Chemical Engineering Science 63 (2008) 3960 – 3965

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

Observation and modelling of capillary flow occlusion resulting from the capture of superparamagnetic nanoparticles in a magnetic field

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ARTICLE INFO

Article history:
Received 22 November 2007
Received in revised form 24 April 2008
Accepted 29 April 2008
Available online 6 May 2008

Keywords:
Biochemical engineering
Biomedical engineering
Fluid mechanics
Numerical analysis

ABSTRACT

The magnetic field mediated capture of 10 nm diameter superparamagnetic nanoparticles, in the form of agglomerates of mean diameter 330 and 580 nm, from microcapillary flows has been observed and modelled. The steady state thickness of the captured layer in microcapillaries of diameter 400–800 μm could be predicted for both the 330 and the 580 nm diameter agglomerates at flow rates of between 0.1 and 0.4 ml min^{-1}. The model provides insight into blockage formation at a constant flow rate as a precursor to the prediction of thrombotic embolism in magnetic directed therapies. Capillary constriction was particularly acute for the 580 nm agglomerates in large microcapillaries (800 μm) with flow rates of 0.1 ml min^{-1}. From this model, agglomerates of diameter 330 nm or less offer the potential for minimal microcapillary occlusion in a range of flow rates.

1. Introduction

The magnetic field mediated targeting of superparamagnetic nanoparticle linked therapeutic agents to specific sites of disease in the body is an exciting prospect. Intentional embolization with magnetic particles has been used therapeutically with some success to selectively stop blood supply to tumours, causing them to necrotize (Sako et al., 1986). However, in drug delivery settings excessive nanoparticle accumulation might block small blood capillaries, causing a thrombotic embolism, which is undesirable.

Magnetic nanoparticles are already in use clinically as contrast agents in magnetic resonance imaging (Pankhurst et al., 2003). However, to date there appear to have only been three early stage clinical trials of magnetic targeting of paramagnetic nanoparticles in humans. In two of these trials, the chemotherapeutic drug epirubicin linked to 100 nm paramagnetic nanoparticles was administered intravenously. These nanoparticles were successfully targeted with minimal side effects to tumours with an externally applied 0.2–0.8 T magnet placed by the tumour (Lubbe et al., 1999, 1996). Wilson et al. (2004) delivered a sample of intra-arterially administered doxorubicin linked 0.5–5 μm superparamagnetic nanoparticles to tumours in patients with an external 1.5 T magnet placed adjacent to the tumour. Although patients reported short lived abdominal pain during injection of the drug bearing nanoparticles, embolization was not detected in post procedure angiography (Wilson et al., 2004). Whilst tissue penetration of pharmaceutical linked nanoparticles is important in this paper we develop and test a model to assess the effect that the size of the administered paramagnetic nanoparticles has on the constriction of capillaries as a result of magnetic targeting.

2. Materials

$FeCl_3 \cdot 6H_2O$, $FeCl_2 \cdot 4H_2O$, $NH_3 \cdot H_2O$ and HCl were obtained from Fisher Scientific (UK) and PMAA from Sigma Aldrich. The capillary arrays were manufactured in-house from a commercially available plastomer (Dow Affinity®) using a novel extrusion-based process that has been previously described (Hallmark et al., 2005a, b).

3. Methods

A 10 nm superparamagnetic magnetite (Fe_3O_4) nanoparticles were synthesized by co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions upon addition of a base in an oxygen-free, non-oxidizing, environment as described by Xia et al. (2005) using overhead mixing rather than ultrasonication to mix the reaction solution (Darton et al., 2008). To reduce agglomeration of the superparamagnetic nanoparticles, 3% by weight PMAA was added and the pH adjusted to 7.4 (Mendenhall et al., 1996). This resulted in agglomerates, assumed to be spherical, of the 10 nm superparamagnetic nanoparticles of 575 ± 8.0 nm in diameter as measured by a Brookhaven Zeta-sizer. To obtain smaller agglomerates of diameter 328 ± 3.5 nm a sample of nanoparticles in 3% by weight PMAA was sonicated with a 330 W ultrasonic cell crusher (Heat Systems XL-2020) on full power for 10 min. These particle sizes were considered suitable for this work

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doi:10.1016/j.ces.2008.04.057

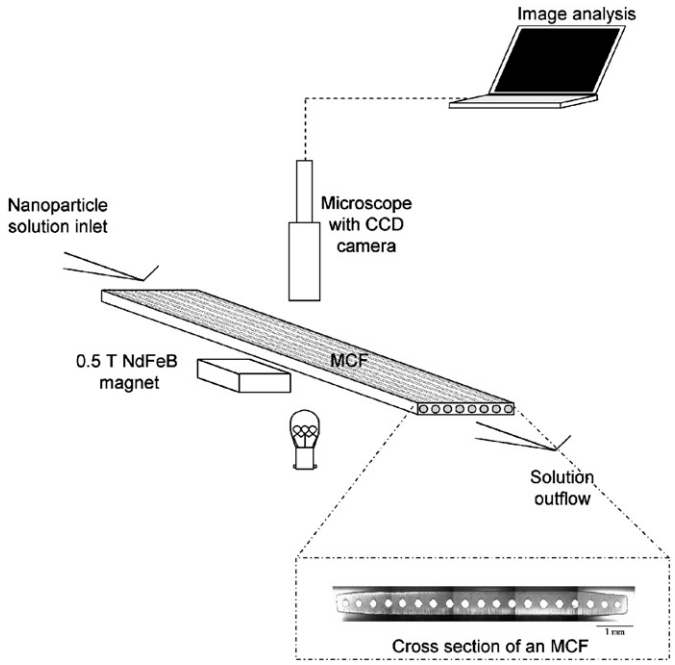

Fig. 1. Schematic diagram of the apparatus to measure magnetic in-flow capture of superparamagnetic nanoparticles.

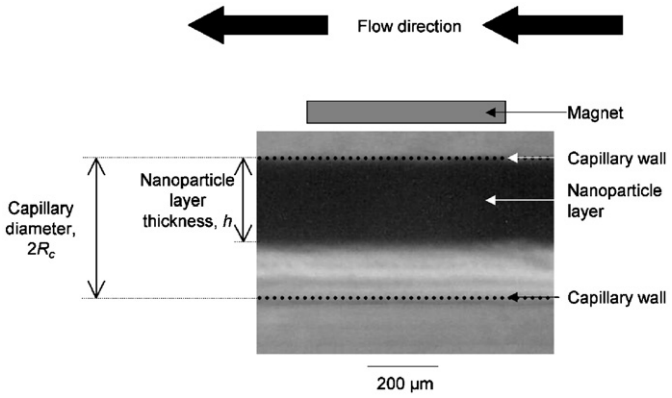

Fig. 2. Photomicrograph of a layer of captured nanoparticles in a microcapillary. The flow direction is from right to left, and the magnet is positioned on the upper wall of the microcapillary.

because they were large enough to enable in-flow capture with a 0.5 T NdFeB magnet but still relatively small to potentially improve tissue penetration at target site. To reduce possible surface coat interactions or unevenness no encapsulation of particles was used. The magnetic properties of the nanoparticles were measured using SQUID magnetometery at 293 K from −1 to 1 T, which showed that the particles were superparamagnetic with a magnetic susceptibility of 1.57×10^{-4}.

Nanoparticle capture was studied in a novel plastic capillary array, termed a microcapillary film or MCF (Hallmark et al., 2005a,b) containing capillaries of 410 μm diameter. The MCFs were fabricated in-house from a commercially available polymer resin, Dow Affinity Plastomer, using a novel extrusion process (Hallmark et al., 2005b). MCFs provide low refraction for optical microscopy and previous research has characterized fluid flows in the material (Hornung et al., 2006). Only one of the 19 available capillaries was used in each film. A typical experiment would proceed as follows. A steady flow of an aqueous solution of PMAA (3% w/w) was first established in the test capillary and its flow rate was accurately controlled by an HPLC pump (Kontron 422). An electro-mechanical injection valve unit (VICI Valco) was used to introduce into the flow 2 ml slugs of 40 mg ml^{-1} superparamagnetic nanoparticles suspended in PMAA solution (3% w/w). Superparamagnetic particles were magnetically targeted with a 0.5 T NdFeB permanent magnet (e-magnets UK, Sheffield). The solution leaving the film was not recycled. The setup of the apparatus is illustrated schematically in Fig. 1.

Experiments were carried out on two sizes of nanoparticle aggregate (330 and 580 nm). Flow-rates less than 1 ml min^{-1} proved optimal for capture and hence flows between 0.1 and 0.5 ml min^{-1} were examined in steps of 0.05 ml min^{-1}. These volumetric flow rates correspond to superficial linear velocities of 1.3 and 6.3 cm s^{-1}, respectively, with steps of 0.6 cm s^{-1}. The Reynolds numbers corresponding to these flow velocities are 1.7 and 8.0, respectively, using a measured fluid viscosity of PMAA solution (3% w/w) of 2.5×10^{-3} Pa s and a density of 1024 kg m^{-3}. Additionally, the physical properties of the PMAA solution (3% w/w) are close to those of blood, with values of blood viscosity reported circa 3.3×10^{-3} Pa s (Lowe et al., 2000) and density between 1043 and 1051 kg m^{-3} (Hinghofer-Szalkay and Greenleaf, 1987).

Nanoparticle capture was observed until one of two criteria were met; either a steady thickness of captured nanoparticles had been held for over an hour after the injected pulse, or the initial layer was eroded by the flow. When a stable layer of captured nanoparticles formed its thickness depended on the flow rate and particle size (Darton et al., 2008). Erosion was the dominant behaviour at higher flow-rates. A photomicrograph illustrating a layer of captured nanoparticles in a microcapillary is shown in Fig. 2.

4. Model

The stability of a steady-state layer of magnetically captured nanoparticles within a flowing fluid depends on the relative magnitude of the forces acting on each nanoparticle within the layer. Two dominant forces act on a stationary nanoparticle at the wall of a capillary: the hydrodynamic force resulting from the flow field around the nanoparticle and the magnetic force due to the presence of a magnetic field gradient. Electrostatic forces and Van de Waal's forces have been neglected as in other work in this area (Ebner et al., 1997). A key assumption in the model is that the captured nanoparticle layer is stable when the magnetic forces are greater than the hydrodynamic forces. When the two forces become equal the nanoparticle layer is assumed to become unstable and subject to erosion.

4.1. Hydrodynamic analysis

Experimental observations reveal that nanoparticles are captured by the magnetic field and form a layer on the capillary wall. With a constant volumetric flow-rate this layer constricts the capillary, resulting in higher fluid velocities and shear stresses on the surface of the nanoparticle layer. The aim of this analysis is to estimate the magnitude of the shear force acting on the nanoparticles resulting from flow field in a constricted capillary. Fig. 3 illustrates schematically the constriction of the flow within a capillary due to a captured layer of particles at the capillary wall.

The cross sectional area of the captured layer is assumed to take the form of a segment of the capillary's circular cross section; its area can hence be shown to be

$$A_{\text{deposit}} = R_c^2 \,\text{Cos}^{-1}\left(\frac{R_c - h}{R_c}\right) - (R_c - h)\sqrt{h(2R_c - h)}, \quad (1)$$

where R_c is the capillary radius and h is the maximum thickness of the captured layer. If this area is subtracted from the total cross