Nanomedicine for the Diagnosis and Treatment of Cardiovascular Disease: Current Status and Future Perspective

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1 Introduction

Cardiovascular disease (CVD) encompasses all pathologies of the heart or circulatory system, including coronary heart disease, peripheral vascular disease and stroke. Cardiovascular diseases are the primary morbidity and mortality cause in the world and seen among nearly 25% of adult population who are over 20 years of age, although it differs in continents and regions. The primary conditions underlying the great majority of cardiovascular diseases are dyslipidemia, atherosclerosis and hypertension.

Treatments for CVD include non-invasive therapy such as prescription medication and lifestyle alterations, or surgical therapy such as coronary artery bypass grafting and angioplasty. Effective drug treatments for heart disease can help lower blood pressure or cholesterol, prevent or dissolve blood clots, relieve and prevent angina symptoms or improve the strength or rhythm of the heart's contractions. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, anti-clotting drugs and beta blockers are the examples of drug classes which are commonly used in CVD. Up to date, these drugs are mostly introduced into the market in conventional formulations such as tablets or capsules. During the past 20 years, with the detailed molecular level understanding of the diseases and the development of sophisticated technologies for nanoscale using, nanomedicine has undergone an explosive growth in the world. Nanomedicine is the application of nanotechnology in monitoring, diagnosing, preventing, repairing or curing diseases and damaged tissues in biological systems and it is gaining importance for the treatment of CVD. In the near future, it is considered that nanomedicine approach will enable establishment of patient-specific “personalized medicine”. It is also considered that gene therapies for cardiovascular applications will have a potential usage in the field of cardiovascular applications in upcoming years. This chapter focuses on recent formulations in cardiovascular therapy with comparison of conventional dosage forms. In addition, future perspectives for the treatment of CVD with nanoparticles will be discussed in details.

2 Conventional Techniques/Methods for Diagnosis, Treatment of the CVD

2.1 Nanoparticles for Diagnostics of CVD

Since everything is made of atoms and molecules, nanotechnology is an interdisciplinary research field which cover all the branches of science and technology (Balzani, 2005; Ilem Ozdemir & Asikoglu, 2012; Linazasoro, 2008; Roco, 2003; Sahoo & Labhasetwar, 2013). Nanoscience and nanotechnologies application have a huge potential to bring benefits in information and communication technologies, electronics, transportation, the production of stronger and lighter materials, biology, medicine, pharmacy and more (Bassecoulard & Zitt, 2007; Karunaratne, 2007; Roco, 2001; Sahoo et al., 2007). Since most of these applications are centered on improving human health nanotechnology has given rise to a whole new field called nanomedicine (Karunaratne, 2007; Sahoo et al., 2007). Nanomedicine is the application of nanotechnology in preventing, monitoring, diagnosing, repairing diseases and damaged tissues in biological system (Bassecoulard & Zitt, 2007; Gupta, 2011). In the few past decades, nanomedicine has been developed into a strong multidisciplinary field, enabling prominent technological advances such as intelligent materials and substances with durable surface coating, faster electronics, responsive biosensors, targeted therapeutics nanovectors, and improved nanodiagnostics. The overall goal of nanomedicine is to diagnose as accurately and early as possible, to treat as effectively as possible with minimal side effects, and to
evaluate the efficacy of treatment noninvasively (Ilem Ozdemir & Asikoglu, 2012; Roco, 2001). When medical check-up had found an indication for a disease, it is important to exclude the “false positives” by applying more specific diagnostic procedures. In this case, specific targeted agents in molecular imaging, plays a crucial role for localization and staging of a disease. The main advantage of nanomedicine is earlier detection of a disease, leading to less severe and costly therapeutic demands, and an improved clinical result.

Nanotechnology application in diagnostics can be subdivided into three areas: in vitro diagnostics, in vivo diagnostics and medical devices. In vitro diagnosis for medical applications has traditionally been a laborious task. Nanotechnology enables the development of smaller, faster and cheaper new generation medical devices (Renzo et al., 2006).

Medical imaging is an essential diagnostic tool over the last 25 years. Molecular imaging and image-guided therapy are now basic tools for monitoring disease.

Since CVD have been the top killers for human beings, rapid and accurate diagnosis of CVD is critically important to save lives. Since the underlying pathological conditions such as plaque formation remain largely unclear, early diagnosis is difficult and morbidity and mortality rate is high (Biana, 2012; Hong & Kang, 2006). The imaging techniques routinely used for cardiovascular disease diagnosis are electrocardiography (ECG), chest X-ray, echocardiography, cardiac catheterization and blood tests (Kakoti et al., 2013). These imaging techniques could only detect changes in the appearance of tissues when the symptoms were relatively advanced. Today, nanotechnology based imaging applications are being refined with the goal of detecting disease as early as possible (Biana, 2012; Renzo et al., 2006).

Nanoparticles have the potential for imaging from its current anatomy based level to the molecular level. So nanoparticle imaging techniques cover advanced optical and luminescence imaging and spectroscopy, ultrasound, and X-ray imaging, magnetic resonance imaging, and nuclear imaging with radioactive tracers most of which depend on targeting agents or contrast agents that have been introduced into the body to mark the disease site (Godin et al., 2010; Renzo et al., 2006).

Fluorescent nanocrystal (also quantum dots) can be used as fluorescent markers for diagnostic purposes. Since quantum dots have unique fluorescent properties they have been studied as optical probes for cardiovascular imaging (Choi et al., 2009; Gupta, 2011; Smith et al., 2004). Quantum dots are defined as particle with physical dimension smaller than the excitation Bohr radius. Since the size, particle absorbed light at a wide range of wavelength and emits almost monochromatic light of a wavelength (Han et al., 2001; Sahoo & Labhasetwar, 2003). Due to their excellent optical properties quantum dots have been improved despite the cytotoxicity and limited clinical safety. On the other hand some research groups have reported that in vivo behavior of particles can be modified by carefully controlling of surface chemistry and particle size. Surface modified quantum dots have been developed for fluorescent imaging of vascular disease inflammatory events in mouse and rats models (Gupta, 2011; Jayagopal et al., 2007).

Ultrasound requires contrast agents to provide backscatter of sound waves to the scanner head (Renzo et al., 2006). For this purpose several contrast agents have been developed for ultrasound imaging. Ultrasound is a sonographic based imaging technique which established in diagnosis of physiological tissues. Stabilized gaseous microbubble contrast agents (~5µm in diameter) have been developed as ultrasound contrast agent. Microbubbles are generally used as imaging agent for vasculature since their size and susceptibility to destruction with clinical ultrasound imaging intensities. Takeuchi et al. have been reported microbubbles which were used for targeting to thrombi. Several researchers have demonstrated the modified bubble system by ligands for specific binding to cells and tissues. Because GPIIbIIIa-expressing fibrinogen binding activated platelets are major players in thrombosis, Alonso et al. have been
developed surface modified GPIIbIIIa-specific antibody gas-filled microbubbles for molecular targeting of thrombus. Cavari et al. have been reported polyvinyl alcohol based bubbles for imaging vascular disease (Gupta, 2011; Wickline & Lanza, 2002).

Nanotechnology based particles have been used as computed tomography (CT) contrast agents tent to the based on high molecular atomic number elements such as gold, iron and bismuth (Cormode et al., 2009; Hainfeld et al., 2006; Hyafil et al., 2007; Rabin et al., 2006; Mukandan et al., 2006). Since CT requires high contrast differences, gold nanoparticles are popular choice for CT (Kim et al., 2007; Mukandan et al., 2006). Gold provides unique properties like, resistant to oxidation under physiological conditions and have particularly plasmon resonance in the visible range of the electromagnetic spectrum. These properties have led to application of gold particles in various diagnostic and therapeutic areas like immuno labeling, radiotherapy and X ray image contrast enhancement. Solid iodine based nanoparticle has been demonstrated to image arteriosclerosis by Hyafil et al (Cormode et al., 2009; Gupta, 2011).

Today, magnetically sensitive nanoparticles have become important tool in diagnostic application of detecting disease as early as possible (Gupta, 2011; Renzo et al., 2006). Since reflexivity properties, paramagnetic and superparamagnetic metals linked carriers such as liposomes, micelles, dendrimers, perfluorocarbon bubbles etc. are used in magnetic resonance imaging (MRI) applications (Wickline & Lanza, 2002). For this purpose, magnetically sensitive carriers made with pure metals having high magnetism (cobalt, iron etc.) or decorated with paramagnetic elements like Gadolinium (Gd). FDA has been approved Gd as a T1 relaxation paramagnetic MRI contrast agent and many research papers have been published about Gd decorated contrast agents in cardiovascular disease imaging.αvβ3is overexpressed in angiogenesis, therefore Winter et al demonstrated the Gd decoratedαvβ3targeted perfluorocarbon nanoparticles imaging potential of vascular disease associated with angiogenic neovasculature (Li et al., 2010; Maiseyenu et al., 2009; Mulder et al., 2006; Rensent et al., 2006; Winter et al., 2006). Many research papers have been demonstrated particles which taken up by macrophage rich atherosclerotic lesions (Jaffer et al., 2006; Tang et al., 2009; Trivedi et al., 2004). Due to Gd decorated liposomes which enriched with PS are phagocytized by macrophages, located at the site of high macrophage activity like atherosclerosis associated inflammation (Maiseyenu et al., 2009). Gd loaded immunomicelles surface modified with antibodies have been reported for MRI of cardiovascular disease (Amirbekian et al., 2007; 2009; Lipinski et al., 2006; Mulder et al., 2007;).

Superparamagnetic iron oxide has been widely used to induce contrast for T2 relaxation MRI. Gd or iron oxide can be chosen as depending on the application. Gd produce positive contrast which can easily visualized while iron oxide induced negative contrast and signal loss and because many sources of signal loss in MRI other than iron oxide it may be hard to ascribe signal loss certainly (Cormode et al., 2009). Superparamagnetic iron oxide has been investigated as MRI imaging agent for atherosclerotic and thrombotic lesions (Frias et al., 2004; Gupta, 2011).

Dendrimers are a class of cascade polymers which are rendered a globular confirmation. In the area of vascular disease dendrimers have been used for loading and imaging MRI etc). Fahmy et al have demonstrated ligand modified dendrimers as MRI imaging probes. Also radioactive Bromine encapsulated biodegradable dendrimers structures were used in positron emission tomography imaging of ischemia in mouse model (Fahmy et al., 2007; Gupta, 2011; Hagooooly et al., 2008).

Nuclear imaging modalities like single photon emission tomography (SPECT) and PET are significant imaging techniques for early diagnose of vascular disease (Cormode et al., 2009). While many radiopharmaceuticals have been developed for cardiovascular imaging, elements were labeled with a radionuclide. In recent years developing of multicomponent nanoparticles are getting popular which combine
nuclear imaging probes and therapeutic agents (McCarthy, 2010). Polysaccharide coated iron oxide nanoparticles have been developed and radiolabeled with Flourșne-18 radionuclide for PET imaging. The most widely use radionuclide Technetium-99m has been conjugated directly to Annexin 5 for imaging arteriosclerosis associated inflammatory events. Also Iodine-125 labeled nanoparticles were investigated as SPECT imaging agent (Chrastina & Schnitzer, 2010; Cormode et al., 2009).

Many of these reports are relatively new and ongoing research, their promising results makes nanomedicine promising in revolutionizing diagnostic modalities for vascular disease. Effective molecular, imaging contrast agents can be synthesized using nanoparticles. Through the design of nanoparticle based probes, highly sensitive, highly reliable imaging techniques have been performed for diagnostic application. In future nanoscale science will play an important role in imaging modalities.

2.2 Nanoparticles for Treatment of Cardiovascular Disease

Cardiovascular disease (CVD) encompasses a class of diseases that involves the heart and vasculature. For decades, CVD has been one of the leading causes of mortality and accounts for virtually 1/3 of all deaths in the world. Therefore, there is pressing a need to develop novel techniques such as nanotechnology for the early detection and treatment of several CVD (McCarthy, 2010).

Nanotechnology offers advantages for CVD mainly in four areas:

i. Targeted therapeutics: delivering drugs where they are needed.

ii. Tissue engineering: building new tissues to replace defective valves, damaged heart muscle, clogged blood vessels, etc.

iii. Molecular imaging: using “smart” imaging agents that identify disease more specifically

iv. Biosensors and diagnostics: improved diagnostic devices for the laboratory, and implantable sensors to detect problems inside the body (Arayne et al., 2007).

The most important clinical applications of nanotechnology are in area of pharmaceutical development and pharmaceutical nanoparticles have gained great importance for the treatment of CVD. In pharmaceutical technology and biomedicine, nanoparticles are typically defined as particles with diameter from 1 to 100 nm and have been exploited for both diagnostic and therapeutic purposes. The ideal size of nanoparticles used as drug delivery systems ranges from 10 to 100 nm. They can be classified into several categories, according to their structure (i.e., nanoparticles, nanospheres, nanocapsules, nanotubes and colloidal carriers such as liposomes or dendrimers), physicochemical properties (i.e., pH sensitive, magnetic, stealth nanoparticles) and the materials used for its synthesis (i.e., natural, synthetic, hybrid, or gold nanoparticles). Nanoparticles can achieve controlled drug release, targeting and increase the effectiveness or bioavailability of many diagnostic or therapeutic agents. In this section, some drugs formulated in nanoparticles for the treatment of CVD are summarized (Arayne et al., 2007; Goldberg et al., 2007).

Endothelial-selective delivery of therapeutic agents would provide a useful tool for modifying vascular function in various cardiovascular diseases and several research groups are interested in this targeting approach (Spragg et al., 1997).

Kona et al. developed a novel nanoparticulate drug delivery system that mimics platelets binding to the injured vessel wall under physiological flow conditions. Glycoprotein Ib (GPIb) was chosen as the targeting ligand and conjugated to nanoparticles because its role in platelet adhesion to the vascular wall under high shear flow conditions is well-recognized. Dexamethasone-loaded biodegradable poly-(d,l-lactic-co-glycolic acid) (PLGA) nanoparticles were formulated using a standard emulsion method. The
results demonstrate that conjugation of GPIb to PLGA nanoparticles increased particle adhesion onto targeted surfaces and increased cellular uptake of these nanoparticles by activated endothelial cells under shear stresses. In addition, these nanoparticles also provided a controlled release of the model drug. Therefore, this drug-loaded, GPIb-conjugated PLGA nanoparticles could be used as a targeted and controlled drug delivery system to the site of vascular injury for treatment of cardiovascular diseases (Sujanya et al., 2012).

Restenosis, the principal complication of percutaneous transluminal coronary angioplasty is responsible for the 35–40% long-term failure rate following coronary revascularization.

Song et al. (1998) investigated the potential usefulness of biodegradable nanoparticles for the local intraluminal therapy of restenosis. NPs containing a water-insoluble anti-proliferative agent U-86983 were formulated from oil–water emulsions using biodegradable polymers such as poly-(lactic acid–co-glycolic acid) (PLGA), and specific additives after particle formation, to enhance arterial retention using either heparin, didodecylmethylammonium bromide, fibrinogen, or combinations. The in vivo studies were conducted with a new dog model for arterial angioplasty. The results support the view that modified nanoparticles along with optimized infusion conditions could enhance arterial wall drug concentrations of agents to treat restenosis.

In other studies; Fishbein and coworkers, prepared tyrphostin inhibitor containing poly (DL-lactide) (PLA) nanoparticles for intrarterial administration by spontaneous emulsification / solvent displacement technique for the treatment of restenosis (Fishbein et al., 2000). Klugherz et al. (1999) have demonstrated transcatheter local delivery of the antirestenotic agent probucol loaded PLGA particles, in rabbit iliac arteries, for enhanced retention, sustained release and increased therapeutic effects. Winter et al. (2008) performed studies to develop a prolonged antiangiogenesis therapy regimen based on theranostic ανβ3–targeted nanoparticles. For this purpose, fumagillin was incorporated into perfluorooctylbromide nanoparticles to elicit acute antiangiogenic effects. The impetus for this study is the observation in animal models that chronically high systemic doses of a water-soluble version of fumagillin resulted in a decrease in neovascularization and plaque development, thus a targeted nanoagent may allow for localized delivery requiring decreased dosing.

Liposomes are spherical platforms that use natural lipids and/or synthetic polymers and cholesterol as building blocks to form the bilayer structure. They possess a hydrophilic core surrounded by a hydrophobic membrane and they are in size from 50 nm to several microns (Ruiz-Esparza et al., 2013). Currently, in the drug market, there is no liposomal formulation approved for the treatment of cardiovascular disease. However, several innovative examples of liposomal technologies have been developed for the treatment of cardiovascular disease and researches are going on.

Joner et al. (2008) have developed cationic liposomal nanoparticles of prednisolone that specifically bind to chondroitin sulfate proteoglycans that are expressed within the subendothelial matrix but not vascular endothelial cells. In vivo studies were conducted with atherosclerotic New Zealand white Rabbits which were implanted with bare metal stents. Results showed that site-specific targeting by this nanoparticle steroid in injured atherosclerotic areas might be a valuable and cost-effective approach for the prevention of in-stent restenosis.

Cardiovascular diseases are not as much benefited from nanotechnology in terms of drug delivery as the field of cancer and others. There are still unmet aspects of cardiovascular drug delivery that need to be worked upon.
3 New Techniques/Methods for Diagnosis, Treatment of the CVD

3.1 Therapeutic and Theranostic Nanoparticles for Cardiovascular Disease

The theranostics has been identified as recognition of heterogeneous diseases requires more personalized solutions (Espina et al., 2009). Theranostics entitles to the fusion of therapy and diagnostics, with the purpose of optimizing efficacy and safety, as well as updating the process of drug development. The increasing of number of scientific inventions has made the development of theranostics possible. The theranostic agents have a number of advantages, as they potentially allow for the concomitant determination of agent localization, release, and efficacy. Whereas the use of these agents in cancer treatment has received the majority of the attention, their use in cardiovascular disease is increasing.

In the field of biology, the human genome project and the development of biomarker initiatives have improved the understanding of disease progression. Genotyping or gene expression technologies make it possible to transfer this newly needing biological knowledge into the development of diagnostic tests. Theranostics allow doctors with high medical value testing for science-driven treatment decisions; enhance patient safety by identifying patients who won't respond to a drug or who have an adverse effect; increase the efficiency of drug development, helping pharmaceutical companies by developing new drug; and positive effect on health economics, thus selecting optimal and cost effective therapy by doctors. Although such a thought on this field has much potential in improving healthcare, there are some objections that must be corrected before it offers to routine use in the clinic (Falk, 2008; Buxton, 2009; Nazem & Mansoori, 2008; Couvreur & Vauthier, 2006).

The disease elimination can be improved by using theranostic agents to perform localized cytotoxicity with little collateral damage. The control of drug dosing, location, and time is an important purpose for drug delivery development, as enhanced therapeutic effect while reducing side effects. Systems responsive to a stimulus such as temperature, pH, applied magnetic or electrical field, ultrasound, light, or enzymatic action have been proposed as triggered delivery systems (McCoy et al., 2010). Recently, light has been used to release therapeutic agents from delivery systems or activate agents that produce cytotoxic effect. For instance, light-activatable agent (Visudyne) that has been approved by the food and drug administration (FDA) is widely used for the treatment of age-related macular degeneration (AMD, is the major cause of blindness among the elderly in the developed world) (Amirbekian et al., 2007).

Atherosclerosis is occurring over a number of decades that often goes undetected until the onset of clinical symptoms. Atherosclerotic lesions offer a plethora of potential targets, including specific inflammatory cell types. Various nanotechnology applications are being developed for the treatment of atherosclerosis, including nanocarriers drug delivery systems and devices such as mechanical stents, possessing nanoscale components. Targets for imaging of atherosclerotic plaques contain endothelia, macrophages, fibrin, collagen III, and markers of angiogenesis (Botnar et al., 2004; Cyrus et al., 2006). Along with the development of novel strategies for treatment of CVDs, efforts are being spent to apply nanotechnologies for ex-vivo and in vivo detection of CVD signals. The awareness of precursor signal of CVD reduces the many fatalities associated with the diseases.

The main nanocarrier classes researched as therapeutic and ‘theranostic’ agents for atherosclerosis are liposomes with different surface characteristics, polymeric nanoparticles and micelles, perfluorocarbon nano-emulsions and cross-linked iron oxide (CLIO) particles conjugated to therapeutic molecules (Danenberg et al., 2002; Stephan et al., 1997; Hedman et al., 2003; Lanza et al., 2006) For example, a prolonged anti-angiogenesis therapy was reported using theranostic avb3-integrin-targeted paramagnetic nanoparticles in hyperlipidemic animals (Winter et al., 2006; 2008) MRI data showed that the neovascu-
lar signal has reduced for 3 weeks with histological evaluation, pointing toward the potential of this strategy for efficient antiangiogenic therapy and simultaneously evaluating plaque stability. Another example for angiogenesis therapy is fibrincoated perfluorocarbon nanoparticles. These nanoparticles can also be used for acoustic or MRI imaging with targeted thrombolysis (Marsh et al., 2007). Hua et al. (2010) have developed the targeting perfluoropropane-containing liposomes to activated platelets via a peptide (RGDS) derived from the α-chain of fibrinogen. Initially, the peptide and rtPA were each modified with distinct fluorescent labels to obtain tracking of the microbubbles and thrombolytic drug. When injected into healthy rabbits, the thrombolytic drug was visualized within the liver by using ultrasound imaging. This may demonstrate the additive effect of microbubble rupture on the ultimate lysis of clots. There is also a disadvantage about the nanoparticles. They can affect the walls of blood vessel. The vascular endothelium could be a barrier and unwanted target for nanoparticles to be delivered to other organs (Lukyanenko, 2007). In this respect, the transport of nanoparticles across vessel walls, organelle-targeted delivery of nanoparticles, and other effects of nanoparticles on vessel cells may affect the CVDs. These factors should be considered in future for nanomedicine research.

3.2 Biomarkers in Cardiovascular Disease

Biomarkers are an important tool in clinical practice, helping to improve patient care. For example, biomarkers have showed that a significant impact in early detection of sub-clinical disease (e.g., prostate-specific antigen screening for prostate cancer), diagnosis of acute or chronic syndromes (e.g., B-type natriuretic peptide in heart failure), risk stratification (e.g., cardiac troponin in acute coronary syndromes), and monitoring of disease or therapy (e.g., hemoglobin A1c in diabetes mellitus) (Catalona et al., 1991; Maisel et al., 2002; Anderson et al., 2007 Goldstein et al., 2004).

Local inflammation in the vessel wall plays a key role in the development of atherosclerosis (Hansson, 2005). Therefore, inflammatory biomarker could be prognostic biomarkers in CVD. Epidemiological and clinical studies have shown strong and consistent relationship between biomarkers of inflammation, evaluated by high sensitivity C-reactive protein (HsCRP), and risk of cardiovascular events in patients with cardiovascular especially ischemic heart disease (Harutyunyan et al., 2011; Mathiasen et al., 2010; Mygind et al). However, when HsCRP is used in general population studies, HsCRP does not always seem to have a significant prognostic value in detecting future cardiovascular disease (Olsen et al., 2007).

YKL-40 is an acute phase protein and a new potential biomarker of inflammation in CVD patients, which is expressed by several cell types of the immune system (Johansen, 2006). Macrophages in atherosclerotic plaques express YKL-40, and the highest expression was found in macrophages in early atherosclerotic lesions. Some studies have showed that serum YKL-40 is increased in patients with acute myocardial infarction YKL-40 is associated with both early and late phases in the development of atherosclerosis. It has been demonstrated that YKL-40 stimulates the maturation of monocytes to macrophages and then is hidden by macrophages during the late stages of differentiation (Johansen, 2006; Rehli et al., 2003).

The role of the activation of the sympathetic system and the renin-angiotensin-aldosterone system (RAAS) in the development of CV diseases has been extensively explored. Renin is the first limiting step of the RAAS and plays an important role in CVD. There are new progresses in pharmacological inhibition of RAAS by using angiotensin-converting enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARBs). However, whether plasma renin has a direct prognostic role in predicting CVD risk, it can be offered as a biomarker to improve CV risk stratification which is a topic of discussion.
Starting from the observations, an association between increased rennin levels and CV risk has been supported. Bruner et al. (1972) indicated that hypertensive patients with low renin activities protected when compared to those patients with high rennin and suggested that renin could be a potential risk factor for the development of CVD. Although rennin has shown the positive effect on CVD according to literatures, rennin does not completely satisfy the criteria suggested by the American Heart Association criteria for the evaluation of novel biomarkers (Hlatky et al., 2009).

4 The Comparison of Conventional Formulation and New Nanomedicine Therapy of Cardiovascular Disease

This review identified a significant number of nanomedicine products approved for CVDs in-human use. It is difficult to extrapolate these numbers directly, because growth in medical industries is so heavily influenced by swings in the economy and regulatory processes. However, some definite trends related to the future of nanomedicine. The most prominent theme throughout is the relative adolescence of the field. Although all the applications identified represent significant technological advancements, they are only scratching the surface of the potential available, and the continued refinement and combination of these technologies will lead to the truly transformative capabilities envisioned for nanomedicine.

One of the major concerns regarding the use of nanotechnology in the body is the question of persistence. Conventional therapeutics are generally processed by the body and the metabolites are excreted soon after administration, but some nanoparticles have demonstrated persistent in vivo deposits for months or years. Examination of the in vivo applications and products identified demonstrates a much higher prevalence of “soft” (157 applications and products) versus “hard” (30 applications and products) nanostructures (Goel et al., 2009; Rx Media, 2013; Walkey & Chan, 2011). Some samples of conventional formulations and nanomedicines in the market were shown in Table 1.

5 Future Perspectives

The ability to detect and treat CVD is the main concern of clinical medicine. With the advantage of nanotechnology, and the generation of multifunctional agents, it becomes possible to perform both actions simultaneously. There are many advantages to this approach, such as ability to determine agent localization, release, or efficacy.

Nanomedicine approaches keep great promise in revolutionizing therapeutic and diagnostic modalities in the clinical treatment of CVD. The previous review and studies have attempted to emphasize the various nanomedicine fabrication and formulation strategies in this area. Many of these reports are still based on in vitro or preclinical small animal model in vivo investigations. Further studies will certainly help to test its clinical usefulness in predicting cardiovascular events.

References

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<th>Drugs</th>
<th>Conventional formulation</th>
<th>Nanomedicines</th>
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| Lipid increasing drug - Isosorbit monohydrate | Monoket long retard tablet 40 mg (Adeka, Turkey)  
Monodur tablet 60 mg (Astra Zeneca, Canada) | Monolong SR microplet capsule 40 mg (Ali Raif, Turkey)  
Mono corax microplet capsule 60 mg (corax, Germany)  
Monisol microplet capsule 60 mg (Zorka, Russia)  
Monitan microplet capsule 60 mg (Wyeth, Canada) |
| Antihypertensive drug - Diltiazem hydrochlorure | Diltiazem ampoule 25 mg (Mustafa Nevzat, Turkey). | Altiazem SR microplet 60 mg (Nobel, Turkey)  
Dilatam SR microplet 60 mg (Abic, Israel)  
Coramil SR microplet 60 mg (Sanofi, Sweden) |
| Lipid increasing drug - Phenofibrate | Lipidil tablet 200 mg (Fournier, Germany, Canada)  
Lipofene tablet 200 mg (Teofarma, Italy) | Feno-micro microplet 250 mg (Apotex, Hungary)  
Lipofene SR microplet 250 mg (Nobel, Turkey) |

**Table 1:** Conventional formulations and new nanomedicines for CVD therapy (90).


Balzani V., Small, I, 278, 2005.


Rx MediaPharma interactive drug information resource, 2013.


