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On the suitability of nanocrystalline ferrites as a magnetic carrier for drug delivery: Functionalization, conjugation and drug release kinetics

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Abstract

Superparamagnetic nickel ferrite nanoparticles functionalized with polyvinyl alcohol, polyethylene oxide and polymethacrylic acid (PMAA) polymers and subsequently conjugated with doxorubicin anti-cancer drug are studied for their use as a magnetic carrier for drug delivery. Fourier transform infrared spectroscopy enabled examination of the ability of the nanoparticles to be functionalized with polymers and conjugated with doxorubicin drug. The functionalized polymer-coated nanocrystalline nickel ferrites retain the magnetic characteristics of non-functionalized nanocrystalline nickel ferrites (superparamagnetism, absence of hysteresis, remanence and coercivity at room temperature), encouraging their application as a magnetic carrier for drug delivery. The PMAA-coated nanoferrites are demonstrated as being a potentially superior magnetically targeted drug carrier based on FTIR results and drug release kinetics in the absence and presence of an external magnetic field.

Keywords: Superparamagnetic nanocrystalline ferrites; Functionalization; Conjugation; Drug delivery

1. Introduction

There is a strong interest in the potential utilization of magnetic nanoparticles in biomedical and diagnostic applications, including magnetic resonance imaging, hyperthermia tumor treatment, separation of DNA, cell separation and site-specific gene and drug delivery [1–8]. The magnetic nanoparticles in reality could bear on their surface or in bulk a pharmaceutical drug that could be appropriately directed to the target organ and released. These applications require that the nanoparticles be characterized by a combination of properties, namely, adequate magnetic saturation, biocompatibility [9] and interactive functions at the surface. Superparamagnetic nanocrystalline ferrites are potential materials for biomedical applications since they do not retain magnetization before and after exposure to an external magnetic field, reducing the possibility of particle aggregation. Additionally, an external magnetic field supplies energy and helps the magnetic moments in overcoming the energy barrier. This energy is dissipated as heat when the particle moments relax to their equilibrium orientation position and leading to heating of the particle ensemble [10], an aspect beneficial for the treatment of hyperthermia [11]. Furthermore, the superparamagnetic ferrite nanoparticles exhibit superior chemical stability (oxidation resistance) and biocompatibility compared with metallic magnetic materials with higher magnetization [12].

A potential and primary advantage of using magnetic nanoparticles is the use of localized magnetic field gradients to attract the particles to a selected site and retain them at the site until the completion of therapy, subsequently followed by their removal. The particle suspension may be

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injected intravenously, and then blood circulation would be used to transport the particles to the region of interest for treatment. This route necessitates that the particles do not aggregate, which may block their spread or distribution. Thus, the primary requirement is that of stable and well-dispersed particles in the nanometer size range. Once the particles are injected into the bloodstream they are rapidly coated by the plasma proteins, a process known as opsonization [13]. Generally, opsonization renders the particles recognizable by the body's major defense system, the reticulo-endothelial system (RES). The RES is a diffuse system of specialized cells that are phagocytic associated with the connective tissue framework of the liver, spleen and lymph nodes [14,15]. The body's RES, mainly the macrophage cells in the liver, usually take up these nanoparticles due to their hydrophobic surface. The macrophage cells of the liver, and to a lesser extent the macrophages of the spleen and circulation, play a critical role in the removal of opsonized particles. Thus, the usage of magnetic nanoparticles in vivo requires surface modification to ensure particles are non-toxic, biocompatible and stable to the RES.

Particles with a hydrophobic surface are efficiently coated with plasma components (hydrophobic surface), leading to hydrophobic–hydrophobic interaction, which encourages their rapid removal from the circulation. However, particles that are more hydrophilic resist the plasma protein coating process [16]. This characteristic is advantageous in the synthesis of superparamagnetic nanoparticles for drug delivery, where the superparamagnetic nanoparticles are coated with a layer of hydrophilic polymer chain. After coating the nanoparticles, they do not have a free hydrophobic surface and the opsonization process is inhibited. The polymer coatings that can be considered are dextran, polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), oleic acid, polymethacrylic acid (PMAA) and polyoxamines. The role of the dense brushes of polymers is to inhibit opsonization, permitting longer circulation times [17–19]. Another approach to avoid the RES is to reduce the particles size.

In the absence of any surface coating, superparamagnetic nanoparticles have a large surface area to volume ratio and may have the tendency to agglomerate and adsorb plasma proteins. On agglomeration or on being covered with adsorbed plasma proteins, they are rapidly cleared by macrophages in the reticulo-endothelial system before they arrive the target cells [20]. A possible method to increase the circulation time of nanoparticles in the bloodstream is to utilize the above approach of coating the nanoparticles with hydrophilic polymer to minimize or eliminate the protein adsorption [21]. The polymer coating provides stability to the nanoparticles in solution and also helps in binding the drug to the surface of nanoparticles for varied biomedical applications. The nature of the surface coating and its subsequent geometric arrangement on the nanoparticles determines the overall size of the colloid and plays a significant role in biokinetics and biodistribution of nanoparticles in the body. However, the nature of coating or derivatization depends on the application if it is aimed at the inflammation response or anti-cancer agents. In addition to the above aspects, the functional groups of the polymer on the nanoparticle surface merit consideration for drug delivery applications because they are used as further binding sites for drugs such as diagnostic or pharmacologically active substances.

In summary, the application of functionalized superparamagnetic nanoparticles in drug targeting and delivery requires that the entities have the potential to strongly interact with cells and be delivered inside cells. The objective of the present work is to describe the suitability of nanocrystalline ferrites as a magnetic carrier for drug delivery. The aspects that are important to enable the use of nanoparticles for biomedical applications, notably, functionalization, conjugation and drug release behavior, are discussed.

2. Experimental

2.1. Synthesis of functionalized $NiFe_2O_4$ nanoparticles

Nanocrystalline nickel ferrites ($NiFe_2O_4$) were synthesized by the reverse micelle method and the detailed procedure is described elsewhere [22,23]. In brief, two microemulsion systems were firstly prepared in this method. Microemulsion system I consisted of 2 ml of 30% NH_4OH + 2.4 ml of water + 66 ml of 0.50 M AOT-iso-octane, sonicated for 10 min. Microemulsion system II, containing 0.384 g of $FeSO_4 \cdot 7H_2O$ and 0.192 g $NiSO_4 \cdot 6H_2O$ dissolved in 8 ml of water + 66 ml of AOT-iso-octane, was sonicated for 10 min. The two microemulsions were subjected to rapid mechanical stirring for 75 min. The metal hydroxides are precipitated within the water pools of reverse micelles and oxidized to ferrite. Then the resulting microemulsion was washed several times with the 50% mixture methanol and acetone. The resulting liquid was separated and the ferrite product centrifuged. The resulting solid product was washed with methanol and distilled water, and dried in an oven at 90 °C for 30 min. The nanocrystalline nickel ferrites obtained by the above method has a narrow size range [22,23].

The surface property of the magnetic nanoparticles is an important key characteristic because the surface is modified with biocompatible hydrophilic polymer for use as a drug-carrying vehicle. The nanocrystalline ferrites synthesized by the reverse micelle process were dialyzed for 2 days with 0.01 M nitric acid and stored at 4 °C for subsequent functionalization with hydrophilic polymer.

2.1.1. Polyvinyl alcohol and polyethylene oxide functionalized nanocrystalline nickel ferrites

To obtain nickel ferrite nanoparticles coated with PVA or PEO, the requisite amount of dialyzed nickel ferrite nanoparticles were mixed with PVA or PEO solution (requisite amount of PVA or PEO was dissolved in 40 ml

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