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Review Article

MAGNETIC NANOPARTICLES IN VARIOUS BIOMEDICAL APPLICATIONS

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ABSTRACT

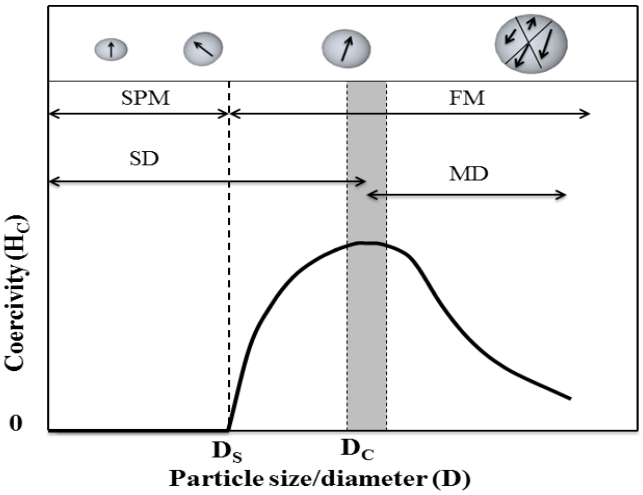
This review article presents an overview of the role of magnetic nanoparticles (MNPs) in various biomedical applications. Various synthesis techniques of magnetic nanoparticles have been discussed in compliance with their suitability in biological applications. Utilizing the magnetic property of the nanoparticles, several biomedical technology applications have been developed such as magnetic resonance imaging (MRI), separation of biomolecules, biosensing, bacteria inhibition, magnetic field stimulated drug delivery, magnetic hyperthermia therapy etc. Among the various applications, this article comprises a detailed review mainly focused on the potentiality of the MNPs in magnetic field stimulated drug delivery technique and hyperthermia therapy. The present difficulties/limitations and remaining challenges of these techniques have also been outlined in this article.

Keywords: Drug release, Hyperthermia therapy, Magnetic nanoparticles, Stimuli-responsive technique, Targeted drug delivery.

1. INTRODUCTION

Recently the research in MNPs has gained immense interest due to its growing applications in various fields of modern technology. The magnetic property of the NPs utilized in different ways in various technological applications. The essential use of the particles in electronics (such as in sensors, storage media etc.) and biotechnology make them attractive to the researcher. Potential applications of the MNPs can be found in various useful biomedical applications such as in magnetic resonance imaging (MRI), tissue engineering, bio-analysis, molecular detection, magnetic drug targeting, hyperthermia therapy etc. [1-3]. Biocompatibility, biodegradability, colloidal stability, controllable size, homogenous dispersion in a liquid medium, easy surface functionalization and tunable magnetic property are the key requirements of the NPs for their different type of prospective biomedical applications. For *in vivo* applications the MNPs are promising material as they can be directed and localized by the force of a remote external dc magnetic field. The magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), and cubic spinel ferrite of Mn, Fe, Zn, Co, etc. are the most extensively studied MNPs as they have been widely used in numerous biotechnological applications [4]. Till date, the use of Iron and its oxides in biological applications are well established as they are nontoxic in nature [5], biodegradable [6] and also possess good magnetic properties. To get enhanced magnetic property spinel metal ferrite/mixed metal ferrite MNPs such as $CoFe_2O_4$, $Mn_{0.6}Zn_{0.4}Fe_2O_4$, $Cu_{0.3}Zn_{0.5}Mg_{0.2}Fe_2O_4$ etc. have also been investigated, however, it requires proper surface modification for biocompatibility [7-9]. To make the particles biocompatible and to stabilize them *in vivo,* proper surface coating is necessary. Various types of organic surface ligands such as polyethylene glycol, polyvinyl alcohol, dextran, carboxydextran, aminosilanes etc. have been commonly used for coating [10-11]. Depending on the requirement, the magnetic property of the MNPs can be manipulated by proper tunning of their size and shape which makes them useful in biomedical technology applications. By controlling size and shape during the synthesis process the coercivity (H_C), saturation magnetic moment (M_S), magnetic susceptibility (χ) etc. of the MNPs can be tuned to the desired level for its applications [12-13]. A drastic change of H_C with the particle size is observed for these particles. The ferromagnetic behaviour of the particles changes into superparamagnetic with the decrease of their

size/diameter. With particle size reduction from a larger diameter, the H_C increases and reaches a maximum at a critical diameter D_C.



SPM = Superparamagnetic, FM = Ferromagnetic
SD = Single-domain, MD = Multi-domain

Fig. 1: Schematic representation of variation of coercivity with particle size for nanoparticles [13]

With further reduction of particle diameter, coercivity reduces to zero (Fig. 1). With the decrease in particle size, the multi-domain particles become single domains below a critical diameter D_C. The coercivity of the single domain particles becomes zero at particle diameter less than D_S and the particles become superparamagnetic. However, these critical diameters D_C and D_S are not constant for all materials. They depend on anisotropy constants, saturation magnetization and exchange interactions of the neighbouring spins which are the property of the materials [14-17]. In large MNPs (particle size greater than D_C) multi-domain structure exists, several small regions (domains) which are spontaneously magnetized. The magnetic domains are separated by domain walls. Generally, for these multi-domain particles, the magnetization reversal occurs by domain wall motion which is a relatively easy process that causes lower coercivity. Superparamagnetic or ferromagnetic particles can produce heat when experiencing an AC magnetic field. The heat can be used to heal the affected tumor cell, called magnetic hyperthermia therapy. The generated local heat can also be used as a stimulus to control the release of drugs [18-20]. However, critical and proper investigations are required before using the NPs for this purpose. The process of synthesis of MNPs plays a crucial role in tunning their different property like size, shape, porosity bio-compatibility, chemical stability etc.

2. SYNTHESIS OF MAGNETIC NANOPARTICLES

Among various synthesis techniques, the most common is wet chemical method. A flowchart for the synthesis of ferrite and magnetite nanoparticles in wet chemical method has been shown in Fig. 2. The wet chemical method is classified into hydrolytic and non-hydrolytic approaches. In the hydrolytic approach, the coprecipitation technique is most significant as it has several advantages over other methods. For example, from alkaline coprecipitation of ferrous chloride and ferric chloride in the proper ratio, controlled size Fe_3O_4 can be obtained. In this method, the particle size can be varied within a range from 3-20 nm by tunning different experimental conditions like temperature, pH, etc.

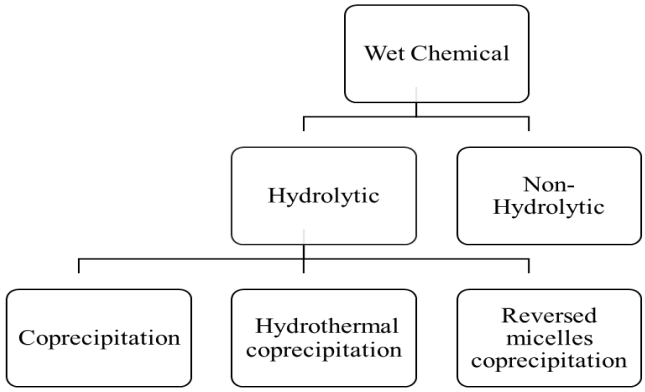


Fig. 2: Flowchart for the synthesis of ferrite and magnetite nanoparticles in wet chemical method

The advantages of this method are: it requires low-cost materials, can be performed direct synthesis in water and the synthesis process is flexible as particle size can be varied by tunning the experimental parameters. To achieve good magnetic properties in MNPs, the coprecipitation method under hydrothermal conditions can be used [21]. In this synthesis process, the particle size of MNPs is controlled by the reaction parameters like solvent, temperature, and duration. The main disadvantage of this process is the non-uniform size distribution of the MNPs. The reverse micelles coprecipitation technique has been widely used to get uniform size distribution of MNPs in the range of 4-14 nm. Different shapes and morphological structures of MNPs can also be obtained in this synthesis method [22-23]. Here micelles are used as a capping agent. To get

high-quality ferrite MNPs, non-hydrolytic routes are also becoming popular among researchers. Uniform size and high crystalline MNPs with good magnetic properties can be obtained in this synthesis route [24]. Besides those synthesis methods, there are other approaches also, such as microemulsions, [25] sol-gel synthesis, [26] microbial method, ball milling technique etc., which can be found in the literature.

3. SURFACE MODIFICATION OF THE MNPS

Surface modification of the MNPs is needed to induce some necessary properties for *in vivo* biological applications. MNPs experience magnetic dipole attraction that agglomerates the particles. To prevent agglomeration suitable coating of MNPs is also a necessary criterion. The important properties like biocompatibility, stability, nontoxicity, monodispersing etc. are achieved by proper surface modification/ functionalization of the NPs. The selection of proper coating (functionalization) material is very crucial as the MNPs derived from the different approaches of synthesis have different properties in their cores and surfaces. Depending on the synthesis process, the core of the NPs may be hydrophobic or hydrophilic and the surface property will depend on the nature of atoms/molecules on the surface. Based on the nature of the application of the MNPs and the chemistry of the initial particle surface there are several coating strategies have been developed. Coating materials can be categorized as organic coating and inorganic coating. Organic coating is organic spices including surfactant and polymers. Some widely used organic coating materials are dextran, polyvinyl alcohol (PVA), polyethylene glycol [PEG], surfactants (CTAB) etc. [27] Coating with high molecular weight polymers prevents the particles against agglomeration and improves colloidal stability by reducing the inter-particle magnetic dipole-dipole interaction [28]. The organic coating can also enhance/modify the magnetic property of the MNPs as the inter-particle distance changes [14]. Amphiphilic copolymer (MPEG-PLGA) coated magnetite nanoparticles showed no cytotoxicity along with substantial stability and superparamagnetic property [29]. Xie, J. et al. reported that core-shell structured Mn-Zn ferrite MNPs, coated with PEG-phospholipids exhibit good biostability and biocompatibility [30]. These functionalized MNPs also show an excellent heating effect under an AC magnetic field which is an important criterion in magnetic hyperthermia therapy. Silica is an important inorganic coating material for its optical transparency and non-toxicity. Magnetic properties of the MNPs, such as magnetization, and magnetic susceptibility also modified by inorganic coating like silica, carbon etc.

4. BIOMEDICAL APPLICATION OF THE MNPS

Over the last few years, the rapid advancement of nanotechnology has made a huge impact in the field of nanoparticle-based biomedical applications. Utilizing the property of the MNPs, several technologies have been developed in this field such as magnetic resonance imaging (MRI), bioseparation, biosensing, bacteria detection and sequestration by magnetic capture, monitoring stem cell migration, hyperthermia, drug delivery etc. In this article, the role of MNPs in magnetic hyperthermia and magnetic field-triggered drug delivery technique has been discussed and reviewed in detail.

4.1. Magnetic hyperthermia

In recent years the magnetic nanoparticle hyperthermia technique in tumor/cancer therapy has been investigated intensively due to its effectiveness and reduced adverse side effect [31]. In this technique, the heat released by MNPs under the application of an AC magnetic field is used to heal the targeted cells. Depending on the behaviour of magnetization reversal in an assembly of MNPs, the mechanism/process of heat release is classified into three categories. These are hysteresis loss, relaxation of magnetic moments and viscus loss. The heat produced in ferromagnetic NPs by hysteresis loss process is much higher than the other two. Generated heat (E) due to hysteresis losses in a complete cycle of magnetization is obtained by calculating the area of the close loop under the M vs H curve (Eq. -1).

$$E = \int_{-H_{max}}^{+H_{max}} M(H)dH \qquad \text{Eq. - 1}$$

Where M(H) is the magnetization of the MNPs and H_{max} is the maximum value of the magnetic field.

Specific absorption rate (SAR) is an important parameter that is actually a measure of heat release per second and can be determined by the product of E and frequency of ac magnetic field (f) (Eq. 2).

$$SAR = E \times f \text{ (in the unit of Watt per gram)} \qquad \text{Eq.-2}$$

The hysteresis loop area which is a direct measure of SAR value generally proportional to the coercivity of the particles [32]. Size, shape and magnetocrystalline anisotropy (K) of the MNPs play important role in coercivity. The dependence of coercivity of nanoparticles with their size is already shown in Fig. 1. In single domain MNPs domain walls are absent and the magnetization reversal occurred by coherent rotation of

the magnetization vector (MS) according to Stoner and Wohlfarth model [13]. Some anisotropy forces due to crystal, surface or shape anisotropy tend to restore the magnetization reversal. It is well established that single domain particles at a critical size (D_C) the anisotropy energy barrier is maximum and consequently shows maximum coercivity. For example, $CoFe_2O_4$ MNPs show a maximum coercivity of around 4.5 KOe at their critical size (D_C) which is about 20 nm [14]. Lee et al. reported a large saturation magnetization (M_S) value of ~75 emu/g and a maximum coercivity (H_C) of ~48 Oe in Fe_3O_4 MNPs when the particle size reached ~120 nm [33]. A large number of reports can be found in literature where particle sizes in the range of 20-100 nm have been used for this purpose. However, H_C of fine particles have a relation to particle size but it is not only a parameter that determines H_C rather it has a complex dependence on various parameter such as surface spin canting, aspect ratio, separation of the particles etc. [13], [14], [33] When the single domain particles become small enough, the barrier potential energy, ΔE (=KV) for magnetization reversal becomes small compared to the thermal fluctuation energy K_BT (Where V is the volume of each particle with anisotropy constant K and K_B is the Boltzmann constant). Consequently, thermal fluctuations overcome anisotropy forces and spontaneously reverse the magnetization of the particles from one easy direction to another even without any magnetic field. This is known as the superparamagnetism of nanoparticles. Generally, the average size of superparamagnetic particles is less than 20 nm. Superparamagnetic particles have special importance in biomedical applications as the particles do not have any magnetic moment without a magnetic field which prevents them from agglomeration. In superparamagnetic particles, heat is generated mainly due to Neel relaxation mechanism and viscus loss. In particles with a small diameter, the magnetization vector changes its direction over the anisotropy barrier under the application of an AC magnetic field causing heating due to Neel relaxation. In this process, the imaginary part of ac susceptibility plays an important role. Polymer-coated Fe_3O_4 superparamagnetic NPs of size about 20 nm showed an SLP of 118 W/g at 26.67×10^3 A/m ac field with a frequency of 265 KHz [34]. A significant number of investigations have been reported in the literature regarding specific power loss of different MNPs as a function of applied field and frequency [35-36]. SLP can also be enhanced by increasing both fields (H) and frequency (f) as it is proportional to the square of the term $H \times f \times L$, i.e. $(HfL)^2$. Where L is the diameter of the current loop [37]. But, to avoid unwanted heating in the patient body due to the induction of eddy current the value of ($f \times H$) should be within 4.85×10^8 A/m·s as per Brezovich limit. Therefore, selection of amplitude and frequency of ac field is crucial in hyperthermia therapy and it is desirable to enhance SLP by improving the property of the NPs not by increasing the value of $f \times H$. A successful hyperthermia treatment on human patients by utilizing an AC magnetic field of 18 kA/m at a frequency of 100 KHz has been reported by Gneveckow et al. [38] Small size (particle diameter < 100 nm) ferromagnetic or superparamagnetic NPs also generate heat on account of friction with the surrounding medium when rotating itself physically in a viscous medium under the application of ac magnetic field known as viscus loss (Brownian mechanism). Finally, in hyperthermia therapy, the magnetic field induced heat by small size (<100 nm) encapsulated ferromagnetic or superparamagnetic NPs is utilized to heal cancer/tumor cells. To enhance SLP, choosing suitable particles is very much necessary with the proper choice of ac field and frequency.

4.2. Magnetic field triggered drug delivery

As the anti-cancer drug is harmful to both the healthy and cancer cells, during cancer chemotherapeutic treatment, the drugs require to be delivered specifically into cancer/targeted cells to heal those cells without affecting the normal living cells. To achieve the purpose and other challenges, novel drug delivery technologies have been developed. Attaching the drug/therapeutic agent suitably on the carrier/vehicle then directing the carrier/drug complex to the desired site and finally controlled release of the drug, are the key mechanism of drug delivery. Controlled release of the drug at a lower systematic dosage at a specific site minimizes the adverse side effect of this therapy [39-41]. Different types of carrier/vehicle such as polymer-coated nanoparticles, nanocapsules, liposomes, hydrogels, dendrimers etc. have been developed based on the applications of the drug delivery systems (DDS) [42]. Among various type of carriers, MNPs has achieved immense attention as they can be directed and guided externally by a dc magnetic field and also produce heat under ac magnetic field. Utilizing those unique properties of the MNPs magnetic field triggered DDS has been developed. A schematic representation of magnetic field-triggered DDS has been depicted in Fig. 3. In MNPs-based targeted drug delivery, first, the drugs are loaded or attached with MNPs to produce the drug/carrier complex. The magnetic drug/carrier complex is then injected into the bloodstream.

Afterward, high-gradient external DC magnetic fields are employed to guide and concentrate the drug at the tumor location [43]. After targeting the carrier/drug complex at desired location the release of the drug is controlled by different stimuli. For example, electric field, heat, pH, light, enzymes, etc. are used as stimuli to control the release of the drug [44-46]. It is proposed that the generated heat in MNPs carrier under the application of an AC magnetic field could be a stimulus for controlled drug release [47-49]. In this process, the release of drug is controlled externally with the proper application of an AC magnetic field which reduces side effects compared to other invasive techniques of drug release. However, several numbers of studies have been reported to investigate magnetic field stimulated drug delivery technique using MNPs as carrier [50] but it requires more intensive study of this phenomenon with many possible magnetic materials before practical application.

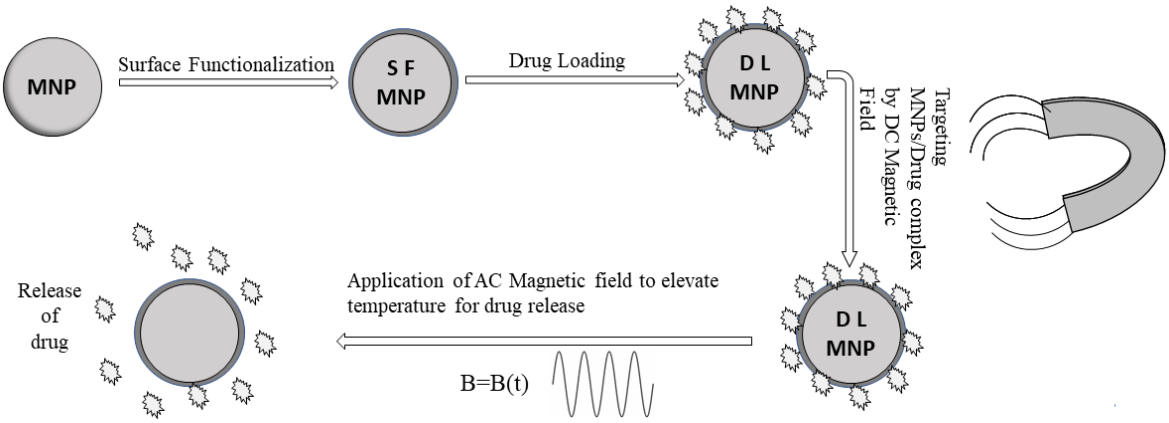


Fig. 3: Schematic representation of magnetic field triggered drug delivery technique

5. CONCLUSION

With the advancement of nanoscience and nano-technology, the use of NPs in biomedical applications has increased and made considerable progress in this field. In this review, the applications of MNPs in different biomedical applications are summarized. The basic magnetic properties of the MNPs have been discussed in view of their biomedical applications. Various synthetic techniques of magnetic nanoparticles with surface modification procedures have been discussed considering their suitability in biological applications. Magnetic nanoparticles achieved special attention in the field of DDS for their biocompatibility, nominal cytotoxicity, chemical stability and their ability to be guided under the influence of an external magnetic field. MNPs-based hyperthermia therapy has several advantages over conventional hyperthermia treatment. However, choosing the value of the magnetic field with proper frequency is required for successful clinical application. Magnetic field-triggered DDS has achieved superiority over the other DDS for its targeting specificity, controlled release and less adverse side effects. To make this technology a useful clinical tool a large number of basic and clinical researches needs to be done. Developing biocompatible MNPs with a broad range of multifunctional properties for various kinds of biomedical applications will play a crucial role in this field in the future.

Conflict of interest

None declared

6. REFERENCES

1. Zhang H, Li J, Hu Y, Shen M, Shi X, Zhang G. *J. Ovarian Res,* 2016; **9** (19).
2. Sun, M, Sun B, Liu Y, Shen QD, Jiang S. *Sci. Rep.* 2016; **6**: 22368.
3. Ambrogio MW, Thomas CR, Zhao YL, Zink JI, Stoddart JF. *Acc. Chem. Res,* 2011; **44**(10): 903-913.
4. Xue P, Sun L, Li Q, Zhang L, Guo J, Xu Z, Kang Y. *Colloids and Surfaces B*: *Biointerfaces,* 2017; **160**: 11-21.
5. Laurent S, Forge D, Port M, Roch A, Robic C, Elst LV, et al. *Chem. Rev,* 2008; **108** (6): 2064-2110.
6. Durán JDG, Arias JL, Gallardo V, Delgado AV. *J. Pharm. Sci,* 2008; **97**(8): 2948-2983.
7. Dey C, Ghosh A, Ahir M, Ghosh A, Goswami MM. *Chem Phys Chem,* 2018; **19**(21): 2872-2878.
8. Dey C, Baishya K, Ghosh A, Goswami MM, Ghosh A, Mandal, K. *J. Magn. Magn. Mater,* 2017; **427**: 168-174.

9. Ansari M, Bigham A, Hassanzadeh-Tabrizi SA, Ahangar HA. *J. Magn. Magn. Mater,* 2017; **439**: 67-75.
10. Berry CC, Wells S, Charles S, Curtis ASG. *Biomaterials,* 2003; **24**(25):4551-4557.
11. Liu TY, Hu SH, Liu KH, Liu DM, Chen SY. *J. Controlled Release,* 2008; **126**(3): 228-236.
12. Lutz JF, Stiller S, Hoth A, Kaufner L, Pison U, Cartier R. *Biomacromolecules*, 2006; **7**(11): 3132-3138.
13. Cullity BD. *Introduction to Magnetic Material, 2nd ed. London: Addison-Wesley*; 1972.
14. Pal D, Mandal M, Chaudhuri A, Das B, Sarkar D, Mandal K. *J. Appl. Phys*, 2010; **108**:124317.
15. Li Q, Kartikowati CW, Horie S, Ogi T, Iwaki T, Okuyama K. *Scientific Reports,* 2017; **7**: 9894.
16. Kamble RB, Varade V, Ramesh KP, Prasad V. *AIP Advances,* 2015; **5**: 017119.
17. Nayek C, Manna K, Bhattacharjee G, Murugavel P, Obaidat I. *Magnetochemistry,* 2017; **3**(2): 19.
18. Yavuz MS, Cheng Y, Chen J, Cobley CM, Zhang Q, Rycenga M, et al. *Nat. Mater,* 2009; **8**: 935-939.
19. Choi SW, Zhang Y, Xia YA. *Angew. Chem,* 2010; *Int. Ed.* 49, 7904-7908.
20. Ge J, Neofytou E, Cahill T J, Beygui RE and Zare RN. *ACS Nano.* 2012; **6**: 227-233.
21. Ge S, Shi X, Sun K, Li C, Uher C, Baker J, et al. *J. Phys. Chem. C,* 2009; **113**(31): 13593-13599.
22. Goswami MM. *Sci Rep,* 2016; **6**: 35721.
23. Mandal M, Pal D, Mandal K. *Colloids and Surfaces A*: *Physicochem. Eng. Aspects*, 2009; **348**: 35-38.
24. Cai W, Wan J. *Journal of Colloid and Interface Science,* 2007; **305**(2): 366-370.
25. Chin AB, Yaacob II. *Journal of Colloid and Interface Science,* 2007; **305**(2): 366-370.
26. Albornoz C, Jacobo SE. *J. Magn. Magn. Mater,* 2006; **305**(1): 12-15.
27. Butterworth MD, Illum L, Davis SS. *Colloids Surf. A,* 2001; **179**: 93-102.
28. Portet D, Denizot B, Rump E, Lejeune JJ, Jallet P. *J. Colloid Interface Sci,* 2001; **238**: 37-42.
29. Ding G, Guo Y, Lv Y, Liu X, Xu L, Zhang X. *Colloids and Surfaces B: Biointerfaces*, 2012; **91**: 68-76.
30. Xie J, Zhang Y, Yan C, Song L, Wen S, Zang F, et al. *Biomaterials,* 2014; **35**(33): 9126-9136.
31. Johannsen M, Gneveckow U, Thiesen B, Taymoorian K, Chie HC, Wald¨ofner N, et al. *Eur. Urol,* 2007; **52**: 1653-1662.
32. Dutz S, Hergt R, Murbe J, Muller R, Zeisberger M, Andra W, et al. *J. Magn. Magn. Mater,* 2007; **308** (2): 305-312.
33. Lee JS, Cha JM, Yoon HY, Lee JK, Kim YK. *Sci. Rep.* 2015; **5**: 12135.
34. Hedayatnasab Z, Abnisa F and Wan Daud WMA. *IOP Conf. Ser.: Mater. Sci. Eng*. 2018; **334**, 012042.
35. Goswami MM, C Dey, A Bandyopadhyay, D Sarkar, M Ahiret et al. *J. Magn. Magn. Mater,* 2016; **471**(1): 376-381.
36. Joshi HM, Lin YP, Aslam M, Prasad PV, Schultz-Sikma EA, Edelman R, et al. *J. Phys. Chem. C,* 2009; **113**: 17761-17767.
37. Sun J, Wang W, Yue Q. *Materials,* 2016; **9**: 231.
38. Gneveckow U, Jordan A, Scholz R, Brüss V, Waldöfner N, Ricke J, et al. *Med. Phys.* 2004; **31**: 1444-1451.
39. Allen TM, Cullis PR. *Science,* 2004; **303**: 1818-1822.
40. Price PM, Mahmoud WE, Al-Ghamdi AA, Bronstein LM, *Front. Chem,* 2018; **6**: 619.
41. Vargason AM, Anselmo AC, Mitragotri S. *Nat Biomed Eng*, 2021; **5**: 951.
42. Mishra N, Pant P, Porwal A, Jaiswal J, Samad M A, Tiwari S. *Am. J. Pharm Tech Res,* 2016; 6(1).
43. Singh D, McMillan JM, Kabanov AV, Sokolsky-Papkov M, Gendelman HE. *Nanomedicine (Lond),* 2014; **9**: 501-516.
44. Yavuz MS, Cheng Y, Chen J, Cobley CM, Zhang Q, Rycenga M. *Nat. Mater,* 2009; **8**: 935-939.
45. Karthik S, Puvvada N, Prashanth Kumar BN, Rajput S, Pathak A, Mandal M, et al. *ACS Appl. Mater. Interfaces,* 2013; **5**: 5232.
46. Choi SW, Zhang Y, Xia YA. *Angew. Chem*, *Int. Ed.* 2010; **49**: 7904-7908.
47. Liu JF, Jang B, Issadore D, Tsourkas A. *Nanomedicine and nanobiotechnology*, 2019; **11**(6): e1571.
48. Hua X, Yang Q, Dong Z, Zhang J, Zhang W, Wang Q, et al. *Drug Delivery,* 2017; **24:** 511.
49. kianfar E. *Supercond J. Nov Magn*, 2021; **34:** 1709-1735.
50. Pal D, De D, Das A, Chaudhuri A, Goswami MM. *J. Adv. Sci. Res,* 2020; **11**(03): 170-175.