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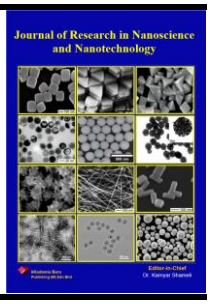

Magnetic Nanoparticles In Hyperthermia Therapy: A Mini-Review

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ABSTRACT

The activation of MNPs for hyperthermia therapy via an external alternating magnetic field is an interesting method in targeted cancer therapy. This mini-review explains new developments and implications of magnetic nanofluids mediated magnetic hyperthermia for their potential use in future clinical settings. The external alternating magnetic field generates heat in the tumor area to eliminate cancer cells. Depending on the tumor type and targeted area, several kinds of MNPs with different coating agents of various morphology and surface charge have been developed. The tunable physiochemical characteristics of MNPs enhance their heating capability. In addition, heating efficiency is strongly associated with the amount of the applied magnetic field and frequency. The great efforts have offered promising preclinical trials of magnetic hyperthermia via MNPs as a smart nanoagent. MNPs are very appropriate to be considered as a heating source in MHT and prospective research in this field will lead to tackle the problems from chemotherapy and introduce promising therapeutic techniques and nanodrug formulations for remotely controlled drug release and anticancer effects. This mini-review aims to pinpoint synthesis and structural analysis of various magnetic nanoparticles examined for magnetic hyperthermia therapy and controlled drug release in cancer treatment.

Keywords:
Magnetic Nanoparticles, Magnetic Hyperthermia, Nanofluids, Drug Delivery Systems, Cancer Therapy

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1. Introduction

Since two decades ago, nanotechnology has gained its privileges in nanomedicine [1, 2]. Currently, the scientific association has broadly attempted to obtain advanced synthetic methods for the preparation of innovative nanomaterials [3-5]. Cancer may lead to 10 million mortality each year, and its escalating burden can cause 13.1 million death by 2030 [6]. However, using smart nanomaterials and advanced devices might decrease worldwide cancer effects. As an unique multifunctional nanomaterials, magnetic nanofluids have been widely examined for cancer therapy

[7, 8], magnetic resonance imaging (MRI) [9, 10], MHT [10-12], and thermoablation [13], targeted drug delivery [14], bioseparation [15], biosensing [16], cell labeling [17], and targeting and immunoassays [18]. This is due to the advantages of magnetic nanoparticles (MNPs) including low cost of preparation, high physical and chemical stability, biocompatibility, and biodegradability [19-21]. For therapeutic and biomedical applications, MNPs especially Fe_3O_4 and γ-Fe_2O_3 generally have small and narrow size distribution as well as high magnetization [22]. The magnetization of Fe_3O_4 appears from antiferromagnetic coupling (super-exchange through oxygen) between the Fe^{3+} ions in octahedral and tetrahedral interstices, whereby the magnetic moments of the Fe^{2+} ions (in octahedral positions) provide the magnetization of the unit cell [23].

2. Magnetic Hyperthermia Therapy

Magnetic hyperthermia therapy (MHT) has shown a great potential for cancer treatment at *in vitro* and also *in vivo*, however, it is still under clinical trial [24]. The primary target of MHT is to deliver heat to destroy cancer cells at the secure hyperthermia range between 42-48 °C [25]. The main challenge of this therapy is controlling the medium temperature rise known as hyperthermia temperature, which can be performed by variation of the external alternating magnetic field (AMF) parameters such as frequency and magnetic field. Furthermore, particle size and shape, interparticle interactions, chemical composition, and concentration of the MNPs are important factors in MHT [25]. MNPs are exposed to the magnetic field (typically 50-1000 kHz) to produce a moderate temperature range of 42-48 °C for 30-60 min that causes necrotic cancer cell death without damages to the normal cells [26]. Based on the concentration of MNPs assemblies, the interparticle interaction may be understood theoretically by the simulation method of the specific absorption rate (SAR) value. For this purpose, the ferrofluid samples are exposed to an external alternating magnetic field (AMF) in order to assess their heating capabilities or SAR value. In MHT, alteration of AMF strengths not only may control hyperthermia temperature (T_H) but also tunes the magnetic properties of MNPs [25]. It is worth mentioning that MNPs in a low-viscous medium may trigger a magnetic response of anisotropic particles to be physically rotated through the Brownian heating loss mechanism for increments of hyperthermia temperature and SAR values [27]. The induced heating capability of MNPs samples is assessed by SAR (Eq. 1), which is defined as the amount of heat generated by an unitary amount of material per unit time under the exposure of AMF with defined field strength and frequency [28]:

$$\mathrm{SAR} = \left(\frac{C_m . m_m}{\mathrm{m_{Fe}}}\right)\left(\frac{\mathrm{dT}}{\mathrm{dt}}\right) \quad (1)$$

where C_m is the specific heat capacity of the ferrofluids that is comprised of the specific heat capacity of the medium and iron oxides. Further, m_m is for the total mass of the ferrofluids containing of medium, MNPs samples, and m_{Fe} indicates the iron mass per unit mass of MNPs sample (based on Fe ratio). The dT/dt achieved from the initial slope of the temperature and time curves using the linear fitting method. The magnetic nanofluids were placed at the center of a helical coil with several-turned loops having inner diameter, outer diameter, and length, which connected to a water-cooled induction heating instrument (Figure 1). The hyperthermia conditions were provided by an external AMF with three varied currents, which corresponded to the frequencies.

The magnetic field strengths (H) are determined using Eq. (2):

$$\mathrm{H} = \frac{\mathrm{n \cdot i}}{\mathrm{L}} \quad (2)$$

where n, i, and L are respectively defined the number of coil turns, applied current (A), and the inner diameter of the coil turns (m).

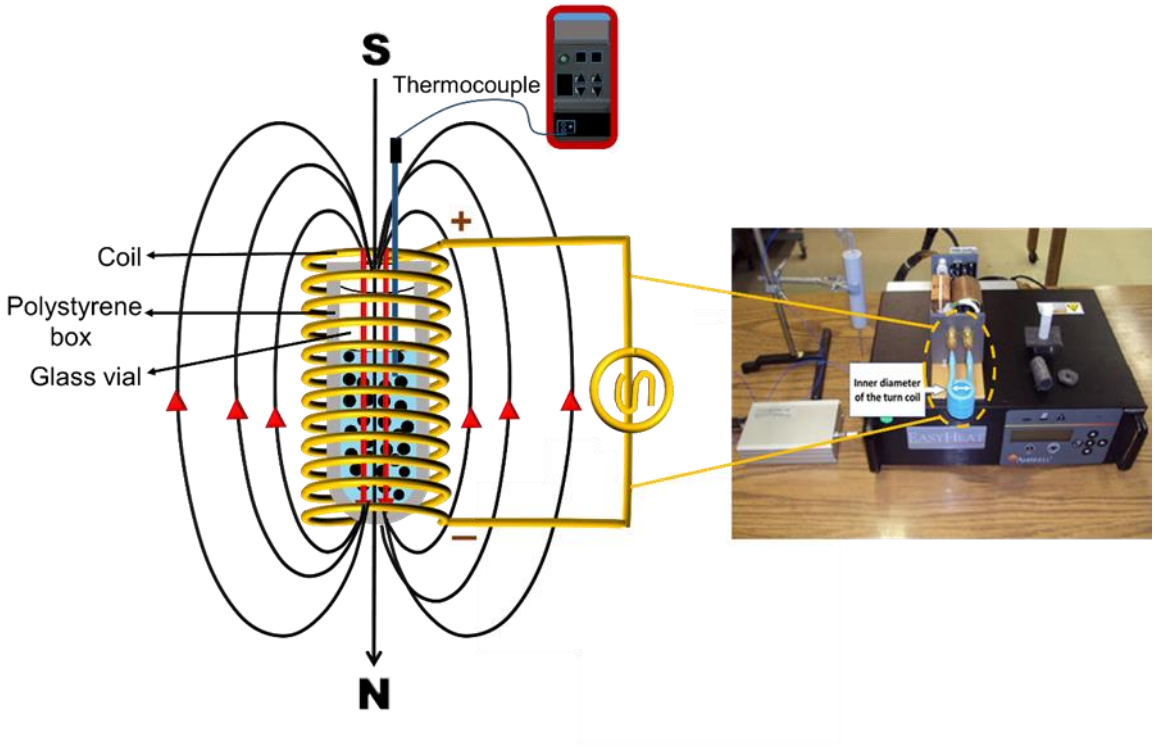

Figure 1: The schematic of induction heating instrument for magnetic hyperthermia

3. Coated magnetic nanoparticles for combined therapy of hyperthermia and chemotherapy

In magnetic hyperthermia, nanofluids of bare MNPs may show several disadvantages such as low colloidal stability, fast oxidation or sensitivity to air and humidity, self-agglomeration, due to dipole–dipole attractions between the naked NPs, which subsequently enhances the particle size, low biocompatibility, and weak biodegradability. The above disadvantages can be tackled by the surface functionalization and coating the MNPs. In addition, the biocompatible and nontoxic layers on MNPs are not only preserve the physiochemical characteristics of MNPs, they also introduce new functionalities from both MNPs and coater for an effective MHT, controlled-drug loading and also controlled-drug release performances. The organic and inorganic materials can be considered as coating agents for MNPs. As organic materials, surfactants, polymers, and biological molecules; and as inorganic materials metals, metal oxides and silica can coat MNPs [29].

For example, a hybrid complex loaded with holmium and anticancer drugs for evaluations of its surface modifications, morphology, and magnetic characteristics as well as interactions with the biological membranes and the cytotoxicity [30]. It was indicated that the round-shaped superparamagnetic iron oxide nanoparticles (SPIONs) (~15 nm) was effectively stabilized and also modified via doxorubicin (Dox) or epirubicin. The amount of drugs encapsulated into the synthesized SPIONs was investigated with thermogravimetry. The slight aggregation in SPIONs was caused by the drying process onto a Formvar film covering the mesh for Transmission Electron Microscopy

(TEM) analysis. It is indicated in Figure 2a that the SPIONs possess almost regular dispersity similar to the following samples. Figure 2b corresponds to the morphology studies of the SPIONs coated with citric acid (SPION@CA). The advantage of the citric acid coating was shown in an increase loading of anticancer drug. Figure 2c and d indicates the SPION@CA_Dox and SPION@CA_Epi, respectively. The organic layer (citric acid) with loaded drugs (Dox) for both TEM images Figure 2c and d are visible. Both Dox and epirubicin have dissimilar densities compared to the magnetic core, so they can be seen with the lighter layer coating core. The thickness of the organic shell was found to be less than 2 nm.

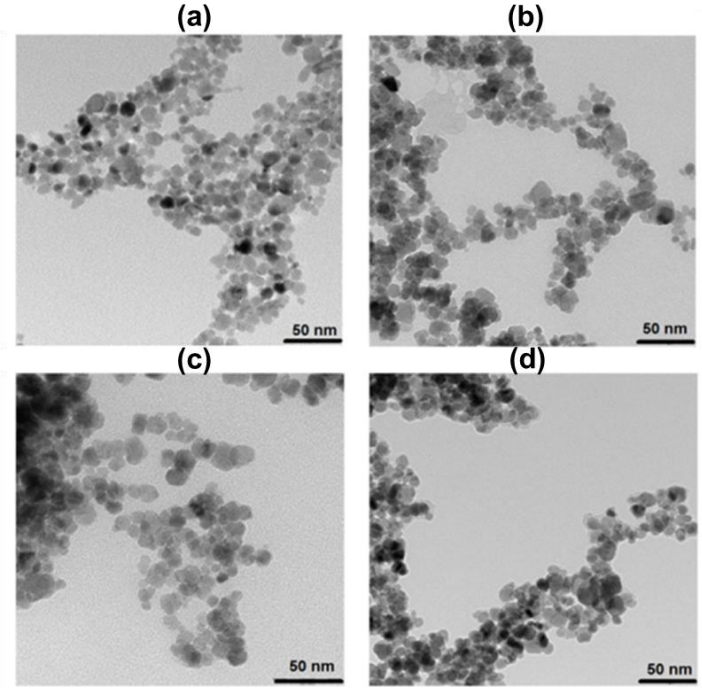

Figure 2: TEM images of particle size distributions (a) bare superparamagnetic iron oxide nanoparticles (SPIONs), (b) SPION@CA, (c) SPION@CA_Dox, and (d) SPION@CA_Epi (scale bar = 50 nm) [30].

The coating agent such as polymer may cover the surface of MNPs to avoid agglomeration, and decrease the possibility of a blockage in the blood vessels since the dispersity of MNPs is enhanced. Table 1 indicated different studies using coated MNPs for MHT and controlled drug release. The coated MNPs with high colloidal stability can enhance blood circulation and then deliver the MNPs to the targeted tissue. The surface of coated MNPs with low sensitivity to air and humidity can show positively good absorption of proteins. Above all, the coating can display as a barrier for quick clearance of MNPs from the blood stream to safely reach the targeted tissue [29].

The organic groups can functionalize MNPs by using functional groups include carboxyl, aldehyde, hydroxyl, and amino groups. These forms of coatings can maintain the magnetic characteristics, whereas, the features of organic materials can form the material with core shell and matrix [31]. As a popular coating structure with a moderate cost, core-shell can have various core forms include hexagonal, spherical, multiple, and even movable within the hollow shell (Figure 3) [31].

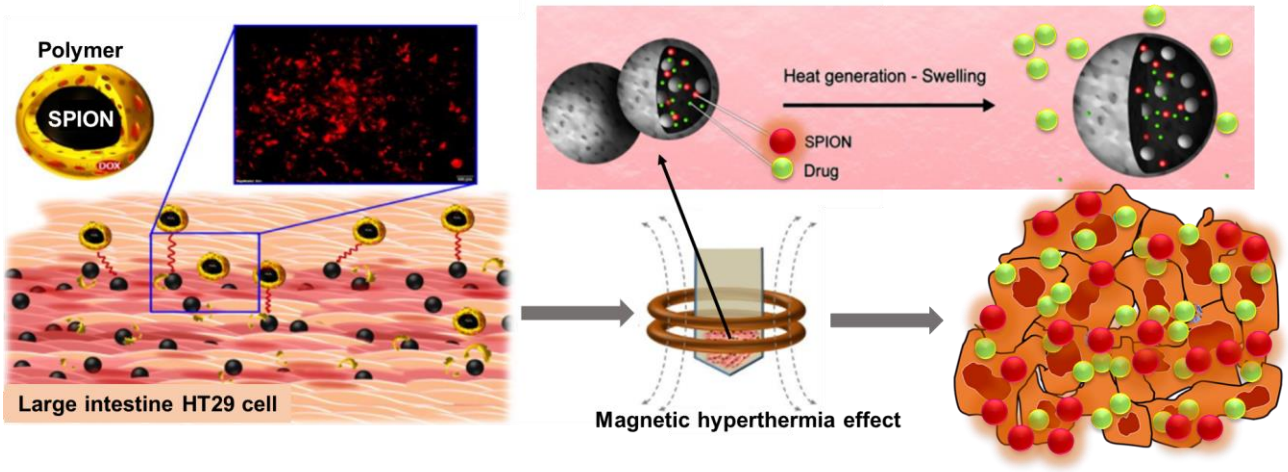

Figure 3. The schematic of polymer coated SPION for magnetic hyperthermia effects and controlled drug release against HT29 human colon cancer cells.

Table 1. Different studies using MNPs for effect on combined therapy of MHT and chemotherapy.

Magnetic nanoagent	Anticancer drug	Tumor cell lines	% Cell death after			Ref.
			MHT	Chemotherapy	Effect on combined therapy	
Polyethylene glycol (PEG)--ironplatinum (FePt)-Fe_3O_4	Doxorubicin	HeLa	47	52	80	[32]
Dimercaptosuccinic acid (DMSA)-Fe_3O_4	Doxorubicin	MDA-MB-231	43	37	60	[33]
Fe_3O_4/SiO_2	Doxorubicin	4T1	65	40	80	[34]
Monoclonal antibody conjugated Fe_3O_4	Doxorubicin	GTL-16	-	20	78	[35]
Silica-Fe_3O_4	Maytansinoid	IC21	15	20	78	[36]
Oleosome-$ZnFe_2O_4$	Carmustine	SK-BR-3	40	60	80	[37]

Coated MNPs with multifunctional encapsulating material may allow drug and ferromagnetism to be jointly delivered in one nanoparticle (Figure 4a-i). It was reported that the effective encapsulation of both Fe_3O_4 and Dox with agar as a drug carrier to obtain Dox-Fe_3O_4@agar [38]. The Fe_3O_4 encapsulated in the carrier maintained an acceptable saturation

of magnetization (41.9 emu/g) and had superparamagnetism. The MNPs encapsulated in the gel still maintained good heating capacity., that the magnetocaloric temperature reached 43 °C only after five min. In addition, Dox-Fe_3O_4@agar indicated a maximum release rate of 85%±3% in 56 min at pH 7.0 to simulate the intestinal environment (Figure 4g). In addition, Dox release from Dox-Fe_3O_4@agar complex via Dox's red fluorescence property against HT29 cells after 1 h treatment by fluorescence microscopy (Figure 4a-f). The results showed that the HT29 cells in the control sample did not show fluorescence (Figure 4a and d). Nevertheless, when cells were cultured with the Dox alone for 1 h, the HT29 cell image showed red fluorescence (Figure 4e). In addition, after culture for 1 h in the Dox-Fe_3O_4@agar treatment group (Figure 4c), red fluorescence could be observed (Figure 4f), which demonstrates that Dox-Fe_3O_4@agar effectively releases Dox and could be applied to cells. This can be seen clearly with the merged images shown as the insert in Figure 4d–f. It was shown also that using fluorescent microscopy that Dox entered HT29 human colon cancer cells and reduced cell viability by 66%. As hyperthermia was induced with an auxiliary external magnetic field, cancer cells could be further killed, with viability of only 15.4%. The above study could show that agar is an effective anticancer drug carrier for controlled drug release and anticancer treatment. The SAR values of the nanofluid samples exposed to different AMF strengths are provided in Figure (4h). The SAR values increased considerably with increasing AMF strengths due to the heating loss mechanisms [39], which is also in line with previous research reports such as bare superparamagnetic Fe_3O_4 [28] and polycaprolactone-coated Fe_3O_4 [11] and γ-Fe_2O_3 [40].

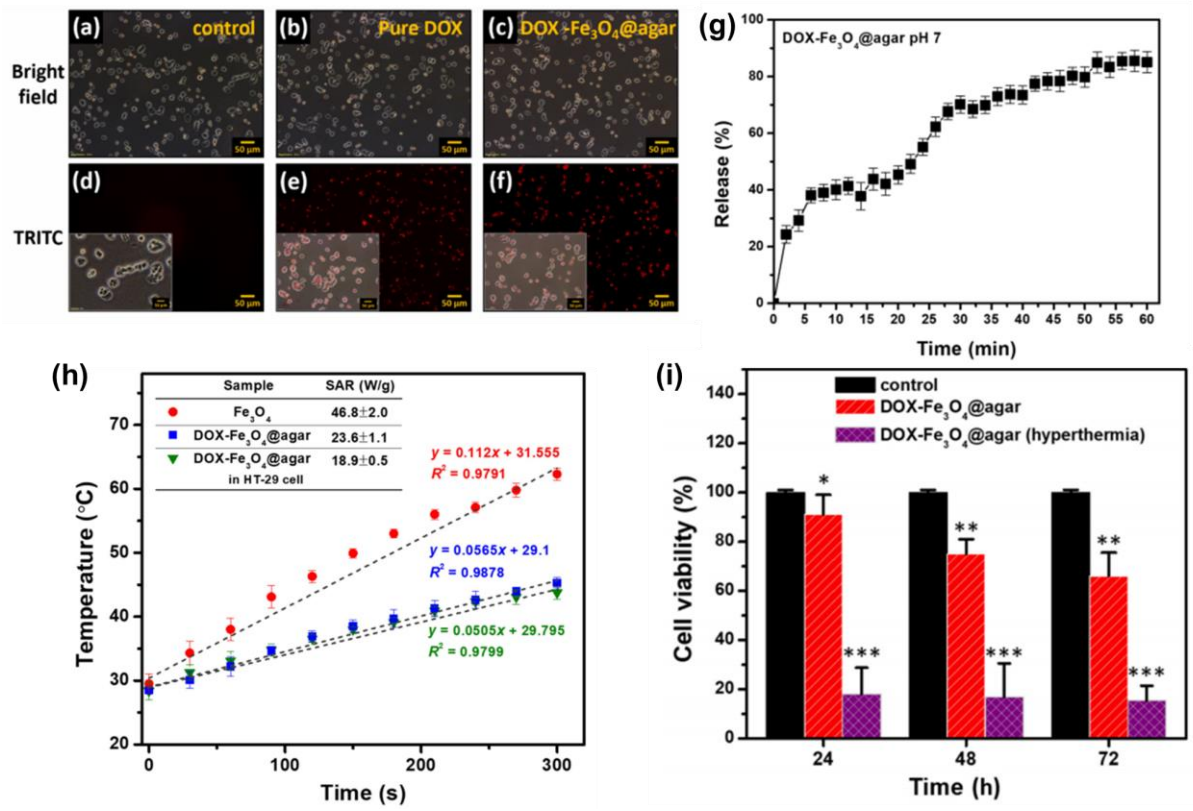

Figure 4. Fluorescence microscopy images of HT-29 cells after 1 h of incubation with pure DOX and DOX-Fe_3O_4@agar (on tetramethylrhodamine (TRITC) channel, at original magnification 100-fold); (a,d) control

HT-29 cells, (b,e) pure DOX-treated cells, and (c,f) DOX-Fe_3O_4@agar-treated cells. Insert: Merged images of HT29 cells from bright and TRITC images. (h) Temperature achieved by Fe_3O_4, DOX-Fe_3O_4@agar, and DOX-Fe_3O_4@agar in HT-29 cells. Here, 5 mg of sample is dispersed in 1 mL of DMEM (applied field = 400 A, f = 250 kHz). Inset shows the SAR values. (i) Cell survival of HT 29 cells treated with magnetic hyperthermia determined by MTT assay. The samples are control, pure DOX-treated (12 μg/mL), and DOX-Fe_3O_4@agar-treated (12 μg/mL) cells (n = 3). Statistical analysis was performed using one-way ANOVA followed by Duncan's test. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ versus control [38].

Oltolina et al., [41] loaded Dox on biomimetic MNPs mediated with magnetosome proteins (BMNPs) for in vitro and in vivo cancer treatment of mammary carcinoma model, in which hyperthermia improved cancer cell death and controlled drug release. The interaction of BMNPs with 4T1 cells was examined by TEM at various time points. The TEM images indicated that with exposure of magnetic field to the cells, some BMNPs interacted with the cell membrane and also to be internalized. In addition, the study obtained that AMF-induced hyperthermia is a valid therapy to decrease tumor size. The decrease of the tumor weight was only obtained from Dox-BMNPs + AMF, showing hyperthermia enhanced targeting drug release for a potent antitumor efficacy.

4. Conclusions

MNPs are low-cost and thermos-sensitive to use in magnetic fluid hyperthermia therapy. Types and magnetic characteristics of magnetic nanofluids along with applied parameters of an external magnetic field importantly influence the controlled heating mechanism. Improving the applied heat efficiency in magnetic hyperthermia is strongly related to the MNPs features such as size, shape, structure, and viscosity of the nanofluids. This review provided the basics of magnetic hyperthermia, mechanisms of heat losses, thermal doses for hyperthermia therapy, and strategies to improve heating efficiency. It is vital to build a bridge between the synthesis/coating of magnetic nanoparticles and their practical application in magnetic hyperthermia.

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