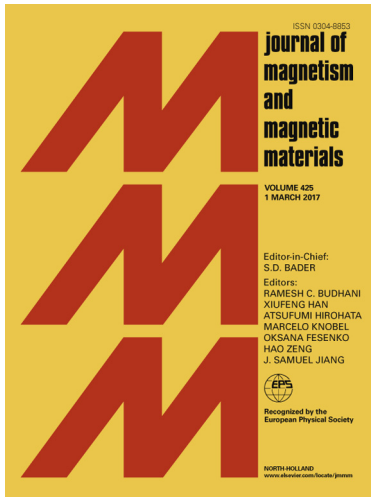

Microfluidic approaches for the production of monodisperse, superparamagnetic microspheres in the low micrometer size range

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ABSTRACT

The preparation of small, monodispersed magnetic microparticles through microfluidic approaches has been consistently challenging due to the high energy input needed for droplet break-off at such small diameters. In this work, we show the microfluidic production of 1-3 μm magnetic nanoparticle-loaded poly(D, L-lactide) (PLA) microspheres. We describe the use of two approaches, using a conventional flow-focusing microfluidic geometry. The first approach is the separation of target size satellite particles from the main droplets; the second approach is the direct production using high flow rate jetting regimes. The particles were produced using a polymeric thiol-ene microfluidic chip platform, which affords the straightforward production of multiple chip copies for single-time use, due to large feature sizes and replica molding approaches. Through the encapsulation of magnetite/maghemite nanoparticles, and their characterization with scanning electron microscopy (SEM) and vibrating sample magnetometry (VSM) measurements, we show that the resulting particles are monosized, highly spherical and exhibit superparamagnetic properties. The particle size regime and their magnetic response show potential for in vivo intravenous applications of magnetic targeting with maximum magnetic response, but without blocking an organ's capillaries.

1. Introduction

There are many potential *in vivo* applications for magnetic nanoparticles (MNPs) including therapeutic applications such as drug delivery (with the drug being encapsulated or bound to the MNPs) and magnetic hyperthermia (where the entire MNP heats up under the influence of an alternating magnetic field). Furthermore, diagnostic applications such as the imaging of receptor expression and cell types by magnetic particle imaging, MRI contrast and biosensing for diseases detection also benefit from MNPs [1]. For magnetic targeting under the influence of an external magnetic field, the typically used 20-100 nm sized particles are not ideal, as the magnetic force acting on a single particle is too small to overcome the blood stream's inertial and shear forces. Therefore, accumulation in the target tissues (e.g., a tumor) or a target organ (e.g., the pancreas) requires high magnetic fields and field gradients [2]. The easiest solution to overcoming these challenges in magnetic drug targeting is to increase the particle size, i.e., moving from nanoparticles to microparticles.

For *in vivo* intravenous administration, the magnetic microspheres (MMS) must be smaller than red blood cells, which have an average size of 6.5 μm, and should be spherical, monodisperse and superparamagnetic. Any capillary blockage can thus be avoided, both with and without an applied magnetic field, and allow for efficient and predictable magnetic targeting. An optimal targeting particle size might be one based on nature, namely the size of thrombocytes (blood platelets), which have a maximum size of between 2-3 μm [3], and typically circulate in the blood stream for 8-9 days [4]. This size regime effectively bypasses lung capillaries [5,6], while showing greater localization to the endothelium than the sub-micron counterparts [7]. Our lab favors the use of biodegradable monodisperse MMS, as they combine the defined magnetic targetability, the capability of encapsulation and controlled release of drugs with low toxicity, FDA-approval, and biodegradability once the MMS have done their job. Up to now, our lab made monodisperse MMS with a microfluidic glass chip at sizes between 8 - 50 μm [8], and later with a co-flow method to yield sizes up to 700 μm [9]. Smaller MMS had to be prepared by a solvent evaporation/extraction batch method, which yielded very broad size distributions between 1-2 μm [10]. The aim of the present study was to explore the production of small monodisperse MMS, which could be used in the bloodstream, would not clog the capillaries, and would be able to react to an external magnetic force. To ensure monodispersity and the continuous production of particles, microfluidic methods were utilized for the MMS production. We decided on investigating both direct and indirect microfluidic methods to produce MMS sized in

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the low micrometer range (1-3 μm). The direct method utilizes flow focusing, where an inner non-miscible solvent stream breaks up into monosized droplets after passing through an orifice, as shown in **Figure 1**. The indirect method refers to the collection of satellite particles that arise commonly in the just described microfluidic droplet generator in conjunction with the primary droplets.

Direct production of MMS of the size regime investigated here (~2 μm) has been realized by bulk methods [10], electrospray [11], and commercial flow focusing nozzles [12]. However, to our knowledge, a simple microfluidic chip has not yet been employed. This is partly because microfluidic production of small droplets is extremely difficult to achieve owing to the high energy input needed for droplet breakup. This generally requires small feature sizes as the production of droplets smaller than one-tenth of the orifice is rare [13], making the microfluidic chip fabrication costly and labor intensive. Indirect production of small MS through the collection of satellite droplets has been demonstrated [14-16], albeit for non-magnetic particles. Satellite particles are formed through the surface instabilities of the dispersed phase [17-19], and are generally considered problematic as the primary droplet polydispersity rapidly increases resulting in lower quality sample yield. However, if the aim is to produce small