Intrinsically radiopaque porous microspheres for improved transarterial chemoembolization

Ketie Saralidze, Menno L.W. Knetsch, Leo H Koole.
Maastricht University, Department of Biomedical Engineering/Biomaterials Science, Maastricht, The Netherlands.

Statement of Purpose: Polymeric microspheres are applied for a wide range of clinical treatments. These particles are being used as fillers for augmentation of soft tissue, as bulking agents. Additionally, microspheres are used for embolization therapy. Transarterial chemoembolization (TACE) based on selective intravascular infusion of embolic agent loaded with chemotherapeutic drug through catheter directly into arterial vessels nourishing the tumor. Occlusion-induced ischemia, in combination with local drug delivery and a targeted cytotoxic effect induces tumor necrosis. The hepatocellular carcinoma (HCC) is the sixth most prevalent and the third most frequent cause of cancer-related death. According to GLOBOCAN, there were approximately 748,300 new cases of primary liver cancers in 2008.[1] There are several commercial embolization microspheres on the market. These are composed of poly(vinyl alcohol) (Contour SE, Bead Block, DC beads) or tris-acryl-gelatin (Embosphere). These spheres are available in a wide range of sizes, and can be loaded with the anti-tumor drug doxorubicin (DC Bead).[2] The tumor is thus attacked in two ways: 1) by blocking arterial blood flow and 2) local release of doxorubicin. Commercial embolization microspheres have some disadvantages namely they are radiolucent, i.e. X-ray invisible, and they have limited drug-loading capacity. Here we present preliminary data on a range of new microspheres that combine radiopacity, i.e. X-ray visibility, with increased drug loading capacity.

Methods: Microspheres were prepared by suspension polymerization as described earlier.[3] Radiopacity of the microspheres was due to incorporation of the iodine containing monomer 2-[4-iodobenzoyloxy]-ethyl methacrylate (4IEMA).[4] The monomer mixture was supplemented with pMMA dissolved in toluene, before polymerization of the microspheres.[5] The pMMA could be extracted from the solid microspheres, resulting in microporosity. We synthesized microspheres with 30%, 50%, 60% and 70% porosity. The microspheres were loaded with rhodamine and doxorubicin.

Results: Synthesis of radiopaque, hydrophilic and porous microspheres was successful. The particles displayed fine porosity (1-5 μm) as can be seen from Figure 1.

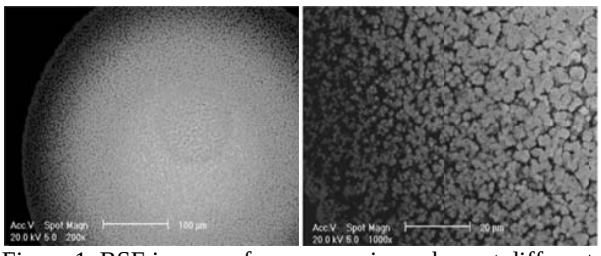

Figure 1. BSE images of a porous microsphere at different magnifications.

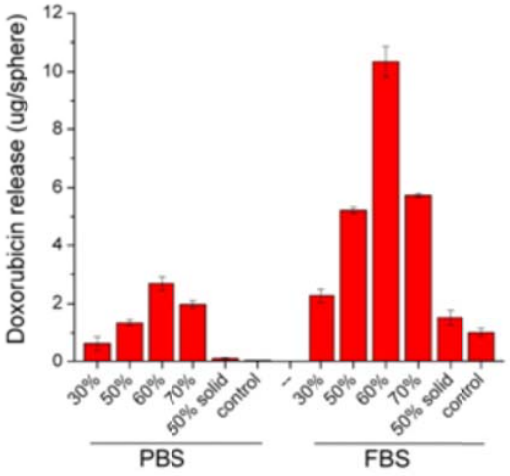

Figure 2. Endpoint release doxorubicin in phosphate-buffered saline (PBS) or fetal bovine serum (FBS). n=4

Radiopacity of the microspheres was confirmed by X-ray fluorimetry. The microspheres could be filled with rhodamine or doxorubicin (Figure 2).

The release-profile was dependent on the medium in which the experiment was performed. Release in serum was faster than when determined in buffer.

The release profiles of the drugs demonstrate an initial burst release followed by a slow release for up to at least 48 hours. Since doxorubicin has limited (thermo) stability, release for more than 2 days is probably not effective. The porosity of these microspheres increased the drug-loading capacity 2- to 3-fold, as compared to the published data for the doxorubicin containing DC beads.[6]

Conclusions: The new microspheres demonstrate that it is possible to combine two functionalities into embolization particles: (i), radiopacity for non-invasive monitoring and (ii), temporary depot for a drug which is to be released inside the tumor's arterial vessel bed, following embolization. These combined features may be useful to improve TACE. We hypothesize that both features, when combined, will help to make minimally invasive intervention to attack solid tumors more safe and effective. Our next step will be to assess the performance of these microspheres *in vivo* in an animal tumor model.

References: [1] Ferlay J. Int. J. Cancer 2010;127: 2893-2917. [2] Malagari K. Expert Rev. Anticancer Ther. 2008;8: 1643-1650. [3] Saralidze K. Biomacromolecules 2006;7: 2991-2996. [4] Kruft MA. J. Biomed. Mater. Res. 1994;28: 1259-1266. [5] Jayakrishnan A. J. Biomed. Mater. Res. 1990;24: 913-927. [6] Lewis AL. J. Vasc. Interv. Radiol. 2006;17: 335-342.