High-Gradient Magnetic Capture of Ferrofluids: Implications for Drug Targeting and Tumor Embolization

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One of the perspective methods of cancer chemotherapy is magnetic targeting of drugs to tumors. This task is usually accomplished using small permanent magnets attached near the desired sites. In this study a new much more effective approach is proposed which is based on a strong magnetic gradient using a ferromagnetic wire placed in a strong magnetic field. Feasibility of this approach has been evaluated by the formation of ferrofluid seals and measurement of maximum pressure the formed seal can resists. Using this method it is possible to capture even superparamagnetic particles with nanosize dimensions, therefore the method may have an interesting applications in biomedical sciences.

Introduction

Due to the limitations of currently available chemotherapeutic methods, the delivery of anticancer drugs to the target site represent a very attractive treatment approach, which can substantially increase therapeutic efficacy and reduce toxic side effects in the treatment of solid tumors. One of the promising concepts is magnetic targeting. Using large unilamellar liposomes with encapsulated ferrofluid we have recently achieved a 26-fold increase of drug concentration in the left kidney of the rat to which a small SmCo magnet was attached compared with the non-targeted right kidney (Babincová *et al.,* 2000).

Another important factor which enhance the effect of chemotherapy is embolization, or in the other words, mechanical obstruction of tumor due to the enhanced concentration of ferrofluids in the tumor-feeding vessels and the succesive necrosis of tumor body. Moreover ferrofluids obstructing feeding vessels represents barrier which delay outflow of activated drug and minimize further adverse effects of a drug on healthy tissues.

The force exerted on a magnetisable particle is determined by the absolute value and direction of the gradient of the induction of magnetic field $\vec{B}$ (Svoboda, 1987)

$$\vec{F} = \frac{V \cdot \chi}{\mu_O} (\vec{B}.\vec{\nabla})\vec{B} \qquad (1)$$

where V is the volume and χ susceptibility of magnetic particle, and μ_0 is the magnetic permeability in vacuum. From this expression it is clear that both magnetic induction as well as its gradient should be maximised. To achieve this goal a high-gradient magnetic separation (HGMS) technique was developed. The typical HGMS device consists of a steel-wool matrix magnetised by an external field (Parker, 1976). Another successful approach consists in placing a ferromagnetic wire parallel to the flow tube (Badescu *et al.,* 1996). Our aim in this study was to evaluate the suitability of such a method for magnetic drug targeting and tumor embolization.

Material and Methods

We have used four kinds of ferrofluids. Small unilamellar magnetoliposomes (De Cuyper and Joniau, 1988) with the diameter of 20 nm (SUM), fluidMAG (Chemicell, Berlin, Germany) of 100 nm, large unilamellar magnetoliposomes (Babincová, 1993) with 700 nm (LUM), and beadMAG (Chemicell, Berlin, Germany) with 1000 nm. The experimental setup for the study of seal formation under the influence of non-homogeneous magnetic field is shown in Fig. 1. A plastic tube (inner diameter 1.5 mm) is going through a peristaltic pump (flow rate 1 ml/min). The maximum pressure that the formed seal can resist is measured using a pressure gauge made from vertical transparent tube, and from the height h attained the pressure is calculated as $P = \varrho_{fluid} gh/\varrho_{Hg}$, where ϱ_{fluid} and ϱ_{Hg} are densities of the used fluid and of mercury, respectively (Sheng *et al.,* 1999).

The magnetic field was generated using a water-cooled electromagnet with a 2 × 8 × 17 cm gap, with ferromagnetic wires of 2 cm length and

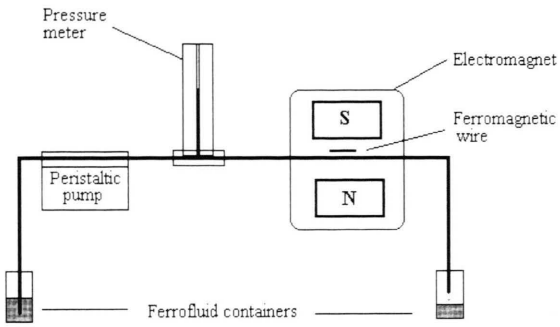

Fig. 1. Setup for the measurement of ferrofluid pressure resistance.

0.98 mm diameter, made from an FeNi alloy (saturation magnetization 1.8 T) mounted alongside the plastic tube in the middle of the gap.

Results and Discussion

When the maximum resistant pressure was reached, the ferrofluid seal was broken and the pressure dropped to the initial value. Dependence of this maximal pressure on the strength of magnetic field created by electromagnet is shown in Fig. 2. The maximal pressures which are able to withstand the seals formed from larger particles are substantially higher and their time of formation is substantially shorter (approx. seconds) as compared with small ferrofluid particles (formed in min), and moreover the induction of applied magnetic field should be in this case stronger than 0.5–0.6 T. It should be emphasized that using permanent magnets (or electromagnets without the wire) is possible to form a seal only using LUM or beadMAG. For the small superparamagnetic SUM and fluidMAG particles is necessary to use high-gradient magnetic technique. The field gradient ∇B created by the ferromagnetic wire with saturation magnetization M_s = 1.8 T and radius a = 1 mm is may be estimated using the approximate formula (Svoboda, 1987) $\nabla B = M_s / a = 1.8 \,.\, 10^3$ T/m, which is almost a four magnitude larger than the gradient generated near the surface of a small permanent magnet (Babincová *et al.*, 2000). Therefore the force acting on the ferrofluid particles flowing in the plastic tube simulating the blood network is sufficient to induce seal formation. Sealing of blood vessels supplying the tumors (embolization) would induce tumor necrosis, and moreover ferrofluid particles may be efficiently heated using a high-frequency magnetic field (Néel and Brown effects, Babincová *et al.*, 1999) which also may be useful for tumor eradication. Clinical whole-body magnetic resonance imaging machines (MRI) are generating magnetic fields with induction of ~1.5 T (research MRI machines with induction > 5 T are also available). Using ferromagnetic wires mounted near the desired sites (e.g. tumors) ferrofluids (carrying anticancer drugs, β-emitting isotopes, etc.) may be targeted with an efficiency 3–5 magnitudes larger than using permanent magnets. Our preliminary (unpublished) experiments with the high-gradient magnetic targeting of ferrofluids to a given site of a rat tail seems to support the applicability of this approach *in vivo*. Our main topical goal is to develop this technique for a magnetic site-specific gene targeting using recently synthesized transMAG ferrofluid particles (Chemicell, Berlin, Germany).

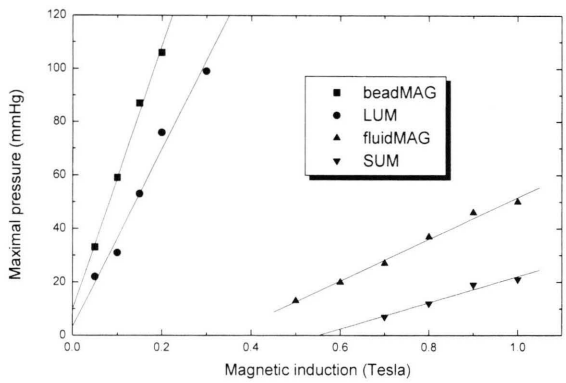

Fig. 2. Maximal pressures obtained at various values of magnetic induction for large unilamellar magnetoliposomes (LUM), small unilamellar magnetoliposomes (SUV) and commercial (Chemicell, Berlin, Germany). ferrofluid particles beadMAG (large diameter) and fluidMAG (small diameter).

Acknowledgments

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