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Exothermic effect of dextran-coated Fe_3O_4 magnetic fluid and its compatibility with blood

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ABSTRACT

The magnetic fluid (MF) for hyperthermia should be superparamagnetic, non-toxic and biocompatible. The compatibility between blood and dextran-stabilized Fe_3O_4 MF was first investigated; then the influences of the MF concentration and the magnetic field intensity on the heating ability was studied; at last the effects of temperature, shear rate and applied magnetic field on the viscosity of blood and MF/blood mixtures was measured. The results revealed that the viscosity and coagulation time of blood are almost unaffected by small addition of dextran-stabilized Fe_3O_4 MF, showing good compatibility with blood. The Fe_3O_4 MF under alternating magnetic field can generate enough energy to heat tumor tissue for hyperthermia therapy.

1. Introduction

Magnetic fluids (MF) are stable colloidal suspensions that are composed of single-domain magnetic nanoparticles (MNPs) dispersed in appropriate solvents. The MF has some peculiar properties, which can be used in many biomedical applications, such as (a) cellular therapy in cell labeling, separation and purification [1]; (b) drug delivery systems [2–8]; (c) contrasting enhancement in magnetic resonance (MR) imaging [9–12]; (d) localized therapeutic hyperthermia [13] and (e) biosensors [14]. One of the most important properties of MF is that the MF composed of MNPs could release heat in an alternating magnetic field. Thus the MF becomes a promising material for hyperthermia to kill tumors, which takes advantage of the fact that tumor tissue is more sensitive to heat than normal tissues [15–17]. MF hyperthermia involves the introduction of MNPs into the tumor tissue and irradiation with an external alternating magnetic field to increase the temperature of the tumor to 42–46 °C therefore to kill tumor cells [18,19]. In addition, magnetic nanoparticles can be drawn to a particular part of the human body under the influence of magnetic field. The MNPs can be an implantable nanoscaled device filled with drug molecules encapsulated by nanoporous membrane, so MF could serve as an excellent drug delivery system [20]. These properties make the MF a promising material for cancer treatment.

For biomedical applications of MF, it is important that the surface-modified MNPs have water-soluble and functionalized groups on the surface to enhance the MF compatibility with organism, especially with blood. The branch of biorheology focusing more specifically on blood is termed hemorheology. Its purpose is therefore to study the flow of blood, in interaction with its surrounding environment, in both macro- and microcirculation [21]. Blood, which is a suspension of red blood cells (erythrocytes) (RBCs), white blood cells (leukocytes) and platelets in plasma, is known to be a non-Newtonian fluid with non-linear stress–strain rate relationship and is treated as an electrically conducting MF which also exhibits magnetic property [22,23]. Şincai et al. investigated the effects of two kinds of MF on the blood properties in dogs' vein, and demonstrated that blood had excellent compatibility with the water-based MF, while low compatibility with the alcohol-based MF [24]. Attempts have been made to investigate the effect of magnetic field on biological suspensions [25]. The orientation of paramagnetic sickled erythrocytes with deoxygenated hemoglobin S was first observed by Murayama in a homogeneous static magnetic field of 0.35 T [26].

In this study, dextran-stabilized MF with high saturation magnetization was synthesized at the presence of dextran-T20 based on our previous publication [27]. The compatibility between blood and MF and the viscosity of blood and MF/blood mixture were investigated. In addition, the influences of the concentration of magnetic

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fluid and electrical current of magnetic field on the heating ability were studied.

2. Experimental

2.1. Materials

All chemicals are analytical graded and used without further purification. Iron (III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), iron (II) sulfate heptahydrate ($FeSO_4{\cdot}7H_2O$), aqueous ammonia (25 wt%), hydrazine hydrate ($N_2H_4{\cdot}H_2O$, 50 wt%), dextran T20 (Mw ≈ 20,000) were all purchased from the SCRC (Sinopharm Chemical Reagent Co., Ltd.). Human blood was provided by the No. 1 Subsidiary Hospital of Soochow University. Deionized water was employed throughout the experiments.

2.2. Preparation of dextran MF

The synthesis of dextran-coated Fe_3O_4 MNPs was based on our previous study [27–29]. In typical synthesis, a mixture of dextran and iron (III) chloride hexahydrate dissolved in 30 mL of deionized water was put into a three-neck flask equipped with a mechanical stirrer, and 0.5 mL hydrazine hydrate was added into the flask. After the mixture was stirred and mixed completely, some sulfate heptahydrate was added. After 15 min, sulfate heptahydrate was dissolved completely, and some ammonia solution was quickly dropped into the mixture with vigorous stirring under argon protection, followed by quickly dropping additional ammonia solution until the pH of the solution reached 10. Soon afterwards the solution was stirred for an additional 3 h in argon atmosphere at the temperature of 60 °C. The black suspension was cooled and purged by centrifugation at a speed of 7000 rpm for 20 min to separate large particles from the suspension, then the liquid at the top of the separation tube was taken out. Excess ammonia, hydrazine and its leftovers, iron cation and dextran macromolecules were removed by dialysis using a membrane bag with a 14,000 cut-off molecular weight for 24 h. The deionized water was replacing every hour.

2.3. Preparation of MF/blood mixture

In biomedical applications, MF is usually injected into the blood vessel through vein infusion. Taking account of the trace dosage of MF contrast to body fluid, the amount of blood and MF differs very much. In the present investigation, MF/blood mixture was prepared by mixing dextran-stabilized MF and blood together at a constant ratio of 1:19 (v/v) under continuous oscillation. For a typical procedure, 0.5 mL of dextran-stabilized MF was infused into 9.5 mL of blood slowly under oscillation. 30 min later, garnet MF/blood mixture was obtained.

2.4. 2-Dimensional transient bio-heat transfer method

The temperature field of the magnetic fluid under the AC magnetic field is modeled using the Pennes equation [30] as follows:

$$\delta_{ts}\rho C\frac{\partial T}{\partial t} + \nabla\cdot(-k\nabla T) = \rho_b C_b\omega_b(T_b - T) + Q_{met} + Q_{ext} \quad (1)$$

where δ_{ts} is unsteady parameter, ρ the density of the tissue, C the specific heat (J/(kg K)) of the tissue, k the thermal conductivity (W/(m K)), ρ_b the blood density (kg/m^3), C_b the blood specific heat (J/(kg K)), ω_b the perfusion rate (1/s), T_b the arterial blood temperature (°C), and Q_{met} and Q_{ext} are the heat sources from metabolism of organism and external heating of applied magnetic field, respectively (W/m^3). According to the paper reported by Rosensweig [31], the heating source generated by the Fe_3O_4 particles under the alternating magnetic field is described as:

$$P = \pi\mu_0\chi_e H_0^2 f\frac{2\pi f\tau}{1+(2\pi f\tau)^2} \quad (2)$$

where μ_0 is the permeability of free space, $4\pi\times10^{-7}$ T m/A; χ_e the equilibrium susceptibility; H_0 ($=B_0/\mu_0$) and f are the amplitude and the frequency of alternating magnetic field. When both mechanisms act simultaneously, the effective relaxation time τ is the given by

$$\tau = \frac{\tau_N\cdot\tau_B}{\tau_N+\tau_B} \quad (3)$$

where τ_N and τ_B are the Néel relaxation and the Brownian relaxation time, respectively. For super-paramagnetic particles, the generated energy of Fe_3O_4 MFs results from relaxation processes: the loss due to the change of reorientation (Neel loss, τ_N) and frictional loss (Brown loss, τ_B). τ_N and τ_B are written as:

$$\tau_N = \tau_0\exp\left(\frac{KV_M}{k_bT}\right)$$
$$\tau_B = \frac{3\eta V_H}{k_bT} \quad (4)$$

where τ_0 is the average relaxation time in response to a thermal fluctuation, approximately to 10^{-9} s, η the viscosity of MFs, V_M the volume of MNPs, V_H the hydrodynamic volume of MNPs, K the anisotropy constant of 8 kJ/m^3, k_b the Boltzmann constant ($=1.38\times10^{-23}$ J/K), and T is the temperature. The MNPs' volume V_M and the hydrodynamic volume including the ligand layer V_H are written as

$$V_M = \frac{\pi D^3}{6}$$
$$V_H = \frac{\pi(D+2\delta)^3}{6} \quad (5)$$

where D is the diameter of the MNPs and δ is the ligand layer thickness, such as surfactant layer.

According to the Langevin equation [31], the equilibrium susceptibility χ_e is expressed as:

$$\chi_e = \chi_i\frac{3}{\xi}\left(coth\,\xi - \frac{1}{\xi}\right) \quad (6)$$

In the above equations, ϕ is the volume fraction of the magnetic fluids, M_d the domain magnetization of the MFs, M_s the saturation magnetization of the MFs when all magnetic dipoles with moment $m = M_dV_H$ are aligned with the magnetic field, and the Langevin function parameter is expressed as: $\xi = \mu_0M_dHV_M/kT$, $M_s = Nm = \phi M_d$ and $H = H_0\cos2\pi ft$.

The initial susceptibility, which is defined under magnetic fields of very low intensities $H\to0$ and very low frequencies $f\to0$, is expressed as $\chi_i = \mu_0\phi M_d^2V_M/3kT_0$, where T_0 is the initial temperature. The temperature rise is calculated as $\Delta T = P\Delta t/\rho c_p$ where ρ and c_p are the effective density and the effective specific heat of the magnetic fluids calculated as $\rho = \phi\rho_1 + (1-\phi)\rho_2$ and $c_p = \phi c_p + (1-\phi)c_p$, where subscripts 1 and 2 represent the Fe_3O_4 MNPs and the carrier liquid (water in this paper), respectively.

2.5. Model, mesh and boundary conditions

We established a model of concentric circles to simulate the heat transfer. As shown in Fig. 1, the inner circle with diameter of R_{in} = 1 cm stands for the necrosis area of tumor, the outer circle with diameter of R_{out} = 1.5 cm stands for the normal area of tissue with rich vessels. In this model, the medium is supposed to be stagnant and no diffusion existed between two domains. Refined triangle meshes are used to discretize the model.