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Review Article

Delivery of Nanoparticles for the Treatment of Cardiovascular Diseases

Abstract

Cardiovascular diseases are still one of the major causes of death for the people in the world. Biomedical implantable devices are the basic approach on the treatment of cardiovascular diseases. However, unexpected and serious complications can be observed in the case of their usage. Nanotechnology gives a promising perspective to overcome these drawbacks. Nanoparticulate drug delivery systems have develop superior medical solutions and offer better prospects to patients. This review comprehensively summarizes the recent situation, the benefits and the role of nanocarriers in cardiovascular implant technology.

Introduction

Nanotechnology is a promising and emerging field which uses nanoparticles to facilitate the treatment and/or diagnosis of various diseases such as cancer [1,2], diabetes [3], osteoarthritis [4], brain and retinal diseases [5], cardiovascular diseases [6,7] and bacterial infections [8,9]. Nanoparticles are defined as colloidal particulate dispersions or particles ranging from 10 to 1000 nm in size [10,11]. A similar definition was made by Buzea et al. They described the nanoparticles as "particles with at least one dimension smaller than 1 micron and potentially as small as atomic and molecular length scale" [12]. Different types of nanostructure systems are designed for drug delivery and also the manipulation and the fabrication of biomedical implantable devices have been extensively investigated over the past decades. For this reason, the utilization of the nanoparticulate drug delivery systems in the field of biomedical is predicted to spread rapidly in recent years. [13] Biomedical implants obviously provide a wide range of medical cures for many of the disorders, such as cardiovascular diseases. Vascular grafts, defibrillators, heart valves, pacemarkers and stents are the most common cardiovascular implantable devices used in the medical field. However, the present implant technology is facing a major difficulty of being perceived by the human body as foreign substances. Nanotechnology provides a medical solution to revolutionize the biomedical implant technology exactly by modifying and designing their structures thereby to overcome these problems [14]. The topic of this review article is to designate the role and the importance of nanocarriers in cardiovascular implant technology.

Nanotechnology and Cardiovascular Implantable Devices

Among the various diseases, cardiovascular diseases are still the major cause of mortality in the developed countries. Nanotechnology-based systems have promised new opportunities to diagnose and treatment cardiovascular diseases. Stents are the first option for the cardiovascular therapy [15]. A stent is a tubular device used to support a segment of a blood vessel or any other anatomical lumen so as to preserve or regain its patency. Balloon angioplasty was the common choice to open the blocked vascular vessels before the introduction of coronary stents as bare metallic stents [16]. However, both stent implantation and balloon angioplasty are still cause of various complications, such as elastic recoil, vascular smooth muscle cell migration and proliferation, platelet aggregation, and at last thrombus formation [17,18]. These complications were eventually overcome by the modifications in the stent technology and could be ameliorated by the introduction of therapeutic compounds. In this context, drug eluting stents have been developed through coating the surface of the stents by a matrix polymer, bearing therapeutic agents that regulate the cell division and prevent thrombosis. Sirolimus-, biolimus-, everolimus- and paclitaxel-polymer combinations have been the major surface modifiers which are used for the surface coating and the manufacturing of the drug eluting stents [19,20]. Among them, paclitaxel-eluting TAXUS® and sirolimus-eluting CYPHER® are the most under-researched implanted stents in this field. The conducted randomized clinical studies have demonstrated that these systems had indicated their therapeutic efficiencies by reducing the risk of in-stent restenosis [21,22]. Even though the surface coating of the stents by drug-polymer combination has solved the problem of in-stent restonosis, a new critical problem surfaces after then –late stent thrombosis. This trouble is partly due to the introduction of the stent surface as a foreign substance by human body and also partly due to the incorporation of the polymers, which even they have biodegradable structure, causes inflammation and increases the sensitivity to thrombosis [23,24]. In fact, the majority of the drug eluting stents over bare metallic stents is still contradictive for these reasons. At this point, the researchers have found the solution in nanotechnology. The combination of nanotechnology with cardiovascular device provides a key to the solution by inducing the endothelial cells proliferation, while suppressing the vascular smooth muscle cell proliferation at the same time. From this perspective, nanostructured stents seem more effective in the treatment of cardiovascular disease compared to nanocarrier based stent coatings. When nanoparticles are associated with stents, the particles leaves from the stent surface, penetrate to

the injured epithelium and are taken up by the arterial tissues [25]. The major benefits of the nanoparticulate drug delivery systems are tabulated in (Table 1).

Nanoparticles Coated Biomedical Devices

The first study on this field belongs to Labhasetwar and his group. In 1997, they investigated the potency of developed polymeric nanoparticulate drug delivery systems on the treatment of restenosis by using an ex-vivo arterial model. They prepared poly(lactide-co-glycolide) (PLGA) polymeric nanoparticles and modified their surfaces by a cationic agent. The ex-vivo model study demonstrated that the arterial uptake of surface coated nanoparticles was 10-fold higher than that of the non-coated nanoparticles [28]. Although this research did not contain an in-vivo experiment, it had been a major driving force in providing a basis to incorporate nanocarriers on stent surfaces for restenosis treatment. As a continuation of this study, the same researchers designed another experiment and produced anti-restetonic drugs encapsulated polymeric nanoparticulate formulations. They evaluated the uptake ability of these systems in an ex-vivo model utilizing dog carotid arter. This study demonstrated that the arterial uptake is size-dependent and the particles of *ca.*100 nm diameter penetrated to the artery wall better than those of 200 nm. It was also reported that when the artery was not washed, approximately 26 percent of the nanoparticles had been retained, whereas if the nanoparticles contanct was followed by washing with Ringer's solution, the retention dropped to 6 percent. This result indicated the possibility to wash away the coated nanoparticles from the stent surface through vascular flow [29]. At the same year, they investigated the arterial retention of the polymeric nanoparticulate systems into porcine coronary arterials through an in vivo model. However, they found a reduction on the uptake capacity of nanoparticles, compared to ex-vivo model findings [30]. In 2002, Labhasetwar and his research team evaluated the uptake potency and the localization of the nanoparticles through endothelial cells. They reported that the nanoparticles preferentially localized in the cytoplasma of the cells and the nanoparticles of about 70 nm particle size showed a 27 fold higher uptake than that of the particles which had aproximately 200 nm diameter [31,32]. Similar results were reported by different researchers. Luderer *et al.* prepared sirolimus loaded poly(D,L-lactide) nanoparticles with a diameter of *ca.* 250 nm. They concluded that the developed nanoparticles seemed more effective than the free drug in inhibiting smooth endothelial cell proliferation without affecting the endothelial cell multiplication [33].

In 2004, Westedt and co-workers firstly designed the nanoparticle coated catheter balloons which releases nanocarriers locally and shows a biphasic drug release. Westedt and his team evaluated the arterial uptake ability of the fluorescent labeled nanoparticles which were released from a microporous balon catheter. In conclusion, they observed a higher uptake of nanoparticules [34]. This viewpoint brought another perspective and a new approach of "coating the nano-sized carriers on the stent surface instead of coating of nanoparticles on ballons" has emerged. In 2009, Nakano *et al.* [35] firstly reported the development of nanoparticle-eluting stents. They prepared nanoparticle formulations and coated their surfaces with chitosan to achieve electrodeposition. Then, the nanoparticles were coated on a metallic stent surface by a cationic electro-deposition coating technique. Chitosan coating also gave a cationic surface charge to the nanoparticles, thus this cationicity further helps intracellular uptake because of interaction with negatively charged cellular membranes. *In vivo* study results performed on the porcine model indicated that fluorescein isothiocyanate (FITC)-encapsulated nanoparticles coated stents showed fluorescence in neo-intima and media layers compared to solely FITC-polymer coated stents which did not have any fluorescence.

Joo et al., [36] also developed a novel simple coating process to coat of nanoparticles on the stents surfaces. They called this technology as "Ring Shaped Surface Tension Method". It relies on the principle that a liquid is held between two very closely spaced surfaces in the form of a meniscus, as a result of capillarity. A specially designed ring trails along the immobilized stent surface held along its axis, just like a ring slides over a finger. The nanoparticle suspension was injected between the stent surface and the ring. The deposition occurred at the wedge where the meniscus met the surface when the ring was moved up or down [16]. Uniform deposition of the nanoparticles on the stent surface was observed through the scanning electron microscopy images. The major benefit of this coating process is that the amount of drug on the stent surface can be modified by various ways [36].

In 2013, concercium of Concept Medical Research Private Ltd., Envision Scientific Private Ltd. and Professor Lemos's working team have reported a new cardiovascular implantable stent. This system consists of a polymer-free novel phospholipid based sirolimus encapsulated nanocarrier system coated on stand-alone balloon catheters and on stents with precrimped balloons [37]. Calcium-phosphorous based components rarely settled at the nanoparticle surface and lead to the release of the encapsulated drug through the pH changes. However, precilinical studies were performed solely on the nanosystem caoted ballons. The clinical phase trials of these systems are still going on to initiate its clinical use.

In summary, the current coating technologies of nanoparticles on cardioavscular implantable stents is an up and coming treatment strategy for the therapy of cardiovascular diseases. Recent

Table 1: The superiorities of nanoparticles on cardiovascular implantable devices [14,26,27].

Cardiovascular implantable devices	Advantages
Nanoparticles coated biomedical devices	-Minimizing the changes of local drug toxicity by providing sustained release -High tissue uptake attributed to their sub-micron and sub-cellular size -Higher biocompatibility and lesser toxicity through avoiding the polymer usage -Protection of chemically labile drugs by providing an inert casing
Nanostructured biomedical devices	-Mimics the sub-micron topography of the internal tissue enhancing biomaterial-blood or tissue compatibility -Enhances the proliferation of endothelial cells -Suppresses the proliferation of vascular smooth muscle cells

developments in this field will further boost the transition of these strategies to the market.

Nanostructured Biomedical Devices

In recent years, a great amount of research is carried out on the nanostructured biomedical implants which designed by the way of surface topography. The first study in this field belonged to Reed *et al.* in 1998 [38]. They evaluated the integration of microstructure technology with vascular coronary stents that enables delivery of antirestenotic drugs into coronary arteries by piercing through the plaque. However, this system was not able to transport the drugs into the arterial layers on the contrary of nanoparticles. A solution for this problem came from Wang *et al.* [39]. Wang and co-workers stressed on a polymer free stent coating by opting for a composite coating of carbon nanotubes and magnetic mesoporous silica nanoparticles. Iakovou *et al.* [40] developed an alternative approach - create a nanotopology – instead of coating nanotubes on to stents. This approach involved the design of a metallic stent surface to create a nanostructure. With carving out a polymer-free surface, the risk of polymer-induced thrombosis disappeared and thus, the major complication of the currently marketed stents will be overcomed. Iakovou *et al.*, also emphasized with this study that the risk and the rate of the formation of thrombosis were significantly lower in bare metallic stents than drug-eluting stents [40]. This in itself puts into question the practice of forming a drug-polymer matrix on the stent surface; it does pave a way to effectively provide a long term drug concentration locally but stems an altogether new problem of thrombosis [41].

Various research groups currently work on the manufacturing technologies of fully metallic wires with nanostructured surface features. High temperature chemical vapor deposition is a well-known technique for chemically etching surfaces that results in desired surface properties. Recently, Loya *et al.* explored radio frequency plasma for the creation of radially emanating metallic nanopillar structures on stent surfaces creating a dense and porous texture capable of affecting vascular cells [42,43]. Such metallic nanostructures on stent surfaces may provide an opportunity to improve the safety of stent usage, with a polymer-free approach which reduced the risk of thrombus formation in patients. The stent applications which composed of nanostructuring metallic surfaces may possibly lead to reutilization of bare metallic stents [44].

An important perspective on the design and engineering of the stents is their interaction with the endothelial cells and their effects on endothelialization process. Jia *et al.*, investigated the effectiveness of the nanostructured stainless steel stents on endothelialization mechanism of the cells [45]. Paclitaxel loaded nanostructured stainless steel stents was successfully prepared in this concept. *In vivo* studies, which were performed on a porcine model, demonstrated that (i) the prepared stents lead to rapid re-endothelialization, (ii) they promoted vessel healing with less deposition of fibrin, and (iii) they reduced inflammatory responses when compared to a polymer based sirolimus stent and a bare metallic stent.

In summary, the technology to chisel a metallic stent surface with a nanoscale positively alters the vascular cell responses to specifically boost the adhesion and proliferation of the required cell type, especially endothelial cells leading to re-endothelialization and recede that of the vascular smooth muscle cells that lead to an adverse response. These are expected not only to eliminate the risk of stent related thrombosis, but also to contribute to the restoration of physiological function of treated vessels.

Conclusion and Future Perspectives

Cardiovascular disesases are still remained overly significant in human life. Over the years, cardiovascular biomedical implantation technology has made gradual progress. Utilization of nanoparticulate drug carriers on implantable stent technology is a promising approach for the treatment of cardiovascular diseases. For this reason, future aspects in this field should focus to minimize the toxic effects of drugs, find out new strategies to deliver the nanoparticles by using non-polymeric materials, and move the coating technologies to an endustrial scales. These recent developments on the nanoscale biomedical implants described in this review will allow us to reach these technologies to the market in the near future.

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