DEVELOPMENT OF SURFACE MODIFIED SUPER PARAMAGNETIC IRON OXIDE NANOPARTICLES

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ABSTRACT

Super paramagnetic iron oxide nanoparticles (SPIONs) coated with biocompatible materials are used for *in vivo* applications, such as contrast agent for magnetic resonance imaging (MRI), for tumor therapy or cardiovascular disease. Biomedical application requires the biocompatible SPION, which is stable and well dispersed in water at physiological pH or in physiological salinity. Many different approaches are used for generation of functionalized nanoparticles in order to obtain the required properties for biomedical uses. In order to obtain biocompatible SPION, SPIONs with size 15-25 nm have been synthesized and these SPIONs have been coated with poly (ethylenimine) (PEI), poly (vinyl alcohol) PVA and Pluronics p-123(PEG-PPG-PEG).High resolution Field Emission Scanning Electron Microscope FESEM, X-Ray diffraction studies, Fourier Transform Infra Red Spectroscopy FTIR, Laser Scattering Particle Size Analyzer and Vibrating Sample Magnetometer VSM were employed to investigate the morphological, crystalline and magnetic properties of nanoparticles. For biomedical applications such as MRI, drug-delivery and hyperthermia, the nanoparticles have to be biocompatible, have a large enough moment for targeting and display super paramagnetic behavior .Owing to their non-toxicity and strong magnetic susceptibility, magnetite and maghemite Nanoparticles have been extensively researched for biomedical applications. Below a certain Size (15 nm for magnetite), magnetite nanoparticles display super paramagnetic behavior with zero remanence and zero coercivity. Vibrating Sample Magnetometer studies were carried out to study the effect of phase transformations on the magnetic properties of the nanoparticles. The samples were analyzed by VSM at room temperature to find the saturation magnetization, Ms, remnant magnetization, Mr and coercivity, Hc of various polymer coated Iron Oxide nanoparticles. The poly (ethylenimine) coated iron oxide nanoparticles showed better results with low coercivity and low remnant field compared with uncoated and poly vinyl alcohol coated iron oxide nanoparticles. The PEI-coated iron oxide nanoparticles, PVA-coated particles and Pluronics –coated particles were found to be well dispersed in water as they have a hydrophilic outer surface containing hydroxyl and amine group. This hydrophilic outer surface will enhance their bio activity. Therefore they become a very good drug carrier for biomedical applications.

Key words: SPIONS, poly (ethylenimine), Pluronics p-123, Field Emission Scanning Electron Microscope, Vibrating Sample Magnetometer

I. INTRODUCTION

The major application of nanotechnology on which most of the research is focused on are biomedical applications. The other major field is nanoelectronics which includes both top-down and bottom-up approaches.

One important application is development of a novel drug delivery system. A drug delivery system used to consist the active component and an outer coating to maintain its stability inside the human system, but there exists quite a few issues on its stability and side effects. These two problems can be solved very well if the specificity and circulation time of the drug are increased. There are quite a few methods to achieve this; one such method is being attempted in this project[1].

The project discussed in this report deals about synthesis, surface modification and characterization of Iron Oxide nanoparticles and the variations observed in their magnetic properties due to size reduction and surface modification.[9] SPIONS are at present effectively replacing the Gd+ ions as the contrast reagents in Magnetic Resonance Imaging, MRI as their saturation magnetization is high and also show very low hysteresis. It is now being tried to treat cancers by using it as a drug carrier. The super paramagnetism is shown by various inorganic particles but the compound focused on here is Iron oxide nanoparticles

in the iron are found to be in Fe3+ state[2]. Iron oxide nanoparticles are the most commonly used super paramagnetic contrast agents in MRI. The dipolar interactions between two super paramagnetic cores and surrounding solvent protons result in an increase in both longitudinal and transverse relaxation times[3].For biomedical applications, SPIONS should have a narrow size distribution, while the surface of the particles should be coated with biocompatible hydrophilic materials so that the coated SPIONS can form an aqueous dispersion at physiological pH 7.4. Commonly stabilization of the ferrofluids is achieved by optimizing the electrostatic repulsion of similarly charged surfaces .With the aim to form stable non-toxic aqueous dispersion of SPION, coating of the magnetic nanoparticles with biocompatible polymers has drawn recent interest. Some of them include poly (ethylenimine) PEI, Pluronics[4], Poly (vinyl alcohol) PVA and Poly (acrylic acid) PAA.

II. OBJECTIVE

The major problem on which current research on cancer cells are focused is lower specificity of the drugs employed and the stability of the drugs after administration into the human system. These two issues can be well answered if the ability of the drug carrier to evade the immune response and ability to target exactly the required target tumor affected cells rather acting on the normal cells are well explained. My work contains the synthesis route of SPIONS and characterization of its properties which proves that they can act as an effective molecular probe in many biomedical applications like MRI. In this report the synthesis of SPIONS and incorporation of biocompatible moieties onto it is discussed in detail.

And the biocompatible coatings on SPIONS were three different polymers namely

- Poly(vinyl alcohol)-PVA

- Poly (ethylenimine)-PEI

- Pluronics-P123

The various characterization techniques employed were Fourier Transform Infrared spectroscopy FTIR, X-Ray diffraction measurements XRD, particle size analyzer PSA, Field emission Scanning electron microscope FESEM, finally the Vibrating Scanning Magnetometer.

These characterizations were done in order to analyze the size, size distribution, surface morphology, chemical composition, crystal properties and magnetic properties. The above said properties were studied in detail as the particles can be tested with cancer cells.

III. MATERIALS AND METHODS

A. Materials

Ferric chloride anhydrous ($FeCl_3$), ferrous sulphate hydrates ($FeSO_4$), Ammonia (7%), Poly (vinyl alcohol), poly (ethylenimine), Pluronics (p-123) all were purchased from Sigma Aldrich and Merck & Co.

B. Reagents

Precursor solution containing Anhydrous Ferric chloride & Ferrous sulphate hydrate:

The Ferric chloride anhydrous ($FeCl_3$), Ferrous sulphate hydrate ($FeSO_4$) were purchased from Sigma Aldrich. The powders were mixed in a 2:1 ratio by weight and then added into a 50 ML beaker containing 15 ML deionized water.

PVA solution1 %

The polymer poly vinyl alcohol was purchased from Merck & Co. A 0.1 g of PVA was weighed and added to 10 ML of deionized water and then mixed with the precursor solution.

Ammonia 7 % solution

Ammonia solution was diluted using deionized water up to 7 %.

Pluronics p-123 5 % solution

Pluronics p-123(PEG-PPG-PEG) was purchased from Sigma Aldrich. And 0.5 g of it was dissolved well in 10 ML deionized water until true solution was obtained.

Poly (ethylenimine) PEI solution 5 %

Poly (ethylenimine) was purchased from Sigma Aldrich and 0.5 g of it was dissolved in 10 ML deionized water to obtain clear 5% solution.

C. Methods

Synthesis of Iron Oxide Nanoparticles

The synthetic route of Iron oxide nanoparticles were followed from a standard protocol handled by *Cheng et al[12]*.In that he employed ammonia 25% but

here it was 7% ammonia. The synthesis was carried out in two steps

- Iron oxide nanoparticles were obtained in the form of clusters due to the bridging effect of poly (vinyl alcohol) and

- Redispersion was carried out using ultra sonicator by the electrostatic repulsion effect.

In a typical synthesis, 1.9g $FeCl_3$, 1.1gFeSO$_4$ .7H$_2$O were dissolved into15ML deionized water and stirred under a flow of nitrogen. A 0.1g PVA was dissolved into 10ML deionized water and then mixed with the above solution. Under continuous stirring, the pH value of the mixed solution was gradually raised from 6to 11 by adding 7% ammonia solution drop by drop. After the black iron oxide particles precipitated, the slurry was stirred for another 10min and then incubated at 85°C for 60 min. Then the product was deposited magnetically and washed several times with deionized water to eliminate impurities.[12]

Surface Coating of Iron Oxide Nanoparticles

1.5222 g Fe$_3$O$_4$ NPs were sonicated in 100 mL ethanol/water (volume ratio, 1:1) solution for 30min to get uniform dispersion. Then 5% poly (ethylenimine) solution was added to the dispersion under N$_2$ atmosphere at 40°C for 2 h. After that the solution was cooled to room temperature. The prepared PEI-modified Fe$_3$O$_4$ NPs were collected with a magnet, and washed with ethanol, followed by deionized water for three times. Finally, PEI-modified Fe$_3$O$_4$ NPs were dried under vacuum at 70°C. Similarly 5 % Pluronics p123 was also coated onto the surface of nanoparticles in a similar manner.[7]

D .Characterization Techniques

- The morphology, size and structure of the synthesized nanoparticles were determined by high resolution Field emission Scanning Electron Microscope FESEM from JEOL.

- X-Ray diffraction studies were carried out by BRUKER XRD and PANalytical X'per PRO XRD ($\lambda = 1.55$ Å) at 40 kV and 100 mA.

- The Fourier transform Infrared Spectroscopy from Perkin Elmer F100 was used to obtain the chemical composition and nature of functional groups present on the surface of the particle.

- The magnetic properties were studied using VSM 7300, Lakeshore vibrating sample magnetometer.

IV. RESULTS AND DISCUSSION

The synthetic route of the Iron oxide nanoparticles coated with polymers is illustrated in Figure 3.1. Polyvinyl alcohol was firstly mixed with ferric, ferrous salts and re dispersed using ultra sonicator. As an ammonia solution was added into the mixed solution gradually, the burst nucleation happened promptly and generated a large amount of iron oxide nanoparticles in the solution. However, due to the bridging effect of PVA, Iron oxide nanoparticles coated with polymers were flocculated to form large clusters, which facilitated the separation and purification of Iron oxide nanoparticles by magnetic sedimentation. In order to disperse the flocculated Iron oxide nanoparticles in aqueous solution again, Iron oxide cluster suspension kept in sonicator.

A.   Estimation of Morphology of particles using Field Emission Scanning Electron Microscope

The samples were prepared by coating with a conducting material like platinum or gold. These coatings were performed using Sputter coating technique. Then samples were placed in the sample holder for imaging under the electron beam in a FESEM. The imaging was done and images were obtained in various magnifications up to 100,000. The morphology, size and structure of the nanoparticles were characterized using JEOL FESEM. The four various particles synthesized under different conditions were characterized. This analysis showed clearly the advantage of using a surfactant to stabilize the shape of the particles and to obtain a narrow size distribution.

The first set of experiments were done using 1% poly vinyl alcohol solution alone without any polymer which when washed with water resulted in uncoated Iron oxide nanoparticles. Which resulted in clusters with size ranging from 25-30 nm.The second set of experiments was done using 5 % Pluronics p-123 solution, which showed good size distribution but the size was quite big of the order of 45-50 nm.The third set of experiments was done using Poly (ethylenimine) 5 % solution. Which resulted in much lower sized particles of the range from 20-30nm.The fourth set of experiments was done without using any surfactant and

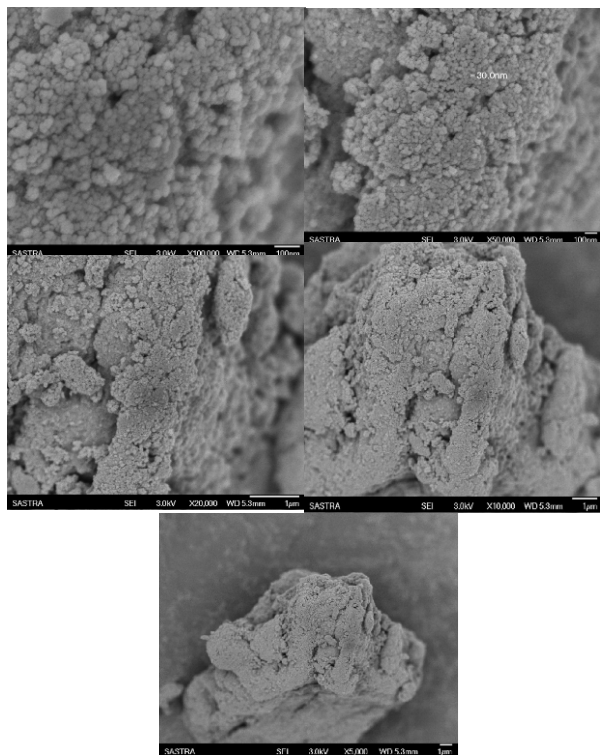polymer which resulted in an irregular morphology of particles.

Fig. 1.1 FESEM images of PVA-coated Iron Oxide Nanoparticles at five various magnifications (*A*) × 100,000 (*B*) × 50,000 (C) × 20,000 (D) × 10,000 (E) × 5,000. The re-dispersed nanoparticles after treating with ultrasonic waves were evident from the images and they were in the size range of 25-30 nm

B.   Estimation of Crystallite Size of the Iron Oxide Nanoparticles Using X-Ray Diffractometer

The X-ray diffraction studies of Iron oxide nanoparticles were analyzed using Bruker and PANalytical x'per PRO X-Ray diffractometer. Both are Powder X-Ray analyzers. The main objective of the analysis was to determine the grain size of the particles when coated with different polymers.

The equation used to calculate was Scherrer equation

$$Dp = 0.94 \lambda$$

$$\beta 1/2 \cos \theta$$

$$Dp = \text{ particle size},$$

$$\beta 1/2 = \text{ Full Width at Half Maximum (FWHM)},$$
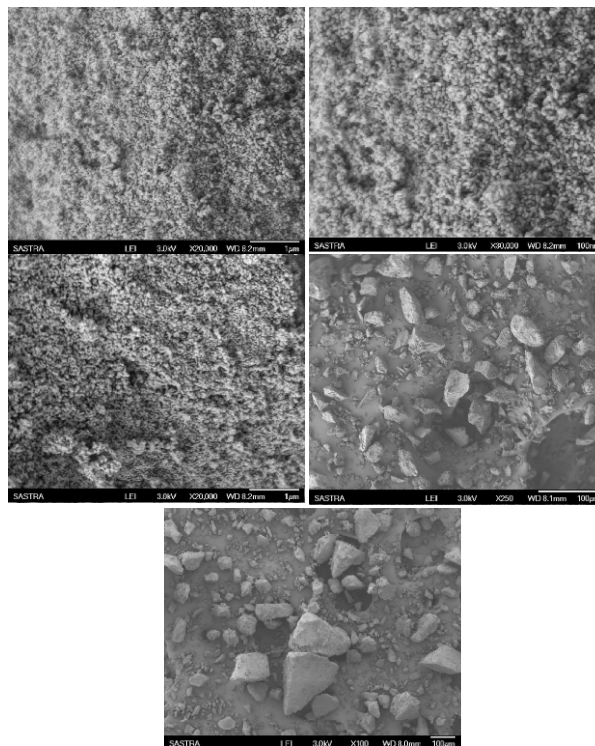
Fig. 1.2 FESEM images of Pluronics p-123-coated Iron Oxide Nanoparticles at five various magnifications (A) × 30,000 (B) × 20,000 (C) × 20,000 (D) × 250 (E) × 100. Uniformly distributed Iron oxide nanoparticles were observed from the images of size ranging from 40-50 nm

$$\lambda = 1.542 \mathring{A} \text{ for copper target}$$

Thus the phases of these iron oxide nanoparticles were verified to the database and found to contain mostly Fe^{3+} atoms and some Fe^{2+} ions.

The standard Miller Indices of Magnetite nanoparticles were found to match with the analyzed particles, the XRD spectra for each sample was compared with the JCPDS# 19-629 standard d values in lattice spacing for Iron Oxide nanoparticles. Some of the matched d **values** were

2.94 Å, 2.92 Å, 2.902 Å for 220 in all the three samples,

2.502 Å, 2.490 Å, 2.502 Å for 311,

2.085 Å, 2.0805 Å for 400,

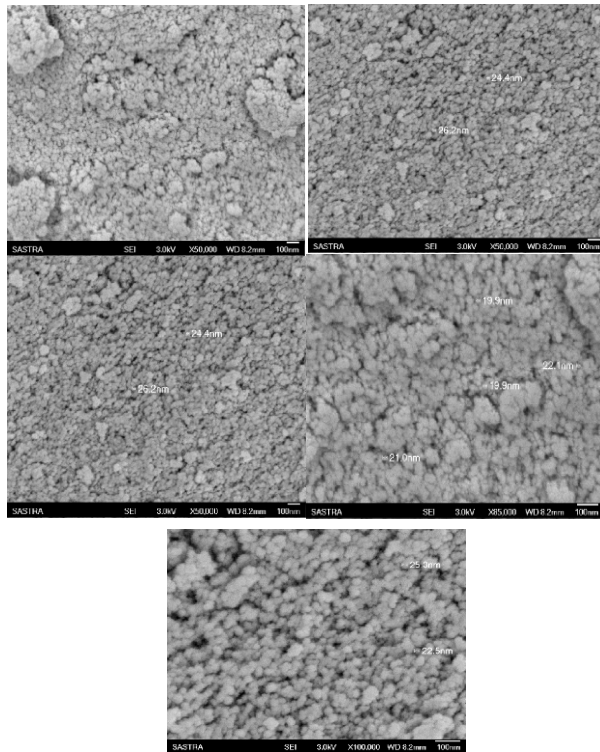1.698 Å, 1.781 Å for 422,

1.598 Å, 1.603 Å, 1.604 Å for 511 and

Fig. 1.3 FESEM images of PEI-coated Iron Oxide Nanoparticles at three different magnifications (A),(B),(C) × 50,000 (D) × 85,000 (E) × 100,000. Uniformly distributed PEI-coated Iron oxide nanoparticles were observed from the images of size ranging from 20-25 nm
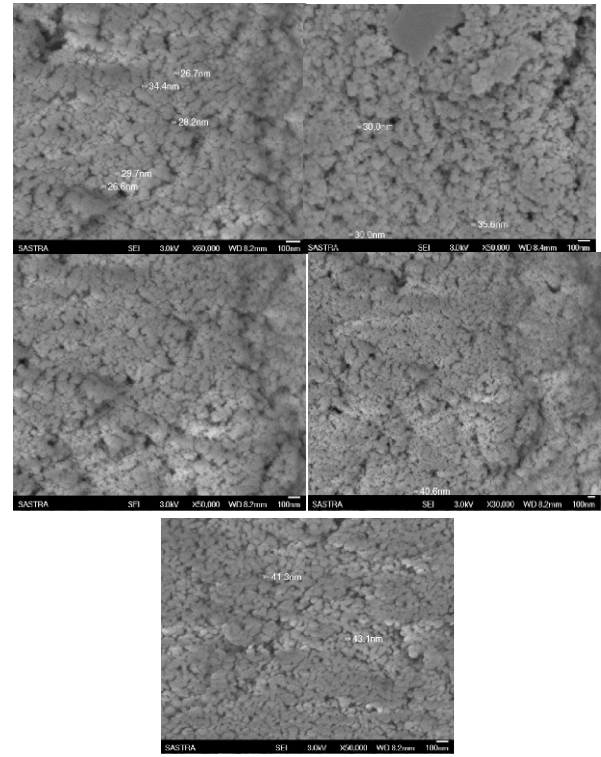

Fig. 1.4 FESEM images of uncoated iron oxide nanoparticles with random size distribution which was due to the absence of surfactant. The size ranges were from 25- 50 nm which is not a uniform size range. The spherical morphology is also not clearly seen in these particles which is evident from the images.
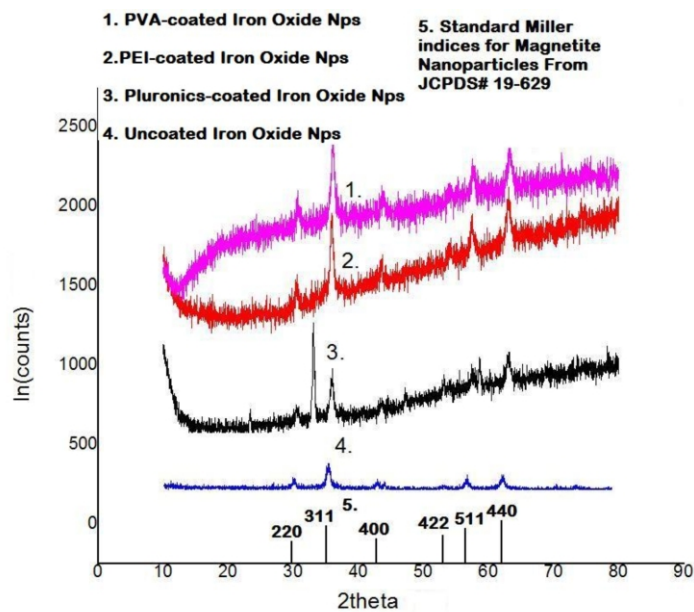
Fig. 2.1 XRD spectra of various Polymer-coated iron oxide nanoparticles. 1. PVA-coated Iron Oxide Nanoparticles 2. PEI-coated Iron Oxide Nanoparticles 3. Pluronics p-123 coated Iron Oxide Nanoparticles 4. Uncoated Iron Oxide Nanoparticles 5. Standard Miller Indices from JCPDS# 19-629

1.469 Å, 1.473 Å, 1.474 Å for 440

Their Crystallinity was found to be high because of the presence of more number of peaks. From all the particles the PEI-coated Iron Oxide nanoparticles were well matched with the standard d values of magnetite nanoparticles. And the grain sizes were calculated using Scherrer formula.[1]

C. Estimation of the nature of functional group present on the surface of the Iron Oxide nanoparticles using Fourier Transform Infra Red spectroscopy

The nature of chemical functional groups present on the surface of the nanoparticles was determined by Fourier Transform Infra red spectroscopy. The samples were analyzed using Perkin Elmer Spectrum F100. Each of the samples showed the characteristic peaks for the functional groups present in all the three polymers such as poly (ethylenimine), Pluronics p-123. 3401.16 O-H Alcohol (3600-3200(b) stretch) 2923.04 C-H Alkanes (2960-2850(s) stretch) 1060.02 C-O Alcohol (1000-1260(s) stretch) 579.05 Fe-O Iron Oxide are the peaks obtained for PVA-Coated iron oxide nanoparticles showing the peaks for the functional groups present in PVA. Similarly FTIR spectra Fig 2.2 shows the characteristic peaks of the functional groups present in other polymers.

D. Estimation of super paramagnetic property of Iron Oxide Nanoparticles using vibrating sample magnetometer VSM:

Discrete magnetic nanoparticles are candidates for numerous applications such as multi-terabit in-2 magnetic storage devices, magnetic refrigeration systems, ferrofluids, catalysts, contrast enhancement agents in magnetic resonance imaging (MRI), site specific drug-delivery and also hyperthermia agents. For biomedical applications such as MRI, drug-delivery and hyperthermia, the nanoparticles have to be biocompatible, have a large enough moment for targeting and display super paramagnetic behavior. Owing to their non-toxicity and strong magnetic susceptibility, magnetite and maghemite Nanoparticles have been extensively researched for biomedical applications. Below a certain size (15 nm for magnetite), magnetite nanoparticles display super paramagnetic behavior with zero remanence and zero coercivity.
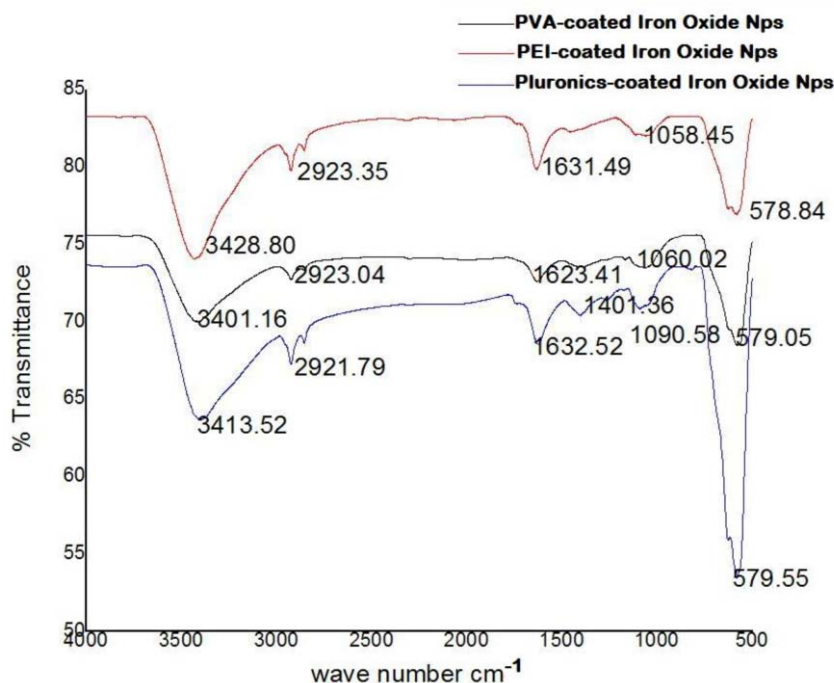

Fig. 2.2 FTIR spectra of three different polymer–coated Iron oxide nanoparticles.
1. PVA-coated Iron oxide Nanoparticles 2. PEI-coated Iron Oxide Nanoparticles 3. Pluronics p-123- coated Iron Oxide Nanoparticles
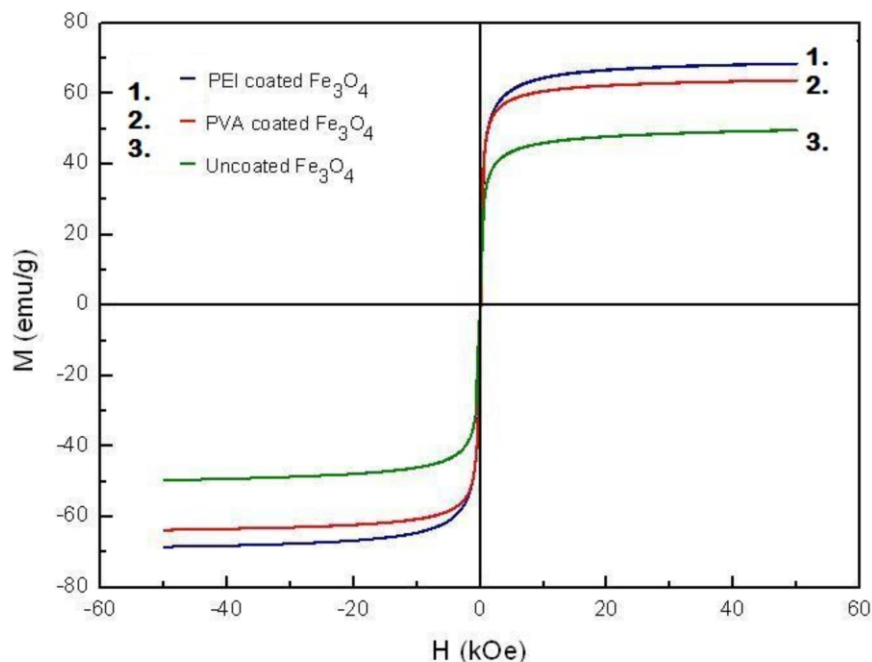
Fig. 3.1 The Vibrating Sample Magnetometer analysis of various polymer-coated Iron Oxide Nanoparticles.
1. PEI- Coated Iron oxide nanoparticles 2.PVA-coated Iron Oxide Nanoparticles 3.Pluronics-coated Iron oxide nanoparticles 4.Uncoated Iron Oxide nanoparticles
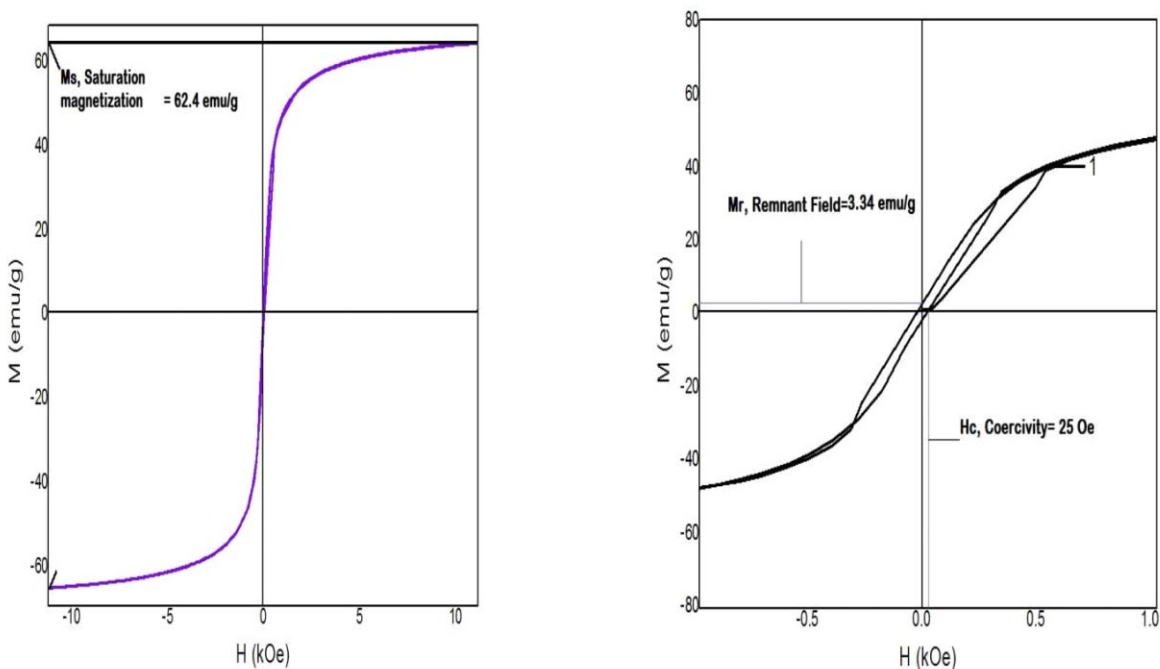

Fig. 3.2 Vibrating Sample Magnetometer analysis for PEI-coated Iron Oxide nanoparticles. The particles exceed the bulk magnetite Ms, value giving 62.4emu/g thus suitable for biomedical applications. By expanding the origin. Hc, coercivity was calculated to be 25 Oe and the remnant field Mr, 3.34 emu/g which is a low value thus proving that these particles are in super paramagnetic state at room temperature
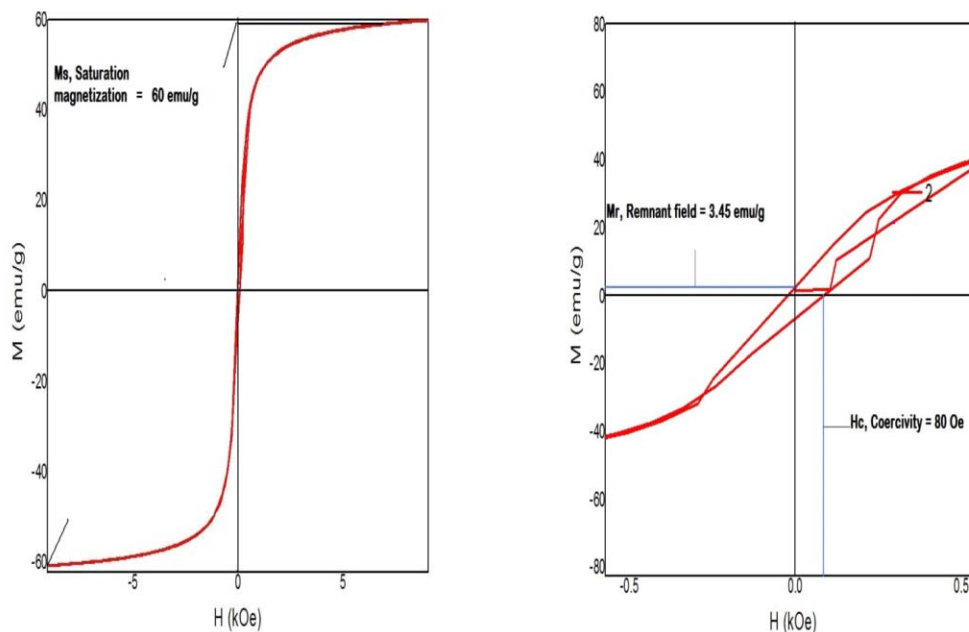
Fig. 3.3 Vibrating Sample Magnetometer analysis for PVA-coated Iron Oxide nanoparticles. The particles exceed the bulk magnetite Ms, value giving 60 emu/g thus suitable for biomedical applications. By expanding the origin. Hc, coercivity was calculated to be 80 Oe and the remnant field Mr, 3.45 emu/g which is a low value thus proving that these particles are in super paramagnetic state at room temperature
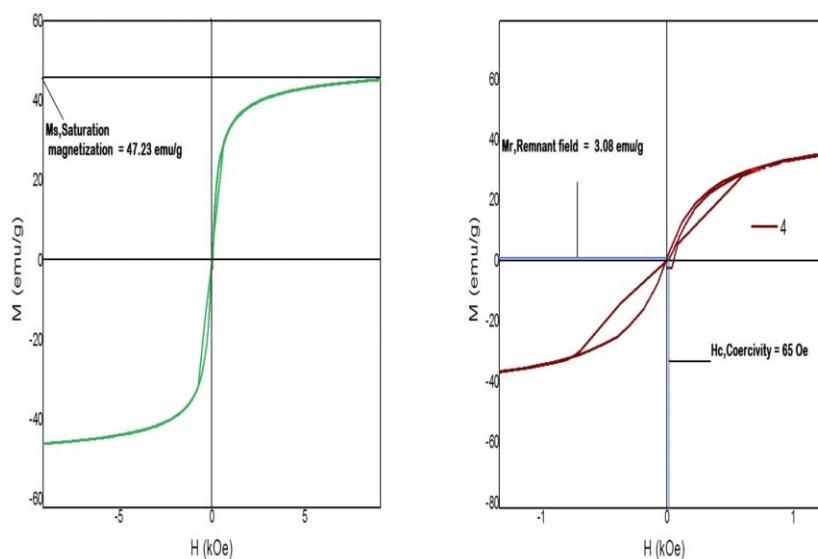

Fig. 3.4 Vibrating Sample Magnetometer analysis for Uncoated Iron Oxide nanoparticles. The particles show saturation magnetization of Ms, value giving 47.23 emu/g lesser than polymer coated particles. By studying the origin. Hc, coercivity was calculated to be 65 Oe and the remnant field was Mr, 3.08 emu/g which is a low value thus proving that these particles are in super paramagnetic state at room temperature

Vibrating Sample Magnetometer studies were carried out to study the effect of phase transformations on the magnetic properties of the nanoparticles. The samples were analyzed by VSM at room temperature to find the saturation magnetization, Ms, remnant magnetization, Mr and coercivity, Hc.[14]

V. CONCLUSION

In this study, a facile and an effective method of preparation and modification of magnetite Nanoparticles with poly (vinyl alcohol) PVA, poly (ethylenimine) PEI, and Pluronics p-123 were performed in order to

produce a super paramagnetic material with the required properties.

By the flocculation and re dispersion method a PVA-coated SPIONS of size ranging from 25-30 nm were obtained. In a similar well known synthesis and surface activation route the PEI-coated SPIONS and Pluronics p-123-coated SPIONS were obtained. The sizes of PEI-coated particles were much lesser ranging from 15-22 nm and that of Pluronics-coated particles were ranging from 35-50 nm. Additionally uncoated Iron Oxide nanoparticles were also synthesized and their sizes were found to be from 50-80 nm. Their crystalline nature, existing phase and grain size were characterized by X-Ray Diffractometer. All the four types of particles were studied under Vibrating Sample Magnetometer VSM to find their super paramagnetic properties. Except that of Uncoated and Pluronics-coated others were found to be super paramagnetic at room temperatures.

By studying all these properties and also confirming the presence of hydrophilic functional groups on their surface these nanoparticles by FTIR. These Polymer-coated super paramagnetic Iron Oxide Nanoparticles can be used as an excellent contrast agent in MRI and also DNA and RNA sequences can be complexed with them for cancer therapies. These tailored nanoparticles can be further tagged and employed as a good targeting molecular probe in cancer diagnosis and treatment. The basic idea behind preferring Poly (ethylenimine) as one of the coating was to attempt development of a Aptamer- SPION bio conjugate for enhanced uptake of drugs in cancer cells. But as the Aptamer which was intended to work on is still in its clinical trials the bio conjugates were unable to be developed. Thus the major application of these nanoparticles will be in combination with an Aptamer which can be very effective in inhibition of DNA replication in cancer cells thereby reducing the cell proliferation.

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