SnapShot: Nanoparticles of Biodegradable Polymers for Cancer Treatment

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Fig. 1. (Left) Molecular structure of TPGS, a PEGylated Vitamin E, which has desired hydrophobic-lipophilic balance that makes it an effective emulsifier and an ideal copolymer component for nanoparticle formulation [9].

Fig. 2. (Right) Scanning electron spectroscopy of paclitaxel-loaded, PLA-TPGS NPs, which are of 238±15 nm in diameter with 10% drug loading. The drug encapsulation efficiency is 95.9%.

Fig. 3. (Left) Atomic force microscopy of paclitaxel-loaded, TPGS-emulsified PLGA nanoparticles, which shows a single nanoparticle of smooth surface morphology [7].

Fig. 4. (Right) X-ray photoelectron spectroscopy of paclitaxel-loaded PLA-TPGS NPs showing the chemical structure of the NP surface [9].

Fig. 5. (Left) Differential scanning calorimetry of paclitaxel formulated in Taxol® (the upper curve) versus the NP formulations, which shows that the physical status of the drug has been changed from crystalline to amorphous [7].

Fig. 6. (Right) In vitro accumulative drug release profiles of paclitaxel-loaded, PVA- or TPGS-emulsified PLGA NPs, which are adjustable by the various composition and formulation parameters.

Fig. 7. (Left) Confocal laser scanning microscopy of a single MCF-7 breast cancer cell incubated with coumarin-6-loaded, TPGS-emulsified PLGA nanoparticles for 2 hr. The nucleus is in red and the fluorescent nanoparticles are in green [4].

Fig. 8. (Right) Effects of particle size and surface coating on Caco-2 cellular uptake of polymeric NPs. Note that NPs of 100-200 nm in diameter and the NPs coated by TPGS resulted in best effects [6].

Fig. 9. (Left) In vivo pharmacokinetics after i.v. administration of paclitaxel formulated in PLA-TPGS NPs vs Taxol®. One shot of the former realized 336 hr chemotherapy compared with 22 hr for Taxol®.

Fig. 10. (Right) Xenograft tumor model – C6 tumor size after intratumoral injection of Taxol and Paclitaxel formulated in TPGS-emulsified PLGA NPs at 10 mg/kg dose on day 11, 16 and 21 [4].

Fig. 11. (Left) In vitro viability of SK-BR-3 breast cancer cells treated with placebo PLGA/MMT NPs with or without HER2 decoration and the paclitaxel formulated in Taxol®, the Pac-PLGA/MMT NPs and the Pac-PLGA/MMT-HER NPs at the same 2.5 mg/ml drug concentration after 24, 48, 72 h culture, respectively (n = 6) [12].

Fig. 12. (Right) In vitro viability of MCF-7 cells after 24h treatment at 25μg/ml concentration of paclitaxel formulated in the NPs of PLA-TPGS and 0%, 16.7%, 33.3% folic acid copolymers in comparison with that in Taxol® [11].
Nanomedicine, the application of nanotechnology to medical science, will radically change the way we diagnose, treat and prevent diseases. A typical example is cancer, which is a leading cause of death and has now become the most significant cause of death in most Eastern countries. In spite of this, there has been no substantial progress in the past 50 years in fighting cancer. The cancer death rate in US was 1.939‰ of the total population in 1950 and still 1.940‰ in 2001, 1.934‰ in 2002, 1.901‰ in 2003, 1.858‰ in 2004. The current way we treat cancer is very much like that we did 30 years ago, still surgery followed by radiotherapy and chemotherapy. We are in crisis in the fight against cancer. Nanomedicine, cancer nanotechnology and chemotherapeutic engineering bring new hope to make cancer curable by targeted therapy at its very origin, which will deliver therapy of high dose just to cancer cells of very limited total amount and leave healthy cells untouched [1-4].

New systems of biodegradable polymeric nanoparticles for controlled and targeted delivery of imaging and/or therapeutic agents have been developed. We have successfully completed a full spectrum of research of TPGS-emulsified PLGA nanoparticles and nanoparticles of PLA-TPGS copolymers for controlled and targeted delivery of anticancer drugs with paclitaxel as a model drug, which include preparation and characterization of drug-loaded nanoparticles; in vitro drug release and cytotoxicity; in vitro cellular uptake of nanoparticles; in vivo pharmacokinetics, biodistribution and xenograft tumor model. TPGS-emulsified PLGA nanoparticles and nanoparticles of PLGA-TPGS copolymers can have the desired physicochemical and pharmaceutical properties for drug delivery. They have high drug encapsulation efficiency, desired drug release profile, high cellular adhesion and adsorption, desired pharmacokinetics including large AUC and long half-life in the circulation system [5-10]. Moreover, they provide preferable surface modification for successful conjugation to functional molecules such as folate and herceptin for targeted delivery of imaging and therapeutic agents [11-13].

In vitro evaluation of the toxicity of HT-29 cancer cells demonstrates that paclitaxel formulated in TPGS-emulsified nanoparticles could be 46 times more effective than Taxol® after 24 hours of treatment at the same paclitaxel dose of 10 mg/kg. In vivo pharmacokinetics show that the drug formulated in PLGA nanoparticles could achieve 3.9 times higher therapeutic effect judged by the area-under-the-curve (AUC) and 23.0 times longer half-life than Taxol®. One shot can realize sustainable chemotherapy of 336 hours compared with 22 hours for Taxol® at a single 10 mg/kg dose. The xenograft tumor model confirmed the advantages of the nanoparticle formulation versus Taxol®. Moreover, the drug tolerance for the animals increased 400%.

With respect to targeted delivery, preliminary results show that the IC50, the drug concentration needed to kill 50% of the cancer cells in a designated period, of the SK-BR-3 breast cancer cells for paclitaxel formulated in the herceptin-decorated PLGA/MMT NPs could be 12.74 times higher than that formulated in the bare NPs and 13.11 times higher than Taxol®, and that the in vitro therapeutic effects increased 8.68% for MCF-7 breast cancer cells [12]. The folate-decorated nanoparticles significantly promote targeted delivery of the drug formulated in the folate-decorated PLGA-TPGS NPs. The cytotoxicity increased 31.1% compared with the bare PLGA-TPGS NP formulation after 24 h treatment at the same 25 μg/ml paclitaxel concentration. C6 glioma cell line experiment confirmed these advantages.

There have been two major concerns on nanotechnology for biomedical applications: feasibility and safety. Can nanoparticles escape from recognition and elimination by the body defense system, i.e. the reticuloendothelial system (RES)? If yes, is there any negative impact on health? Our research relieves the first concern. As for safety, 90% of the nanoparticles of common interest in biomedical applications are non-degradable, e.g. metal and inorganic nanoparticles. Nanoparticles of biodegradable polymers should be much less harmful.

REFERENCES


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