RESEARCH

Iron Sulfide Nanoparticles: Synthesis, Characterization, and Molecular Docking Studies of Its Interaction with Bovine Serum Albumin and Human Serum Albumin

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Abstract

Nano-sized iron sulfides have garnered great scientific interest as they possess a wide range of varieties, topologies, and physiochemical qualities. Particularly, iron sulfides (FeS) in the nanometer range size demonstrate enzyme-like activity by imitating organic enzymes that require an iron-sulfur cluster as a cofactor, increasing their potential for use in biomedicine. Here, sodium dithionite was used as the sulfur source and iron chloride ($FeCl_3 \cdot 3H_2O$) as the iron source to create iron sulfide nanoparticles through the chemical precipitation method. The synthesis of the prepared FeS nanoparticles was confirmed by using various spectroscopic studies, i.e., TEM, SEM, DLS, VSM, XRD, and EDX, validating their size, shape, hydrodynamic diameter, magnetic properties, phase composition, and elemental composition respectively. The average particle size obtained from TEM was around 83 nm, and quasi-shaped morphology was observed from SEM. The presence of iron and sulfur within the synthesized nanoparticles was confirmed by EDX. Molecular docking is an effective tool to model the interactions between a protein and small molecules at the atomic level. The ability of a nanoparticle (ligand) to interact with proteins to form a protein–ligand complex plays a crucial role in the dynamics of proteins. The binding of nanoparticles with protein may inhibit or enhance (or have no effect) the biological function of the protein. Thus, it becomes necessary/important to know whether a particular nanoparticle should be used for drug delivery or not. The binding information obtained from the molecular docking of nanoparticles and proteins may be used to decide about the same. We have studied the interaction of ferrous/iron sulfide (FeS) with bovine serum albumin (BSA) and human serum albumin (HSA) proteins through molecular docking. The binding of ferrous/iron sulfide was studied separately with both the selected proteins. Findings demonstrated that four hydrogen bonds involving hydrogen atoms from four distinct amino acid residues of BSA protein (Arg194, Ser343, Asp450, and Ser453) are predicted by the preferential binding of FeS nanoparticles to BSA protein. However, binding to HSA involved only one hydrogen bond. We have further planned to extend our docking studies to study the interaction of BSA and HSA with anticancer drugs and drug-conjugated FeS nanoparticles. The constructive outcomes of the above studies could be used to perform in vitro studies.

Keywords Iron sulfide · Drug delivery · Bovine serum albumin · Human serum albumin · Proteins · Molecular docking

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1 Introduction

Nanomaterials are the broad term for particles with sizes between one and hundred nanometers (nm). In the past few decades, nanotechnology has been investigated as a primary platform in the endeavor to design a drug delivery system. Nanomedicine is a branch of nanotechnology that deals with nanomaterials having a size of several hundred nanometers or less and are employed as drug delivery agents. Based on global cancer data, 18.1 million cases of cancer were reported in 2020, with 9.3 million cases occurring in males and 8.8 million instances in women. Chemotherapy relies on the bloodstream to deliver anti-cancer medications to the tumor. Conventional chemotherapy for cancer treatment has detrimental effects on the entire body and does not sufficiently enrich the therapeutic agents in the tumor location. As a result, one treatment option being researched in lieu of chemotherapy is targeted drug delivery. By directing the medication to the precise location of the cancer, targeted drug delivery seeks to both decrease adverse effects and increase the amount of medication given to the tumor site [14–17]. Consequently, it is imperative to create therapeutic strategies that more precisely target the tumor, protecting adjacent tissues and increasing the efficacy of the administered medication [18, 26]. Gold [29] and biopolymer [27, 28] coated magnetic nanoparticles find significant applications in targeted drug delivery for cancer treatment. Both these coatings help in the easy conjugation of anticancer drugs to the magnetic nanoparticles. The potential for significant advancement in cancer diagnosis, detection, and therapy has led to a vigorous evaluation and use of cancer nanotechnology in cancer management and treatments. Nanotechnology has been used in the field of cancer since its inception, giving researchers insight into investigating novel approaches to the disease's detection, prevention, and treatment. The application of nanotechnology has made it possible to create nanometer-scale devices, or nm-sized devices, that can be used to encapsulate helpful drugs that have demonstrated outstanding outcomes but are typically harmful because of the doses meant for prolonged usage. Furthermore, instances exist whereby these devices can be effortlessly coupled with many functional moieties to enhance localization and delivery precision [25]. Chemotherapy techniques for cancer are arguably the most important studied use of nanomedicine. The use of nanoparticle drug carriers is thought to offer several advantages over standard chemotherapy treatments, including increased efficacy, decreased side effects, and increased tumor specificity for a wide range of cancer types. Although the consensus is that nanoparticles are more effective and have better biodistribution than free drug particles, actual clinical outcomes have not supported this theory. Sadly, although preclinical research and literature have demonstrated the great potential of the drug delivery system now being developed globally, they have mainly fallen short of expectations in the clinic. One explanation for the underwhelming clinical results of nano-sized drug carriers is the multiple obstacles to drug delivery that the nanoparticle must overcome while traveling from the administration site to the interior of the tumor. Only particular routes allow nanoparticles to enter cells; these routes frequently depend on erratic interactions between ligands and cell receptors to deliver the medication and nanoparticle to the lysosome for digestion. The body employs many methods, including mononuclear phagocyte system clearance, to eliminate non-self-particles from blood and tissue, which also affects drug carriers [19]. However, few drug-loaded liposomal nanoformulations co-encapsulated with gold nanoclusters have represented better biodistribution and decreased toxicity making them a suitable theranostic nanostructure for cancer treatment [2]. Cobalt nanoparticles show potential application in the biomedical field owing to their intriguing chemical, magnetic, and electrical properties in the nm range [4, 27, 28]. Magnetite (Fe_3O_4) and other iron-based magnetic nanoparticles have been extensively researched because of their special characteristics, which include biocompatibility, stability over time, and sensitivity to magnetic fields. With the help of an external magnetic field, drug-loaded iron oxide nanoparticles can amass at the tumor site in targeted drug delivery systems. This may result in progressively more effective medication delivery to the tumor location, eliminating cancer cells without endangering healthy cells [11, 12]. The obstacle of cellular uptake can be overcome by combination treatment where nanoparticles in combination with an electric field work together resulting in progressive cellular uptake of nanoparticles by cancerous cells [1]. Superparamagnetism is a crucial characteristic shown by Fe_3O_4 below 20 nm size which increases its efficacy as a biomedical agent. These nanoparticles exhibit few limitations such as hydrophobic surface chemistry, dispersibility loss, and magnetism loss. All these issues can be tackled by the surface functionalization of magnetic nanoparticles by various organic and inorganic moieties such as carbon, silica, gold, and silver [8, 9]. Besides iron oxide, effortless synthesis, magnetic properties, and ultrasmall size are a few characteristics attributed to iron sulfide nanoparticles that make them suitable agents for biomedical interaction [30, 13, 31]. However, before using a particular nanoparticle as a drug delivery agent, it is necessary to ensure how they interact with proteins within the body. This is because one of the most important aspects of protein dynamics is the capacity of a nanoparticle to bind with proteins to create a protein-nanoparticle complex. Proteins can have their

biological functions enhanced, inhibited, or unaffected by the attachment of nanoparticles to them. One such structure-based drug design technique is molecular docking, which models molecular interactions and forecasts the binding mechanisms and affinity between ligands and receptors. Molecular docking has emerged as a crucial tool in computer-assisted drug design in recent years, since it may significantly increase efficiency and lower research costs while predicting binding affinity and analyzing interactive mode (Fan and Zhang 2019). Molecular docking is a useful technique for simulating atomic-level interactions between proteins and tiny molecules. A choice regarding the selection of drug delivery agent may be made using the binding data gleaned from the molecular docking of proteins and nanoparticles [6, 22, 23]. As per molecular docking studies for nanoparticle-protein interaction have been conducted on iron oxide nanoparticles [3, 7], but to the best of our knowledge, negligible literature is present for docking studies of FeS nanoparticle-protein interaction.

Here, we have worked on the synthesis of iron sulfide nanoparticles by chemical precipitation method and investigated their shape, size, elemental composition, magnetic behavior, and phase composition by SEM, TEM, EDX, VSM, and XRD respectively. We have also studied the interaction of ferrous/iron sulfide (FeS) with bovine serum albumin (BSA) and human serum albumin (HSA) proteins through molecular docking.

2 Methods

The current study aimed at studying the interaction of iron sulfide nanoparticles with bovine serum albumin (BSA) and human serum albumin (HSA) proteins through molecular docking to investigate nanoparticle interaction with these proteins. Laboratory synthesis of iron sulfide nanoparticles was also carried out.

3 Materials

Sodium dithionite ($Na_2S_2O_4$) as sulfur content and ferric chloride ($FeCl_3,6H_2O$) as iron precursor were used in the present study after purchasing them from Alfa Aesar. Double-distilled water (DDW) was used throughout the experiment, which was conducted at room temperature and atmospheric pressure.

4 Synthesis of Iron Sulfide Nanoparticles

Room temperature synthesis was carried out using the precipitation method where iron chloride ($FeCl_3.6H_2O$) served as iron precursor and sodium dithionite ($Na_2S_2O_4$) as sulfur content. A 1:1 volume ratio solution was prepared by dropwise addition of 1.0 M sodium dithionite solution to 1.0 M $FeCl_3,6H_2O$ solution followed by decanting the solution and washing the precipitates with water to get the pure precipitates of iron sulfide nanoparticles without any side products. The precipitates were oven-dried at 120 °C in an airless environment for a period of 10–12 h and stored in powdered form for further characterization purposes.

5 Characterization

Carbon-coated 200-mesh copper grids (Ted Pella, USA) were used for transmission electron microscopy (TEM) and EDX (energy dispersive x-ray spectroscopy) to measure the size and elemental composition of iron sulfide nanoparticles (FeSNPs). The morphology of FeSNPs was verified using scanning electron microscopy (SEM). Dynamic light scattering (DLS) measurements using the MALVERN ZETA-SIZER equipment from the NANO-ZS series were also used to analyze size. Phase composition was observed by engaging XRD (Brukar D_8 Discover X-ray spectrometer, over the 2θ° range from 20 to 80° at a rate of 2.31/min, using Cu-Kα radiation (λ = 1.54060 A˚).

6 Molecular Docking Study

The interaction of ferrous/iron sulfide (FeS) with bovine serum albumin (BSA) and human serum albumin (HSA) proteins has been studied through molecular docking. The crystal structure of serum albumin proteins BSA (PDB ID – 4F5S, Fig. 1a) and HSA (PDB ID – 1AO6, Fig. 1b) are obtained from the RCSB protein database [5]. The crystal structure of both proteins has two monomers in an asymmetric unit. For both the proteins, chain A is selected for molecular docking. The single chains of BSA and HSA consist of 583 and 585 amino acid residues, respectively. The water molecules are removed from the selected structures. The hydrogen atoms are added to the amino acid residues of both proteins. The energy of the selected structures is minimized to remove unfavorable steric repulsions that may have developed due to the addition of hydrogen atoms. The crystal structure of ferrous/iron sulfide is acquired from PubChem [20, 21] in standard database format. OpenBabel (O'Boyle et al. 2011) is utilized to convert standard database format to pdb format. The binding of ferrous/iron sulfide is studied separately with both the selected proteins. The pdb files of the protein and ferrous/iron sulfide are uploaded on the PatchDock server [24] for clustering RMSD 1.5 Å and complex type protein-small ligand with default settings. The structures of protein–ligand complex obtained from molecular docking are visualized using VMD [10].

Fig. 1 Crystal structures of a chain of the selected serum albumin proteins. **a** Bovine serum albumin (BSA, PDB ID – 4F5S) and **b** human serum albumin (HSA, PDB ID – 1AO6)
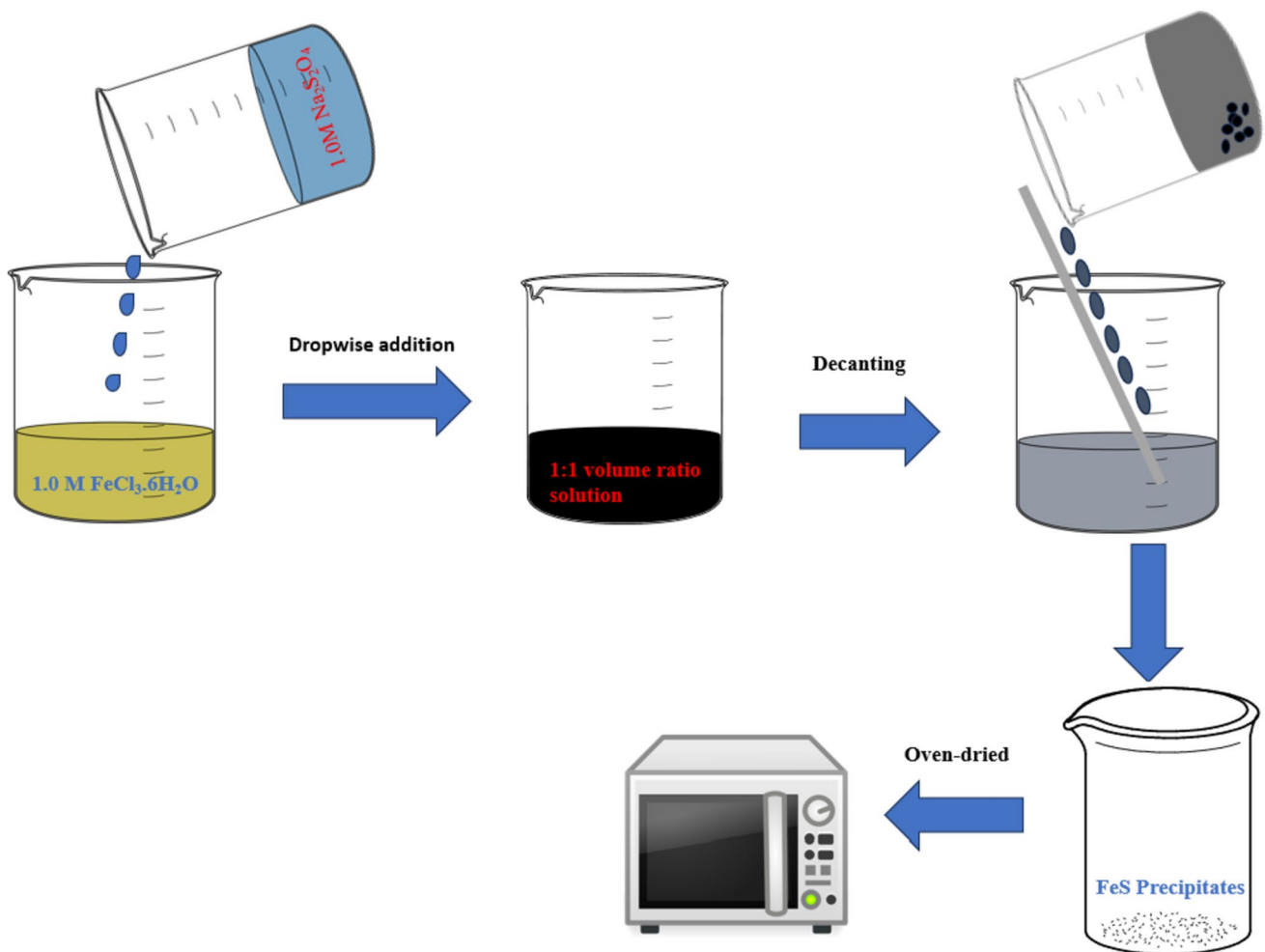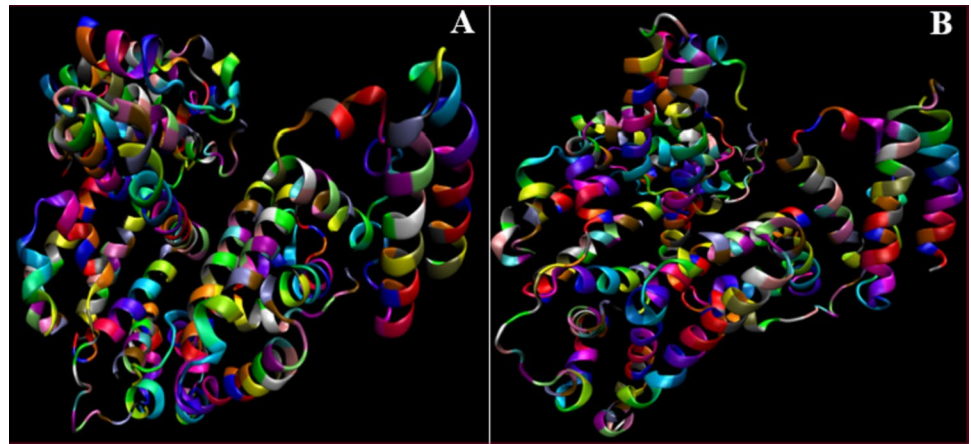
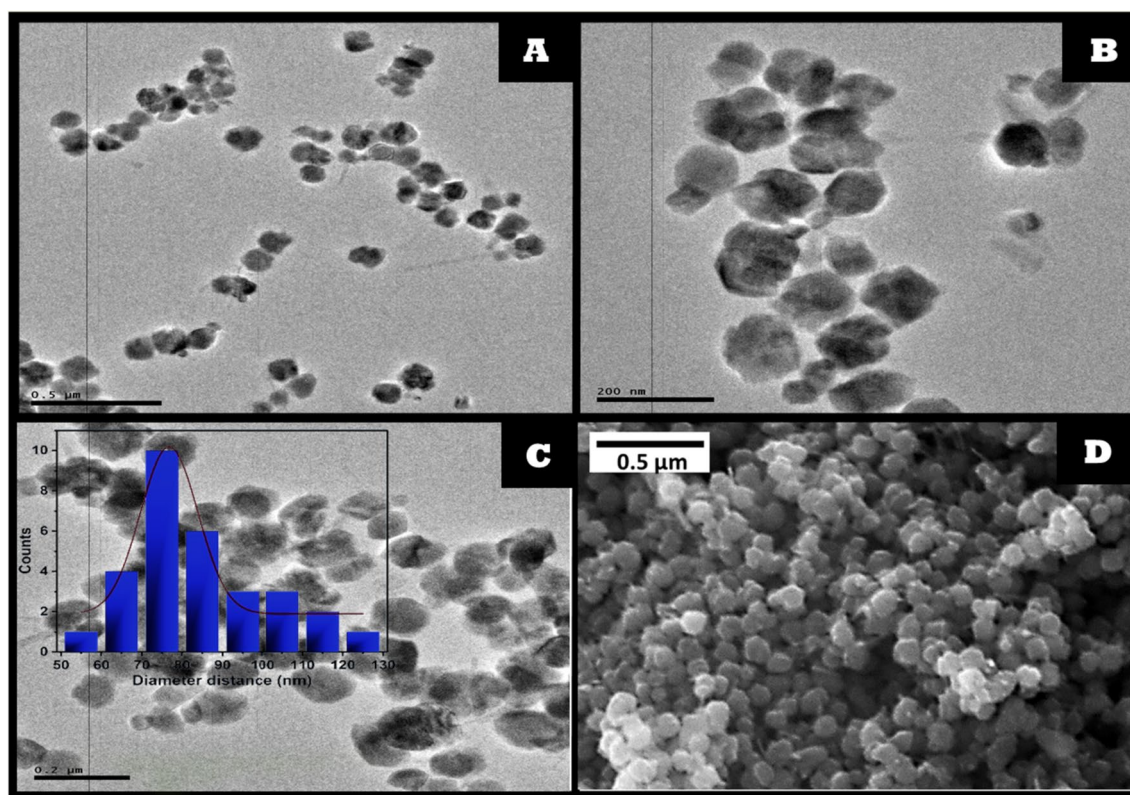**Scheme 1.** Schematic representation for synthesis of FeSNPs

Fig. 2 a, b TEM images FeS NPs (scale bar = 0.5 μm, 200 nm respectively), **c** TEM images FeS NPs along with size distribution histogram showing an average size of about 83 nm (scale bar = 0.2 μm), **d** SEM data shows quasi-spherical morphology

7 Result and Discussion

FeSNPs were synthesized by adopting the chemical precipitation method where $FeCl_3.6H_2O$, $Na_2S_2O_4$, and $NaBH_4$ were used as iron precursor, sulfur precursor, and reducing agent respectively (Scheme 1). Figure 2 a, b, and c show the TEM micrographs of FeSNPs. The average size of nanoparticles was calculated to be 83 nm (Fig. 2c). The inset of Fig. 2c represents the size distribution histogram of FeSNPs obtained from ImageJ software representing a mean size of 83 nm. SEM (Fig. 2d) studies illustrated the quasi-spherical morphology of the synthesized nanoparticles.

The size of the FeSNPs was further calculated with DLS measurements (Fig. 3a) giving the hydrodynamic diameter around 88–92 nm. The higher value of hydrodynamic diameter is due to the formation of an electric double-layer around the solvated particles. XRD analysis (Fig. 3b) was undertaken to assess the phase constitution of the synthesized nanoparticles. The diffraction peaks were observed at 110, 002, 120, 211, 030, and 113 which were in good correspondence with the characteristic peaks of FeSNPs (JCPDS card no.01–076-0181).

EDX analysis represents the elemental composition showing the presence of iron and sulfur within the synthesized nanoparticles (Fig. 4 a and b). Vibrating sample magnetometry was used to evaluate the magnetic properties of the synthesized nanoparticles. A small hysteresis loop was seen (Fig. 5a) which indicates a small degree of ferromagnetism in FeSNPs. It can be seen from Fig. 5b that the particles are well dispersed in an aqueous medium pointing towards its colloidal stability as they do not settle down. Figure 5c shows that these particles can be controlled by an external magnetic field as they move toward the glass surface on exposure to bar magnetic. All these characterization studies pointed toward the successful synthesis of FeSNPs.

The synthesis of the nanoparticles was done as we want to use these nanoparticles as drug delivery agents. For this, we need to confirm how these nanoparticles interact with proteins within the body. The ability of a nanoparticle (ligand) to interact with proteins to form a protein–ligand complex plays a crucial role in the dynamics of proteins. The binding of nanoparticles with protein may inhibit or enhance (or have no effect on) the biological function of the protein. Thus, it becomes necessary/important to know whether a particular nanoparticle should be used for drug delivery or not. The molecular docking is an effective tool to model the interactions between a protein and small molecules at an atomic level. The binding information obtained from the molecular
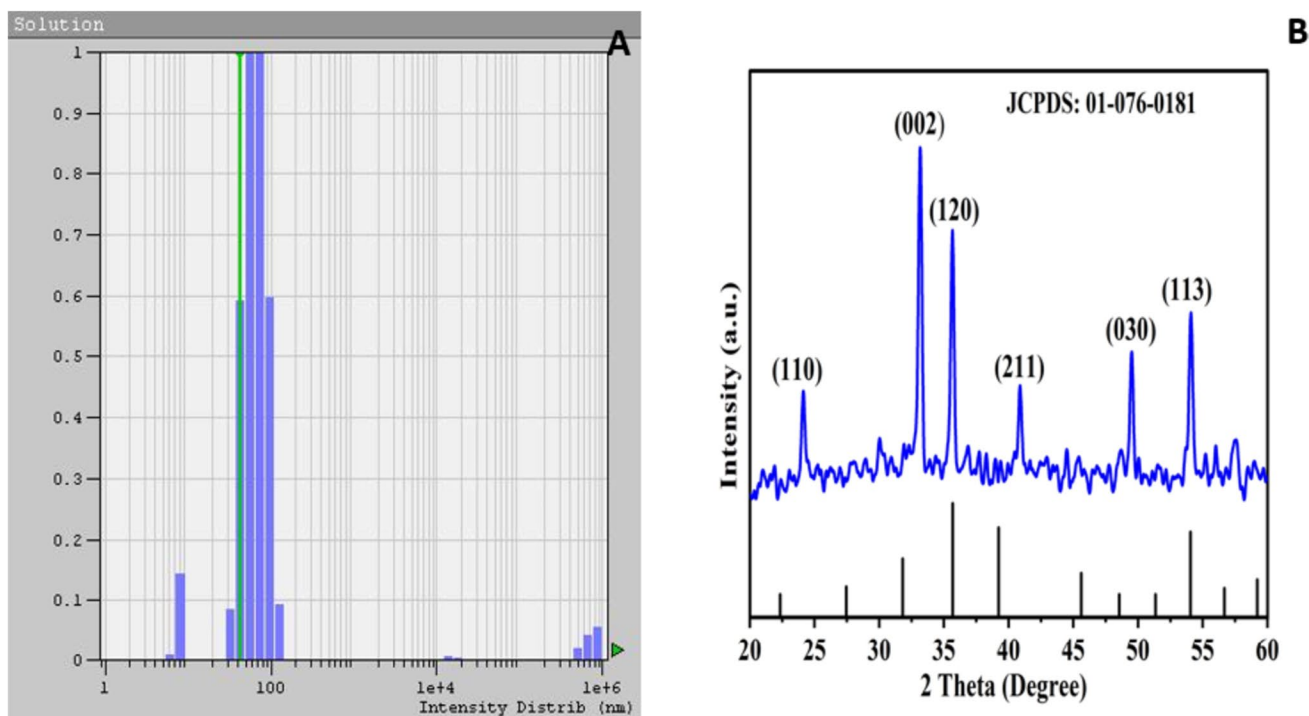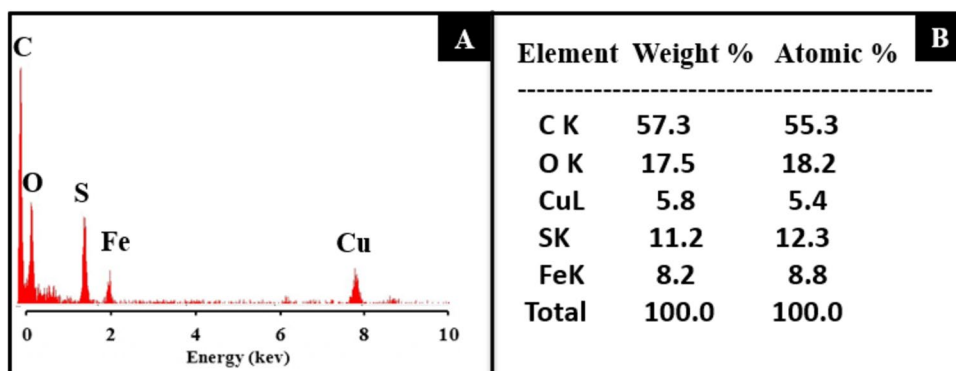
Fig. 3 **a** The data of DLS showing hydrodynamic diameters and size distribution by plotting the graph between intensity vs. diameter of the nanoparticle of aqueous dispersion of FeSNPs. **b** Power X-ray diffraction (XRD) of FeSNPs

Fig. 4 **a, b** EDX spectra and elementary analysis data of FeSNPs

docking of nanoparticles and proteins may be used to decide about the same. Figure 6 shows the structures of BSA-FeS (Fig. 6a) and HSA-FeS (Fig. 6b) complexes.

The binding of FeS with BSA and HSA gave atomic contact energy of -30.11 kcal/mol with an approximate interface area of 166 Å^2 and -22.51 kcal/mol with an approximate interface area of 197 Å^2, respectively, for the solution with the highest geometric shape complementarity score. The pdb files of the best solution of BSA-FeS and HSA-FeS complexes are utilized to obtain their LigPlots (Laskowski and Mark B 2011), which represent ligand–protein interactions in two-dimension. Figure 7a shows that the preferable binding of FeS nanoparticle to BSA protein predicts four hydrogen bonds involving hydrogen atoms from four

different amino acid residues of BSA protein (Arg194, Ser343, Asp450, and Ser453). However, only one hydrogen bond is predicted involving a hydrogen atom of Tyr407 amino acid residue of HSA for the preferable binding of FeS nanoparticle to HSA protein as shown in Fig. 7b.

8 Conclusion

FeSNPs were prepared through the precipitation method for use in drug delivery applications. TEM, SEM, and DLS analysis confirmed the shape and size of the synthesized nanoparticles. XRD profile and EDX analysis further confirmed the formation of FeSNPs. The binding information of
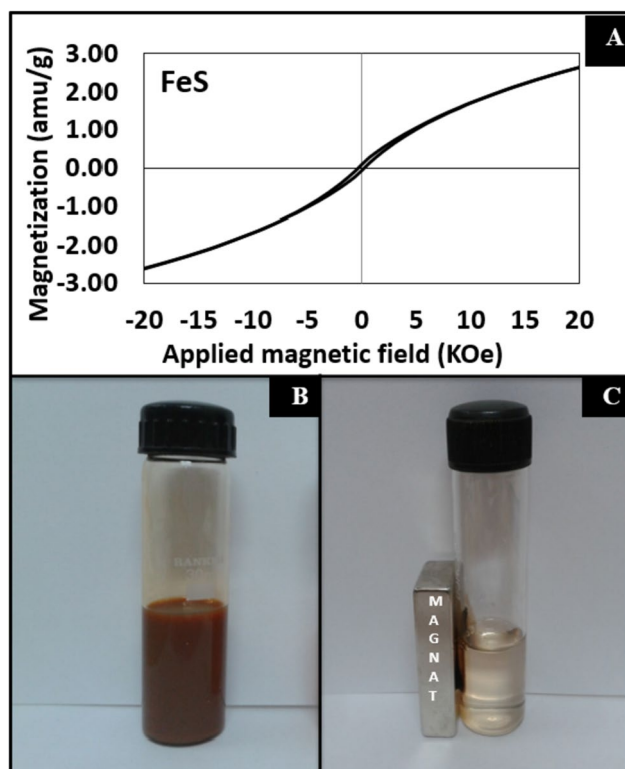
Fig. 5 **a** Magnetization curve of ferromagnetic FeSNPs. **b** Photograph showing dispersion of FeSNPs in aqueous medium. **c** Photograph showing migration of FeSNPs under the influence of magnetic force
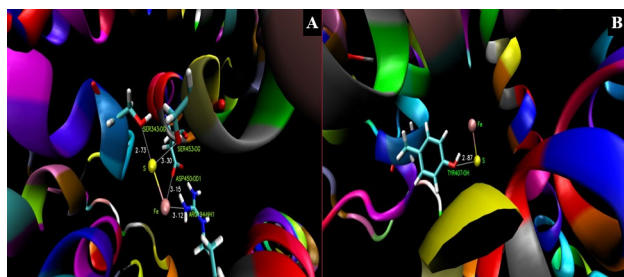

Fig. 6 **a** Schematic representation of interactions between FeS and BSA at the BSA-FeS nanoparticle interface. **b** Schematic representation of interactions between FeS and HSA at the HSA-FeS nanoparticle interface

Fig. 7 **a** The two-dimensional graphical representation of amino acid residues involved in interactions with FeS in BSA-FeS nanoparticle complex. **b** The two-dimensional graphical representation of amino acid residues involved in interactions with FeS in HSA-FeS nanoparticle complex

ahead toward experimental studies to confirm the cytotoxicity and binding efficiency of FeSNPs and drug-conjugated FeSNPs by performing in vitro studies. The positive outcomes of all the above interaction-based studies would help in the development of a drug delivery platform for the successful treatment of cancer.

Data Availability No datasets were generated or analyzed during the current study.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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nanoparticles with proteins is necessary to confirm whether a particular nanoparticle should be used for drug delivery or not. We investigated the binding of FeSNPs with BSA and HSA and revealed an appreciable interaction of these nanoparticles with both proteins. The future perspective includes molecular docking of an anticancer drug (doxorubicin) with serum albumin (BSA & HSA). Molecular docking of drug-conjugated FeSNPs with serum albumin (BSA & HSA). The results of these docking studies would pave the way to move
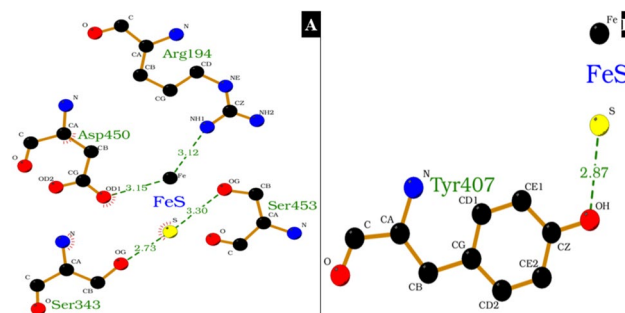
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