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Personalized medicine

Holmium–lipiodol–alginate microspheres for fluoroscopy-guided embolotherapy and multimodality imaging

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ABSTRACT

Embolotherapy is a minimally invasive transcatheter technique aiming at reduction or complete obstruction of the blood flow by infusion of micro-sized particles in order to induce tumor regression. A major drawback of the current commercially available and clinically used microspheres is that they cannot be detected in vivo with medical imaging techniques, impeding intra- and post-procedural feedback. It can be expected that real-time monitoring of microsphere infusion and post-procedural imaging will result in better predictability and higher efficacy of the treatment. In this study, a novel microsphere formulation has been developed that can be visualized with fluoroscopy, X-ray computed tomography (CT) and magnetic resonance imaging (MRI). The microspheres were prepared with the JetCutter technique and consist of alginate (matrix-forming polymer), holmium (cross-linking and MRI contrast agent), lipiodol (radiopaque contrast agent) and Pluronic F-68 (surfactant). The mean size (±SEM) of the hydrated holmium–lipiodol–alginate microspheres (Ho–lip–ams) was 570 ± 12 μm with a holmium content of 0.38 ± 0.01% (w/w). Stability studies showed that the microspheres remained intact during incubation for two weeks in fetal calf serum (FCS) at 37 °C. The inclusion of lipiodol in the microspheres rendered excellent visualization capabilities for fluoroscopy and CT, whereas the holmium ions, which keep the alginate network together, also allow MR imaging. In this study it was shown that single sphere detection was possible by fluoroscopy, CT and MRI. The Ho–lip–ams were visualized in real-time, during infusion in a porcine kidney using fluoroscopy, and post-procedural, the deposition of the microspheres was examined with fluoroscopy, (cone beam rotational) CT and MRI. The different imaging modalities showed similar deposition patterns of the microspheres within the organ. The combination of intra-procedural visualization, multimodality imaging for patient follow-up and the possibility of quantification offers a new and promising method for more safe, efficient and successful embolization treatment.

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1. Introduction

Embolotherapy, i.e., intra-arterial injection of embolic agents, has gained an important position in the treatment of a wide variety of conditions affecting different organs of the human body, such as uterine fibroids, arteriovenous malformations (AVM), as well as kidney and liver tumors. Embolotherapy is a minimally invasive transcatheter technique aiming at reduction or complete obstruction of the blood flow by infusion of micro-sized particles of a predefined size in order to induce tumor regression. Several embolotherapy agents are commercially available and clinically used, ranging from heterodisperse, irregularly shaped, polyvinyl alcohol (PVA) particles (Derdeyn et al., 1995), to spherically shaped and uniformly sized microspheres such as Embosphere (Merit Medical, South Jordan, Utah, USA) (Merit Medical, 2014,http://www.merit.com/products/media.aspx?type=brochure&id=279542; Spies et al., 2001, 2004, 2007), Embozene (CeloNova BioSciences, San Antonio, USA) (CeloNova BioSciences, 2014, http://celonova.com/our-company/about-celonova/; Stampfl et al., 2008, 2012) and LC beads (BTG International Ltd., London, UK) (BTG International Ltd., 2014, http://www.btg-im.com/products/usa-323/lc-bead-70/about-lcbead). In general, these microspheres with a size range of 40–1300 μm are introduced into the feeding artery of the tissue via fluoroscopy-guided catheterization, resulting in uniform artery occlusion with a predictable penetration depth (Chiesa and Hart, 2004;

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Rasuli et al., 2008). Beside these 'bland' embolization particles, which neither possess image possibilities nor contain additional chemotherapeutic drugs, microspheres can be loaded with therapeutic compounds. The inclusion of chemotherapeutic drugs in embolization agents (e.g., microspheres) provides a locoregional drug delivery approach called transarterial (chemo) embolization (TACE/TAE). Currently, several drug-eluting beads (DEB) which contain doxorubicin (DEBDOX™) (Lewis and Holden, 2011) or irinotecan (DEBIRI™) (Lewis and Dreher, 2012) are commercially available for the treatment of liver cancer. A major drawback of the currently clinically available bland- and drug-loaded-microspheres, however, is that they cannot be visualized in vivo using medical imaging techniques, prohibiting any feedback on the microsphere distribution during and after the treatment. A microsphere formulation that can be visualized both by X-ray and MRI techniques, is expected to increase both the safety and the efficacy of embolotherapy procedures. More precisely, X-ray visibility offers the opportunity to real-time monitor the microsphere infusion using fluoroscopy, providing direct feedback for the interventional radiologist, which facilitates minimization of non-targeted delivery. However, if detailed knowledge of the microspheres with respect to the target and non-target tissue is required, MRI may be used as a complementary post-treatment technique, since MRI provides superior soft tissue contrast and may be highly sensitive to dedicated contrast agents (Seevinck et al., 2007). The goal of this study was to develop a multimodal imageable microsphere formulation for embolotherapy and to investigate its multimodality imaging properties in an in vitro and ex vivo model. To this purpose, alginate microspheres were prepared, incorporating lipiodol to provide X-ray visibility, and holmium, a paramagnetic element, which renders it an MRI-contrast agent.

2. Materials and methods

2.1. Materials

All chemicals and polymers were of commercial sources and were used as obtained. Sodium alginate (Protanal LF 240 D, Ph. Eur.) was a generous gift from FMC Biopolymer Ltd. (Girvan, Ayrshire, United Kingdom). Pluronic F-68 was obtained from Sigma–Aldrich (Steinheim, Germany). Holmium (III) chloride hexahydrate ($HoCl_3 \cdot 6H_2O$; 99.9%) was purchased from Metall rare earth Ltd. (Shenzhen, China). Lipiodol®, a radiopaque contrast agent composed of iodinated ethyl esters of fatty acids from poppy seed oil with a total iodine content of 37% (w/w) (Lewis et al., 2012), which is frequently used for TAE/TACE procedures (Lewandowski et al., 2011), was purchased from Guerbet (Lipiodol Ultrafluide, Guerbet, Aulnay-Sous-Bois, France). Agarose multipurpose (MP) was obtained from Roche Applied Science (Mannheim, Germany). Manganese(II) chloride tetrahydrate ($MnCl_2 \cdot 4H_2O$; ACS reagent) and nitric acid (65%) were obtained from Merck (Darmstadt, Germany).

2.2. Alginate microsphere preparation

For the preparation of alginate microspheres, the JetCutter technique was used (Prusse et al., 2000), resulting in spherical particles with a predetermined size. Briefly, sodium alginate was dissolved in demineralized water under magnetic stirring at a concentration of 2% (w/v). Subsequently, lipiodol or poppy seed oil was added to the alginate solution under vigorous stirring to prepare a 1:1 alginate: oil (w/w) emulsion. 1% (w/v) Pluronic F-68 was added as a surfactant to stabilize the emulsion. Next, the alginate–oil emulsion was processed with the JetCutter which was equipped with a cutting tool consisting of 40 wires with a diameter of 100 μm. A nozzle diameter of 250 μm was used and the rotor speed was set to 4000 rpm. The droplets were allowed to solidify in solutions containing 25 mM of the chloride salt of holmium to form holmium–lipiodol–alginate microspheres (Ho–lip–ams) and holmium–poppy seed oil–alginate microspheres (Ho–pso–ams). The preparation of Ho–lip–ams is illustrated in Fig. 1. Non-ethiodized poppy seed oil was used as control. The alginate microspheres were allowed to cross-link for 2 h under gentle magnetic stirring. After three washing steps to remove excess cations, in which the microspheres were dispersed in surplus demineralized water, mildly vortexed and centrifuged to remove the excess water, the microspheres were collected and stored in demineralized water at room temperature.

2.3. Microsphere characterization and stability

Morphological examination and size distribution of Ho–pso–ams and Ho–lip–ams were investigated with light microscopy (magnification 4 × 10). To calculate the average size and its distribution, the diameters of 100 randomly selected microspheres were determined. For the determination of the total holmium content of the Ho–lip–ams, 500 mg of Ho–lip–ams was collected by

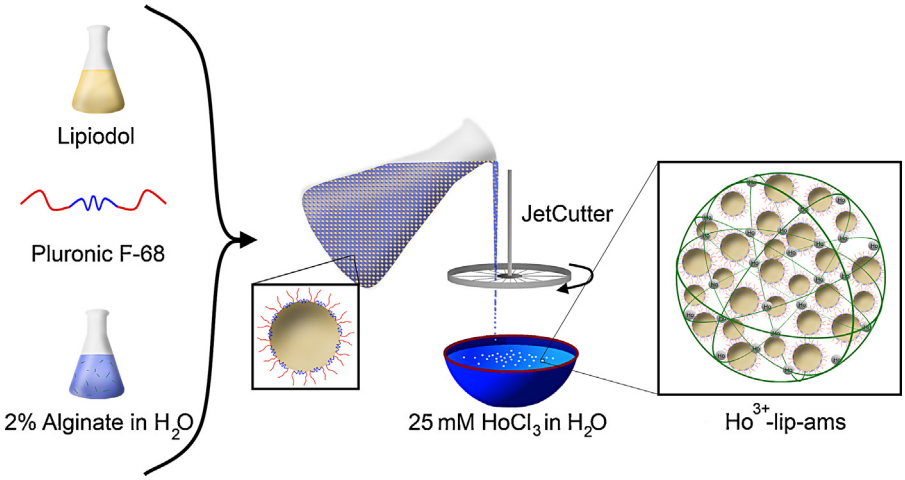

Fig. 1. Schematic drawing of Ho–lip–ams preparation. Lipiodol and water for injection are emulsified with Pluronic F-68. Next, the emulsion is processed with the JetCutter. The formed droplets fall into the holmium chloride solution resulting in the formation of holmium-cross-linked alginate microspheres entrapping lipiodol emulsified droplets (Ho–lip–ams).

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