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Evaluation of casein coated iron oxide magnetic nanoparticles

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Abstract

Theranostic systems offer a promising approach for early cancer diagnosis and treatment. Here we report the investigation of Na-caseinate-coated iron oxide magnetic nanoparticles (MNP) for potential use in theranostics. The MNP were synthesized in a continuous flow, coated with Na-caseinate, and crosslinked enzymatically for improved stability and drug loading. To evaluate their magnetic suitability for magnetic particle imaging (MPI) and hyperthermia, we conducted DC magnetization measurements, magnetic particle spectroscopy (MPS), and AC-magnetometry. Results show that Na-caseinate coating has minimal impact on magnetic behavior, with a stable magnetization saturation (Ms) of 109(5) $A \cdot m^2/kg(Fe)$ for both coated and uncoated particles. The MPI signal (A3*) decreased by less than 15%, with a slight 2% drop in the A5/A3 ratio. Additionally, Na-caseinate coating improved salt stability without altering magnetic performance, supporting their potential for theranostic applications in drug delivery, MPI, and hyperthermia.

I. Introduction

Theranostic systems use nanoparticles for both imaging and therapy, offering great potential to improve early cancer diagnosis and treatment for millions worldwide. Due to their reactivity to external magnetic fields, magnetic nanoparticles (MNP) can be used in magnetic particle imaging (MPI), magnetic resonance imaging (MRI) or in hyperthermia treatment. Iron oxide nanoparticles offer good biocompatibility but suffer from low stability in physiological media [1]. Even though tannic acid is used as stabilizer further coating can improve stability and functionality. Casein, the primary protein in milk, shows great potential for drug delivery applications and enhancing magnetic nanoparticles functionality [2]. Previous studies have demonstrated that using casein with MNPs enhances their biocompatibility and *in vivo* performance. Here we report a direct way of coating MNPs and their evaluation regarding stability and magnetic behavior [3].

II. Methods and materials

II.I. Production and coating of MNP

Iron oxide nanoparticles were synthesized by mixing iron chloride, sodium nitrate, and sodium hydroxide in a caterpillar micromixer, with tannic acid as a stabilizer. The nanoparticles were purified using magnetic separation. For casein coating, MNPs were mixed with a 10 mg/mL Na-caseinate (Na-Cas) solution in carbonate buffer (pH 8.5) at 60 °C for 16 h. The casein coating was then crosslinked enzymatically with transglutaminase at 40 °C for 1 h, followed by purification over a magnetic column.[3]

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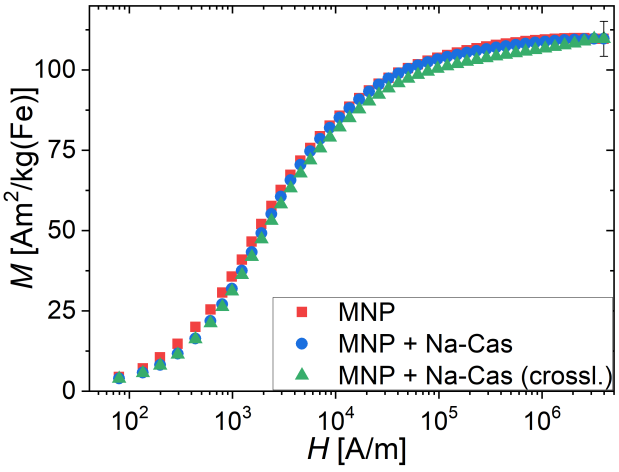

Figure 1: DC magnetization curves at room temperature for MNP systems: MNP (red), MNP + Na-Cas (blue), and MNP + Na-Cas (crossl.) (green), with $\log_{(10)}$ field scale.

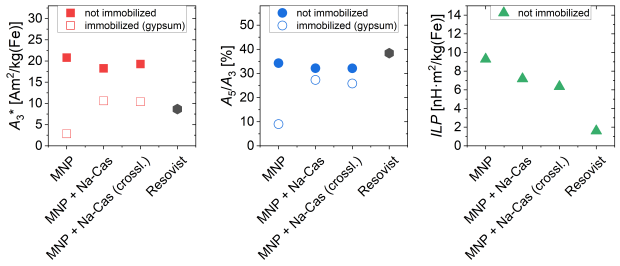

Figure 2: A3*, A5/A3, and ILP-values of uncoated and coated MNP and the MRI contrast agent Resovist as a reference.

II.II. MNP investigation

DC magnetization measurements of MNP samples were performed at room temperature (295 K) using a SQUID (MPMSXL, Quantum Design, USA) magnetometer, applying a magnetic field up to 5 T. Saturation magnetization (MS) was calculated with a 5% uncertainty. Magnetic particle spectroscopy (MPS) measured MNP response under a sinusoidal field at 37 °C, with parameters A3* and A5/A3 providing insights into size, anisotropy, and aggregation with a 25 mT field at 25 kHz. AC-magnetometry assessed hyperthermia potential with 40 µL MNP samples at 100 kHz and 24 kA/m, calculating specific and intrinsic loss power (SLP and ILP) from hysteresis loop area, with a 3% uncertainty in triplicate measurements [3].

III. Results and discussion

Iron oxide nanoparticles (24.9 nm ± 5.3 nm) were synthesized and coated with Na-caseinate (size increase ∼4 nm). The coated MNPs showed improved stability in salt solutions, successful drug encapsulation, and biocompatibility with uptake in SCL-1 cells.

All MNP systems (MNP, MNP+Na-Cas, MNP+Na-Cas (crosslinked)) showed a saturation magnetization (MS) of about 109(5) A·m²/kg(Fe) (Fig.1), similar to bulk magnetite, indicating high crystallinity.

This is higher than previous studies reporting MS values of 44.86–60 A·m²/kg(Fe). The consistent MS values suggest casein coating and crosslinking do not affect magnetic behavior, though slightly reduced magnetization at lower fields may result from weaker interactions in coated systems. This suggests the MNPs are well-suited for imaging and diagnostic applications. Shown in Fig.2, MPS revealed a slight decrease in A3* of 15% for casein-coated MNPs (20.79 to 18.27 A·m²/kg(Fe)), still significantly higher than Resovist (8.67 A·m²/kg(Fe)).

Minimal changes of 2% in A5/A3 indicate the coating has little effect on MPI performance. The coating also reduced the impact of immobilization on A3* and A5/A3, making casein-coated MNPs suitable for MPI in biological environments. AC-magnetometry showed that uncoated MNPs had a high ILP (9.29 ± 0.28 nH·m²/kg(Fe)), while casein-coated MNPs had 7.18 ± 0.22 nH·m²/kg(Fe), both superior to Resovist. These ILP values suggest strong heating potential for hyperthermia, allowing lower MNP concentrations for effective treatment. Casein-coated MNPs thus show strong potential for both hyperthermia and MPI applications.

IV. Conclusion

Casein-coated MNPs show excellent magnetic behavior with minimal impact from the casein layer, maintaining stability in the presence of salts and in immobilized states. The system's non-toxicity, stability, and high magnetic performance make it a promising theranostic agent, with future studies focusing on drug transport and particle degradation for clinical applications.

Acknowledgments

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Author's statement

Authors state no conflict of interest. The findings reported here are the highlights from our recently published paper (Ref. 3: 10.1039/D4RA02626H).

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