Multifunctional nanoparticles based on PEO-polyacetal diblock copolymers for drug delivery

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Modern nanoparticle-based drug delivery systems (DDS) are considered a promising therapeutic platform because of their potential to enhance the efficacy of drugs in anticancer and antiviral therapy. Besides their therapeutic action, modern nanoparticulate materials have been also used in biomedical imaging allowing drug targeting and the assessment of the therapeutic effect. Modern nanomedicine combines the above two actions in a single entity known as theranostic nanoparticles, which allow simultaneous diagnosis of the disease site, drug delivery to cure the disease and monitoring of the drug response. An appealing approach employs the use of stimuli-responsive DDS that exhibit an abrupt drug release in the presence of physiological gradients (endosomal pH drop, reducing agents such as glutathione, etc) or externally-controlled triggers, such as temperature, light or ultrasound activation. Light and ultrasound, are convenient stimuli to externally activate a DDS as they are considered generally safe, versatile and can be delivered effectively to nearly all parts of the body [1, 2].
In the present study, we demonstrate for the first time, a theranostic degradable nanoparticle comprising a self-assembled poly(ethylene glycol)-polyacetal diblock copolymer. The polymer nanoparticles are sensitive to four external stimuli which induce their disassembly following the main chain scission of the hydrophobic block by (i) UV (365 nm), and potentially infrared (1064 nm), light irradiation due to the presence of nitrobenzyl moieties along the polymer main chain, (ii) high frequency diagnostic ultrasounds (1 MHz) at relatively low doses and (iii) mildly acidic conditions (pH 5.5) which cleave the acetal bonds and (iv) a reducing environment which break the disulfide bonds present along the polymer main chain. In addition, the polyacetal block contains cobalt complexes which are super paramagnetic and stable in biological conditions [3]. Relaxivity studies confirmed that the system behaves as a T_2 weighted MRI contrast agent with an unusually high relaxivity ratio (r_2/r_1 = 160).

In detail, the polymer was synthesized by a two-step acid catalysed polycondensation reaction of 1,4 nitrobenzenedimethanol (NBD), butynediol (BD) and 2-hydroxyethyl disulfide (HED) with a divinyl ether derivative as the four comonomers (first step), and was subsequently end-capped with poly(ethylene oxide) (PEO) (figure 2) at the vinyl ends of the semitelechelic precursor polymer (second step). The polyacetal block was synthesized by mixing the diols (70% NBD, 10% BD, 20% HED) and the vinyl ether comonomer at equimolar ratio in the presence of pyridinium p-toluenesulfonate (PPTS, 1%) as the catalyst. Next, the polymer was end-capped with monohydroxy terminated PEG (5 kDa) catalysed again by PPTS (1%) to afford the final block copolymer structure. Finally, the block copolymer was treated with dicobalt octacarbonyl to introduce the MRI functional groups along the polyacetal block. The final product was isolated in good yield (ca. 80%) and was characterized by GPC and ^{1}H NMR spectroscopy. The M_n of the polymer was found to ~12,000 by GPC with a polydispersity index of 1.3. The final diblock copolymer comprised a 5 kDa hydrophilic PEG block and a hydrophobic polyacetal block which contained 9 NBD units, 2.5 BD units and 1.5 HED units, and was self-assembled in water to form photo-, ultrasound- redox- and pH-sensitive nanoparticles as multi-stimulus-activated drug delivery vehicles (Figure 1).

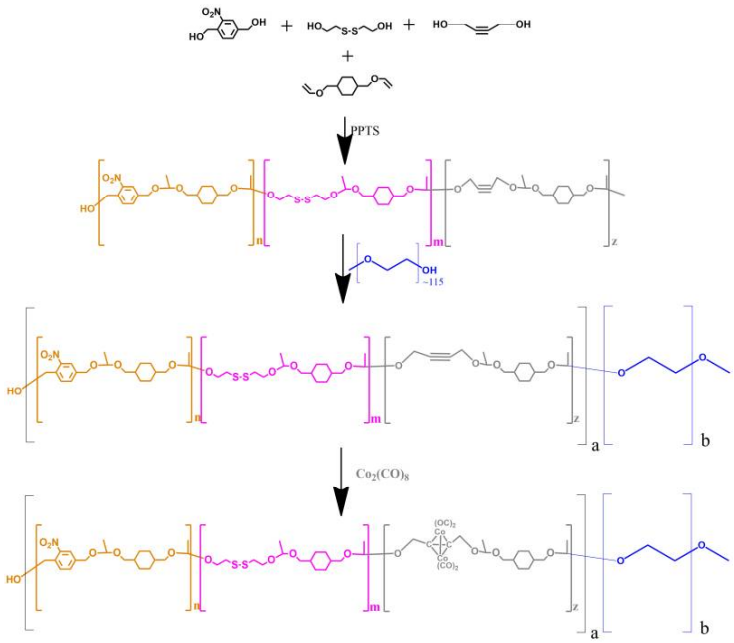

Figure 1. Synthetic route followed for the synthesis of the tetra-stimuli-responsive diblock copolymer.

The superparamagnetic behavior of the nanoparticles was verified by ^{1}H NMR spectroscopy. For this, we applied conventional inversion recovery and CPMG pulse sequences on the water protons in order to study the T1 and T2 relaxation of the water peak, respectively. Furthermore, the degradation of the diblock copolymer upon light irradiation, the application of ultrasounds and in the presence of reducing conditions were monitored using GPC and ^{1}H NMR spectroscopy. Finally, nanoparticles loaded with the model cancer drug camptothecin were prepared and the drug release profile upon application of the above stimuli was studied.

In conclusion, we have developed a new multi-responsive polymer that responds individually to four different stimuli, while also exhibiting a super-paramagnetic behavior, and demonstrate its potential in the development of "smart" nanocarriers with ideal properties as contrast agents for MRI.

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References

1. Pasparakis G., Manouras T., Vamvakaki M., Argitis P. Harnessing photochemical internalization with dual degradable nanoparticles for combinatorial photo–chemotherapy, *Nature comm.,* **2014**, *3623*.
2. Manouras T., Vamvakaki M. Field responsive materials: photo-, electro-, magnetic- and ultrasound-sensitive polymers, *Polym. Chem*., **2018**, *8*, 74-96.
3. Mukherjee S., Dinda H., Shashank L., Chakraborty I., Bhattacharyya R., Sarma J., Shunmugam R. Site-Specific Amphiphilic Magnetic Copolymer Nanoaggregates for Dual Imaging, *Macromolecules*, **2015,** *48*, 6791-6800.