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The effects of synthesis method on the physical and chemical properties of dextran coated iron oxide nanoparticles

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HIGHLIGHTS

- IONPs coated with dextran were synthesized via co-precipitation method variations.
- The synthesis method greatly affected the physical and chemical properties.
- The simultaneous semi-two-step method was the most reproducible method.
- The two-step method resulted in the greatest variation between batches.
- The effects of solution viscosity were studied for the one-step method.

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ABSTRACT

Iron oxide nanoparticles coated with dextran were synthesized via four variations on the co-precipitation method. The methods ranged from *in situ* formation of the nanoparticles within the dextran solution to the adsorption of dextran to the nanoparticle surface following nucleation and extensive washing. The timing of the addition of dextran into the reaction mixture was found to greatly influence the physical and chemical properties of the magnetic nanoparticles. Batches of dextran coated iron oxide nanoparticles were synthesized by each method in triplicate, and the nanoparticles were further crosslinked with epichlorohydrin. The properties of the nanoparticles such as size, percentage of dextran coating, stability in solution, crystallinity, and magnetic properties were evaluated. The simultaneous semi-two-step method injected the reducing agent and the dextran solution into the reaction vessel at the same time. This method resulted in the greatest batch-to-batch reproducibility of nanoparticle properties and the least variation in nanoparticles synthesized in the same batch. The two-step method resulted in the greatest variation of the characteristics examined between batches. The one-step method was synthesized with both five grams and one gram of dextran to investigate the effects of solution viscosity on the resulting nanoparticle characteristics. The one-step method with five grams of dextran resulted in nanoparticles with significantly smaller crystal sizes (5.4 ± 1.9 nm) and lower specific adsorption rate (SAR) values (138.4 ± 13.6 W/g) in an alternating magnetic field (58 kA/m, 292 kHz). However, this method resulted in nanoparticles that were very stable in PBS over 12 h, which is most likely due to the greater dextran coating (60.0 ± 2.7 weight percent). For comparison, the simultaneous semi-two-step method generated nanoparticles 179.2 ± 18.3 nm in diameter (crystal size 12.1 ± 0.2 nm) containing 18.3 ± 1.2 weight percent dextran with a SAR value of 321.1 ± 137.3 W/g.

1. Introduction

Nanoparticle research has been driven by the need for new technological applications in data storage, biomedical sciences, drug delivery, and therapeutics. Iron oxide nanoparticles represent a class of materials with such applications and are very promising due to their potential biocompatibility and magnetic properties which can be used for magnetic resonance imaging, magnetically

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mediated hyperthermia, etc. [1,2]. The magnetic differences of iron oxide nanoparticles compared to the bulk material are a consequence of inter and intra particle interactions. Additionally, when the iron oxide nanoparticles are of a single domain, they exhibit superparamagnetism by which they do not retain magnetization in the absence of an externally applied magnetic field [3].

While the increased surface-to-volume ratio is an attractive property of superparamagnetic iron oxide nanoparticles, it also leads to considerable difficulty as a result of the tendency of nanoparticles to aggregate to reduce their surface energy by forming strong magnetic dipole interactions between the particles [4]. Monodispersed particles with high magnetic saturation are required for many biological applications, so it is often of interest to functionalize the nanoparticles with a coating layer to prevent agglomeration [5]. The coating layer can also be designed to increase the circulation time and the biocompatibility of the nanoparticles for use as MRI contrast agents and magnetically mediated hyperthermia [6,7]. Dextran is a biocompatible long chain hydrophilic polymer composed of glucose with mostly α-1, 6 glycoside linkages [8] that strongly physisorb to magnetite nanoparticles in alkaline solutions via non-covalent interactions of the abundant hydroxyl groups resulting in enmeshed nanoparticle cores [3]. The hydroxyl groups of dextran can then be easily crosslinked and functionalized with primary amines to attach various targeting ligands, peptides, or probes [9–12]. Functionalization with primary amines throughout the nanosctructure allows for increased loading capacity and the potential for attachment of multiple targeting ligands, imaging agents or therapeutics into one system [13].

Iron oxide nanoparticles can be synthesized by various methods including co-precipitation [14–16], microemulsion [17], thermal decomposition [12,18–22], and mechanical synthesis [23,24]. The co-precipitation method has traditionally been the most common method and is the primary method by which clinically approved iron oxide nanoparticles are synthesized [25]. Co-precipitation requires the reaction to be performed in an inert atmosphere to prevent oxidation of the Fe^{2+} ions and oxidation of magnetite nanoparticles to maghemite. The surface of magnetite nanoparticles will oxidize to maghemite in the presence of oxygen which reduces the magnetic saturation of the material [26]. The process of co-precipitation involves initial nucleation followed by slow growth as the solutes diffuse to the surface of the crystal [4]. Within the co-precipitation method, there are various procedures that alter parameters of the reaction in order to tune the properties of the iron oxide nanoparticles produced. Variables such as pH, temperature, reaction time, and iron ion ratios have been examined to determine their effects on the size, stability, and heating properties of the nanoparticles. Vayssieres et al. [27] varied the pH of the reaction solution between 8.5 and 12 and found that the resulting iron oxide nanoparticles became smaller as the solution increased in alkalinity. It was also determined that a minimum pH of 10–11 is required for the nanoparticle size to remain stable over time. Murbe et al. [28] addressed the effect of reaction temperature on the physical and chemical properties of iron oxide nanoparticles showing that as the temperature at which initial nucleation occurred increased from 25 to 70 °C, the nanoparticle size also increased from 16 to 39 nm. Additionally, the magnetic saturation of the nanoparticles increased from 76 to 88 emu/g. Frimpong et al. [16] addressed the effects of reaction temperature and staged reactions on the magnetic properties of citrate capped iron oxide nanoparticles, and they also found that as temperature increased, the nanoparticle crystal size also increased. The saturation magnetization was also influenced by the reaction temperature and method as the one-step method resulted in nanoparticles with a lower magnetic saturation value and decreased heating capabilities than the two-step reactions. A significant amount of research has been completed on dextran coated iron oxide nanoparticles, specifically on varying the molecular weight of the dextran. Xu et al. [29] formed iron oxide nanoparticles in the presence of dextran with a molecular weight of 20 or 40 kDa. The 40 kDa dextran resulted in a viscous reaction solution, so the 20 kDa nanoparticles were preferred. However, the magnetic saturation of the nanoparticles was lower than expected due to significant agglomeration of the nanoparticles and a wide range of hydrodynamic radii. Although the effects of reaction temperature, time, pH, and dextran molecular weight have been analyzed, the time and method of dextran addition into the reaction solution has not yet been evaluated. Therefore, this manuscript seeks to determine the effects of the timely addition of dextran to the reaction mixture on the physical and chemical properties of the dextran coated iron oxide nanoparticles.

It is desired to understand the effects of dextran on the properties of iron oxide nanoparticles in order to develop a protocol that results in consistent and desired properties. As depicted in Fig. 1, four co-precipitation methods were developed to synthesize dextran coated iron oxide nanoparticles which were further crosslinked with epichlorohydrin to increase the thermodynamic stability of the dextran on the surface of the nanoparticles [30]. The methods varied by the time of dextran addition to the reaction mixture: from *in situ* formation of the iron oxide nanoparticles to formation followed by extensive washing prior to dextran adsorption. Three batches of nanoparticles were synthesized via each method in order to address the variability within a single method as well as the differences between the methods. All other parameters such as pH, reaction temperature, and dextran molecular weight were kept constant among the methods. After synthesis, both the dextran coated and epichlorohydrin crosslinked nanoparticles were characterized for size, dextran weight percent, stability, crystallinity, and heating ability in the presence of an alternating magnetic field. Each of these properties is important to evaluate prior to *in vivo* studies should the nanoparticles be used for biological applications. It is also important to develop protocols for iron oxide nanoparticle synthesis that result in consistent properties of the nanoparticles such as desired size, stability in solution, crystallinity to allow for heating in an AMF as well as image contrast, and dextran coating to increase circulation and biocompatibility. This article addresses the development of a synthesis method that results in consistent and desirable properties of iron oxide nanoparticles.

2. Materials and methods

2.1. Materials

Iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), iron (II) chloride ($FeCl_2 \cdot 4H_2O$), 9–11 kDa dextran, epichlorohydrin (ECH) were obtained from Sigma Aldrich (St. Louis, MO). Ammonium hydroxide (NH_4OH) was purchased from EMD Chemicals (Gibbstown, NJ). Phosphate buffered saline solution (PBS) (10×) was purchased from EMD Millipore (Billerica, MA). All materials were used as received.

2.2. Dextran coated iron oxide nanoparticle synthesis via two-step method

A modified one-pot co-precipitation method [16] was used to prepare dextran coated IONPs. $FeCl_3 \cdot 6H_2O$ and $FeCl_2.4H_2O$ were combined in a 2:1 M ratio (2.2 g and 0.8 g, respectively) and dissolved in 40 mL deionized (DI) water and sealed in a three-neck flask under vigorous stirring and an inert nitrogen environment. 5 g of dextran was solubilized in 20 mL of DI water. The solution was heated to 85 °C at which 5 mL of NH_4OH was added dropwise to the

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