Aggregation of Magnetic Nanoparticles in Biological Solvents Evaluated by HTS-SQUID Magnetic Immunoassay System

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***Abstract*—Magnetic nanoparticles (MNPs) have been studied for various medical applications by taking advantage of their unique magnetic properties. Magnetic immunoassay (MIA) is a technique for the rapid detection of target biomarkers by antigen-antibody reaction between antibody-modified MNPs and the target biomarker. In this study, we aim to improve the accuracy of the MIA, we evaluated the AC magnetic properties of MNPs in the biological solvents. To measure the magnetic signal of MNPs, we used the developed HTS-SQUID magnetic immunoassay system. First, we evaluated the instability of the HTS-SQUID magnetic immunoassay system using pellets of manganese (II) fluoride. The results show that the device instability due to operating time does not affect the measurement of magnetic signal changes in MNPs due to biological solvents. Since the magnetic properties of MNPs depend on particle size and viscosity, we measured the time evolution of the magnetic signal of Resovist in glycerin, human serum, sheep whole blood, and NaCl. It was found that the magnetic signal of Resovist decreased exponentially with ions contained in the solvent. The results are fitted as the exponential double function, suggesting that the magnetic signal of MNPs in biological solvents is affected by the aggregation of MNPs in the blood and that there are at least two steps in the mechanism of the aggregation.**

***Index Terms*—Aggregation, HTS-SQUID, magnetic nanoparticles, magnetic properties.**

I. Introduction

MAGNETIC nanoparticles (MNPs) have been studied for various biomedical applications such as contrast agents [1], hyperthermia [2], and magnetic separation of cells and DNA [3] because of their unique magnetic properties. Among these, the magnetic immunoassay (MIA) method has been extensively studied as a new technique for detecting specific proteins (biomarkers) [4], [5], [6], [7]. Optical methods such as Enzyme-Linked Immuno-Sorbent Assay (ELISA) are the main methods used to detect biomarkers [8], but the MIA method does not require a rinsing process to remove unreacted antibodies and non-biomarker substances in the blood, so it is possible to detect biomarkers more quickly and easily than conventional methods [9].

Rosenweig advocated that MNPs respond to magnetic fields by Brownian relaxation, in which MNPs themselves rotate, and Néel relaxation, in which the magnetic moment inside MNPs rotates [10]. Brownian relaxation time τ_{B} and Néel relaxation time τ_{N} are expressed by the following equations

$$\tau_{\mathrm{B}} = 3\eta V_{\mathrm{H}}/kT \tag{1}$$

$$\tau_{\mathrm{N}} = \tau_0 \exp\left(KV_{\mathrm{M}}/kT\right) \tag{2}$$

where η is viscosity, V_{H} is hydrodynamic volume, k is Boltzmann's constant, T is temperature, τ_0 is in the range of 10^{-9} to 10^{-11} s, where K is magnetic anisotropy energy to keep magnetization in a particular direction and V_{M} is core volume. When both relaxation processes are present, MNPs respond by a mechanism dominated by short relaxation times, and the effective relaxation time τ_{eff} is expressed by the following equations [11].

$$\tau_{\mathrm{eff}} = \tau_{\mathrm{B}}\tau_{\mathrm{N}}/(\tau_{\mathrm{B}} + \tau_{\mathrm{N}}) \tag{3}$$

In the MIA method, the concentration of target biomarkers is evaluated by measuring the magnetic signal of MNPs functionalized by specific antibodies. Since the Brownian relaxation time shown in (1) changes before and after the binding of the MNPs to the target biomarker by antigen-antibody reaction, the magnetic signal of the MNPs decreases depending on the concentration of target biomarkers. However, as we reported in the past that the magnetic signal of MNPs is also reduced to about half in 0% to 10% v/v human serum [12], MNPs form aggregates by shielding their surface charges with sodium and chloride ions in the blood [13]. This phenomenon is indistinguishable from an increase in particle size due to antigen-antibody reaction, and it may lead to worse accuracy of the MIA method, Therefore, to quantitatively evaluate the magnetic signal of MNPs in biological samples, it is necessary to evaluate the change in the magnetic properties of MNPs due to aggregation. The static properties of MNPs have been extensively studied by many researchers using magnetic sensors and microscopes such as scanning electron microscopy [14], [15], [16], [17]. In addition, since particles larger than 4 μm may cause a blockage of blood capillaries in vivo [18], MNPs

Manuscript received 10 November 2022; revised 10 January 2023; accepted 20 January 2023. Date of publication 25 January 2023; date of current version 8 February 2023. *(Corresponding author: K. Yamashita.)*

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Color versions of one or more figures in this article are available at https://doi.org/10.1109/TASC.2023.3239830.

Digital Object Identifier 10.1109/TASC.2023.3239830