made of poly(amino acid). Multilayered coatings prepared using poly(L-lysine) (PLL), poly(L-glutamic acid) (PLGA) and methylene blue as a drug substance demonstrated the ability to release the drug during several hours in an environment of pH = 5.5. Jiang et al. [27] also investigated nanocoatings (thickness measured in nanometers) of PLL and PLGA made by LBL method. In this research as a drug substance, cefazolin, gentamicin, and methylene blue were used. The loading and release drug substances may be tunable by the number of deposition layers, pH of coating preparation and post-treatment procedures. Multilayered coating with a methylene blue showed low-pH triggered drug release profile [27]. In controlled release drug systems used to fight the inflammation around the implant, it is important that the system remains stable at the neutral pH and the drug substance is released under the influence of an acidic environment. Niu et al. [28] using the LBL method prepared coatings made of poly(allylamine hydrochloride) (PAH) – porphyrin conjugate and thiol-modified poly(acrylic acid) (PAA). Drug substance – porphyrin – was released at pH=4.5. Additional modification through cross-linking the thiol groups of prepared

coatings changed the pH value, at which the drug was released, to 6. So this type of structure, through additional cross-linking, allows obtaining the desired release profile of the drug. Kharlampieva et al. [29] found that combining poly(4-vinylpyridine) derivative with poly(methacrylic acid) (PMA) is an appealing way to create the low pH-sensitive system, which degrades at acidic pH. Wood et al. proposed hydrolytically degradable LBL coatings made of poly(β-amino ester) and heparin or chondroitin sulfate as a drug substance. The release of the drug from 20-layer coating occurred for a slightly acidic environment in a sustained manner for more than 10 days [30]. Liu et al. [31] fabricated coatings that were relatively stable at neutral pH and degraded during several days under the influence of a low-pH environment. These coatings were made of citraconate-modified PAH.

Summary

Smart coatings, which release drug substances, can solve the problem of biofilm formation on the surface of implants and the development of bacterial infections. Such targeted therapy will enable the therapeutic dose of the drug to be delivered to the inflamed sites without exposing the other tissues to the drug. There are many methods that allow the creation of intelligent coatings from a wide range of materials, in particular, biopolymer coatings, which release drug substances with bactericidal activity. The properties of the coatings produced strongly depend on the parameters used in the manufacturing process, therefore, when designing such systems it is necessary to identify all determinants. Most of the research is currently focused on the production of repetitive coatings, with the desired mechanical properties, high biocompatibility and the desired release profile of the drug substance without the burst release phenomena. Future research should be performed to develop new intelligent biomaterials and converting them using available techniques into controlled drug delivery systems. Extensive clinical studies of produced structures and their possible modification by tuning the parameters of their manufacturing process are also necessary.

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