# Clustering of iron oxide nanoparticles into poly(ethylene oxide)-*block*-poly(ε-caprolactone) nanoassemblies as ultrasensitive MRI probes

A. Hannecart[1], D. Stanicki[1], L. Vander Elst[1, 2], L. Mespouille[3], R. N. Muller[1,2], S. Laurent[1,2]

[1]NMR and Molecular Imaging Laboratory, General, Organic and Biomedical Chemistry Department, University of Mons, B-7000 Mons, Belgium
[2]Center for Microscopy and Molecular Imaging, B-6041 Charleroi, Belgium
[3]Laboratory of Polymeric and Composite Materials, University of Mons, B-7000 Mons, Belgium

## Introduction

Polymer vesicles, called polymersomes, are hollow spheres formed by the self-assembly of amphiphilic polymers with long hydrophobic blocks (Fig 1.). Thanks to their high robustness, polymersomes have emerged as promising nanocarriers. The objective of this project is to study the self-assembly of $PEO_{2000}$-*b*-$PCL_{12650}$ copolymers with ultrasmall iron oxide nanoparticles (USPIO). A composition close to $PEO_{2000}$-*b*-$PCL_{12000}$ was chosen owing to the tendency of these copolymers to form a vesicular morphology. Several studies have reported the formation of poly(ethylene oxide)-*block*-poly(ε-caprolactone) (PEO-*b*-PCL) based vesicles due to their high potential for biomedical applications. However, to the best of our knowledge, no work has be done on the incorporation of USPIO into nanoassemblies produced from PEO-*b*-PCL copolymers with long PCL blocks.

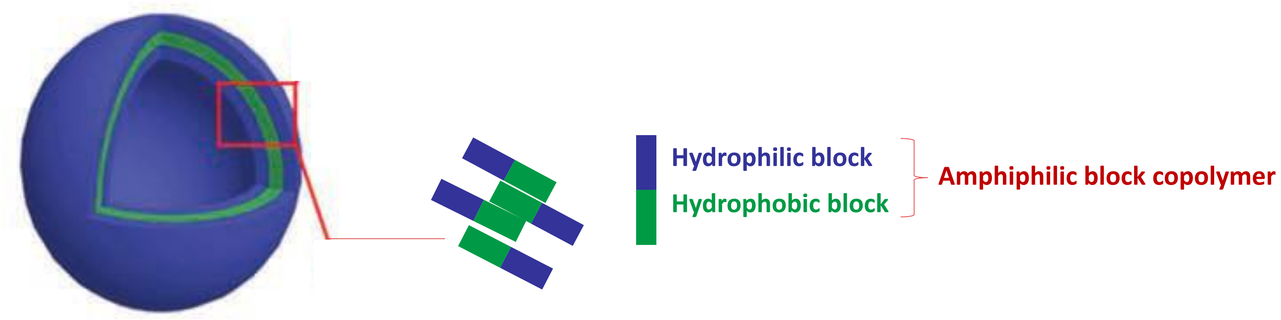


***Figure 1.*** *Schematic representation of a polymersome*

## Material and methods

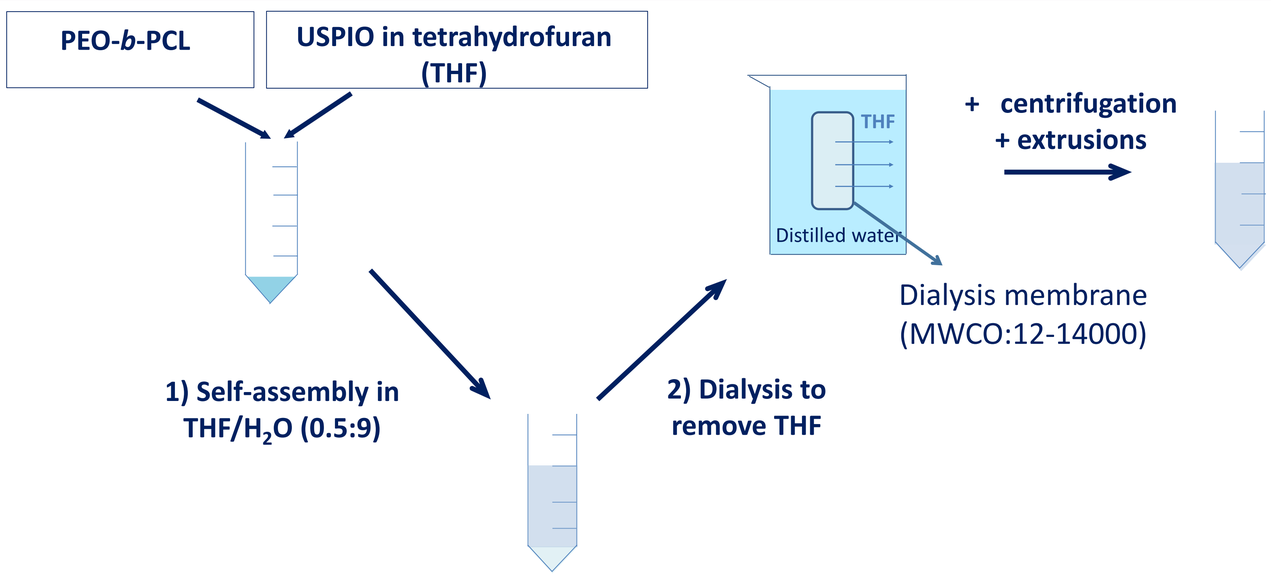


***Figure 2****. Self-assembly of $PEO_{2000}$-b-$PCL_{12650}$ with USPIO by the nanoprecipitation method*

USPIO (magnetic core size of 4.2 nm and 7.5 nm) were produced by thermal decomposition of iron(III) acetylacetonate in the presence of surfactants in an organic solvent at high temperature (>200°C).

Nanoprecipitation of $PEO_{2000}$-*b*-$PCL_{12650}$ with iron oxide nanoparticles was performed by varying the initial nanoparticle concentration (Fig. 2). The best results were obtained by mixing 10 mg of copolymer with 500 µl of THF containing USPIO ($[Fe]_0$ = 40 mM for $d_{USPIO}$ = 7.5 nm, $[Fe]_0$ = 80 mM for $d_{USPIO}$= 4.2 nm).

## Results and discussions

### Size and morphology

Dynamic light scattering (DLS), transmission electron microscopy (TEM) and cryo-TEM analyses (Fig. 3) showed that nano-objets produced by the self-assembly of $PEO_{2000}$-*b*-$PCL_{12650}$ with USPIO are spherical, possess a high USPIO content and a diameter close to 100 nm

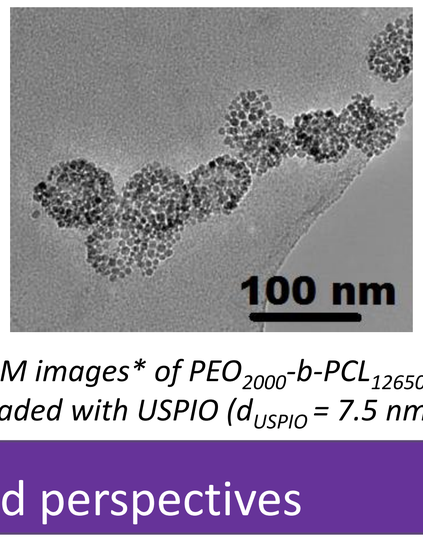


***Figure 3****. Cryo-TEM images* of $PEO_{2000}$-b-$PCL_{12650}$ nanoassemblies loaded with USPIO ($d_{USPIO}$ = 7.5 nm)*

### $r_1$ and $r_2$ relaxivities

The efficiency of a MRI (magnetic resonance imaging) contrast agent is quantified by its longitudinal and transverse relaxivities ($r_1$ and $r_2$). $T_2$-weighted contrast agents decrease MRI signal intensity where they accumulate. The most effective $T_2$-weighted contrast agents are those characterized by the higher $r_2/r_1$ ratio. Incorporation of USPIO into PEO-*b*-PCL nanoparticles leads to a significant increase of $r_2/r_1$ ratios ($r_1$ decreases due to a reduced accessibility of water protons to USPIO and $r_2$ increases due to USPIO clustering) (table 1).

**Table 1.** *Relaxivities ($r_1$ and $r_2$) at 37°C and 60 MHz*

| | $r_1$ ($s^{-1}mM^{-1}$) | $r_2$ ($s^{-1}mM^{-1}$) | $r_2/r_1$ | $r_1$ ($s^{-1}mM^{-1}$) | $r_2$ ($s^{-1}mM^{-1}$) | $r_2/r_1$ |
|---|---|---|---|---|---|---|
| | USPIO (THF) | | | USPIO loaded in $PEO_{2000}$-*b*-$PCL_{12650}$ (water) | | |
| **$d_{USPIO}$ = 7.5 nm** | 12.9 | 37.8 | **3.0** | 1.22 | 198 | **162** |
| **$d_{USPIO}$ = 4.2 nm** | 7.8 | 17.9 | **2.3** | 0.28 | 110 | **389** |

## Conclusions and perspectives

USPIO possessing two different diameters (d = 4.2 nm and d = 7.5 nm) were produced by the thermal decomposition method and incorporated into $PEO_{2000}$-*b*-$PCL_{12650}$ nanoassemblies by a nanoprecipitation method. Extrusions were performed to produce 100 nm diameter polymeric nanoparticles with a narrow size distribution which is ideal for *in vivo* applications. These polymeric nanoparticles were loaded with a high USPIO content by optimizing the initial USPIO concentration and are characterized by very high $r_2/r_1$ ratios which demonstrates that they are promising candidates as $T_2$-contrast agents. Further research will focus on the incorporation of an anti-cancer drug into these nanocarriers and the attachment of an active targeting group such as an RGD-containing peptide to their surfaces.

2nd International Electronic Conference on Medicinal Chemistry
1-30 November 2016

sponsors: MDPI pharmaceuticals

*The authors thank O. Ersen and D. Ihiawakrim from Institut de Physique et Chimie des Matériaux of Strasbourg for cryo-TEM analyses.