Lipiodol-loaded poly(oxyethylene)-*block*-poly(oxypropylene)-*block*-poly(oxyethylene) triblock copolymers/polyethylene glycol-nanoparticles

LPNCs

Kenneth T. Cheng, PhD[1]

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Chemical name:	Lipiodol-loaded poly(oxyethylene)-*block*-poly(oxypropylene)-*block*-poly(oxyethylene) triblock copolymers/polyethylene glycol-nanoparticles	
Abbreviated name:	LPNCs	
Synonym:	Lipodol-Pluronic/PEG-NP, Lipodol-Poloxamer/PEG-NP, Lipodol-PEO-PPO-PEO/PEG-NP	
Agent Category:	Nanoparticles	
Target:	Non-targeted probe, the reticuloendothelial system (RES)	
Target Category:	Non-specific filling of blood vessels and tissues, phagocytosis by the RES	
Method of detection:	Computed tomography (CT) and planar X-ray	
Source of signal:	Iodine (I)	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on PubChem SID (3730533) for more information.

Background

[PubMed]

1 National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

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Lipiodol-loaded poly(oxyethylene)-*block*-poly(oxypropylene)-*block*-poly(oxyethylene) (PEO-PPO-PEO) triblock copolymers/polyethylene glycol (PEG)-nanoparticles (LPNCs) are X-ray contrast agent preparations developed for contrast enhancement in computed tomography (CT) imaging (1). Lipiodol is an iodized poppy seed oil (ethyl esters of iodized fatty acids of poppy seed oil with 480 mg of iodine/ml) that can be used as an X-ray contrast agent for lymphography and hysterosalpingography. It is commercially available for investigation but has not been approved by the United States Food and Drug Administration for clinical use in humans.

X-ray imaging techniques (planar and CT) depend on tissue density differences that provide the image contrast produced by X-ray attenuation between the area of interest and surrounding tissues (2). Contrast enhancement (opacification) with the use of contrast agents increases the degree of contrast and improves the differentiation of pathological processes from normal tissues. Because iodine, an element with high atomic density, causes high attenuation of X-rays within the diagnostic energy spectrum, water-soluble and reasonably safe iodinated contrast agents in intravenous injectable forms have been developed for clinical applications (3, 4). Water-soluble, intravenous X-ray contrast agents are generally organic iodine compounds that contain one or more tri-iodinated benzene rings. When injected intravenously, they are largely distributed in the extracellular fluid space and excreted unchanged by the kidneys. Contrast enhancement of a region of interest depends on the route of administration, delivery of the agent to the area by blood flow, and the final iodine concentration in the region (5, 6).

Intravenous injection of water-soluble X-ray contrast agents can be performed in conjunction with dynamic CT to improve the detectability of tissue pathologies (4, 5, 7). However, there are many limitations associated with this approach because of their nonspecificity and rapid extravasation from the circulation. Nanoparticle contrast media have also been developed to improve the circulation time and target specificity of contrast agents (8, 9). One possible approach involves encapsulation of water-soluble or -insoluble X-ray contrast agents in various nanoparticle carriers (1, 8, 10, 11). Although these nanoparticle carriers are naturally taken up by the reticuloendothelial system, they can be modified with specific targeting moieties to increase the affinity of nanoparticles for target tissues, organs, and cells (1, 11-13). Among the nanoparticle carriers, PEO-PPO-PEO triblock copolymers are macromolecular surfactants composed of poly(oxyethylene)-*block*-poly(oxypropylene)-*block*-poly(oxyethylene) (Pluronic or Poloxamer series). Through hydrophobic interactions between the PPO blocks, these surfactants undergo self-assembly into spherical micelles in aqueous solution above a critical temperature (14). These nanoparticles can expand and shrink rapidly in response to temperature changes (15-17). Bae et al. (14) prepared LPNCs with the use of a new class of PEO-PPO-PEO/PEG nanoparticles to encapsulate lipiodol oil. LPNCs have an inner hydrophobic oil phase stabilized by a covalently cross-linked PEO-PPO-PEO/PEG shell layer. Kong et al. (1) reported that this LPNC nanoparticle preparation has effective X-ray attenuation properties and longer circulation time than those of conventional water-soluble contrast agents. The authors suggested that the conjugation of an appropriate targeting moiety might lead to the active targeting of LPNCs to a specific tissue or organ.

Synthesis

[PubMed]

Bae et al. (14) reported the synthesis of LPNCs by the use of an emulsification/solvent evaporation method (15, 16). LPNCs were prepared by cross-linking the outer shell layers of PEO-PPO-PEO/PEG copolymer ($(PEO)_{100}(PP)_{65}(PEO)_{100}$, Pluronic F127, *Mw* = 12,600) micelles reactively preactivated with amine. F127 was chosen because of its high hydrophilic/lipophilic balance value, high extractability in the aqueous phase, relatively low toxicity, and characteristic self-assembly into micelles. Briefly, F127 was first preactivated with *p*-nitrophenyl chloroformate (p-NPC) at its two terminal hydroxyl groups (1). Lipiodol was dissolved in dichloromethane and then mixed with the activated PEO-PPO-PEO/PEG copolymer. The mixture was added dropwise to a solution of amine-functionalized polyethylene glycol (pH 9) with six branches ($PEG\text{-}amine_2$). This was sonicated for 3 min to form an oil-in-water emulsion, and it was then neutralized by hydrochloric acid. At this stage, the NPC group of the activated F127 was conjugated with the primary amine groups of the $PEG\text{-}amine_2$ in the outer shells of the LPNCs. Residual dichloromethane was quickly removed from the resultant oil-in-water emulsion with a rotary evaporator. During this solvent removal process, the influx of water and the concomitant outflow of methylene chloride caused a phase separation into micelles. Methylene chloride exuded into the outer aqueous, phase-produced, oil-filled core at the interiors of the micelles. Cross-linking of the micelle outer shell layers by the $PEG\text{-}amine_2$ prevented the fusion of the micelles with other micelles. The preparation was dialyzed using a dialysis membrane with a molecular mass cutoff of 50 kDa and then finally filtered by a 0.45 μm filter. The encapsulation efficiency of lipiodol was ~82% at a 100% F127/lipiodol weight ratio (w/w) (1). The authors suggested that there was no volume transition at the 100% (w/w) ratio of lipiodol/F127 (1, 14). The mean amount of encapsulated lipiodol was 71.1 ± 4.2% (w/w) of dried LPNCs.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The LPNC *in vitro* hydrodynamic diameter, dispersion stability, and volume transition in aqueous solution were evaluated with dynamic light scattering (1). The mean hydrodynamic diameters of LPNCs were 153.2 ± 14.4 nM ($n = 3$) and were stable for 72 h at 9–37°C. The morphological characteristics of LPNCs were examined with scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The SEM study showed that LPNCs maintained their spherical shape with a mean diameter of 150.4 ± 22.4 nm, and that LPNCs were well segregated and dispersed. The TEM study also showed well-dispersed LPNCs with high electron density and an average size of 146.3 ± 26.8 nm. At an LPNC concentration of 400 mg/ml, strong X-ray attenuation characteristics were demonstrated. There was no significant viscosity or aggregation at this concentration. In a release test of LPNCs in phosphate-buffered saline (pH 7.4)

containing 0.02% (w/v) Tween 20 at 37°C, no significant lipiodol outflow into the aqueous phase occurred during a period of 72 h (1).

The *in vitro* cytotoxicity of LPNCs was tested in A549 cells by the 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide inner salt assay (1). The effective concentration of reducing the cell viability by 50% (EC_{50}) was 0.196 mM iodine. In comparison, the EC_{50} for iopromide, a clinically used water-soluble CT contrast agent, was 0.0648 mM iodine.

Animal Studies

Rodents

[PubMed]

Kong et al. (1) evaluated the X-ray contrast performance of LPNCs in mice by injecting 200 µl (400 mg/ml) LPNCs intravenously into healthy nude mice. CT imaging showed that the LPNCs contrast enhancement resulted in the clear delineation of the cardiac ventricles and major arterial and venous structures for 4 h after administration. Most LPNCs accumulated in the spleen and liver within 24 h. The contrast enhancement of the spleen and liver gradually faded during the time period of 24–72 h. Histological analysis at 72 h after administration showed decrement of lymphatic cells in the spleen, liver, and lymph nodes. Kong et al. (1) suggested that this supported the belief that there was nonspecific scavenging of LPNCs in the reticuloendothelial system.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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