Polymeric Nanoparticles in Cardiovascular Diseases

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Nanoparticles, including biodegradable polymeric nanoparticles, are able to increase the efficiency and reduce the degradability of natural polyphenols, thus increasing their beneficial abilities in the target tissues. Resveratrol-, quercetin-, or curcumin-loaded polymeric nanoparticles have been shown to markedly reduce reactive oxygen species formation, the inflammatory process, apoptosis, lipid peroxidation, cardiac hypertrophy, and even to delay myocardium injury due to ischemia/reperfusion. Thus, polymeric nanoparticles represent a promising tool for the delivery of natural polyphenols to target tissues and enhance their desirable effects in the cardiovascular system.

Keywords: nanoparticles, cardiovascular diseases, polyphenol

1. Introduction

Recently, the use of polymeric nanoparticles has been based on nonbiodegradable polymers, such as polyacrylamide, polystyrene, and poly (methyl) methacrylate[1]. For such particles, inflammatory responses and chronic toxicity were observed, and therefore, research has focused on biodegradable polymeric nanoparticles with reduced toxicity, higher biocompatibility, and a better ability to regulate drug release kinetic patterns. With the exception of natural polymers like chitosan, albumin, alginate, and gelatine, the synthetic polymers mainly include poly (lactide) (PLA), poly (lactide-co-glycolide) copolymers (PLGA), poly (ε-caprolactone) (PCL), and poly (amino acids)[2][3][4][5]. These biodegradable synthetic polymers should fulfil two major requirements: performance and safety[6].

Firstly, polyethylene glycol (PEG)-coated synthetic copolymers conjugated with active mediators have been shown to yield drug delivery systems with positive properties[7][8]. PEG coatings form a hydrated ring which prevents protein interactions and reduces opsonization, resulting in an increased circulation time and lower activation of the immune system[9]. Furthermore, a conjugation of glycoprotein Ib (GPIb) to PLGA nanoparticles has been shown to increase nanoparticle adhesion to the targeted surface, cellular uptake of nanoparticles, and controlled release of the active substances[10][11]. PLA is relatively hydrophobic, which allows it to be used for implants like stents, screws for bone fixations, but also for drug delivery systems[12]. Polymeric nanoparticles have been reported to cross the intestinal barrier after oral administration and therefore, it is effectively used for oral drug delivery[13].

2. Drug/Polyphenol-Loaded Polymeric Nanoparticles

Nowadays, targeted nanoparticle delivery systems in the field of cardiovascular disease are under intensive investigation. Minimizing the side effects while maximizing the drug effectiveness by targeted delivery poses a challenge not only in atherosclerosis, but also in hypertension, myocardial infarction, and heart failure (for a review, see References[10][11]). First, a liposome drug delivery system has been proven to be a successful option for the treatment of angina pectoris. Encapsulated amiodarone, an anti-arrhythmic drug, in conventional liposomes demonstrated a reduced morality rate due to arrhythmia and negative hemodynamic changes in rat models of cardiac ischemic/reperfusion procedure[14]. Later, treatment of aliskiren (a renin inhibitor)-loaded PLA nanoparticle decreased the blood pressure of SHR much more significantly than the powdered form[15]. Similarly, nanostructured lipid carriers and solid lipid nanoparticles improved the oral bioavailability of a calcium channel blocker, nisoldipine[16]. PLGA and PCL seem to be effective delivery systems for nifedipine and felodipine since they significantly reduced blood pressure in hypertensive rats[17][18]. Innovative NO-releasing polymeric nanomaterials are among the new potential solutions in the development of qualitatively new antihypertensive drugs[19]. Osako et al. demonstrated that the PEG–PLGA copolymer is able to deliver a NF-κB decoy oligodeoxynucleotide, which is directed against the NF-κB binding site in the promoter region[20]. This copolymer has been demonstrated to prevent monocrotaline-induced NF-κB activation in a rat model of monocrotaline-induced pulmonary arterial hypertension[21].

Still, the key problem with using nanoparticles is their toxicity. The small size and large surface area to volume ratio makes them very reactive. Nanoparticles may even generate ROS and other free radicals, resulting in an increased oxidative load and inflammation[22]. Recently, natural polyphenols-loaded nanoparticles have been the focus of interest thanks to their antioxidant properties, which additionally may exceed the prooxidant effects of some nanoparticles. Among them, resveratrol, quercetin, and curcumin, are the most frequently studied.

In the study by Singh and Pai[23], resveratrol-loaded PLGA nanoparticles had better oral bioavailability and absorptivity in rats in comparison with the pure drug[23]. Similarly, Siu et al.[24] documented that resveratrol-loaded galactosylated PLGA nanoparticles had better bioavailability and in vitro anti-inflammatory activity in rats and lipopolysaccharides-induced macrophage cell line RAW 264.7 cells, respectively[24]. Oral administration of resveratrol loaded into N-trimethyl chitosan conjugated with palmitic acid nanoparticles in Balb/c mice provided a 3.8-fold increase in resveratrol bioavailability compared to the pure drug. This increase was attributed to the muco-adhesive and high absorption effects of the polymeric nanoparticles, as well as to the ability to prevent resveratrol degradation[25]. Cheng et al.[26] reported that dual-shell polymeric nanoparticles, multistage continuous targeted drug delivery carrier (MCTD)-NPs, which utilize a multistage continuous targeted strategy to deliver ROS scavengers specifically to the mitochondria of ischemic cardiomyocytes, increased the distribution of resveratrol in the ischemic myocardium and reduced infarct size in myocardial ischemia/reperfusion injury in rats[26].

Quercetin-loaded PLA nanoencapsulation demonstrated a higher water solubility and sustained release of the drug, leading to better bioavailability and stability of quercetin. Ghosh et al.[27] suggested that oral treatment with quercetin-loaded PLGA might play a protective role against oxidative damage in ischemia reperfusion induced in young and aged rats[27]. Wang et al.[28] layered a bioactive polymer (PLGA layers) onto superparamagnetic SiN to control the medication discharge profile. The PLGA layer on the outside of SiN can act as a gate-keeping layer to direct the medication discharge from SiN. They demonstrated that SiN@QC-PLGA nanobio-composite properties improve the practical similitude to the local myocardium, permitting cell enlistment, attachment, expansion, and articulation of heart proteins, which can be utilized in anticipation of atherosclerosis and other cardiovascular diseases[28].

Using curcumin-loaded PLA–PEG copolymer nanoparticles, El-Naggar et al.[29] demonstrated that curcumin-loaded nanoparticles had better anti-inflammatory and antioxidant effects in a streptozotocin-induced diabetes model than pure curcumin[29] In a similar model, curcumin-loaded chitosan nanoparticles promoted diabetic wound healing[30]. Carlson et al.[31] studied the cardio-protective effects of a combination of curcumin and resveratrol co-loaded into polymeric micellar in a cell model of doxorubicin-induced cardiotoxicity. The combination has been shown to markedly reduce apoptosis and ROS formation in the above cell model[31]. Similarly, curcumin-loaded copolymer PEG-Poly (ethylene glycol) methyl ether-block-poly(d,l lactide)-block-decane strongly inhibited apoptosis, lipid peroxidation, and production of NADPH-derived superoxides induced by exposure of cardiomyocytes to palmitate[32]. Curcumin-loaded to the same copolymer has been demonstrated to activate the AMP-activated protein kinase (AMPK)/mammalian target of the rapamycin complex-1/p-p70 ribosomal protein S6 kinase signaling pathway and regulate the expression of downstream proteins[33]. In a study by Nabofa et al.[34], the formulated curcumin-nisin-based PLA nanoparticles provided a significant level of cardio-protection in a guinea pig myocardial infarction model[34].

3. Conclusion

Nowadays, different copolymers and polymeric nanobio-composites are being developed with the aim of decreasing nanoparticle reactivity, toxicity, enhancing pharmacokinetics, and designing controlled release. They represent a promising tool for the delivery of natural polyphenols to target tissues and enhance their desirable effects, which is useful in the treatment of various diseases, including cardiovascular diseases.

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