PLOS ONE

RESEARCH ARTICLE

Magnetic Properties of Polyvinyl Alcohol and Doxorubicine Loaded Iron Oxide Nanoparticles for Anticancer Drug Delivery Applications

Muhammad Nadeem[1,2]*, Munir Ahmad[3,4], Muhammad Saeed Akhtar[5], Amiruddin Shaari[1], Saira Riaz[2], Shahzad Naseem[2], Misbah Masood[6], M. A. Saeed[1]*

1 Physics Department, Faculty of Science, Universiti Teknologi Malaysia (UTM), Skudai-81310, Johor, Malaysia, **2** Center of Excellence in Solid State Physics, University of the Punjab, Lahore, 54590, Pakistan, **3** Department of Medical Physics, Institute of Nuclear Medicine and Oncology (INMOL), Lahore, Pakistan, **4** Physics Department, University of Lahore, Lahore, 54600, Pakistan, **5** Divison of Science and Technology, University of Education, Township Campus, Lahore, Pakistan, **6** Department of Oncology, Institute of Nuclear Medicine and Oncology (INMOL), Lahore, Pakistan

* badaninadeem@gmail.com (MN); saeed@utm.my (MAS)

CrossMark
click for updates

OPEN ACCESS

Citation: Nadeem M, Ahmad M, Akhtar MS, Shaari A, Riaz S, Naseem S, et al. (2016) Magnetic Properties of Polyvinyl Alcohol and Doxorubicine Loaded Iron Oxide Nanoparticles for Anticancer Drug Delivery Applications. PLoS ONE 11(6): e0158084. doi:10.1371/journal.pone.0158084

Editor: Bing Xu, Brandeis University, UNITED STATES

Received: June 21, 2015

Accepted: June 9, 2016

Published: June 27, 2016

Copyright: © 2016 Nadeem et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All required information is within the manuscript.

Funding: This work was funded by the Ministry of Higher Education (MOHE) Malaysia and Universiti Teknologi Malaysia (UTM), Skudai, Johor, Malaysia under grant no. 12H75/4F736.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

The current study emphasizes the synthesis of iron oxide nanoparticles (IONPs) and impact of hydrophilic polymer polyvinyl alcohol (PVA) coating concentration as well as anticancer drug doxorubicin (DOX) loading on saturation magnetization for target drug delivery applications. Iron oxide nanoparticles particles were synthesized by a reformed version of the co-precipitation method. The coating of polyvinyl alcohol along with doxorubicin loading was carried out by the physical immobilization method. X-ray diffraction confirmed the magnetite (Fe_3O_4) structure of particles that remained unchanged before and after polyvinyl alcohol coating and drug loading. Microstructure and morphological analysis was carried out by transmission electron microscopy revealing the formation of nanoparticles with an average size of 10 nm with slight variation after coating and drug loading. Transmission electron microscopy, energy dispersive, and Fourier transform infrared spectra further confirmed the conjugation of polymer and doxorubicin with iron oxide nanoparticles. The room temperature superparamagnetic behavior of polymer-coated and drug-loaded magnetite nanoparticles were studied by vibrating sample magnetometer. The variation in saturation magnetization after coating evaluated that a sufficient amount of polyvinyl alcohol would be 3 wt. % regarding the externally controlled movement of IONPs in blood under the influence of applied magnetic field for in-vivo target drug delivery.

Introduction

Drug loaded nanoparticles (NPs) based cancer therapy possesses the potential to overcome the toxicity of the drug and its poor control on dosing when custom combination therapies are

RETRACTED

employed [1–4]. Since all the drugs used for cancer therapy have some side effects, which usually arise due to non-specificity of drug actions. For instance, in tumor therapy, side effects of cytotoxic drugs like bone marrow depression and reduction in immunity could be harmful to an extent that the therapy termination is mandatory [5, 6].

Precise and targeted delivery of drugs to the tumor have got much importance in order to address the limitations of traditional therapies; therefore, search for drug delivery methods has been prompted in last few years. The selectively targeted chemotherapeutic agents to the tumor can provide more effective cancer therapy. The problems associated with conventional chemotherapy can be avoided by using magnetic drug delivery system *i.e.* IONPs carriers targeted by an external magnetic field [7–11]. Alexiou *et al.* showed that magnetically targeted drug delivery can completely reduce the tumor in rabbits without any side effects. Furthermore, the applied drug dose could cut down as compared to that one is used regularly [7, 12].

The development of IONPs for target drug delivery needs to address the issues such as size and shape of the particles, surface coating and drug loading, in-vivo distribution of particles and most importantly the magnetic behavior of these particles [13, 14]. Issa *et al.* reported in 2011, that clusters of nanoparticles formed in the blood stream due to the high surface to volume. The absorption of plasma proteins on the nanoparticles surface results in activation of the clearance mechanism by macrophage cells before they approach the site to be targeted [15]. Recently, Obaidat *et al.* and Issa *et al.* presented concise reviews on surface effects in magnetic nanoparticles concerned with biomedical applications and for efficient hyperthermia respectively [14, 16]. Previously, authors reported that IONPs without any surface modification can stay in the blood for almost 4 hours and can evade reticulo-endothelial (RES) system [17]. The only issue with these particles is, without surface modification they are unable to load the sufficient amount of drug [18].

Various kinds of biocompatible and hydrophilic polymers including dextran [19], poly ethylene glycols (PEG) [20], PVA [21] and poly vinyl pyrrolidone (PVP) [22] can be used to functionalize the surface of IONPs to increase the circulation time and drug loading. The surface modification affects the magnetic properties of IONPs. The magnetic properties mainly saturation magnetization depends on the size of IONPs and surface effects that become significant as the size decreases [14, 23].

In most of the established medical applications, 10 nm is the preferred size of nanoparticles. At this size limit, the magnetic energy of the nanoparticles minimized up to the extent that they become single magnetic domain. Obaidat *et al.* observed the superparamagnetic behavior of nanoparticles when synthesized at the above mentioned scale without surface modification and their fast response to applied magnetic field keeping the remanence and coercivity negligible [16]. However, surface modification of nanoparticles can contribute in varying the size and magnetic behavior. Surface spin disorder was reported to occur in IONPs and lead to high magnetic anisotropy [24], which was initially explained in terms of a dead magnetic layer at the surface [25] and afterwards to the disordered surface spin [26, 27]. On the application of high magnetic fields, this disordered surface spin in nanoparticles could be a hurdle to attain saturation [28, 29]. The reduction in saturation magnetization with increasing PVA concentration was also reported by Kayal *et al.* [30]. The dilution effect of absorbed water whether it comes from PVA or DOX along with hydroxyl content (-OH) enormously affects the surface of nanoparticles by distortion in the alignment of surface spins [31].

Several studies presented the synthesis and characterization of PVA coated iron oxide nanoparticles but the upper limit of PVA concentration was not reported yet. In the present work, PVA is chosen for coating the magnetic nanoparticles, and Doxorubicin drug (DOX) is used as an anti-cancer agent. The main goal and novelty of the present work is to conjugate the DOX with PVA coated (3 and 6wt%) iron oxide nanoparticle carriers to study the magnetic behavior

RETRACTED

for in-vivo target drug delivery and to speculate judiciously the maximum concentration of PVA related to evaluation of saturation magnetization that would be necessary for the controlled movement of IONPs in blood under the influence of applied magnetic field. Generally, there is no minimum saturation magnetization reported so for regarding controlled movement of IONPs in blood but at much smaller values of magnetization; the applied external magnetic field required for controlled movement might reach to very high value [32].

Experimental Section

Chemicals

All reagents, iron (II) chloride, iron (III) chloride, sodium hydroxide and polyvinyl alcohol were purchased from MD Interactive Enterprise (JM051032-V) Malaysia and used without further purification. De-ionized water was used as a solvent in all experiments. Doxorubicin hydrochloride (DOX-HCl) was used for the drug loading.

Instruments

Bruker D8 Advance Diffractometer with Cu-Kα (λ = 1.5406 Å) radiation was used for X-ray powder diffraction measurements. XRD data was recorded across a 2θ range of 20° to 80° using a step size of 0.02°. TEM, HRTEM, and selected area electron diffraction (SAED) images were collected using JEM-2100 transmission electron microscope with accelerating voltage of 200 kV. Compositional analysis was carried out by EDS. Lake Shore's 7407 Vibrating Sample Magnetometer was used to obtain the magnetic measurements at room temperature with an applied magnetic field ranging from 0 to 10 kOe. FTIR spectroscopy (PerkinElmer Spectrum) with a resolution of 4 cm^{-1} was used to investigate the binding energies of all the PVA coated, and DOX loaded samples at room temperature.

Syntheses of uncoated and polymer (PVA) coated iron oxide nanoparticles

Uncoated iron oxide nanoparticles were synthesized by co-precipitation method. The synthesis methodology was same as reported by the author's previous work published elsewhere [33]. Firstly, 240 mL solution of $FeCl_2.4H_2O$ (0.6 M) and $FeCl_3.6H_2O$ (1.08 M) was prepared in deionized water. The prepared solution was stirred at 600 rpm for 25 min. to have complete dissolution of reactants at 60°C. The obtained solution has iron (II) chloride and iron (III) chloride with a molar ratio of 1:1.8. Afterward, this solution was poured drop wise in separately prepared 400 mL solution of NaOH (1.6 M) and maintained at stirring (800 rpm) for 25 min. at 60°C. As the reaction proceeds, a black precipitate of IONPs was formed but remained suspended in a base solution having pH of 11. The black precipitates were collected in the beaker with the help of strong permanent magnet and washed four times with deionized water. All the residual were removed with washing and the final pH of uncoated IONPs suspension lowered down to 7.2. The particles were then dried in vacuum oven at 40°C before characterization. It is worth mentioning that to avoid oxidation of iron from Fe^{2+} to Fe^{3+}, synthesis was performed with a slightly low ratio of Fe^{+3} rather than utilizing the nitrogen environment as reported earlier [30].

The coating of PVA on IONPs was performed with slight modifications in reformed method as proposed by Kayal *et al.* [30]; 3 wt.% PVA coating was achieved at 80°C by adding deliberately one gram of dried nanoparticles and three grams of PVA in nighty six grams of DI water and complete dissolution of PVA was achieved under vigorous stirring. The final solution had the ratio of IONPs: PVA = 1:3 and temperature was then allowed to decrease by

RETRACTED

switching off the temprature controller. The solution remained stirred for 20 hours at room temperature in order to achieve coating. 3 wt. % PVA functionalized IONPs were separated with the permanent magnet and washed three times with deionized water. Finally, pure PVA coated IONPs were separated and dried at 35°C after removal of all the residual with washing. 6 wt. % PVA coated IONPs were also obtained by repeating the above mentioned procedure with only one variation i.e. molar ratio of IONPs: PVA = 1:6. The aqueous suspension of prepared uncoated nanoparticles (on left) and PVA coated IONPs separated with 200 nm filter (on right), and the effect of the external magnetic field are illustrated in Fig 1.

Loading of doxorubicin on uncoated and PVA coated iron oxide nanoparticles

Doxorubicin hydrochloride (DOX-HCl) anticancer drug was loaded onto the uncoated and 3/6 wt. % PVA coated IONPs. The DOX loading of IONPs was carried out by dissolving 10 mg of DOX in 100 ml of distilled water by shaking with orbital shaker for 10 minutes followed by the addition of 50 mg IONPs particles and vigorous stirring (300 rpm) at 25°C for 22 hours [34]. A strong permanent magnet was used to separate the DOX loaded IONPs, which were then dried in vacuum oven at 40°C. Fig 2 shows the aqueous suspension of DOX loaded PVA coated IONPs and effect of external magnetic field on them.

Results and Discussion

Crystallographic structure and Morphology

XRD patterns of uncoated, 3 wt. % and 6wt. % PVA coated, 3 wt. % and 6wt. % PVA coated DOX loaded IONPs are shown in Fig 3A–3E. XRD analysis reveals that all the samples are polycrystalline in nature with broad diffraction peaks due to the nano-size of the crystallites. The peaks along (220), (311), (400), (422), (440), (422), (511), (440) and (533) lattice planes correspond to the standard pattern of face centered cubic spinel Fe_3O_4 (JCPDS card No. 82–1533). The phase purity of complexes is evident from the absence of (210) and (300) planes corresponding to the maghemite (γ-Fe_2O_3). The observed decrement in the intensity of diffraction peaks reveals that with the increasing concentration of PVA and DOX loading, the

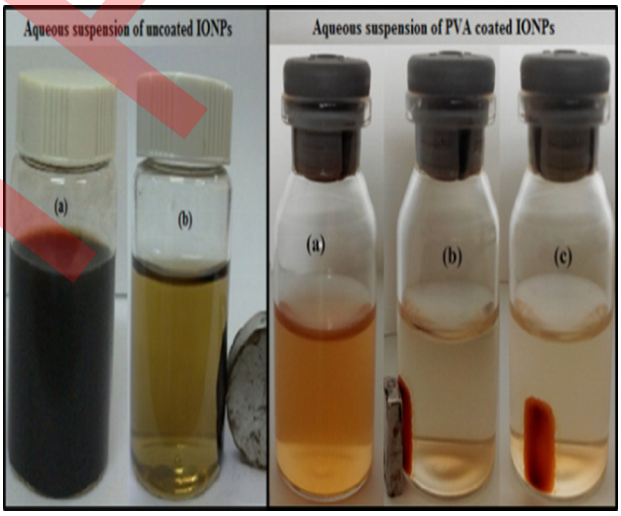

Fig 1. Aqueous suspension and effect of the external magnetic field on both uncoated and PVA coated IONPs.

doi:10.1371/journal.pone.0158084.g001

RETRACTED

Fig 2. Aqueous suspension of DOX loaded PVA coated IONPs (a) and the effect of the external magnetic field on these particles (b).

doi:10.1371/journal.pone.0158084.g002

crystallinity of the complexes decreases due to "masking" effect of the polymer. Fig 3B–3E shows the broadening of XRD peaks due to a reduction in crystallite size of PVA coated and DOX loaded IONPs [5, 35].

Microstructure of the nanoparticles was further studied in detail with the help of transmission electron microscopy (TEM), high resolution transmission electron microscopy (HRTEM) and selected area electron diffraction (SAED). HRTEM image (Fig 4A) confirms the crystalline nature of the uncoated IONPs. The experimentally calculated inter planner spacings 0.2521, 0.4862 and 0.2958 nm corresponding to the (311), (111) and (220) planes respectively are in fair agreement with that expected for face-centered cubic spinel structure of Fe_3O_4. SAED

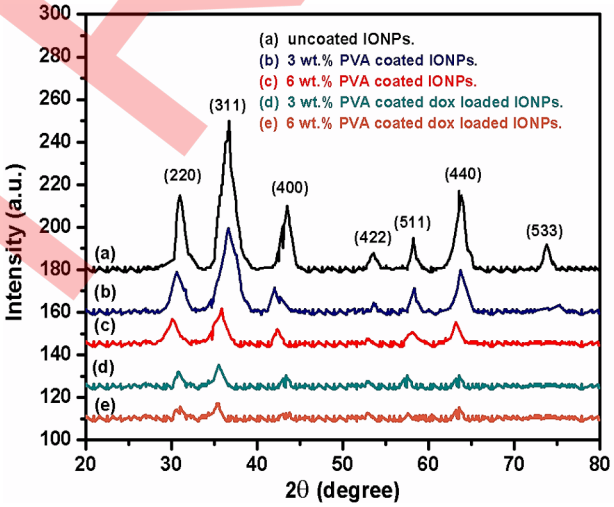

Fig 3. XRD patterns of IONPs complexes. (a) Uncoated IONPs, (b) 3 wt. % PVA coated IONPs, (c) 6wt. % PVA coated IONPs, (d) 3 wt. % PVA coated DOX loaded IONPs and (e) 6 wt.% PVA coated DOX loaded IONPs.

doi:10.1371/journal.pone.0158084.g003

RETRACTED

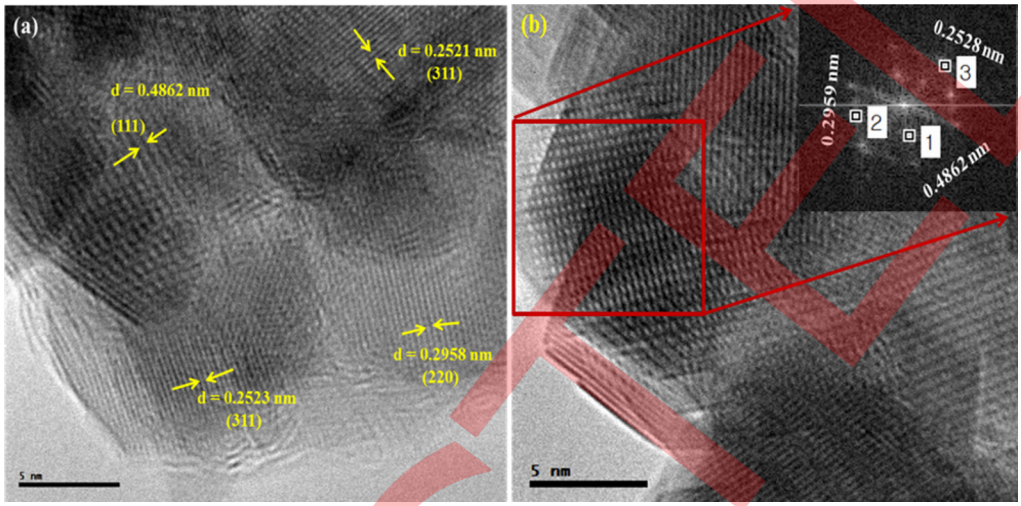

Fig 4. HRTEM (a) and SAED (b) images of uncoated IONPs.

doi:10.1371/journal.pone.0158084.g004

pattern (Fig 4B) shows a set of points obtained by diffraction of electrons from various planes of cubic Fe_3O_4 [36].

Compositional analysis

The compositional analyses of the complexes were carried out by obtaining the energy dispersive spectra (EDS) as shown in Fig 5. The EDS analysis confirms that iron, carbon, and oxygen are the core elements in the uncoated, PVA coated and DOX loaded IONPs. The weight and atomic percentages along with binding energies of iron, oxygen, and carbon in IONPs complexes are depicted in Fig 5A–5C. Fig 5(A) reveals that the wt. % of iron and oxygen in uncoated IONPs are 71.14 and 28.86 respectively. The data obtained from EDS spectra is also

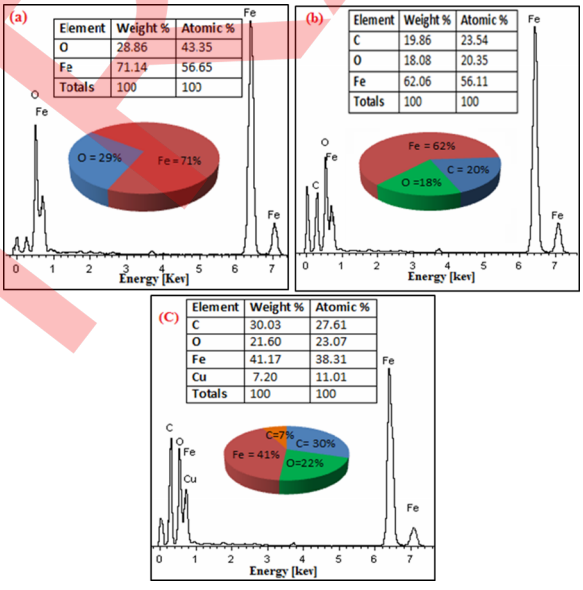

Fig 5. EDS spectra along with atomic and weight percentage of elements in IONPs complexes. (a) uncoated (b) 3 wt.% PVA coated and (c) DOX loaded 3 wt.% PVA coated IONPs.

doi:10.1371/journal.pone.0158084.g005

RETRACTED

presented in the form of chart and table (insets of Fig 5A–5C) for reader's convenience. Fig (5B) shows the wt. % of iron, oxygen, and carbon in 3 wt. % PVA coated IONPs as 62.06, 18.08 and 19.86 respectively. For DOX loaded 3 wt. % PVA coated IONPs, the wt. % of iron, oxygen and carbon is 41.17, 21.60 and 30.03, respectively as shown in Fig (5C). The presence of PVA and confirmation of DOX loading are evident from the decrement in iron peaks and appearance of additional peak of carbon along with the ratios between atomic and weight percentages of carbon and oxygen (Fig 5B and 5C). The appearance of copper surely comes from copper grid used for sample preparation. The binding energies of iron for all the complexes are presented by peaks observed at the energy values of 0.7, 6.5, and 7 keV [37, 38].

Conjugation of drug and polymer attachment with IONPs

The FTIR is a suitable technique to find the attachment of polymer (PVA) to the IONPs and conjugation of the drug (DOX) with the PVA coated IONPs. Fig 6(A) exhibits the spectra of uncoated IONPs in which the absorption peak at 3403 cm^{-1} corresponds to O–H stretching (ν) vibrations and the peak at 1630 cm^{-1} belongs to H–O–H bending (δ) vibrations due to adsorbed water on the surface of uncoated IONPs. The absorption band of uncoated IONPs at 620 cm^{-1} attributes to the stretching vibrations of M_{Th}–O–M_{Oh}, where M_{Th} and M_{Oh} are the tetrahedral and octahedral positions occupied by the metallic particles. Fig 6B & 6C) reveals the spectra of pure PVA polymer and DOX with various absorption peaks accordingly with the database[39].

The spectrum of IONPs coated with 3 wt.% PVA given in Fig 6 (D) shows the absorption peaks at 3375 cm^{-1} attributing to stretching vibration of O–H band (alcoholic). The band at 2926 cm^{-1} belongs to asymmetric CH_2 stretching vibration where the additional peak at 2853 cm^{-1} is due to the symmetric C–H stretching vibration. The absorption peak at 1630 cm^{-1} divulges the H–O–H bending (δ) vibrations resulted from adsorbed water. Furthermore, the peaks at 1420 cm^{-1} and 836 cm^{-1} are related to C–C stretching vibrations and CH_2 rocking respectively. The contribution of metal is confirmed from the appearance of ν(M–O–C (M = Fe)) band at 1058 cm^{-1} along with the absorption peaks at 605 cm^{-1} and 550 cm^{-1} resulted from stretching vibrations of M_{Th}–O–M_{Oh} [40].

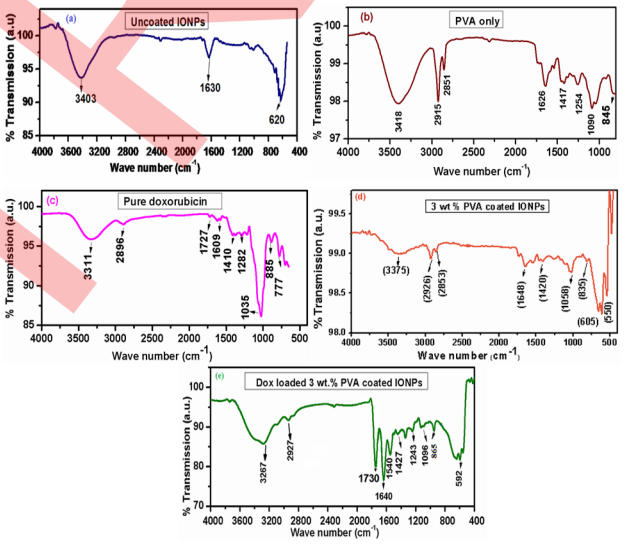

Fig 6. FTIR spectra (a) uncoated, (b) Pure PVA, (c) Pure Doxorubicin, (d) 3 wt.% PVA coated and (e) DOX loaded 3 wt.% PVA coated IONPs.

doi:10.1371/journal.pone.0158084.g006

RETRACTED

The FTIR spectrum of 3 wt.% PVA coated IONPs after DOX loading is shown in Fig 6(E). The N–H stretching vibrations (3267 cm−^{1}), which are appeared in DOX loaded sample and overlap with that of alcoholic O–H band (3375 cm^{-1}) observed in case of 3 wt.% PVA coated IONPs [41]. By comparing the FTIR spectra of pure DOX with that of DOX loaded 3 wt. % PVA coated IONPs, one can conclude that shift of band at 3375 cm−^{1} to subordinate frequency 3267 cm^{-1} confirms the conjugation of DOX with PVA coated IONPs. This conjugation can be further explained by the interaction of–OH groups of PVA with–NH_2 groups of DOX via hydrogen bonding. The N–H stretching vibrations in DOX loaded 3 wt. % PVA coated IONPs appear at a lower frequency *i.e.* 865 cm−^{1} compared to that observed in pure DOX at 885 cm−^{1} validates the above mentioned conjugation [42].

Size effect

For in-vivo bio-distribution, the size of nanoparticles has major significance, which decides the routes and retention time of these particles in the body. The size, surface morphology, coating and the size distribution of the synthesized nanoparticle complexes were studied comparatively in detail with a transmission electron microscope (TEM). The TEM images (Fig 7A–7C) show the average diameter of nanoparticles for all complexes. For uncoated IONPs, TEM image (Fig 7A) discloses that the agglomeration is still there even after dispersion in ethanol and shape of the nanoparticles is not completely spherical. The average diameter obtained for uncoated IONPs is 11.018 nm. The ability of PVA molecules to disperse the IONPs when coated with a polymer (3 wt. % PVA) is confirmed by the observation of well individualized PVA wrapped IONPs with spherical shape (Fig 7B). The PVA coated nanoparticles with an average diameter of 9.644 nm are obtained, and one can conclude that PVA supports to avoid agglomeration

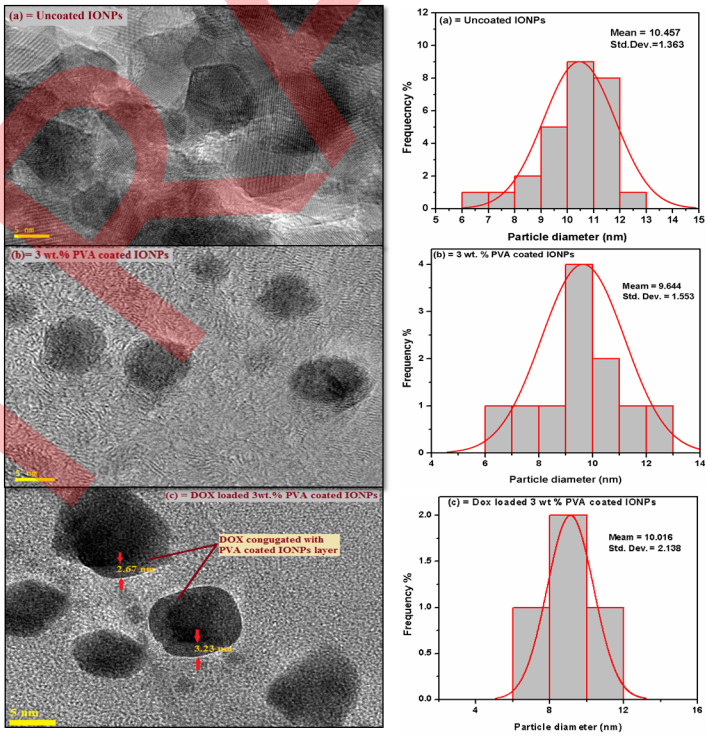

Fig 7. TEM images and size distribution of IONPs complexes (a) uncoated, (b) 3 wt. % PVA coated and (c) 3 wt. % PVA coated DOX conjugated IONPs.

doi:10.1371/journal.pone.0158084.g007

RETRACTED

and reduces the particle size up to some extent as reported earlier [13, 43]. It is important to mention here that, when DOX is loaded onto the PVA coated IONPs; their average diameter is observed to increase slightly by conjugation of DOX and becomes 10.42 nm (Fig 7C). This conjugation of DOX with PVA coated nanoparticles can be further confirmed by the existence of 2.5–3.5 nm thick layers around the particles. Thus the size of the IONPs obtained in the present study is fine enough to escape engulfment by the Reticulo-endothelial System (RES) of the body or circulating macrophages, thus having a better therapeutic efficiency due to increased residence time in the blood [44] and IONPs can behave as a "single super spin", which is good for magnetically targeted drug delivery [37].

Magnetic properties

The magnetic study of all samples reveals that the IONPs exhibit superparamagnetic behavior since hysteresis curves (Fig 8) show the absence of remanence and coercivity. The observed high magnetic response of these particles originates from the size dependent magnetic properties as expected. The existence of single magnetic domain in IONPs complex when the particles are small enough results in novel property termed as "single super spin" [45–47]. Saturation magnetization (M_s) of uncoated, PVA coated and DOX loaded IONPs was observed at an applied field of 10000 Oe. Saturation magnetization (M_s) of uncoated IONPs (Fig 8A) has a value of 70.07 emu less than that of bulk magnetite 88 emu [48–50]. The saturation magnetization of DOX loaded IONPs before polymer coating is about 62 emu that is less than that of uncoated IONPs. For 3 and 6 wt. % PVA coated IONPs, saturation magnetization (Ms) is found to be reduced significantly to values of 54.42 and 35.07 emu, respectively. The rapid decrease in Ms with increasing concentration of PVA polymer coating is established earlier [51]. This is due to the radical–OH group of PVA and dilution effect from adsorbed water. TEM shows that after PVA coating, the size of the particles reduces and the surface effects might cause Ms to decrease [31]. Literature suggests that, if surfactant is coated on IONPs, the surfactant layer can be considered as a dead layer at the surface and observed reduction in magnetization would cause by the quenching of surface moments [52]. Boyer *et al.* [53] proposed

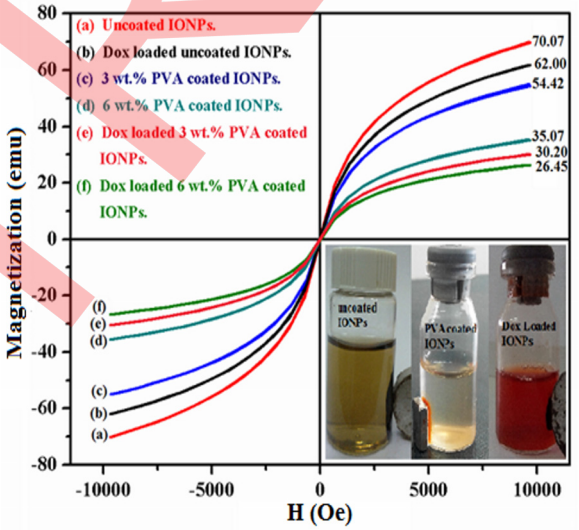

Fig 8. Magnetic profile of IONPs complexes at room temperature, (a) uncoated, (b) DOX loaded uncoated, (c) 3wt. % PVA coated, (d) 6wt. % PVA coated, (e) DOX loaded 3wt. % PVA coated and (f) DOX loaded 6wt. % PVA coated IONPs.

doi:10.1371/journal.pone.0158084.g008

RETRACTED

that the hydroxyl environment of blood might also result in a reduction of saturation magnetization of nanoparticles during the in-vivo study. However, DOX loading on IONPs can change the alignment of surface atomic spins caused by the broken exchange that ultimately reduces the coordination between surfaces spins [35]. Thus, drug loading and polymer coating on IONPs can reduce the M_s to 26.45 emu but the magnetic behavior remains unchanged *i.e.* superparamagnetic. The observed magnetic characteristics of IONPs are decent for delivering the drug to the target site when these particles are guided magnetically.

Conclusions

Superparamagnetic IONPs suspensions in ultra-pure water were prepared with an effective and simple scheme employed in reformed co-precipitation method. To avoid oxidation of iron from Fe^{+2} to Fe^{+3}, synthesis was performed with a slightly low ratio of Fe^{+3} rather than utilizing the nitrogen environment. TEM pattern clearly indicates a mean particle size of ~10 nm for iron oxide particles. High resolution transmission electron microscopy (HRTEM) and selected area electron diffraction (SAED) confirms the crystalline nature of IONPs. PVA coating and DOX loading was confirmed by XRD, TEM, EDS and FTIR. The saturation magnetization being the most important factor for target drug delivery via IONPs guided by external magnetic field has been optimized depending on the PVA concentration and magnetic studies suggest that the PVA concentration of 3 wt. % after DOX loading resulted in saturation magnetization having fine enough value. Since, at higher concentrations of PVA, one may lose the control over the drug delivery via external magnetic field due to a reduction in the saturation magnetization. It would be difficult to guide the particles having smaller magnetizations in the blood vessels where the environment is completely different based on skin, tissue etc. The synthesized IONPs seem to have potential applications in diagnostic and therapeutic fields of biomedicine.

Acknowledgments

The authors would like to acknowledge the Ministry of Higher Education (MOHE) Malaysia and Universiti Teknologi Malaysia (UTM) Skudai, Johor, Malaysia for financial support under grant no.12H75/4F736.

Author Contributions

Conceived and designed the experiments: MN MAS MA. Performed the experiments: MN MAS MA MSA. Analyzed the data: MN MAS MA AS. Contributed reagents/materials/analysis tools: MN MAS MA SR SN. Wrote the paper: MN MAS MA MSA MM.

References

1. Sakulkhu U, Mahmoudi M, Maurizi L, Salaklang J, Hofmann H. Protein corona composition of superparamagnetic iron oxide nanoparticles with various physico-chemical properties and coatings. Scientific reports. 2014; 4.
2. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Annual review of medicine. 2012; 63:185–98. doi: 10.1146/annurev-med-040210-162544 PMID: 21888516
3. Yan Y, rnmalm M, Caruso F. Particle carriers for combating multidrug-resistant cancer. ACS nano. 2013; 7(11):9512–7. doi: 10.1021/nn405632s PMID: 24215340
4. Ma L, Kohli M, Smith A. Nanoparticles for combination drug therapy. ACS nano. 2013; 7(11):9518–25. doi: 10.1021/nn405674m PMID: 24274814
5. Mahmoudi M, Simchi A, Imani M, Milani AS, Stroeve P. Optimal Design and Characterization of Superparamagnetic Iron Oxide Nanoparticles Coated with Polyvinyl Alcohol for Targeted Delivery and Imaging†. The Journal of Physical Chemistry B. 2008; 112(46):14470–81. doi: 10.1021/jp803016n PMID: 18729404

RETRACTED

6. Douziech-Eyrolles L, Marchais H, Hervé K, Munnier E, Soucé M, Linassier C, et al. Nanovectors for anticancer agents based on superparamagnetic iron oxide nanoparticles. International journal of nanomedicine. 2007; 2(4):541. PMID: 18203422
7. Alexiou C, Schmid RJ, Jurgons R, Kremer M, Wanner G, Bergemann C, et al. Targeting cancer cells: magnetic nanoparticles as drug carriers. European biophysics journal. 2006; 35(5):446–50. PMID: 16447039
8. Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2005; 26(18):3995–4021. PMID: 15626447
9. Pankhurst QA, Connolly J, Jones S, Dobson J. Applications of magnetic nanoparticles in biomedicine. Journal of physics D: Applied physics. 2003; 36(13):R167.
10. Alexiou C, Arnold W, Klein RJ, Parak FG, Hulin P, Bergemann C, et al. Locoregional cancer treatment with magnetic drug targeting. Cancer research. 2000; 60(23):6641–8. PMID: 11118047
11. Lübbe AS, Bergemann C, Riess H, Schriever F, Reichardt P, Possinger K, et al. Clinical experiences with magnetic drug targeting: a phase I study with 4′-epidoxorubicin in 14 patients with advanced solid tumors. Cancer research. 1996; 56(20):4686–93. PMID: 8840985
12. Alexiou C, Arnold W, Hulin P, Klein R, Schmidt A, Bergemannand C, et al. Therapeutic efficacy of ferrofluid bound anticancer agent. Magnetohydrodynamics. 2001; 37:318–22.
13. Wahajuddin SA. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. International journal of nanomedicine. 2012; 7:3445. doi: 10.2147/IJN.S30320 PMID: 22848170
14. Issa B, Obaidat IM, Albiss BA, Haik Y. Magnetic nanoparticles: surface effects and properties related to biomedicine applications. International journal of molecular sciences. 2013; 14(11):21266–305. doi: 10.3390/ijms141121266 PMID: 24232575
15. Issa B, Qadri S, Obaidat IM, Bowtell RW, Haik Y. PEG coating reduces NMR relaxivity of Mn0. 5Zn0. 5Gd0. 02Fe1. 98O4 hyperthermia nanoparticles. Journal of Magnetic Resonance Imaging. 2011; 34 (5):1192–8. doi: 10.1002/jmri.22703 PMID: 21928382
16. Obaidat IM, Issa B, Haik Y. Magnetic Properties of Magnetic Nanoparticles for Efficient Hyperthermia. Nanomaterials. 2015; 5(1):63–89.
17. Ahmad M, Rashid K, Nadeem M, Masood K, Ali S, Nafees M, et al. A simple method to prepare aqueous dispersion of iron oxide nanoparticles and their biodistribution study. Journal of Colloid Science and Biotechnology. 2012; 1(2):201–9. doi: 10.1166/jcsb.2012.1021
18. Javed KR, Ahmad M, Ali S, Butt MZ, Nafees M, Butt AR, et al. Comparison of Doxorubicin Anticancer Drug Loading on Different Metal Oxide Nanoparticles. Medicine. 2015; 94(11):e617. doi: 10.1097/MD.0000000000000617 PMID: 25789952
19. Berry CC, Wells S, Charles S, Aitchison G, Curtis AS. Cell response to dextran-derivatised iron oxide nanoparticles post internalisation. Biomaterials. 2004; 25(23):5405–13. PMID: 15130725
20. Zhang Y, Kohler N, Zhang M. Surface modification of superparamagnetic magnetite nanoparticles and their intracellular uptake. Biomaterials. 2002; 23(7):1553–61. PMID: 11922461
21. Cavalieri F, Chiessi E, Villa R, Vigano L, Zaffaroni N, Telling MF, et al. Novel PVA-based hydrogel microparticles for doxorubicin delivery. Biomacromolecules. 2008; 9(7):1967–73. doi: 10.1021/bm800225v PMID: 18533701
22. D'Souza AJM, Topp EM. Release from polymeric prodrugs: linkages and their degradation. Journal of pharmaceutical sciences. 2004; 93(8):1962–79. PMID: 15236447
23. Nikiforov VN, Filinova EY. Biomedical applications of magnetic nanoparticles. Magnetic Nanoparticles. 2009:393–455.
24. Batlle X, Del Muro MG, Labarta A. Interaction effects and energy barrier distribution on the magnetic relaxation of nanocrystalline hexagonal ferrites. Physical Review B. 1997; 55(10):6440.
25. Berkowitz A, Schuele W, Flanders P. Influence of Crystallite Size on the Magnetic Properties of Acicular γ-Fe2O3 Particles. Journal of Applied Physics. 1968; 39(2):1261–3.
26. Batlle X, Pérez N, Guardia P, Iglesias O, Labarta A, Bartolomé F, et al. Magnetic nanoparticles with bulklike properties. Journal of Applied Physics. 2011; 109(7):07B524.
27. Bedanta S, Kleemann W. Supermagnetism. Journal of Physics D: Applied Physics. 2009; 42 (1):013001.
28. Papaefthymiou GC. Nanoparticle magnetism. Nano Today. 2009; 4(5):438–47.
29. Ahmed SR, Ogale S, Papaefthymiou GC, Ramesh R, Kofinas P. Magnetic properties of CoFe2O4 nanoparticles synthesized through a block copolymer nanoreactor route. Applied physics letters. 2002; 80(9):1616–8.
30. Kayal S, Ramanujan R. Doxorubicin loaded PVA coated iron oxide nanoparticles for targeted drug delivery. Materials Science and Engineering: C. 2010; 30(3):484–90. doi: 10.1016/j.msec.2010.01.006

RETRACTED

31. Martinez B, Obradors X, Balcells L, Rouanet A, Monty C. Low temperature surface spin-glass transition in γ-Fe 2 O 3 nanoparticles. Physical Review Letters. 1998; 80(1):181.
32. Dobson J. Magnetic nanoparticles for drug delivery. Drug Development Research. 2006; 67(1):55–60. doi: 10.1002/ddr.20067
33. Nadeem M, Ahmad M, Saeed M, Shaari A, Riaz S, Naseem S, et al. Uptake and clearance analysis of Technetium99m labelled iron oxide nanoparticles in a rabbit brain. IET Nanobiotechnology. 2015.
34. Kuznetsov A, Filippov V, Kuznetsov O, Gerlivanov V, Dobrinsky E, Malashin S. Magn. Polymer Magnetic particles in Biomedical Application. J Magn Mater. 1999; 22:194.
35. Mohapatra S, Pramanik N, Ghosh SK, Pramanik P. Synthesis and characterization of ultrafine poly (vinylalcohol phosphate) coated magnetite nanoparticles. Journal of nanoscience and nanotechnology. 2006; 6(3):823–9. PMID: 16573145
36. Yu H, Chen M, Rice PM, Wang SX, White R, Sun S. Dumbbell-like bifunctional Au-Fe3O4 nanoparticles. Nano Lett. 2005; 5(2):379–82. PMID: 15794629
37. Wang J, Ding J, Jin N, Zhou Y, Li X, Tang M, et al. Pharmacokinetic parameters and tissue distribution of magnetic Fe. International journal of nanomedicine. 2010; 5:861–6. doi: 10.2147/IJN.S13662 PMID: 21042548
38. Rudra A, Deepa RM, Ghosh MK, Ghosh S, Mukherjee B. Doxorubicin-loaded phosphatidylethanolamine-conjugated nanoliposomes: in vitro characterization and their accumulation in liver, kidneys, and lungs in rats. International journal of nanomedicine. 2010; 5:811. doi: 10.2147/IJN.S13031 PMID: 21042545
39. Krimm S. Infrared spectra of high polymers: Springer; 1960.
40. Li P, Yu B, Wei X. Synthesis and characterization of a high oil-absorbing magnetic composite material. Journal of applied polymer science. 2004; 93(2):894–900.
41. Deng J, Peng Y, He C, Long X, Li P, Chan AS. Magnetic and conducting Fe3O4–polypyrrole nanoparticles with core-shell structure. Polymer international. 2003; 52(7):1182–7.
42. Rana S, Gallo A, Srivastava R, Misra R. On the suitability of nanocrystalline ferrites as a magnetic carrier for drug delivery: functionalization, conjugation and drug release kinetics. Acta Biomaterialia. 2007; 3(2):233–42. PMID: 17224313
43. Petri-Fink A, Chastellain M, Juillerat-Jeanneret L, Ferrari A, Hofmann H. Development of functionalized superparamagnetic iron oxide nanoparticles for interaction with human cancer cells. Biomaterials. 2005; 26(15):2685–94. http://dx.doi.org/10.1016/j.biomaterials.2004.07.023. PMID: 15585272
44. Ganguly A, Kundu R, Ramanujachary K, Lofland S, Das D, Vasanthacharya NY, et al. Role of carboxylate ion and metal oxidation state on the morphology and magnetic properties of nanostructured metal carboxylates and their decomposition products. J Chem Sci. 2008; 120(6):521–8. doi: 10.1007/s12039-008-0081-5
45. Dave SR, Gao X. Monodisperse magnetic nanoparticles for biodetection, imaging, and drug delivery: a versatile and evolving technology. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2009; 1(6):583–609. doi: 10.1002/wnan.51 PMID: 20049819
46. Kodama R. Magnetic nanoparticles. Journal of Magnetism and Magnetic Materials. 1999; 200(1):359–72.
47. Huang Z, Tang F. Preparation, structure, and magnetic properties of mesoporous magnetite hollow spheres. Journal of colloid and interface science. 2005; 281(2):432–6. PMID: 15571699
48. Jiang W, Yang H, Yang S, Horng H, Hung J, Chen Y, et al. Preparation and properties of superparamagnetic nanoparticles with narrow size distribution and biocompatible. Journal of Magnetism and Magnetic Materials. 2004; 283(2):210–4.
49. Cullity B. Introduction to Magnetic Materials, Addison-Wesley, Reading, MA, 1972. There is no corresponding record for this reference. 1955.
50. Gomez-Lopera S, Plaza R, Delgado A. Synthesis and characterization of spherical magnetite/biodegradable polymer composite particles. Journal of Colloid and Interface Science. 2001; 240(1):40–7. PMID: 11446784
51. Chastellain M, Petri A, Hofmann H. Particle size investigations of a multistep synthesis of PVA coated superparamagnetic nanoparticles. Journal of colloid and interface science. 2004; 278(2):353–60. PMID: 15450454
52. Huong NT, Giang LTK, Binh NT, editors. Surface modification of iron oxide nanoparticles and their conjuntion with water soluble polymers for biomedical application. Journal of Physics: Conference Series; 2009: IOP Publishing.
53. Boyer C, Whittaker MR, Bulmus V, Liu J, Davis TP. The design and utility of polymer-stabilized iron-oxide nanoparticles for nanomedicine applications. NPG Asia Materials. 2010; 2(1):23–30.

RETRACTED