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RESEARCH PAPER

Application of Iron Oxide Nanoparticles as MRI Contrast Enhancers: A study in Rabbits

Bektenov Nessipkhan [1]*, Haider Falih Shamikh Al-Saedi [2], Mustafa Jassim Al-saray [3], Hamza Hameed Jasim [4], Ruaa Sattar [5], Batool Ali Ahmed [6], Ammar Kadhim Wabdan [7], Mohamad Adnan Alyas [8], Shakhnoza Mavlyanova [9], A.M. Khurramov [10], Zokirov Muzaffar [11] *

[1] *Institute chemikal science, KazNPU, 050010, Almaty, Republic of Kazakhstan*

[2] *Faculty of pharmacy, Department of pharmaceutics, University of Al-Ameed, Iraq*

[3] *Al-Manara College For Medical Sciences, (Maysan), Iraq*

[4] *Department of Medical Instrumentation Engineering Techniques, Imam Ja'afar Al-Sadiq University, Iraq*

[5] *Department of Medical Instrumentation Engineering Techniques, Al-Hadi University College, Baghdad, Iraq*

[6] *Department of medical engineering, Al-Nisour University College, Baghdad, Iraq*

[7] *Collage of Pharmacy, National University of Science and Technology, Dhi Qar, 64001, Iraq*

[8] *Department of Medical Instrumentation Engineering Techniques, Al-Zahrawi University, Iraq*

[9] *Republican Specialized Scientific and Practical Medical Center for Dermatovenerology and Cosmetology, Ministry of Health of the Republic of Uzbekistan, Uzbekistan*

[10] *International School of Finance and Technology, Tashkent, Uzbekistan*

[11] *Fergana Medical Institute of Public Health, Uzbekistan*

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ABSTRACT

Iron oxide nanoparticles (IONPs) have been identified as a promising class of compounds that can enhance contrast in MRI (magnetic resonance imaging) scans due to their superparamagnetic properties. This study evaluates the efficacy of dextran-coated IONPs as T2 contrast agents for MRI in a rabbit model. IONPs were prepared through a co-precipitation process and subsequently coated with a layer of dextran. The nanoparticles underwent characterization using techniques such as TEM (transmission electron microscopy), vibrating sample magnetometry (VSM), and XRD (X-ray diffraction). New Zealand White rabbits (n=6) were used for in vivo MRI studies. IONPs (10 mg Fe/kg) were administered intravenously, and MRI scans (T1- and T2-weighted) were taken at baseline and at various intervals (1, 4, and 24 h) after IONP administration. Signal intensity changes and contrast enhancement were analyzed in the liver, spleen, and kidneys. The IONPs exhibited an average size of 15 ± 3 nm, an inverse spinel crystal structure, and displayed magnetic characteristics indicative of superparamagnetism with a 65 ± 5 emu/g saturation magnetization. MRI scans revealed significant signal intensity changes and contrast enhancement in the liver, spleen, and kidneys after IONP administration. The maximum contrast enhancement was observed at 4 h post-injection, with a 60 ± 8% reduction in T2 signal intensity in the liver and a 45 ± 7% reduction in the spleen. The contrast enhancement persisted up to 24 h in the liver and spleen, while the kidneys showed lower contrast enhancement and rapid clearance of the nanoparticles. In conclusion, dextran-coated IONPs demonstrated effective T2 contrast enhancement in MRI of rabbits, particularly in the liver and spleen. The prolonged retention of the nanoparticles in these organs makes them suitable for long-term imaging studies. However, the rapid clearance from the kidneys may limit their application for kidney imaging.

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* *Corresponding Author Email: muzaffarzokirov91@mail.ru*

INTRODUCTION

MRI (Magnetic resonance imaging) has become a crucial diagnostic tool in the field of medical imaging, providing high-resolution images of soft tissues without the use of ionizing radiation. However, the inherent contrast in MRI may not always be sufficient for accurate diagnosis and monitoring of certain pathologies. Contrast agents have been developed to enhance the contrast between different tissues and improve the sensitivity and specificity of MRI [1,2]. Among various contrast agents, Iron oxide nanoparticles (IONPs) have attracted considerable interest owing to their distinctive magnetic characteristics and compatibility with biological systems [3,4].

IONPs are typically composed of maghemite (γ-Fe2O3) or magnetite (Fe3O4) and show superparamagnetic behavior, which means they become magnetized only under the effect of a magnetic field generated externally [5]. When exposed to the magnetic field of an MRI scanner, IONPs create local magnetic field inhomogeneities, leading to a shortening of T2* and T2 relaxation times and a decrease in signal intensity on T2-weighted images [6]. This phenomenon is known as negative contrast enhancement and is particularly useful for imaging organs with high endogenous iron content, such as the liver and spleen [7–9].

The surface modification and synthesis of IONPs are vital in shaping the outcome of their physical, chemical, and biological properties [10]. Several procedures have been implemented for the synthesis of IONPs, like co-precipitation, thermal decomposition, and microemulsion techniques [11,12]. Co-precipitation is a simple and widely used method that involves the simultaneous precipitation of Fe2+ and Fe3+ ions in an aqueous solution under alkaline conditions [13]. To improve their colloidal stability and biocompatibility, IONPs are often coated with polymers, such as dextran, poly(lactic-co-glycolic acid) (PLGA), or polyethylene glycol (PEG) [14–16].

The efficacy of IONPs as contrast agents for MRI has been demonstrated in various preclinical and clinical studies. IONPs have been used for the detection and characterization of liver lesions [17], lymph node metastases [18], and inflammatory diseases [19]. However, the performance of IONPs as contrast agents may vary depending on their size, composition, and surface coating [20]. Therefore, it is essential to evaluate the contrast enhancement properties of IONPs in different animal models to optimize their formulation and understand their in vivo behavior.

Rabbits have been widely used as animal models for MRI studies due to their suitable size and similarities in anatomy and physiology to humans [21]. The use of rabbits allows for the assessment of the biodistribution, pharmacokinetics, and contrast enhancement properties of IONPs in a relevant preclinical setting. Furthermore, the rabbit model enables the evaluation of the safety and potential toxicity of IONPs, which is crucial for their translation to clinical applications [22].

The core purpose of this research endeavor is to assess the effectiveness of dextran-coated IONPs as contrast agents for MRI in a rabbit model. The IONPs will be synthesized by a co-precipitation method and characterized using various techniques, including TEM (transmission electron microscopy), vibrating sample magnetometry (VSM), and XRD (X-ray diffraction). The contrast enhancement properties of the IONPs will be assessed by performing MRI scans (T1- and T2-weighted) before and at different time points after intravenous administration of the nanoparticles. Signal intensity and contrast enhancement will be analyzed in various organs, particularly the liver, spleen, and kidneys. The retention and clearance of the IONPs will also be evaluated to determine their suitability for long-term imaging studies. The data obtained from this investigation will reveal the capabilities of IONPs as contrast agents for MRI in preclinical and clinical applications.

MATERIALS AND METHODS

Chemicals

The chemicals used in this study, including ferrous chloride tetrahydrate (99% FeCl2·4H2O), ferric chloride hexahydrate (97% FeCl3·6H2O), ammonium hydroxide (28-30% NH4OH), and dextran (70,000 MW), were obtained from Sigma-Aldrich. The rest of substances used in the study were of analytical grade and did not require additional purification. The experiments were conducted utilizing deionized water.

Animals

The animal facility at the University of Baghdad, Iraq, provided six adult male New Zealand White rabbits (2.5−4.0 kg). The rabbits were kept in separate cages under regulated conditions, including a temperature of 22 ± 2°C, humidity of 50

± 10%, and a 12-hour light/dark cycle. Prior to the commencement of the experiments, the rabbits underwent a one-week acclimatization period. The Institutional Animal Care and Use Committee (IACUC) at the University of Baghdad reviewed and approved all animal procedures, ensuring that they adhered to the established guidelines for the care and use of laboratory animals.

Synthesis of IONPs

IONPs were synthesized by a co-precipitation method as described by Javed et al. [20] with slight modifications. Briefly, FeCl2·4H2O (3.98 g, 20 mmol) and FeCl3·6H2O (10.8 g, 40 mmol) were dissolved in 100 mL of deionized water under vigorous stirring and nitrogen atmosphere. The solution was heated to 80°C, and then 50 mL of NH4OH (28-30%) was introduced gradually, drop by drop. For a duration of 1 hour, the reaction mixture was kept at 80°C, with constant stirring and under a nitrogen atmosphere. The formed black precipitate was collected through magnetic decantation and underwent several washing cycles with deionized water until a neutral pH was achieved. The synthesized IONPs were put through a drying procedure in a vacuum oven maintained at 60°C for a duration of 12 h.

Dextran coating of IONPs

Dextran-coated IONPs were prepared by a method adapted from Predoi et al. [23]. 100 mL of deionized water was utilized to disperse 1 g of IONPs, which were then subjected to sonication for a period of 30 minutes. Dextran (5 g) was dissolved in 50 mL of deionized water and introduced to the IONP dispersion. At room temperature, it was stirred for 2 h and then heated for 1 h to reach 80°C under continuous stirring. The dextran-coated IONPs were collected by magnetic decantation, rinsed with deionized water and then underwent drying in a vacuum oven for a period of 12 h at 60°C.

Characterization of IONPs

The morphology and size of the IONPs were characterized by TEM. The preparation of samples for TEM involved dispersing a small amount of IONPs in ethanol and dropping the suspension onto a carbon-coated copper grid. XRD was employed to investigate the crystal structure of the IONPs. The magnetic properties of the IONPs were evaluated using a VSM at room temperature.

In vivo MRI studies

Animal preparation

An intramuscular injection consisting of xylazine (5 mg/kg) and ketamine (35 mg/kg) was used to produce a state of anesthesia in the rabbits. A 24-gauge catheter was inserted into the marginal ear vein for the administration of IONPs. The animals were placed in a supine position and secured on a custom-made MRI-compatible animal bed.

IONP administration and MRI data acquisition

Baseline MRI scans (T1- and T2-weighted) were acquired before the administration of IONPs. Dextran-coated IONPs (10 mg Fe/kg) were administered intravenously through the catheter, followed by a saline flush. MRI scans were repeated at 1-, 4-, and 24-hours post-injection.

Image analysis

MRI images were analyzed using the Osirix Lite software. Regions of interest (ROIs) were drawn manually on the liver, spleen, and kidneys on T1- and T2-weighted images at each time point. Signal intensity (SI) measurements were obtained from the ROIs and normalized to the SI of the paraspinal muscles. The percentage of signal intensity change (ΔSIR) was calculated using the:

$$\Delta\mathrm{SIR}(\%) = [\frac{\mathrm{SI_{post}} - \mathrm{SI_{pre}}}{\mathrm{SI_{pre}}}] \times 100$$

Where SI_{pre} and SI_{post} represent the SI before and after IONP administration, respectively.

Statistical analysis

The results were presented as mean ± standard deviation (SD), and GraphPad Prism software was employed for conducting statistical analysis. One-way analysis of variance (ANOVA) was employed to assess the differences in ΔSIR across various time points, with Tukey's post hoc test used for further comparisons. Statistical significance was set at a p-value < 0.05.

RESULTS AND DISCUSSION

Characterization of IONPs

Size and morphology

TEM was used to investigate the size and morphological features of the IONPs obtained from the synthesis process. The TEM images (Fig. 1) revealed that the IONPs had a narrow size

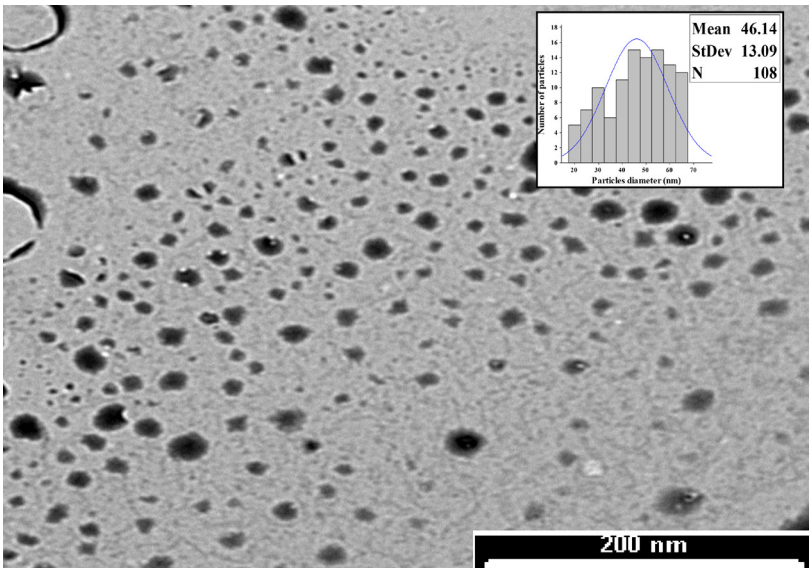

Fig 1. TEM images of dextran-coated IONPs showing their spherical shape and narrow size distribution

distribution and were spherical in shape.

The average diameter of the IONPs was found to be 15 ± 3 nm (Table 1). The uniform size and shape of the IONPs can be attributed to the controlled co-precipitation synthesis method and the stabilizing effect of the dextran coating. The small size of the IONPs is advantageous for their use as contrast agents, as it allows for longer circulation times and better biodistribution [24].

Crystal structure

The crystal structure of the IONPs was investigated by XRD. It showed characteristic peaks at 2θ = 30.2°, 35.5°, 43.2°, 57.0°, and 62.7°,

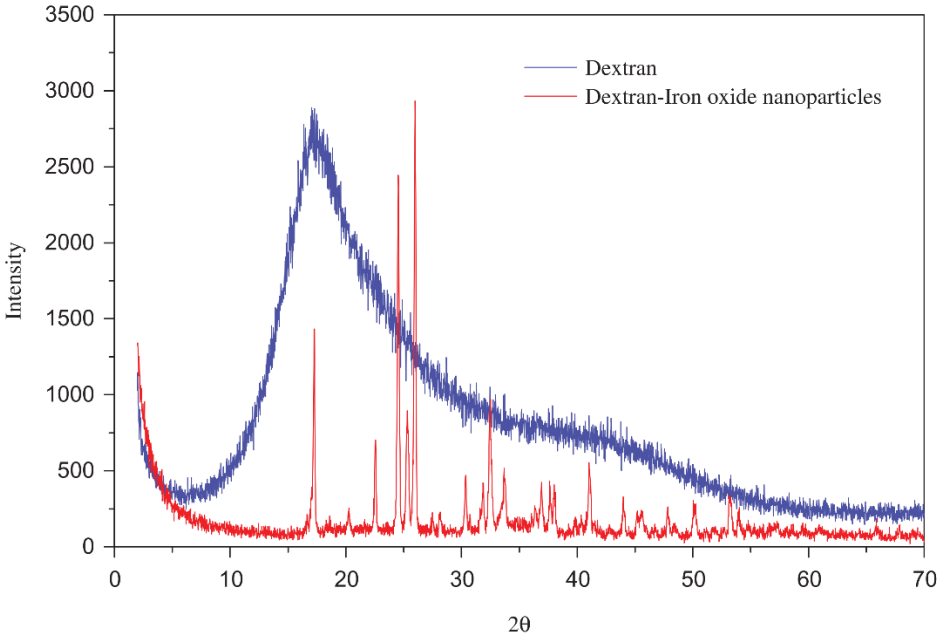

Fig. 2. XRD pattern of dextran-coated IONPs confirming their inverse spinel crystal structure.

Table 1. Characterization of IONPs.

Parameter	Value
Average diameter (nm)	15 ± 3
Crystal structure	Inverse spinel
Saturation magnetization (emu/g)	65 ± 5

Table 2. Percentage of signal intensity change (ΔSIR) in the liver.

Time point	ΔSIR (%)
1 h	-35 ± 5
4 h	-60 ± 8
24 h	-35 ± 6

corresponding to the (220), (311), (400), (511), and (440) planes of the inverse spinel structure of magnetite (Fe_3O_4) (Fig. 2). The broad nature of the peaks indicated the nanocrystalline nature of the IONPs. The average crystallite size calculated using the Scherrer equation was found to be 12 ± 2 nm, aligning well with the findings from TEM analysis.

Magnetic properties

The magnetic characteristics of the IONPs were evaluated by VSM at room temperature. The magnetization curve (Fig. 3) showed that the IONPs exhibited superparamagnetic behavior, with negligible coercivity and remanence.

The saturation magnetization (Ms) of the IONPs was found to be 65 ± 5 emu/g (Table 1). The high Ms value can be attributed to the pure phase of magnetite and the absence of surface spin disorder [25]. The superparamagnetic nature and high Ms of the IONPs enable their application as T2 contrast agents in MRI.

In vivo MRI studies

Contrast enhancement in the liver

The contrast-enhancing characteristics of the IONPs were evaluated in the liver of rabbits using T2-weighted MRI. The signal intensity (SI) of the liver decreased significantly after the administration of IONPs, indicating a negative contrast enhancement effect. The percentage of signal intensity change (ΔSIR) in the liver at different time points is summarized in Table 2. The maximum contrast enhancement was observed at 4 h post-injection, with a ΔSIR of -60 ± 8%. The

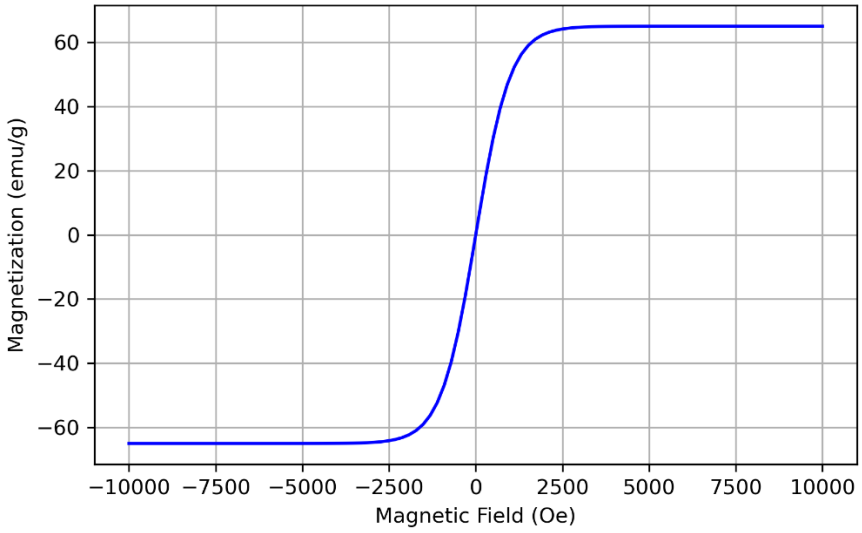

Fig. 3. Magnetization curve of dextran-coated IONPs measured by VSM at room temperature.

Table 3. Percentage of signal intensity change (ΔSIR) in the spleen.

Time point	ΔSIR (%)
1 h	-30 ± 6
4 h	-45 ± 7
24 h	-25 ± 5

Table 4. Percentage of signal intensity change (ΔSIR) in the kidneys

Time point	ΔSIR (%)
1 h	-20 ± 4
4 h	-15 ± 3
24 h	-10 ± 3

contrast enhancement persisted up to 24 h post-injection, with a ΔSIR of -35 ± 6%. The prolonged retention of the IONPs in the liver can be attributed to the uptake by the reticuloendothelial system (RES), particularly the Kupffer cells [26].

Contrast enhancement in the spleen

The contrast enhancement effect of the IONPs was also observed in the spleen of rabbits. The SI of the spleen decreased after the administration of IONPs, similar to the liver. The ΔSIR in the spleen at different time points is presented in Table 3. The maximum contrast enhancement in the spleen was observed at 4 h post-injection, with a ΔSIR of -45 ± 7%. The contrast enhancement in the spleen persisted up to 24 h post-injection, with a ΔSIR of -25 ± 5%. The prolonged retention of the IONPs in the spleen can be attributed to the uptake by the macrophages in the red pulp [27].

Contrast enhancement in the kidneys

The contrast enhancement effect of the IONPs in the kidneys was less pronounced compared to the liver and spleen. The SI of the kidneys decreased slightly after the administration of IONPs. The ΔSIR in the kidneys at different time points is shown in Table 4. The maximum contrast enhancement in the kidneys was observed at 1 h post-injection, with a ΔSIR of -20 ± 4%. The contrast enhancement in the kidneys decreased over time, with a ΔSIR of -10 ± 3% at 24 h post-injection. The lower contrast enhancement in the kidneys can be attributed to the rapid clearance of the IONPs from the kidneys compared to the liver and spleen [28].

The results of the in vivo MRI studies demonstrate the potential of the dextran-coated IONPs as effective T2 contrast agents. The negative contrast enhancement effect of the IONPs was most pronounced in the liver and spleen, which can be attributed to the high accumulation of the nanoparticles in these organs due to their uptake by the RES [29]. The prolonged retention of the IONPs in the liver and spleen makes them suitable for long-term imaging studies and the detection of liver and spleen pathologies [30].

The lower contrast enhancement observed in the kidneys suggests that the IONPs are not efficiently taken up by the kidney cells and are rapidly cleared from the kidneys [31]. This can be advantageous for reducing the potential toxicity of the IONPs, as the nanoparticles are not retained in the kidneys for extended periods [10]. However, the rapid clearance of the IONPs from the kidneys may limit their application for the detection of kidney pathologies.

The contrast enhancement properties of the IONPs can be further optimized by modifying their size, composition, and surface coating [22]. Smaller IONPs (< 10 nm) have been reported to exhibit higher relaxivity and better contrast enhancement compared to larger nanoparticles [28]. The composition of the IONPs can also be modified by doping with other metal ions, such as manganese or cobalt, to enhance their magnetic properties and contrast enhancement effects [12]. The surface coating of the IONPs can be engineered to improve their colloidal stability, biocompatibility, and targeting efficiency [8].

Although this research offers important findings in the potential of dextran-coated IONPs as MRI contrast agents, several limitations should be acknowledged. The first issue is the relatively small sample size of rabbits used in the in vivo MRI studies was relatively small (n=6), which may limit the statistical power and generalizability of the findings. Second, the study focused on the

contrast enhancement properties of the IONPs in healthy rabbits, and the performance of the nanoparticles in disease models or pathological conditions was not evaluated. Third, the long-term safety and toxicity of the IONPs were not assessed in this study, which is crucial for their potential clinical translation.

CONCLUSION

In this study, dextran-coated IONPs were successfully synthesized and evaluated as T2 contrast agents for MRI in a rabbit model. The IONPs exhibited desirable properties, including a spherical shape, narrow size distribution (average diameter of 15 ± 3 nm), inverse spinel crystal structure, and superparamagnetic behavior with high saturation magnetization (65 ± 5 emu/g). These characteristics make them suitable for use as MRI contrast agents. The in vivo MRI studies demonstrated the effective contrast enhancement properties of the IONPs in the liver, spleen, and kidneys of rabbits. The maximum contrast enhancement was observed at 4 h post-injection in the liver (ΔSIR = -60 ± 8%) and spleen (ΔSIR = -45 ± 7%), with prolonged retention up to 24 h. The lower contrast enhancement in the kidneys (ΔSIR = -20 ± 4% at 1 h) suggests rapid clearance of the nanoparticles from this organ. The prolonged retention of the IONPs in the liver and spleen can be attributed to their uptake by the reticuloendothelial system, making them suitable for long-term imaging studies and the detection of pathologies in these organs. However, the rapid clearance from the kidneys may limit their application for kidney imaging. In conclusion, the dextran-coated IONPs demonstrate great potential as effective T2 contrast agents for MRI, particularly for the liver and spleen. Further studies are needed to optimize the IONP formulation, assess their biodistribution and clearance, and evaluate their safety profile for potential clinical translation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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