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NOVEL DRUG DELIVERY SYSTEM IN THE TREATMENT OF CARDIOVASCULAR DISORDERS

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ABSTRACT

Novel drug delivery systems present an opportunity for formulation scientists to overcome the challenges associated with drug therapy of cardiovascular disorders. This provides opportunities in improving the management of patients with cardiovascular disorders. Most of these drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for these agents. The impetus for the development of newer novel drug delivery system apart from therapeutic efficiency is the cost. The development cost of a new drug may be about $250 million and takes about 12 years to reach the market place, whereas an existing drug molecule can get a second life with newer drug delivery system that can be developed in half of the time with 20% cost of the new drug discovery. This paper provides a comprehensive review of the various delivery systems that have been developed for achieving sustained drug release kinetics, specifically targeting drugs to the heart and for addressing formulation difficulties such as poor solubility, stability and drug entrapment. Studies on the active potential of systems for alternative routes of drug administration, i.e., transdermal and buccal are also highlighted. The physico-chemical properties and in vitro/in vivo performances of various systems such as sustained release tablets, nanoparticles, liposome, gene therapy and polymeric hydrogels are summarised. The futuristic approach in the effective treatment of patients with cardiovascular disorders has also high lightened.

INTRODUCTION

It is well known that cardiovascular diseases including the coronary artery disease, heart failure, acute myocardial infarction, arrhythmias are the common causes of morbidity and mortality in the world[1]. Effective treatments of CVD include preventive lifestyle changes, medications and surgical procedures [2-4]. It is necessary to maximize the use of all cardiovascular management strategies to overcome these challenges. Many researches reveals that the problem initiated from simple organoleptic or technological sites to more complex issues involving the targeting of specific tissues and organs. With the aim to reduce dosing frequency, to improve the compliance of the existing pharmacotherapy and to target viral reservoirs, the design of novel drug delivery systems is becoming complementary to new drug discovery. Various drug delivery and drug targeting systems are currently under development to minimize the loss of drug by drug degradation including prevention of harmful side-effects. Such approaches are also fruitful in increasing drug bioavailability and drug accumulated in the required zone.

Among drug carriers one can name cubosomes, liposomes, nanoparticles, mucoadhesives, transdermal patches and micelles. The carriers can be made slowly degradable, stimuli-sensitive (pH or temperature-sensitive) and even targeted (with specified biodegradable hydrogel).With the aim to reduce dosing frequency and to improve the compliance of the existing pharmacotherapy, the design of novel drug delivery systems (NDDS) is becoming complementary to new drug discovery. The goal of the present review is to describe state of NDDS and to thoroughly discuss the challenges in the development of medicines with enhanced biopharmaceutical properties. Numerous reviews discussed different NDDS designed to optimize the delivery of drugs used in cardiovascular disorders. Moreover, present article also highlight the drawbacks based on drugs common molecular features, families of drugs and the qualities that seriously hamper effective pharmacotherapy.

LIPOSOMES

Liposome's ranging in size between 25 nm to several microns. These are microscopic vesicles that comprise one or more phospholipid bilayers which surround an aqueous core. The aqueous core facilitates the entrapment of hydrophilic drugs, while hydrophobic drugs are bound to or incorporated in the lipid bilayer. When administered, liposomes are recognised as being foreign, and are immediately taken up by cells of the mononuclear phagocytic system (MPS).

ATP levels drop by as much as 80% after 15 min in the cardiomyocytes during cardiac ischemia[5]. A similar time scale for the lowering of the intracellular ATP was observed during cardiac hypoxia and inhibition of glycolysis[6]. Liposomes are widely used as nanosized drug delivery vehicles[7]. The accumulation of liposomes as well as other nanoparticular drug carriers in the regions of experimental myocardial infarction was demonstrated[8-12], which proceeds via the enhanced permeability and retention (EPR) effect[13-14]. Liposomes may also "plug" and "seal" the damaged myocyte membranes and protect cells against ischemic and reperfusion injury in vitro [15]. Thus, one can suggest that ATP-L can be used for the "passive" ATP delivery into the infarcted myocardium.

The ability of the liposomes to cross the biological barriers, such as capillary endothelium, and deliver ATP directly into the cell by transporting themselves through endothelial tight junction opening and increased endothelial endocytosis was clearly shown[16,17]. The opening of the endothelial tight junctions is the primary mechanism through which liposomes reach the tissue in the ischemic brain [18,19] and in the liver [20]. Enhanced permeability and retention effect can also facilitate liposome extravasation into ischemic myocardium through damaged blood vessels[10-14]. It was also reported that liposomes could cross a continuous wall of myocardial capillaries in the isolated heart through endocytosis[21]. In an ischemic myocardium, liposomes were found in the cytoplasm of both cardiomyocytes and endothelial cells[8].

Liposomes have been used to deliver a variety of drugs to the arterial endothelial cell wall. As previously outlined a number of drugs have been investigated to treat restenosis. The bisphosphonate agent, clodronate, was delivered using a liposomal formulation consisting of 1:3 distearoyl phosphatidylglycerol (DSPG), 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC) with an average particle size of 190 nm[22]. Results from this study showed that liposomal clodronate successfully inhibited neointima growth in balloon-injured rabbit carotid artery after systemic administration. Other bisphosphonates including, pamidronate, alendronate and ISA-13-1 were tested in a similar liposomal formulation in a balloon-injured rat model[23]. To deliver the liposomes to the target site, the researchers in these studies modified a piece of plastic tubing with a 23-gauge catheter to perform local intraluminal delivery in addition to IV and subcutaneous administration. The results of this study showed that systemic administration not local administration leads to the greatest amount of reduction of neointimal growth, which is

likely due to the mechanism of action of the drugs. These drugs act on macrophages, which are important in the inflammatory mechanism of restenosis[22,23]. Using liposomes to incorporate the hydrophilic bisphosphonates into macrophages is a novel approach for the compound class.

NANOPARTICLES

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale or one billionth of a meter. It is a scientific field devoted to the manipulation of atoms and molecules to construct miniature structures for new molecular assemblies at the nanometer scale size. The application nanotechnology to medicine involves use of devices that will interact with the body at the molecular level. These methods will have high degrees of specificity and can lead to target and tissue specific clinical applications with minimal side effects[24].

Therapeutic applications of nanomaterials in cardiovascular medicine include cardiovascular devices for delivery of drugs and bioactive molecules, or novel technologies for reducing cholesterol accumulation and for dissolving clots[25]. Stent placement is currently the primary intervention for cardiovascular occlusive diseases; however, it may lead to in-stent restenosis[26-28]. Successes in early clinical trials with drug-eluting stents using the anti-proliferative agents have been promising. PLGA NP-coated stents can effectively deliver drugs to vessel walls.

Nanoparticulate delivery systems have been used to treat a variety of disease states. In restenosis treatment, both conventional drugs- and gene-based medicines have been used in nanoparticle delivery to achieve desirable therapeutic results. A nanoparticle delivery system is well suited for the treatment of restenosis since local or targeted delivery can be achieved, lowering systemic toxicity, while reaching specific cell types in sufficient concentrations for the necessary period of time. Biocompatible lipids and polymers also do not create an inflammatory response. In the context of this article, liposomes, polymer-based nanoparticles, and micelles are considered as nanoparticulate carriers. The high shear pressure in the arterial blood supply leads to a very short residence time for the therapeutic agent at the target cells in the arterial wall. The use of nanoparticles allows for the rapid incorporation of the drug and gene into the cell, thus reducing the shear effects of the arterial pressure. Studies using florescent particles have shown a size dependency in arterial wall transfect ion using a SCIMED® REMEDY porous balloon catheter[29].

Three particle sizes were tested and the data showed that the smallest size particles (~110 nm in diameter) had the greatest florescence intensity within the cell. Larger particles showed very little florescence due to short residence time on the arterial wall surface. Other studies showed an increase in inflammatory responses with particles of 5–10 μm in diameter and no therapeutic response, probably due to uptake by the macrophages and other immune cells rather than SMC or endothelial cells[30,31]. Cells can incorporate particles varying from 50–300 nm in diameter based upon a variety of different internalization pathways including nonspecific or receptor-mediated endocytosis[32-36]. Additionally, nanoparticles larger than 300 nm in diameter were found to accumulate in the liver, spleen and lung, rendering them unavailable for arterial delivery upon systemic administration[37]. Other known factors for cellular uptake of nanoparticles include volume, concentration, infusion pressure, and the type of infusion balloon[38,39]. Increased delivery pressure and large volumes can cause an increase in the intimal thickening, while increased particle concentration leads to effective delivery[39]. In addition, the use of cell specific surface modifications, can increase the residence time of the nanoparticles at the desired site.

A significant amount of work has been ongoing and completed in the field of polymer-based nanoparticle drug delivery for the treatment of restenosis. The bisphosphinate agent, alendronate, was encapsulated in a poly(D,L-lactide-co-glycolide) (PLGA) based nanoparticle system with an average size of 223 nm[40]. The presence of calcium ions was found to be critical for the successful entrapment of the hydrophilic drug compound in PLGA matrices, alendronate in this formulation was delivered subcutaneously and by intravenous administration. The results showed reduction in neointimal growth in a balloon injured rabbit model using both routes of administration[40].

Effective prevention of cardiovascular morbidity and mortality will require the development of new diagnostic and therapeutic strategies aimed at treating early and subclinical disease stages. Nanotechnology has also significantly impacted diagnostic intervention in cardiology. The imaging capability of NPs has been involved in the construction of particles with use of imaging-contrast agents, for targeted biomedical imaging of vulnerable plaques, for detection of specific pathologic targets signaling the onset of atherosclerosis and for tracking inflammatory events[41].

The introduction of modern contrast agents is critical in diagnostic ultrasound[42]. Modern ultrasound contrast agents are primarily comprised of microbubble (microspheres with porous or

hollow inner structure) formulation that circulates in the intravascular compartment and are designed to enhance acoustic signals reflected from the blood pool. Therefore, optimal density differences are obtained when the contrast agent is a gas because tissues are primarily composed of liquid. The hollow, biodegradable PLGA microcapsules were developed for use as ultrasound contrast agents to improve ultrasound imaging since it may slowly degrade *in vivo* into lactic and glycolic acid, neither of which produce *in vivo* toxic effects and further degrade into carbon dioxide and water via the tricarboxylic acid cycle[43]. Cui *et al.* fabricated a kind of absorbable PLGA microbubble-based contrast agent (PLGA microspheres with porous or hollow inner structure) by an improved double emulsion-solvent evaporation-method. *In vitro* acoustic measurements demonstrated the good scatter ability of these polymer-based agents. *In vivo* imaging experiments showed PLGA microbubbles could remain stable under high Mechanical Index, which is the ratio of the peak negative pressure and the square root of the frequency. The resistance of PLGA microbubbles to ultrasound destruction allows for their potential applications in left ventricle opacification and myocardium imaging, and demonstrates the ability of PLGA micro-bubbles to detect myocardial perfusion defects[42]. Wheatley *et al.* also developed the PLGA microbubbles used as ultrasound contrast agents. PLGA microbubbles were prepared by an adapted double emulsion w/o/w solvent evaporation process. Significant acoustic enhancements (up to 24 dB) were reported both *in vitro* and *in vivo*. Moreover, the rabbits used in the *in vivo* study did not show adverse side effects from multiple injections of the agent[43,44].

Daidzein is a very good candidate for treating cardio-cerebrovascular diseases, but its poor oral absorption and bioavailability limit its curative efficacy. Li et al., prepared daidzein-loaded solid lipid nanoparticles (SLNs) with PEGylated phospholipid as stabilizer by hot homogenization method. SLNs showed the mean particle size 126±14 nm with entrapment efficiency 82.5±3.7%. In vitro release of SLNs demonstrated a sustained release manner with cumulative release over 90% within 120 h in bovine serum albumin solution (4%, w/v). SLNs showed the better effect on cardiovascular system of the anesthetic dogs by reducing the myocardial oxygen consumption (MOC) and the coronary resistance (CR) in heart compared with oral suspension or intravenous solution. The SLNs demonstrated the best effect on cerebrovascular system by increasing cerebral blood flow (CeBF) and reducing cerebrovascular resistance (CeR) in anesthetized dogs[45].

TRANSDERMAL DELIVERY SYSTEM

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication through the skin for treating systemic illnesses. Since early1980s, this dosage form of transdermal therapeutic system (TTS) has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over others, such as tablets and injections. For examples, it provides controlled release of the drug into the patient, and enables a steady blood-level profile, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms [46-48]. In addition, the dosage form of transdermal patches is user-friendly, convenient, painless, and offers multi-day dosing, it is generally accepted that they offer improved patient compliance[49].

There are currently five transdermal preparations of nitroglycerin available: Nitrodisc, Nitro-Dur transdermal infusion system, Transderm-Nitro transdermal therapeutic system, Deponit transdermal delivery system, and Minitran transdermal delivery system. These preparations are essentially identical in their delivery of nitroglycerin. However, their mechanisms to attain a controlled release differ[50].

So far, few investigations have been carried out with the primary objective to evaluate the efficacy and risk factors of TDDS patches in heart patients[51,52]. However, a study using nicotine patch specifically conducted to evaluate the safety of TDDS on heart patients has showed no additional cardiovascular risks[53]. Nicotine is a ganglion stimulant, which increases the heart rate; so the safe result indicates that patches or adjuvants used in the patches as such do not involve any additional risk for the heart patients.

Courtesy transdermal development, nitroglycerin, a drug that had lost its popularity in the 1960s, was reintroduced for clinical use[54]. Unsuitable for gastrointestinal administration owing to its low oral bioavailability (1%), its use was restricted to sublingual and topical form. Absorption of this drug from these forms was low and variable (26-34%), and inadequate understanding of the pharmacology had raised doubts about its clinical efficacy[54]. Until 1970, the only alternative for the sublingual therapy was an intravenous infusion, occasionally used in the intensive care units on patients undergoing treatment for severe chest pain. In 1981, introduction of the transdermal patch opened up the possibilities of its prolonged and continuous use to prevent the unwarranted attacks of angina.

Transderm-Nitro patches, one of the first two transdermal systems to be marketed, owed their success to a favourable pharmacodynamic parameter of the drug. Effective at low plasma concentration (1.2-11 ng/ml), a dose in the microgram ranges is sufficient to control the angina[55]**.** Presently there are four manufacturers in the market selling the drug in the transdermal form: (Deponit-Schwarz/Lohmann, Nitrodisc-Searle, NitroDur-Key Pharmaceuticals and Transderm Nitro-Ciba)[56]. Support for transdermal therapy has also come from another significant clinical study. Patients of unstable angina who could only be sustained by IV nitroglycerin in the intensive care unit responded to transdermal nitroglycerin, which maintained the antiischaemic effects initially achieved with IV nitroglycerin[57]. Though the utility of the transdermal nitroglycerin is yet to be established in the whole spectrum of coronary heart diseases, it has already improved the quality of life of the ambulant ischemic patients. Special benefits in terms of improvement in haemodynamic abnormalities, reduction in the infarct size and reduction of life-threatening arrhythmias have been noted amongst the users of the products. Finally, the American Heart Association has endorsed the utility of the transdermal form in acute myocardial infarction irrespective of the involvement of left ventricular failure[58].

The other organic nitrate that has been marketed already in the transdermal form is isosorbide dinitrate. As skin is preferentially permeable to the lipid molecule, the fully nitrated lipophilic polyols are acceptable to skin. Bioavailability of isosorbide dinitrate when administered by conventional routes varies significantly. The drug has a short half-life (0.8±0.4 h), demanding frequent administration, and the prescribed dosage regimen is 2.5-10 mg every 2 to 3 h. From transdermal route, a flux of 4.01 mg/h is necessary to achieve the level of clinical efficiency of maintenance therapy[59]. However, in 1984 a Japanese company "Toa Eiyo" had launched frandol tape in the market, containing the drug in adhesive polymer dispersion. The frandol tape, a once-daily transdermal patch, had reduced the inconvenience of frequent administration and gained wider acceptance. Evidence indicates that atherosclerosis is the consequence of an inflammatory response of the arterial wall. Endothelial injury caused by a number of stimuli appears to be an early event in atherogenesis. Serum levels of acute phase reactants such as C-reactive protein (CRP) are increased in patients with a higher risk of development of cardiovascular events. Nitroglycerin acts by a chemical liberation of nitric oxide. The results from several controlled clinical trials have confirmed an anti-inflammatory action of nitroglycerin. The transdermal

patch of GTN has been prepared and improvement in biological markers of arterial inflammation in patients with peripheral vascular disease has been studied. The results of this preliminary study show that nitroglycerin has an anti-inflammatory action in patients with peripheral vascular disease. This may provide a new therapeutic approach to understanding the efficacy of nitro vasodilators in the improvement of atherosclerotic syndromes. The results of this pilot study show that transdermal GTN reduces CRP levels and improves endothelial activation CRP is a potent marker of cardiovascular risk in patients with PVD[60].

SUSTAINED / EXTENDED RELEASE

Dyslipidemia is a major risk factor in the initiation and progression of cardiovascular diseases such as atherosclerosis. Several pharmacological agents have been developed over the past 50 years which target various lipid components such as low density lipoprotein (LDL) cholesterol, triglyceride, and high density lipoprotein (HDL) cholesterol[61].

One extended-release (ER) niacin–simvastatin formulation is available in the US and another formulation has been approved in Europe, with approval pending in the US. Simcor® (Abbott Laboratories, North Chicago, Illinois, USA) is the combination of ER niacin (Niaspan®; Abbott Laboratories, North Chicago, Illinois, USA) and simvastatin (Zocor®, Merck Inc., White House Station, New Jersey) which was approved by the US Food and Drug Administration (FDA) February, 2008. ER niacin–simvastatin is indicated to reduce elevated total cholesterol, low density lipoprotein cholesterol (LDL-C), apolipoprotein (apo) B, non-high density lipoprotein cholesterol (non-HDL-C), or triglycerides, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate[62]. ER niacin–simvastatin is also indicated to reduce triglycerides in patients with hypertriglyceridemia (Frederickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin ER monotherapy is considered inadequate.

Niaspan® is a once-daily, prolonged-release formulation of nicotinic acid which is indicated in many areas for the correction of low HDL-cholesterol. Niaspan® was designed to deliver nicotinic acid at a rate intermediate between the immediate release and earlier sustained-release formulations, and delivers the drug over a period of approximately 8–12 hours[63]. In this way, Niaspan® was intended to minimize the potential of both hepatotoxicity and flushing.

GENE THERAPY

Recent achievements in the cardiovascular area have been made with viral and non-viral gene therapies. A variety of catheter or surgical approaches for in vivo cardiac gene transfer showed promising results in animal and clinical studies. Trans gene expression would be required only during a period of defined risk, such as re-modeling after myocardial infarction. In common with the angiogenic protein therapy, angiogenic gene therapy is getting much interest as an alternative therapy to improve the ischemic heart failure. An animal model with

chronic ischemic myocardium showed an increase in collateral blood flow and an improvement of cardiac function by an injection of plasmid VEGF or FGF[64-65]. The angiogenic gene therapy intensively studied in human clinical trials. The administration of plasmid VEGF into human ischemic myocardium through a small left anterior thoracotomy

resulted in improved heart responses, demonstrating the therapeutic efficacy of this approach[66]. Various isoforms of VEGF have been delivered to patient in clinical studies by different delivery methods. VEGF165 delivered by myocardial injection and intra myocardial transfection to patient demonstrated the significant improvement of ischemic myocardium area with increased perfusion and the reduced angina, respectively[67-68]. The administration of VEGF in those studies resulted in increased level of VEGF in plasma, providing a direct evidence of the transfection and expression of plasmid VEGF. Viral vectors are frequently used to effectively transfect DNA because the expression level of naked DNA in cells is too low due to its poor transfection efficiency. Adenovirus vector-based injection of VEGF121 led to an improvement of angina in all patients and of exercise time with increased VEGF level in plasma in phase I trial[69]. Similar to VEGF, administration of FGF into epicardial fat demonstrated an improvement of angina symptoms and an increase inmyocardial blood flow[70]. Intracoronary administration of FGF-4 using adenovirus vector also showed significantly improved exercise time in treated group compared to placebo group in angiogenic gene therapy (AGENT) trial[71]. The gene therapy has the great potential to the ischemic heart diseases; however, the transfection efficiency, stability and longterm expression of the therapeutic genes should be improved to be practical.

Polymeric hydrogels for delivery of therapeutic proteins

Hydrogels are three-dimensionally structured networks of hydrophilic polymers containing a large amount of water. Hydrogels can be formed through chemical or physical cross linking of

polymers, and have structural similarity to the macromolecular- based components in the body. In addition, hydrogels can be injected into the body via minimally invasive administration, which may reduce the pain of patients[72-73]. Various Natural polymer-based hydrogels which can be used are enumerated in table 1.

Table 1: Natural polymer-based hydrogels for the delivery of angiogenic growth factors

Polymer	Therapeutic protein	Injection route	Effect	Refrences
Gelatin	bFGF	Left ventricular wall	Improved Left ventricular function	[68]
Gelatin	bFGF	Intra-artery	Improved collateral vessels	[69]
Fibrin	bFGF	Ischemic limbs	Increased micro vessel Density	[72]
Hyaluronic acid	VEGF/KGF	Subcutaneous implant	Micro vessel growth	[76]
Alginte	VEGF/PGDF-BB	Local and sequential	Improved cardiac Function	[86]
Chitosan	bFGF	Immobilization On ischemic myocardium surface	Reduced fibrosis/ improved collateral blood flow	[86]

KGF — keratinocyte growth factor; PDGF-BB — platelet- derived growth factor-BB.

DRUG TARGETING

As for any other organ of interest, the targeting of pharmaceuticals to the heart aims at two main objectives: diagnostic imaging of cardiac pathologies and delivery of therapeutics to affected areas. The most important cardiac pathologies include coronary thrombosis and atherosclerosis, myocardial infarction and myocarditis of different etiology.

Monoclonal antibodies provide an effective method for non-invasive detection and visualization of different cardiac disorders, acute myocardial infarction being among them. Taking into account the high frequency of this disease, its fast and specific diagnostics is a matter of primary importance. The general strategy towards monoclonal antibody-mediated infarct visualization was discussed recently by Khaw[74]. The approach used is based on the fact that following myocardial cell death as a result of ischemia, an antibody against intracellular antigen will be

able to differentiate between viable cells with intact membranes and necrotic cells with disrupted membranes. If the antibody is radio labeled, the areas of irreversible myocardial damage can be recognized following the accumulation of antibody-bound radioactivity. Cardiac myosin, which is not, washed away following cell disintegration,was chosen as the target antigen characteristic of infarcted myocardium[75-77]. The efficacy of anti-myosin antibodies labelled with 13'1, In and 99mTc for y-visualization of myocardial infarction was proven in rabbit and dog experiments[80]. Moreover, the radiolabeled Fab fragment of anti-myosin RllDlO antibody is already successfully used in clinical conditions[81-82].

Radiolabeled antimyosin antibody can also be used for the estimation of myocardial damage following open heart surgery, including coronary bypass surgery[83-84]. Spontaneous accumulation of positively charged liposomes in regions of experimental myocardial infarction was described by Caride and Zaret in 1977[85]. Later, this observation was partially confirmed by Kayawake and Kakothe[86], who found predominant accumulation of positively charged liposomes in perfused non-ischemic isolated rabbit heart compared to negatively charged or neutral ones. It was also shown that liposomes concentrate in depolarized myocardial cells[87]. After some additional animal experiments[88-90] it was found that liposome accumulation in ischemic tissues is a rather general phenomenon and might be explained by impaired filtration in ischemic areas, which results in trapping of liposomes within those areas[91]. This observation led to the conclusion that drug-loaded liposomes can be used for 'passive' drug delivery into the ischemic tissues, primarily into the infracted myocardium[92-93].

Liposomes loaded with the thrombolytic enzyme streptokinase were able to accelerate thrombolysis and reperfusion in a canine model of myocardial infarction[94]. Studies with isolated rat cardiomyocytes and isolated perfused rat and rabbit hearts demonstrated that perfusion with high Ca^{2+} (4.5 mM), high K' (8.7 mM), or with a free radical-generating system significantly increases myocardial uptake of positively charged liposomes[95-96]. When liposomes with superoxide dismutase (SOD) were used, they were much more effective in the treatment of myocardium reperfusion injury than native enzyme. The efficacy of liposomal SOD in the treatment of ischemic and reperfusion damages of different organs and tissues including myocardium was repeatedly proved[97-99].

CONCLUSION AND FUTURE APPROACH

Results presented in this review indicate that novel drug delivery systems clearly present an opportunity for formulation scientists to overcome the many challenges associated with drug therapy for cardiovascular disorders. While several novel drug delivery systems have been investigated for cardiovascular disorders, recently there appears to be greater interest and advancement in the use of liposomes and nanoparticles as compared to other systems. While the clinical potential for several NDDS has been reported from *in vitro* and animal studies, there is the lack of data on formulation optimisation and detailed physic chemical/mechanical characterisation of these NDDS. Since cardiovascular disorder treatment involves combination drug therapy, the potential of these novel drug delivery systems for simultaneous loading of various drug combinations needs to be investigated. Although various papers report efficacy studies under in vitro conditions including experimental animal studies, there is the significant lack of data on the clinical applicability (human in vivo studies) and toxicity of these preparations.

Therefore these needs are to be extensively explored. Based on the complexity of the disease and the formulation optimisation and evaluation studies required, multidisciplinary research would be essential for eventual commercialisation of NDDS containing drugs for cardiovascular disorders.

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