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pH-dependent composite coatings for controlled drug delivery system — Review

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Nowadays in case of long-term implants, the most common postoperative complications are bacterial infections, which in consequence may provoke loosening of the implants in the primary phase of stabilization. Bacterial infections are currently the most frequent cause of revision surgery of the implants such as hip joint endoprosthesis, knee joint endoprosthesis and dental implants. In order to provide the local and long-term antibacterial cover in the tissues surrounding the implant, research is performed on materials that are carriers of drugs, which release active substances only in the case of the pH change in the system during inflammation. In consequence, biomaterials ensure antibacterial protection for a long time, not only in short post-operative period. An example of such materials are biopolymers. Biopolymers sensitive to change in pH value of the environment of live tissue that surround the implants can be used as an independent implants or as the coatings on the implants. In this case in the polymer`s matrix is dispersed often used drugs such as doxorubicin, gentamicin, vancomycin and cefuroxime. Drugs are released from this biomaterial according to three main mechanisms: diffusion, swelling and material degradation. This review paper presents the mechanism of bacterial interaction with implant surface and biofilm formation, and mechanism of drugs release from the biological active substance. Therefore, the natural and synthetic polymer materials sensitive to the lower value of pH such as chitosan, Eudragit E 100, Poly (L-histidine) and Poly (4-vinyl pyridine) are described.

Key words: biopolymers, biocomposites, bacterial infections, drug delivery systems, smart coatings.

1. INTRODUCTION

Due to the growing phenomenon of population aging, the number of people who need replacing or repairing damaged tissues by using biomaterials increases. The number of implanted hip joint implants or dental implants is also increasing every year [1]. Metallic biomaterials are the most suitable for replacing hard tissues of the human body. Among them, stainless steels, cobalt alloys, titanium, and its alloys can be distinguished. Due to the highest biocompatibility, corrosion resistance and similar mechanical properties to human bones, titanium alloys are nowadays most often used as materials for implants [2]. The surface of metallic biomaterials is subjected to modifications for further increase their biocompatibility and ensure adequate osseointegration, i.e. binding of the implant to the bone tissue. This type of properties provides coverage of the implant surface with coatings made of ceramic (e.g. hydroxyapatite) or polymeric (e.g. chitosan) biomaterials [3]. The implant surgery itself is associated with the occurrence of infection, which after the implantation process requires antibiotic therapy, in extreme cases reimplantation is necessary. It is important to create coatings that will contain substances with bactericidal activity, e.g. cis-platinum or silver nanoparticles (AgNPs). There are many examples of such coatings in the literature, but the problem is the controlled release of the drug substance from the coating covering the implanted biomaterial [4]. In this paper, the problem of bacterial infections associated with the implantation of the biomaterial into the human body and the ways of limiting the development of these infections with the use of controlled drug delivery systems are discussed.

2. BACTERIAL INFECTION ASSOCIATED WITH IMPLANTS

The process of inserting the implant into the human body, aimed to improve the quality of patient's life, is associated with the risk of side effects such as lack of integration of implanted biomaterial with surrounding tissues, the occurrence of inflammation and in extreme cases the complete rejection of the implant by the body. However, one of the main reasons of unsuccessful implantation is their bacterial infections [5]. Bacterial infections arise as a result of bacteria adhesion to the implant's surface. After placing the implant in the patient's body, there are processes resulting in its integrating with surrounding tissues. At the same time, these processes may be accompanied by the accumulation of bacteria on the surface of the implanted biomaterial. It is important, therefore, that implant integration occurs before significant colonization of the implant by bacterial cells. Bacteria deposited on the surface of the implant are able to create a biofilm, i.e. a coating composed of bacteria, fungi and other microorganisms which are resistant to the human immune system and antibiotic therapy [6]. Adhesion of bacteria to the surface of the implant is preceded by surface adsorption of fine organic compounds and macromolecules (including proteins). Then in the first phase, due to physicochemical forces (van der Waals forces, electrostatic interactions, hydrogen bonds, dipole-dipole interaction or ionic bonds), there is a reversible connection of bacterial cells with the implant surface (1–2 hours after implantation). 2–3 hours after implantation, strong adhesion of the bacteria to the biomaterial surface occurs. Polysaccharides located on, as well as proteins inside the bacterial membrane, facilitate its binding with the substrate. After about 24 hours, a certain group of bacteria begins to secrete a protective layer of exopolysaccharide, which retains nutrients and protects against the response of the human immune system, hence the bacteria in the biofilm are resistant to antibiotics. Some of them are able to leave the biofilm and create new clusters [7, 8].

The occurrence of bacterial infections and local inflammation result, among others, in lowering pH and increasing the temperature in peri-implant tissues. Cancer tissue has a similar property. This characteristic feature of inflamed tissues should be considered when designing a controlled release system of a drug substance, and, in particular, applying biomaterials sensitive to pH changes [9].

Bacteria differ in the structure of their cell wall and can be classified into two groups: Gram-positive and Gram-negative. Structural differences concern the key component of the bacterial cell wall — peptidoglycan. Gram-negative bacteria have a thin peptidoglycan layer (about 2÷3 nm) between the cytoplasmic membrane and the outer membrane. Gram-positive bacteria, on the other hand, do not

have an outer membrane, but the peptidoglycan layer has a thickness of about 30 nm. Despite the thicker layer of peptidoglycan, Gram-positive bacteria are less resistant to antibiotic therapies due to lack of outer membrane [10]. Gram-positive bacteria: *Staphylococcus aureus* and *Staphylococcus epidermidis* and Gram-negative: *Escherichia coli* and *Pseudomonas aeruginosa* are mainly responsible for infections associated with the introduction of the implant into the human body [8].

Except to the bacteria found in the patient's body and on his skin, their source can be surgical instruments, the attire of doctors or contamination in the operating room. Sterilization and aseptic techniques limit the possibility of bacteria getting into the operating field, but they do not provide total protection and bacteria are observed in almost 90% of implantation procedures.

The high resistance of bacteria creating biofilms to conventional antibiotic therapy prompted researchers to modify the surface of biomaterials intended for implants (modification of the surface layer or creating a coating), which will limit their bacterial colonization [11].

3. MECHANISM OF DRUG RELEASE IN POLYMERS

There are three main mechanisms of drug release from biopolymeric systems: diffusion, swelling and material degradation. Diffusion process occurs according to Fick's equations. The drug substance is dissolved in a non-degrading matrix or dispersed when its concentration exceeds the solubility limit of the polymer. Diffusion of a therapeutic substance consists in its spontaneous spreading to the body fluid environment in order to equalize the concentration of diffusing substance in the whole system [12]. Swelling is a process of increase of polymer's volume due to absorption of a solvent. This mechanism is often considered in the case of hydrogel coatings [13]. Biopolymer degradation is defined as a chain breaking process in which polymer chains are cleaved into oligomers and monomers. The term bioerosion also refers to the degradation of biopolymers used in biomedical solutions. Bioerosion is a loss of material in contact with the biological system. Biopolymer erosion can occur on the surface or in the entire volume (bulk bioerosion). Surface degradation is limited to the outer surface of the material, however, in the case of bulk degradation, the biopolymer degrades uniformly throughout the material [14]. Studies on the kinetics of degradation and drug release should take into account the influence of water on created systems, which contributes to the phenomenon of hydrolysis of biopolymer materials. As a result of the degradation of the biopolymer, its chain breaks off and the average molecular weight changes, which allows the quantitative determination of this process [15]. In the case of smart biopolymers sensitive to pH changes, the change in pH triggers a change in the interaction between polymer molecules and solvent or between polymer chains (e.g. electrostatic repulsion) [16]. For example, amino groups of chitosan under the influence of acidic environment undergo protonation, gain a positive charge and as a result of the repulsive action, its degradation occurs [17].

In the development of drug delivery systems *in vitro* release study has been recognized as one of the key ways to evaluate and optimize these systems. However, the main problem associated with release testing is the lack of direct correlation between *in vitro* and *in vivo* release profiles. The human body environment is much more complex than the buffer solutions that are used in *in vitro* studies [18]. Lietchy et al. [12] reported three different types of drug release profiles from polymer materials such as controlled, burst and pulsatile release.

The negative phenomenon associated with the release of the drug substance is a burst release. This is a phenomenon of an initial large release of drug after placing the system in the medium to which this drug is to be released. The burst release often causes, that the concentration of the drug in the release medium reaches a toxic level. This phenomenon is often ignored in published reports and is not included in most mathematical models used to describe the release processes of a drug substance [19].

4. INTELLIGENT AND LOW pH SENSITIVE BIOPOLYMERS

Recently, there has been a significant increase in the use of polymeric materials (natural and synthetic) in biomedical applications. This was due to the development of new biomedical technologies: tissue engineering, regenerative medicine, gene therapy, controlled drug release systems and bionanotechnology. These technologies require the use of biodegradable polymers, i.e. those whose degradation products do not cause any toxic effects, are easily metabolized and removed from the human body. These materials should be characterized by an appropriate period of durability and degradation time, allowing for a full treatment or regeneration of damaged tissues. Biodegradable biopolymers are used for temporary implants (bone screws and plates), porous sponges in tissue engineering, membranes for bone tissue regeneration and carriers of the drug substance. In the case of drug carriers, the drug substance is trapped within the matrix of a biodegradable polymer, from where it is released by diffusion through the polymer layer or degradation of the polymer under the influence of external factors [20]. A special group of biopolymers used as drug carriers is the so-called intelligent biopolymers. These materials under the influence of external stimuli change their physical and chemical properties. Factors that trigger these changes may be temperature change, pH change, UV-VIS radiation, the effect of electric and magnetic fields, or the presence of biochemical substances. The type of functional groups present in its chain determines what kind of factor the polymer is sensitive to. The reaction of the polymer to the environment can be manifested in the form of changing its shape, phase, mechanical or optical properties. These changes concern solutions of polymers, as well as polymeric coatings, applied on a specific surface. In the case of controlled drug release systems, polymers sensitive to temperature and pH change are most commonly used [21]. Polymers sensitive to pH changes may have a linear, branched or network structure. They show a different response to environmental conditions and different ways of organizing depending on their structure. pH-sensitive polymers can be defined as polyelectrolytes containing weak acidic or basic groups that accept or release protons under the influence of pH changes in the environment. pH changes can cause protonation or deprotonation of functional groups of the polymer chain, which can result in flocculation, chain length change or homopolymer precipitation. In some cases, the self-organization of the polymer in micelles, bubbles, gel formation or polymer swelling is also observed [22]. Table 1 lists selected biopolymers sensitive to reduced pH, some of them are described in this paper.

Table 1. Biopolymers sensitive to lowered pH
Tabela 1. Biopolimery wrażliwe na obniżone pH

Low pH-sensitive biopolymer	Natural/synthetic	Reference
Chitosan	Natural	[23, 24]
Eudragit E 100	Synthetic	[25, 26]
Poly(L-histidine)	Synthetic	[27, 28]
Poly(4-vinylpyridine) (P4VP)	Synthetic	[29]
Poly(2-vinylpyridine) (P2VP)	Synthetic	[30]
Poly(vinylamine) (PVAm)	Synthetic	[31]
Poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA)	Synthetic	[32]
Poly(N,N-dimethylamino) ethyl methacrylate (PDMAEMA)	Synthetic	[33, 34]

4.1. Chitosan

Chitosan is one of the natural biopolymers that is abundant in nature, characterized by biodegradability, biocompatibility, ease of modification and sensitivity to reduced pH. Chitosan belongs to the group of polysaccharides and is obtained from chitin (in the process of deacetylation), which is the main building block of crustaceans (shrimps, crabs, lobsters), skeletons of outer mollusks and insects, and cell walls of some fungi. Usually, deacetylation is not complete and chitosan contains a number of acetylamino groups, hence by the chitosan characteristics the parameter of the degree of deacetylation (DD) is determined. The degree of deacetylation of chitosan depends on its reactivity, swelling and solubility. Chitosan has the potential to inhibit the growth of bacteria and fungi, which is mainly dependent on the molecular weight and the type of functional groups of this polymer. Oligomeric chitosan (low molecular weight) can penetrate the cell wall of the microorganism and limit cell growth by inhibiting RNA transcription. Chitosan biodegradation kinetics is influenced by the length of the polymer chain and the decomposition of acetyl groups [35, 36]. Chitosan interacts with predominantly anionic compounds that build the bacterial cell membrane, causing a change in its permeability, which leads to the leakage of intracellular bacteria and ultimately destroys them. The conducted *in vitro* tests confirm the bactericidal activity of chitosan in relation to Gram-positive and Gram-negative bacteria (e.g. *Escherichia coli*, *Salmonella*, *Typhimurium*, *Staphylococcus aureus*) [37, 38]. Chitosan is insoluble in water and most organic solvents. On the other hand, it dissolves in most aqueous solutions of organic acids such as formic acid, acetic acid, lactic acid or citric acid at a pH of less than 6.3. This polysaccharide precipitates from aqueous solutions with a pH > 6.5 in the form of a gelatinous precipitate. The pH-dependent solubility of this biopolymer due to the presence of amino groups can be used in the design of controlled release drug substance systems. Chitosan is not present in the mammalian body but can be metabolized by the action of several enzymes belonging to the group of proteases. The products of this reaction are non-toxic oligosaccharides of varying length, which can then be incorporated into other compounds, metabolized or excreted from the body. The kinetics of the chitosan biodegradation process depends on the degree of crystallinity of the polymer, and this parameter, in turn, is controlled mainly by DD. The lower the DD of the chitosan, the faster the biopolymer degrades [23]. In biomedical applications, chitosan is used as a drug carrier, a scaffold for bone tissue regeneration or wound healing agent. In the case of drug delivery systems, chitosan is used in the form of nanoparticles, hydrogels, microspheres and thin films. The choice of chitosan with appropriate properties (specific molecular weight and DD) is important in the design of controlled drug release systems because it affects the release time of the drug, its therapeutic efficacy and the occurrence of possible side effects [39].

4.2. Eudragit E 100

An interesting group of synthetic biopolymers are so-called Eudragits, products of the company Evonic Industries AG, which are poly(meth)acrylates used mainly in the pharmaceutical industry. These polymers allow obtaining the required release profile of the therapeutic substance through degradation at a specific place in the human body and for the desired time. These polymers are available in various forms: aqueous dispersion, organic solution granules and powders. Eudragits are used in ocular therapeutics, buccal and sublingual drug delivery, delivery to the stomach, intestines, colon drug delivery, transdermal drug delivery, vaginal drug delivery, gene therapy, delivery of vaccines [40]. Eudragits combines with other biopolymers when designing controlled release drug systems. For example, Khatik et al. produced chitosan nanoparticles with curcumin as a drug substance coated with Eudragit S 100 by an oil-in-oil solvent evaporation method using coat/core ratio 2:1. This type of system could help fight colorectal cancer [41]. The sensitivity to reduced pH is shown by Eudragit E 100. First introduced in 1961, belongs to the group of synthetic biopolymers and is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with a ratio of 2:1:1. It has the form of yellow granules with a characteristic odor. It does not dissolve at a neutral pH, but dissolve at a pH below 5. Most often it is used as a coating material for tablets to protect the drug substance, alleviate their unpleasant taste and release the drug substance in the stomach. In addition, it is used as transparent coatings with high adhesion in transdermal delivery systems. It is characterized by good adhesion, low viscosity and it is approved for pharmaceutical applications. Its properties resulting from the cationic nature and the presence of amino groups give a chance to use it as part of a controlled drug delivery system [25, 26]. There is no data in the literature regarding the use of Eudragits as a coating for implants, probably they do not show osseointegrative properties and should not cover the surface of implants that have direct contact with the bone. However, it would be possible to use them as a coating containing a drug substance, e.g. on the upper surface of the dental implant, which could limit the adverse effects of the periimplantitis phenomenon, i.e. inflammatory reactions in the tissues surrounding an implant [42].

4.3. Poly(L-histidine)

Poly(L-histidine) (PHis) belongs to a group of synthetic cationic polypeptides that exhibit sensitivity to a pH-reduced environment. It is used in the pharmaceutical industry, especially in systems that provide drugs for tumors. Due to the presence of imidazole groups, PHis is destabilized when the pH of the environment drops below 6 [43]. It is a biodegradable polymer and its degradation products are not harmful. PHis is often used as a combination of several biopolymers in drug delivery systems. PHis is formed into various polymer structures. Chen et al. [44] made poly(L-histidine)-chitosan/alginate complex microcapsules as carriers for controlled protein drugs release. Zeng et al. [45] proposed pH-sensitive poly(ethylene glycol)-poly-L-histidine hydrogels for controlled gene therapy. The PHis additive provides the sensitivity to reduced pH in this system by controlling the degree of swelling and water uptake. In this study, the increase of PHis content from zero to 20% increased over ten times the swelling ratio of the hydrogel in the pH of 6. PHis can also form micelles. The production of poly(L-histidine)-block-short branched polyethyleneimine for cancer treatment took up Hu et al. [46]. These micelles were developed by deep penetration ability into tumor tissues and pH-sensitivity to treat acidic cancer. Poly(L-histidine) may be used for functionalization of mesoporous silica nanoparticles for pH-triggered controlled drug release. This modification provided an intensive release of the drug in acidic conditions (pH = 5) from nanochannels of mesoporous silica and polymer shell [28].

4.4. Poly(4-vinylpyridine)

Poly(4-vinylpyridine) (P4VP) is a cationic biopolymer, which dissolution properties depend on the deprotonation of pyridine groups. In addition, P4VP exhibits hydrophilic properties for pH less than 5.6, while hydrophilic — above this value in its deprotonated state [47]. P4VP remain stable in physiological pH and degraded in an acidic environment, hence in biomedical applications P4VP is used for the production of antibacterial coatings, gene delivery, biosensors and drug delivery systems. Due to the strong affinity of the pyridine group to metals, poly(4-vinylpyridine) may immobilize metal nanoparticles like AgNPs [48]. Systems containing P4VP, that release drugs, are widely reported in the literature. Rafi et al. [49] created a mesoporous nanosilica drug container that was covered by smart reversible "gatekeeper" — P4VP. In this case, the release profiles were pH-dependent, with decreasing pH, an increase in the release kinetics of the drug substance was observed. P4VP chains

functionalized onto mesoporous nanosilica showed reversible states triggered by pH changes. In acidic conditions, repulsive forces between positively charged polymer chains resulted in an open state and allowed for drug release. A similar solution was used by Fullriede et al. [50]. In this case P4VP was linked with nanoporous silica nanoparticles by bismaleimide. This result also showed the higher release of drug in the acidic environment compared to neutral. Kavitha et al. [51] made P4VP-grafted graphene oxide composite for a drug delivery system. The drug — camptothecin — was not released under physiological conditions, but at acidic conditions with burst release effect. Furthermore, this composite material possessed high biocompatibility, antibacterial properties and low cytotoxicity.

5. IMPLANT COATINGS AS DRUG DELIVERY SYSTEM

There are different types of implant surface modifications that will ensure the antibacterial activity. One of them is micro- and nanostructurization of the surface of implants that imitate natural surfaces (like lotus leaves, dragonfly wings) less susceptible to bacterial adhesion [52]. There are also passive coatings that limit the adhesion of bacterial cells by changing the physicochemical properties (e.g. wettability) of the substrate. However, the effectiveness of this type of coating is limited and depends on the type of bacteria. The alternative is so-called active coatings that release antibacterial agents directly into the tissues surrounding the introduced implant for a limited time. This approach allows the delivery of a therapeutic dose of the drug to the inflamed tissues, without exposing the other tissues of the body (targeted therapy) [53]. One of the disadvantages of local drug delivery is that in the case of long-term implants, the release time of the drug substance is too short, which is related to the limited dose of the drug that can be incorporated into the coating. In addition, the phenomenon of burst release is also a problem, i.e. the rapid release of a large dose of the drug from the coating after the implant is introduced into the body fluid environment [8].

There is a large variety of therapeutic substances that can be incorporated into these types of coatings. Therapeutic substances are most often dispersed in a biopolymer matrix, surrounded by a biopolymer by encapsulation or attached to the implant surface by covalent bonds. In implantology, doxorubicin, gentamicin, vancomycin, penicillin and cefuroxime are often used as a drug substance [54]. Moreover, chlorhexidine (CHX) is used as an antibacterial agent against Gram-positive, Gram-negative bacteria and fungi [55]. CHX finds application in oral drug delivery systems, because has an ability to bind to the enamel and pellicle and thus inhibits the bacterial adhesion and biofilm formation [56]. Enoxacin is an active substance against both Gram-positive and Gram-negative bacteria. Moreover, enoxacin has the ability to inhibit osteoclast formation, which reduces osteoclastic bone resorption [57]. Silver nanoparticles capable of combating a wide range of bacteria are now gaining considerable attention. The mechanism of eliminating bacteria by silver is not fully understood. Due to the strong interaction of silver ions with thiol groups, important enzymes of a bacterial cell can be inactivated. In addition, silver causes changes in the structure of the bacterial cell membrane leading to its destruction. The results of the experiments confirm that the bacterial cell's DNA loses the ability to replicate after being subjected to silver ions [10].

6. SUMMARY

acterial infections associated with the formation of biofilm on the urface of implants are a significant problem and covering these iomaterials with coatings that promote a controlled drug release is ne of the ways to solve it. The use of intelligent materials allows ontrolling the drug release kinetics. Coatings made of biopolymers ensitive to reduced pH allow a rapid increase in the released dose f the drug substance at the moment of inflammation. There are any methods that allow the production of this type of compose coatings. However, it is necessary to develop a technology that allows obtaining reproducible coatings with high biocompatibility, appropriate mechanical properties and a desired release profile of the drug substance, limiting the burst release phenomena. In addition, it is necessary to recreate conditions that simulate the environment of the human body, which would allow the assessment of the behavior of this type of coatings with a long residence time in the body, e.g. as coatings for long-lasting implants. Future research should also focus on clinical studies of this type of composite coatings.

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INŻYNIERIA MATERIAŁOWA MATERIALS ENGINEERING

Kompozytowe powłoki wrażliwe na pH dla kontrolowanego uwalniania leków — Przegląd

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Słowa kluczowe: biopolimery, biokompozyty, infekcje bakteryjne, uwalnianie leków, powłoki inteligentne.

1. CEL I ZAKRES PRACY

W artykule omówiono problem zakażeń bakteryjnych związanych z wszczepieniem biomateriału do organizmu człowieka oraz sposoby ograniczania rozwoju tych zakażeń za pomocą kontrolowanych systemów dostarczania leków, bazując na obszernym przeglądzie najnowszej literatury naukowej.

2. BAKTERYJNE ZAKAŻENIA TOWARZYSZĄCE IMPLANTACJI

Jedną z głównych przyczyn nieudanej implantacji są infekcje bakteryjne. Bakterie osadzone na powierzchni implantu są w stanie wytworzyć biofilm, tj. powłokę złożoną z bakterii, grzybów i innych mikroorganizmów, które są odporne na ludzki układ odpornościowy i terapię antybiotykową. Charakterystyczną cechę tkanek objętych stanem zapalnym, taką jak obniżona wartość pH, można wziąć pod uwagę przy projektowaniu systemu kontrolowanego uwalniania substancji leczniczej za pomocą na przykład biomateriałów wrażliwych na zmiany pH.

3. MECHANIZM UWALNIANIA LEKÓW

Istnieją trzy główne mechanizmy uwalniania leku z układów biopolimerowych: dyfuzja, pęcznienie i degradacja materiału. W przypadku inteligentnych biopolimerów wrażliwych na pH jego degradacja polega na zmianie interakcji między cząsteczkami polimeru i rozpuszczalnikiem lub między łańcuchami polimerowymi (np. odpychanie elektrostatyczne). Na przykład grupy aminowe chitozanu pod wpływem środowiska kwaśnego ulegają protonowaniu, zyskują dodatni ładunek i w wyniku oddziałania odpychającego następuje jego degradacja. Wybuchowe uwalnianie powoduje, że stężenie leku osiąga poziom toksyczny. Zjawisko to jest często ignorowane w opublikowanych raportach i nie jest zawarte w większości modeli matematycznych używanych do opisywania procesów uwalniania substancji leczniczej.

. BIOPOLIMERY INTELIGENTNE I WRAŻLIWE A NISKIE pH

pecjalną grupą biopolimerów stosowanych jako nośniki leków są k zwane „inteligentne" biopolimery. Materiały te pod wpływem bodźców zewnętrznych zmieniają swoje właściwości fizyczne i chemiczne. W przypadku kontrolowanych systemów uwalniania leków najczęściej stosuje się polimery wrażliwe na zmiany temperatury i pH. Wśród takich biopolimerów wrażliwych na obniżone pH najbardziej obiecujące wydają się: chitozan, Eudragit E 100, poli(L-histydyna), poli(4-vinylopirydyna).

5. POWŁOKI POLIMEROWE STOSOWANE JAKO SYSTEMY UWALNIANIA LEKÓW

Istnieją różne rodzaje modyfikacji powierzchni implantu, które zapewnią działanie przeciwbakteryjne. Obejmują one: mikro- i nanostrukturyzację, powłoki pasywne, powłoki aktywne. Istnieje również wiele różnych substancji terapeutycznych, takich jak doksorubicyna, gentamycyna, wankomycyna, penicylina i cefuroksym, które są często stosowane jako substancje lecznicze, chlorheksydyna (CHX) i enoksacyna jako środki przeciwbakteryjne. Nanocząstki srebra zyskują teraz duże zainteresowanie, gdyż również są zdolne do walki z szeroką gamą bakterii. Jednak mechanizm eliminowania bakterii przez srebro nie jest w pełni zrozumiały.

6. PODSUMOWANIE

Infekcje bakteryjne związane z tworzeniem się biofilmu na powierzchni biomateriałów przeznaczonych na implanty stanowią istotny problem i jednym ze sposobów na jego rozwiązanie jest pokrycie tych biomateriałów powłokami, które promują kontrolowane uwalnianie leków. Zastosowanie „inteligentnych" materiałów pozwala na kontrolę kinetyki uwalniania substancji leczniczej. Powłoki wykonane z biopolimerów wrażliwych na obniżone pH umożliwiają szybki wzrost uwalnianej dawki leku w momencie wystąpienia stanu zapalnego. Istnieje wiele metod, za pomocą których można wytwarzać tego typu powłoki kompozytowe. Konieczne jest jednak opracowanie technologii, która pozwoli na uzyskanie powłok o powtarzalnych właściwościach, tj. wysokiej biokompatybilności, odpowiednich właściwościach mechanicznych i pożądanym profilu uwalniania substancji leczniczej.