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Drug Delivery Systems in Hard Tissue Engineering

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Abstract

This paper provides an overview on some of the currently used systems for drug delivery systems with application for hard tissue engineering reported in literature in the last 5 years. These systems have received an increased attention in the last years especially because of their unique properties like antimicrobial or anticancer activity. Also, these systems are continuously studied for the improvement of the therapeutic activity and to decrease undesirable effects. In this paper, are presented the main drug delivery systems reported in literature and the main methods for impregnating of the scaffolds with drugs, their properties and their benefits for hard tissue engineering.

Keywords: Drug delivery systems; Antimicrobial properties; Anticancer activity; Hard tissue engineering

Introduction

Bone tissue reconstruction represents one of the biggest challenges for medicine because lately the world is facing to serious global health problems such as diseases, defects, trauma, the rise of obesity and sedentary lifestyles [1-4]. Bone tissue engineering is a recent field of research associated with regenerative medicine which applies the principles of engineering and the life sciences toward the development of biological substitutes that restore maintain or improve tissue function [5-7]. Until a few years ago, the bone tissue reconstruction was represented by bone grafts which present several limitations like disease transfer, costs, etc. In present, a new generation is required in medicine which consists not only in physical support for bone formation, but also in the presence of biochemical agents for promotes the formation of the bone. One of the biggest advantages of this system is the fact that is able to deliver under control the drugs to the affected tissue [1,8,9].

Until now, numerous porous materials have been investigated, but this materials still presents challenges because its capability to regenerate and remodel itself and mimic the complicated physiochemical attributes of bone. Also, it has been studied the functionality of the scaffolds, by loading biomolecules (drugs, growth factors - GFs) into them to treat bone disorders or to act on the surrounding tissues [10-12].

Three-dimensional bone bioactive scaffolds can be fabricated from a wide variety of bulk biomaterial such as bio-ceramics -tricalciumphosphate (TCP), hydroxyapatite (HA), bio-glasses (BG);or biodegradable polymers - collagen, chitosan, alginate, fibrin, polyesters, polyethylene glycol (PEG) [13-18]. It was demonstrated that their composites represent a good alternative because they combine the advantages of both bioactive ceramics and biodegradable polymers for bone tissue engineering. The reason is very simple, ceramics present weak mechanical properties due to brittleness (hard material with small elongation to failure) and the polymers present a deficiency in the compressive modulus compared with native bone tissue (polymers typically too soft) [8]. So these systems can reduce the disadvantages and offer new advantages in the case of bone tissue reconstruction.

Overview about Drug Delivery Systems in Hard Tissue Engineering

In the past years, these new generation appeared as an alternative solution to many trauma or diseases of bone tissue and are used a wide range of synthetic bone substitutes and biomaterials as scaffold (such as chitosan, alginate, collagen, hydroxyapatite, etc) [19,20].To successfully perform a bone scaffold must present the following characteristics:

- It must be able to be sterilized;

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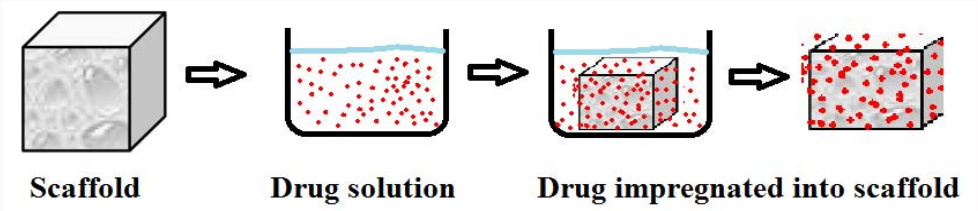

Figure 1: The method which consists in the immersion of the scaffold in drug solution.

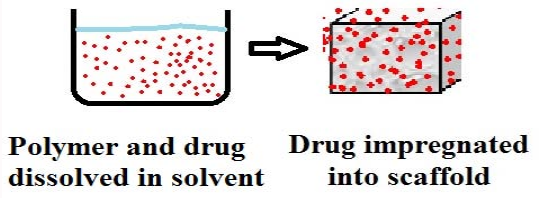

Figure 2: The formation of the system during fabrication.

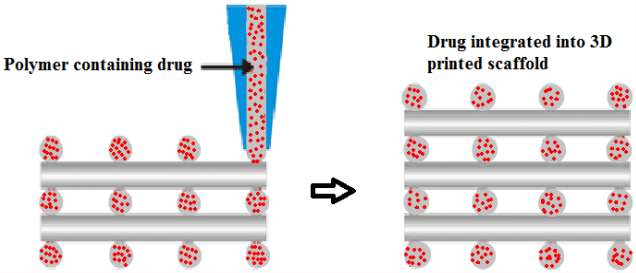

Figure 3: The 3D printing method.

- It must provide mechanical support;
- It must deliver bioactive molecules;
- It must not cause inflammatory reactions;
- It must have interconnected pores to facilitate growth of a new bone;
- It must to promote the osteogenic differentiation;
- It must to degrade as the new bone form;
- It must not cause non-toxic degradation products;
- It must to sustain the bone cell migration [5].

It has been reported several methods for impregnating of the scaffolds with drugs [1]. The first method is the most simple and consists of immersion of the scaffold (with absorbing properties) into the drug solution (Figure 1).

The second method refers to building the system by dissolving the polymer and the drug in solvent during fabrication (Figure 2). It was reported in literature that in the case of these two methods the drug release profiles depends on the scaffold features such as degradation rate, porosity, etc [1].

One new method which has revolutionized the medicine refers to 3D printing. The biggest advantage of this method refers to the accurate control over architecture, shape, size, dose of drugs and location (Figure 3) [1].

Another method very used for the side effects of orthopedic implants is layer-by-layer technology (Figure 4). This method consists in covering the different layers of a certain surfaces and the drugs are caught between these layers (drug A and B). Subsequently, capsules can be formed by decomposition [1].

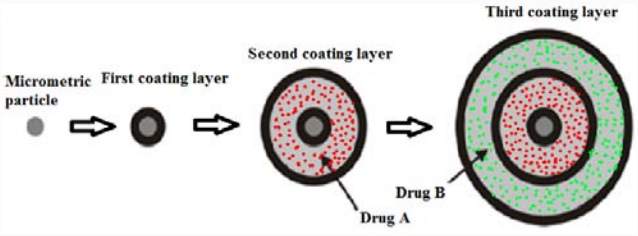

Figure 4: Layer-by-layer method.

One of the most common diseases facing the world now is osteoporosis. Most drugs used to treat this disease have been shown to be ineffective due to their side effects. Thus, to prevent these side effects have tried the use of drug delivery technologies that have been shown to enhance the release profile, reduce toxicity and improve the therapeutic effectiveness of drugs [21]. Also, several drug delivery systems used in hard tissue engineering are presented in Table 1. The main antibiotics used in hard tissue applications are gentamicin, ampicillin, penicillin, oxacillin, kanamycin and methicillin from bone cement. Currently, for this application the researchers are investigating a new type of scaffold containing antibiotic-loaded nanoparticles [22].

Antimicrobial Drug Delivery in Hard Tissue Engineering

Antibiotics are frequently used in the case of bone implants to prevent postsurgical infection or in the case when the infection has been diagnosed [3]. For example, in the case of osteomyelitis, the classic treatment consists in surgical removal of the diseased bone followed by the administration of antibiotics. This method is very complicated because causes weakening of the musculoskeletal support and the antibiotics effectiveness decrease. So, this problem can be resolved by using systems capable of locally delivering antimicrobial agents [2]. Gomes D. and co-workers reported that composite nanostructures such as hydroxyapatite and PLGA are used for the treatment of osteomyelitis and for delivery of antibiotics to the infected bone [23]. Some examples of drug delivery system for osteomyelitis are presented in Table 2.

LogithKumar R and co-workers reported that the antimicrobial activity of chitosan can be improved by modifying its structure and making it ideal for use in hard tissue engineering [24]. Also, it was investigated by a team of researchers the antimicrobial activity of the incorporated vancomycin loaded liposomes into a nano-hydroxyapatite-chitosan-konjacglucomannan scaffold. It was

Table 1: Several systems used in hard tissue engineering [46].

Type	Fabrication method	Materials		Applications
		Core	Shell	
Nanofiber	Co-axial electrospinning	PLGA	Collagen	Dual drug delivery systems for hard tissue engineering
	Co-axial electrospinning	PEO	PCL-PEG	Drug delivery systems for hard tissue engineering
	Co-axial electrospinning	PLLC	Collagen	Dual drug delivery systems for hard tissue engineering
Microfiber	Co-concentric extrusion	Tricalcium Phosphate and alginate	Alginate	Dual drug delivery systems for bone regeneration
Micropheres	Droplet coating	Alginate	Calcium silicate	Protein delivery control for hard tissue engineering
	Co-axial electrodropping	PLGA	Alginate	Dual drug delivery systems for hard tissue engineering (dexamethasone and BMP2)
	Biomimetic approach	Gelatin	Calcium phosphate	Drug delivery systems for hard tissue engineering

Table 2: Example of studies of drug delivery system for osteomyelitis [23].

Class	Material	Antibiotic	Tested on microorganism	Animal model
Bioceramic	Calcium phosphate	Gentamicin	*S. aureus*	Rabbits
	Calcium sulphate	Moxifloxacin	Methicillin resistant *S. aureus*	Rabbits
	Hydroxyapatite	Vancomycin	*S. aureus*	Rabbits
Polymer	Collagen	Gentamicin	*S. aureus*	Rabbits
	PEG, PLGA	Tobramycin, Cefazolin	*S. aureus*	Rabbits
	Polylactide/polyglicolide	Gentamicin	*S. aureus*	Dogs
Bioactive glass	Borate	Vancomycin	Methicillin resistant *S. aureus*	Rabbits
	Boro-silicate	Ceftriaxone– sulbactam	*S. aureus*	Rabbits
Composite	Chitosan, borate glass	Teicoplanin	*S. aureus*	Rabbits
	PLGA, bioactive glass	Ciprofloxacin	*S. aureus*	Rabbits

reported that the scaffold was biocompatible, biodegradable and provides the ability to modify the release profile of the drug by adjusting the ratio between chitosan and konjacglucomannan. It was used a scaffold with a content of 60-70% nano-hydroxyapatite and the content of chitosan and konjacglucomannan was varied to observe the differences. It was observed a slower release of drug at the largest amount of chitosan and konjacglucomannan used. The *in vitro* tests confirmed that the system consisting of vancomycin loaded liposomes and scaffold has inhibited to a greater extent the formation of *S. aureus* biofilms than the drug loaded scaffold [25].

In another study, Hornyák I and co-workers studied the antimicrobial activity of human bone allografts incubated with antibiotic solution (vancomycin) and coated with chitosan. It was observed a sustained release of drug for 50 days. It was reported that the MIC for *Enterococcus faecalis* was 0,2 μg/ml vancomycin and for methicillin resistant *S. aureus* was 2μg/ml vancomycin [26]. Another advantage is that the alginate and the allograft are biodegradable what makes the development of biofilm more difficult [27]. In another study, it was reported a system formed from a chitosan scaffold with bactericidal agents coated with a nano-hydroxyapatite-poly (amide). It was reported a continued release of the bactericidal agents for over 150 hours, the decrease of the extent of bacterial growth and cell adhesion. Also, it was reported that scaffolds made of chitosan/nano-hydroxyapatite/nano-silver particles showed a good antimicrobial activity against Gram-negative and Gram-positive bacterial strains and it was observed that this scaffolds are not toxic to rat osteoprogenitor cells and human osteosarcoma cell lines [28].

González-Sánchez MI and co-workers tried to get the best antimicrobial activity against *Staphylococcus epidermidis* and Methicillin-resistant *Staphylococcus aureus* of osteoconductive acrylate hydrogels by charging silver nanoparticles using three different methods. The first method refers to encapsulating the silver nanoparticles during the synthesis. It was observed that the hydrogels with different cross linking degrees containing silver nanoparticles showed no changes of antimicrobial activity compared with control (Ag 0%) against *Staphylococcus epidermidis* and Methicillin-resistant *Staphylococcus aureus*. The second method refers to the diffusion of the nanoparticles into the composite by diluting the sodium dihydrogen phosphatein the silver nanoparticle suspension. It was observed a slightly higher antibacterial activity compared to control, but it was reported that this results are not statistically significant. The third method used was adsorption of silver nanoparticles into the scaffold by putting in contact the silver nanoparticle suspension with the mineralized hydrogel between 1 and 6 days. It was observed that the samples which was in contact with 1mM silver nanoparticle suspension showed a much higher antimicrobial activity in compare with the samples which was in contact with 0.5mM silver nanoparticle suspension against both *Staphylococcus epidermidis* and Methicillin-resistant *Staphylococcus aureus*. Also, it was reported that the best antimicrobial activity of the scaffolds was for *Staphylococcus epidermidis* and for the samples which were in contact with silver nanoparticles for 2 days, the antimicrobial activity decreased after two days. It was reported that this method does not have a negative impact against osteoblasts and it was one of the few research performed on the acrylate hydrogel with antimicrobial activity with a non-antibiotic based antibacterial [29].

Antitumor Drug Delivery in Hard Tissue Engineering

Gu W and co-workers reported that the organ which produce the highest percentage of mortality and is the most affected by

metastatic cancer is the skeleton [30]. To overcome the limitations of chemotherapy (non-specific biodistribution and targeting) in the case of cancer, the research are rapidly evolving focusing their attention on the drug delivery systems [31]. For example, El-Kady and co-workers synthetized lithium modified bioactive glass nanoparticles by sol-gel method and the nanoparticles were loaded with 5-fluorouracil. The release profile of the drug was in two phases, in the first 24 hours the release was fast and after that the release was slow for 32 days. It was reported that the *in vitro* bioactivity assessment in SBF indicated that this system can be used for bone engineering and the controlled release of lithium ions accelerates bone regeneration [32]. In another study it were synthesized mesoporous silica nanoparticles with dimension of 40 nm anchored by zoledronic acid and loaded with doxorubicin for bone cancer therapy. It was reported that the system had a better bone targeting ability compared with the mesoporous silica nanoparticles. Even if the mesoporous silica nanoparticles present a max loading capacity of 1671 mg/g and a loading efficiency of 83.56%, compared with the system (DOX@MSNs4ZOL) which present a max loading capacity of 1547 mg/g and a loading efficiency of 77.34%, it was reported that DOX@MSNs4ZOL offers the better cytotoxicity against A549 cells and decreased cell migration *in vitro* [33].

Yang L. and co-workers reported that selenium nanoparticles present biocompatibility and anticancer activity and when grow on titanium have the ability to inhibit the growth of cancerous osteoblasts and help the increase of healthy osteoblasts [34]. In another study it was investigated a new drug delivery system formed from calcium phosphate cement and calcium phosphate cement containing caffeine or cisplatin or caffeine and cisplatin. The *in vitro* tests on SOSN2 cells demonstrated that the system formed from calcium phosphate cement, caffeine and cisplatin release greater amount of drug. Also, *in vivo* tests on a male Fischer 344/NSlc 7-week-old rats demonstrated greater tumor growth inhibition when was used the system consisting from calcium phosphate cement, caffeine and cisplatin. Based on these studies the authors reported that this system possess suitable antitumor effects [35].

A new class that treats the cancer bone metastasis is represented by the bisphosphonates which shows an affinity for bone tissue and can be used to deliver other anticancer drugs. In figure 5 is presented a drug delivery system for bone cancer. The system consists in mesoporous silica nanoparticles loaded with anticancer drugs and coated with bisphosphonates. The positive charge of the nanoparticles can be transported and siARN. In the moment of administration the nanoparticles remain to bone cells, they will kill the cancer cells and release drugs or siRNAs. It was reported that poly-l-lysine grafted with beta-cyclodextrin for RIS delivery warned the induction of metastatic cancer in animal models [30].

Wang F and co-workers reported that created a liposomal system conjugated with cyclic arginine-glycine-aspartic acid-tyrosine-lysine peptide (cRGDyk) loaded cisplatin. It was reported, after *in vivo* tests, that this system presents low organ toxicity, high therapeutic efficacy and can be successfully used for therapy of bone metastases [36]. In another study, it was reported an anti-tumoral loaded bone graft material for the treatment of bone cancer. The system consisting of collagen, hydroxyapatite and cisplatin was tested on the osteosarcoma G292 cell line. It was observed that the cytotoxic, anti-proliferative and anti-invasive activities depends on the cisplatin concentration released [37].

A method for destruction of cancer cells is by generating

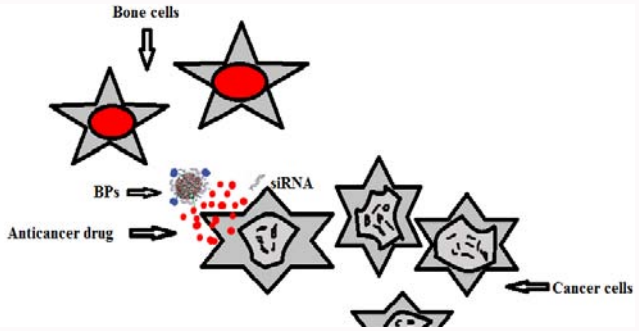

Figure 5: A drug delivery system for bone cancer.

hyperthermia. So, for this are used magnetic nanoparticles loaded to scaffold exposed to alternating magnetic fields combined with anticancer drugs. This method is widely used in hard tissue engineering [1]. Also, Zhang and co-workers created a scaffold consisting of Fe3O4 nanoparticles, mesoporous bioactive glass and polycaprolactone produced by 3D-printing technique. It reported that this system present an excellent apatite-forming bioactivity, good magnetic heating properties and can be used for the treatment of bone tumors [38].

Anti-Inflammatory Drug Delivery in Hard Tissue Engineering

The conventional nanocarriers were replaced by nano-therapeutics due to their advantages such as simultaneous delivery of multiple drugs, the targeting agents present on the surface, etc. These systems can be used to treat different pathologies like inflammatory diseases and can be adjusted depending on the patient. It was reported that the chitin dressings accelerates the wound repair and can regulate secretion of inflammatory mediators like prostaglandin E, IL-8, IL-1 β, etc [39].

In the case of anti-inflammatory applications, some agents very used are steroids or non-steroids (ibuprofen). For example, Paris and co-workers created a scaffold consisting of apatite and agarose polymer loaded with two drugs (ibuprofen and zoledronic acid), during the scaffold fabrication and after consolidation. In the first step, the agarose power was introduced in deionized water and it subjected to magnetic stirring under heat to 90°C. After that, temperature was gradually decreased to 45°C and then the apatite and the drug 1 was added. Then the scaffold was shaped and freeze-dried and then, the drug 2 was injected into the scaffold. It was observed that this system provides a very fast delivery the ibuprofen (reduce the inflammation after implantation) and also, the zoledronic acid (promote bone regeneration). Because, the release of ibuprofen was very fast, the authors have encapsulated the ibuprofen into chitosan spheres. It was reported that due to this change it was obtained a release profile suitable for clinical application [40].In another study it was obtained an anti-inflammatory delivery system for bone applications formed fromporous β-TCP pellets loaded with ibuprofen by physisorption. It was reported that the interaction between porous β-TCP pellets and ibuprofen is weak. *In vitro* tests showed the complete release (100%) of ibuprofen due to Van der Waals forces [41]. Xiao and co-workers reported that an asymmetric coating formed from hydroxyapatite and gelatin on Ti6Al4V alloy implant release ibuprofen at least lasted for 30 days. Also, it was reported that the *in vitro* studies in SBF have led to the formation of apatite and the implant was fully covered after 14 days [42]. In the other hand, Lin and co-workers

release aspirin from a composite formed from PMMA and silica with various 3-(trimethoxysilyl) propyl methacrylate proportion and silica content. It was observed, that the release of the drug in PBS decreased with increasing of the 3-(trimethoxysilyl) propyl methacrylate content and increases with the silica content in the composites [43].

Conclusion and Future Trends

The drug delivery systems represent an emerging area, essential for the treatment of different diseases. They can be synthesized by various methods, depending on the applications for which are required, such as anticancer or anti-inflammatory applications.

It is currently trying to develop controlled release systems loaded with natural products such as medicinal plants or phenolic compounds used to treat different pathologies. Also, Di Marzio and co-workers reported that in the next years the biggest challenge on the development of nano-therapeutics is moving on the research on the systems based of natural products capable of offering a targeted release [44]. Another problem being researched refers to the design and testing of novel methods of controlling the interaction of nanomaterials with the body. The current methods of targeting present the disadvantage that nanomaterials get in certain organs like the spleen and liver [45].

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