

Development and Characterization of Highly Thermostable Ciprofloxacin-Coated Supra-Magnetic Iron Oxide Nanoparticles for Antibacterial Activity

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ABSTRACT

This study aims to provide a comprehensive, cost-effective, environmentally friendly, and time-optimized method for Ciprofloxacin-coated SPIONs, assisted by Poly Lactic-co-Glycolic Acid (PLGA) and poly (ethylene glycol) (PEG). PLGA and PEG were selected due to their biocompatibility, ability to enhance SPIONs stability and biodegradability. Ciprofloxacin is a commonly used antibiotic from the fluoroquinolone category of antimicrobial agents. This medication is widely prescribed to treat various bacterial infections. Ciprofloxacin-coated SPIONs (Cipro-SPIONs) were synthesized using a conventional co-precipitation method, accompanied by thermochemical treatment and post-coating with a ciprofloxacin solution; however, for the first time, direct drug loading was done, which increased the thermal stability of the SPIONs and enhanced the synthesis. PLGA-PEG-SPIONs were first synthesized as a control, demonstrating the highest stability and no agglomeration in this method. However, Ciprofloxacin was coated in a very short time with high stability of Cipro-SPIONs during antibacterial activity. The synthesized Cipro-SPIONs were characterized using several characterization techniques, including TEM, FE-SEM, UV-Vis spectroscopy, DLS, a Zeta analyser, XRD, and ATR-FTIR spectroscopy.

Based on characterization techniques, Cipro-SPIONs have proven suitable for antimicrobial drug delivery due to their small structure, excellent stability, and low cytotoxicity. However, these particles are the first of their kind with the lowest toxicity as compared to other reported methods. Cipro-SPIONs exhibited improved targeted delivery efficiency.

Furthermore, PLGA-PEG-SPIONs are also very useful in vitro and in vivo with the help of Cipro as a coating and stabilizing agent. Our research and characterization results demonstrate that as the Ciprofloxacin (Cipro) loading percentage in PLGA-PEG-coated SPIONs increases, the interaction between Cipro and the SPION surface becomes significantly stronger than previous reported methods. This enhanced binding results in Cipro becoming tightly entangled with the nanoparticles, making it highly resistant to degradation under stable thermal conditions. The robust interaction between the drug and nanoparticles leads to increased stability of the nano-formulation, which is beneficial in terms of prolonged storage and stability; however, it also presents challenges for degradation and drug release. These SPIONs have applications in biology, medical diagnosis, and therapy due to their stability in water and reported neutral pH. This study has also confirmed previous research that the small size of SPIONs allows them to avoid precipitation due to gravitational forces, as demonstrated in this research.

1. Introduction

Supramagnetic iron oxide nanoparticles, typically ranging from 1 to 100 nanometers, have garnered significant attention due to their distinctive magnetic properties and high surface area-to-volume ratio. These properties make SPIONs a promising candidate for a wide range of applications in various scientific and technological domains, also enabling controlled drug release and targeted delivery to cancer cells. Cancer remains a significant global health challenge, necessitating the exploration of innovative therapeutic approaches. Nanotechnology has emerged as a promising avenue, with nanoparticles offering unique and promising properties for drug delivery, specifically targeted delivery of drugs.

In recent years, more focused experiments and research have been performed on supramagnetic iron oxide nanoparticles and their applications in drug delivery. The field continues to evolve towards biomedical applications, especially molecular therapy [1,37]. These include obvious controllable attributes, for example, the size, Fabrication method, shape, magnetic properties, crystal nature, and flexibility of SPIONs with different ligands and targeted cells [38]. The literature demonstrates the use of superparamagnetic iron oxide (Fe_3O_4) and Maghemite ($\gamma\text{-Fe}_2\text{O}_3$) SPIONs, which are controllable in size, have a limited or narrow distribution, are soluble in water, and possess surface functionality [2-7]. For the synthesis of SPIONs, the traditional coprecipitation method is used; in this method, the salts Fe(II) and Fe(III) are co-precipitated in an alkaline solution. It is mandatory to use a coating material such as a polymer or dextran (or its derivatives) to support this method. Surface modification of SPIONs using biocompatible polymers and targeting agents can help prevent these problems, such as aggregation in water, improve their chemical stability, make them biocompatible, and increase their non-specific intracellular uptake. [22,25]. In our research, we have used the same method with Ciprofloxacin and PLGA-PEG coatings. Ciprofloxacin hydrochloride is a fluorinated antibiotic used in medicine to treat bacterial infections [39]. Therefore, it is approved to treat 14 infections, particularly intestinal and urinary infections [41]; respiratory tract infections, typhus, community-acquired pneumonia, bacterial pneumonia, Conjunctivitis, corneal ulcer, bronchitis, acute sinusitis, complex Pyelonephritis, inhalation anthrax, skin or subcutaneous tissue infections tissues and

abdomen [11,12]. It is reported that there are many derivatives of Ciprofloxacin with antibacterial activities; however, few have high antibacterial activities, while others have low antibacterial activities. Ciprofloxacin hybrids with triazolinones replacing the carboxylic acid of cipro possess weak antibacterial activity [27, 28]. When the aromatic amide group replaces the carboxylic acid group of Ciprofloxacin, it shows vigorous antibacterial activity. However, cipro with propyl, ethyl, or methyl acetate ester instead of the carboxylic acid of cipro is excellent for in vitro studies [29]. Some ciprofloxacin derivatives with alkyl groups also exhibit antibacterial activity. Also, some derivatives of cipro are found to be active against fungi [30].

Hence, in this study, we prepared Ciprofloxacin-coated SPIONs (cipro-SPIONs) using the conventional coprecipitation method, followed by thermochemical process and post-coating, and evaluated Ciprofloxacin as the covering for synthesized nanoparticles to get macrophage targeting and stabilization in a physiological environment. In this work, our primary goal is to design functionalized SPIONs that can deliver and enter antigen-presenting cells, enhance their function in the body, and serve as antimicrobial drug delivery agents. This research examines the in vitro and in vivo functions of synthesized SPIONs, their unique properties, and their characterization for antimicrobial drug delivery. The methods of characterization and synthesis in this work are carefully followed and repeated to minimize errors. These SPIONs possess excellent magnetic properties, which are suitable for in vivo resonance imaging, also beneficial for future research in immune-related diseases. Our SPIONs can deliver specific materials to cells with Cipro receptors.

Additionally, these SPIONs have potential applications in biology, medical diagnosis, and therapy due to their stability in water and reported neutral pH. This study has also been supported by previous research, which has demonstrated that the small size of SPIONs allows them to avoid precipitation due to gravitational forces [43]. We have coated our SPIONs with biocompatible polymers during synthesis, which prevents them from aggregating and makes them suitable for drug delivery and medical applications.

Recent studies strongly support our approach. For example, recent work on PEG-PLGA nanoparticles encapsulating ciprofloxacin has demonstrated extended-release profiles with improved

cytocompatibility and reduced toxicity, making such carriers promising for biomedical use [47,48]. Similarly, ROS-sensitive PEG/PLGA nanocarriers have been reported to achieve efficient ciprofloxacin release and enhanced antibacterial activity, highlighting the advantages of polymer-assisted formulations. In parallel, advances in PEG-coated magnetic nanoparticles (Fe_3O_4) emphasize the role of polymeric coatings in stabilizing SPIONs, preventing aggregation, and preserving superparamagnetic properties essential for biomedical applications [45,46].

However, studies reveal that ciprofloxacin-coated SPIONs assisted by Polyethylene glycol (PEG) and Poly Lactic-Co-Glycolic acid (PLGA) with other nano-formulation or derivatives of Ciprofloxacin, such as liposomal or loaded on CNCs, show excellent antibacterial activity when the release percent of these nano-formulations is more than 10 percent. However, with an increase in the release percentage, the bonding might also increase [31,32]. The novelty of our work lies in demonstrating that ciprofloxacin, when directly loaded onto PLGA-PEG-coated SPIONs, forms exceptionally stable interactions with the polymer-magnetic matrix. This strong entanglement enhances thermal stability and enables controlled drug release, which not only sustains antibacterial efficacy but also opens a new avenue for designing SPION-based, PEG-PEG-PLGA-stabilized ciprofloxacin carriers as potential dual-function nanoplatfroms for both drug delivery and targeted MRI contrast, particularly for the detection of macrophage-associated diseases. Our research and characterization results show that when the loading percent of cipro is increased in PLGA-PEG SPIONs, then cipro is tangled with SPIONs very strongly, and it is difficult to degrade those nano-formulations at stable thermal conditions [42]. We assume that the cipro-SPIONs could deliver specific materials to cells that have Cipro receptors. This discovery, therefore, raises the prospect of developing a novel MRI contrast agent in the future that targets macrophages for the detection of immune-related diseases.

2. Materials and Methods

2.1 Material

Sigma-Aldrich Co. (St. Louis, MO, USA) supplied the ferrous chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ > 99%) and ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ > 97%). Polylactic co-glycolic acid (PLGA) and polyethylene glycol (PEG) were also purchased from Sigma Aldrich in high quality. However other

chemical reagents such as dimethyl sulfoxide (DMSO), phosphate buffered saline tablets (PBS), acetone and deuterium oxide (D_2O), benzalkonium chloride (BAC), poly (ethylene glycol) methyl ether (PEG; average M_n 5000 Da), and methoxy polyethylene glycol maleimide (PEG-Mal; average M_n 5000 Da) were purchased in highly purified quality from Fisher Scientific UK. Mentioned chemicals, including Ciprofloxacin, were used without any further purification.

2.2 Methods

Ciprofloxacin conjugated SPIONs were synthesized by co-precipitating $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (2.89 grams, 10 millimolar) and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (1.99 grams, 5.9 millimolar) in 80 mL of oxygen-free water with Ammonium Hydroxide NH_4OH . Ammonium hydroxide (NH_4OH) was used to provide the alkaline medium for the co-precipitation of Fe^{2+} and Fe^{3+} , it also allowed to make quick and stable SPIONs. Sodium citrate acted as both a chelating and stabilizing agent, helping to control particle growth and giving the surface a negative charge to prevent aggregation. To avoid any impurities, the reaction was done inside the glove box under Nitrogen. After 40 minutes, black precipitates formed. Precipitates had a pH of 10; due to this high pH value, the precipitates were washed several times. We repeated washing with high-purity water till the pH dropped to 7. After settling the precipitate using a permanent magnet, the supernatant liquid was removed by decantation. 2 M HNO_3 was then added to the resulting black precipitate. After adding 0.35 M $\text{Fe}(\text{NO}_3)_3$, the reaction mixture was refluxed for 60 minutes. The dialysis process was performed with 0.01 M nitric acid for a full two days, ensuring optimal purification, and the sample was subsequently stored at a stable 4 °C to maintain its integrity. The last step is that the product received is SPIONs. Later, these SPIONs were conjugated with PLGA and PEG. PLGA-PEG polymers were mixed with SPIONs after dissolving in a solvent and left to stir for 6 hours. Later, with the dropwise addition of PLGA-PEG, the solution was gently stirred and put on dialysis. After dialysis, the solution was filtered and characterized as PLGA-PEG conjugated SPIONs. In the final step, the obtained PLGA-PEG SPIONs reaction product was slowly blended with 0.5 mL of ciprofloxacin solution, which accounts for approximately 10% (w/v) of the PLGA-PEG ciprofloxacin delivery. The coating of ciprofloxacin on PLGA PEG SPIONs was optimized by testing drug to polymer ratio, to avoid aggregation, and the perfect ratio was 10% (w/v). After the addition of Cipro, we concluded that the required PLGA-PEG Cipro-SPIONs were obtained. The pH was then adjusted to 7, a neutral pH, which stabilizes the SPIONs.

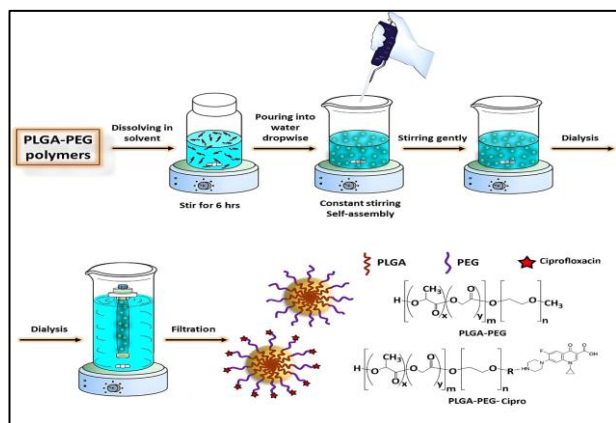


Fig.1. Diagram showing the preparation of PLGA-PEG nanoparticles with Ciprofloxacin

2.3 Preparation of a synthetic urine solution

The previously published methodology was followed in preparing the artificial urine solution. To put it briefly, the following ingredients were stirred into deionized water and allowed to dissolve at room temperature for 12 hours under Nitrogen. Chemicals that were stirred are urea (23 g), uric acid (0.32 g), creatinine (0.9 g), sodium citrate dihydrate (3 g), sodium chloride (6 g), potassium chloride (5 g), ammonium chloride (1.5 g), calcium chloride dihydrate (1 g), magnesium sulfate heptahydrate (1 g), sodium bicarbonate (0.3 g), sodium oxalate (0.04 g), sodium sulfate (2.6 g), sodium phosphate monobasic monohydrate (0.9 g), and sodium phosphate dibasic (0.12 g).

2.4 Sample Preparation for Transmission Electron Microscopy TEM

On a parafilm, a drop of synthesized SPIONs (about 0.51 mg/mL) was pipetted, allowing for the preparation of specimens. Next, a 400-mesh grid of copper coated by a glowing Carbon film was placed so that the carbon side faced up and was exposed to the sample for 60 seconds. The extra solution was wiped away with filter paper. Subsequently, a 2% (w/v) uranyl acetate (UA) solution drop was applied to the parafilm, and the grid was left in contact with the UA-soaked "carbon" side for an additional sixty seconds. The approach has previously been documented to produce high-quality photos of PLGA-PEG nanoparticles.

2.5 Sample Preparation for particle size and zeta potential

To measure the polydispersity index (PDI), the zeta-potential of fluorescein-free PLGA-PEG nanoparticles was measured at a 173° scattering

angle using a dynamic light scattering technique. The dispersion of SPIONs was diluted with ultra-purified water at least 100 times. All measurements have been observed with 0.015 absorbances; however, a refractive index of 1.6 was maintained. At least three analyses of each sample were recorded; however, the Zeta average values were determined.

2.6 Characterization

Further analysis was done by Fourier transform infrared (FT-IR) spectra. The transparent films for SPIONs, Ciprofloxacin, and Ciprofloxacin-coated PLGA-PEG SPIONs were fabricated by applying individual samples onto a silicon wafer. The dimensions of SPIONs were observed using an electrophoretic light scattering spectrophotometer with 90- and 20-degree scattering angles at 25 degrees Celsius. The average particle sizes and morphology of modified supramagnetic iron oxide nanoparticles were determined using a transmission electron microscope (TEM). DLS-Zeta determined size distribution. The thermogravimetric Analysis instrument was routinely used in all phases of research to maintain quality control and production operations. Similarly, UV-visible spectroscopy was done

3. Results and Discussion

3.1 UV-Visible Spectroscopy

The UV-Vis absorption spectra confirmed the successful incorporation of ciprofloxacin into PLGA-PEG-SPIONs. A distinct absorption band in the 270–300 nm region, characteristic of ciprofloxacin, was clearly observed in the PLGA-PEG-Ciprofloxacin-SPIONs formulation, showing significantly higher intensity compared to PLGA-PEG-SPIONs alone. This enhancement indicates effective drug loading and strong interaction between ciprofloxacin and the nanoparticle surface. In contrast, PLGA-PEG-SPIONs without drug exhibited only minimal absorbance, confirming the absence of drug-related signals. Furthermore, cumulative drug release studies revealed that directly loaded Ciprofloxacin-SPIONs exhibited a faster and higher release profile, ensuring more immediate antibacterial activity, whereas PLGA-PEG-Ciprofloxacin-SPIONs demonstrated a slower and more sustained release due to stronger drug-polymer entanglement. This combination of efficient loading and controlled release highlights the potential of PLGA-PEG-SPIONs as a stable and effective platform for antibacterial drug delivery.

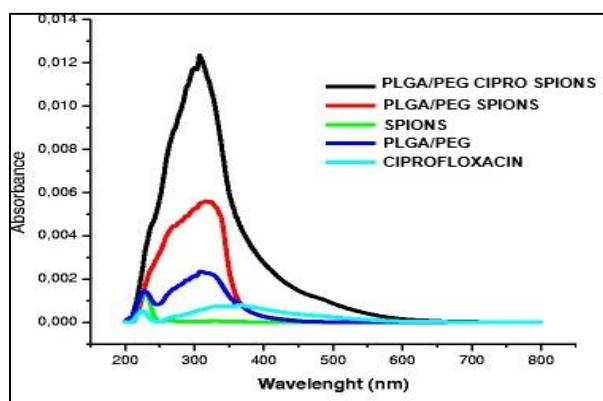


Fig.1. Uv-Visible spectra of PLGA-PEG SPIONs and PLGA-PEG Cipro SPIONs, also showing the spectra of Ciprofloxacin and PLGA/PEG as polymer

3.2 Transmission Electron Microscopy (TEM)

TEM examination confirmed the size and shape of the nanoparticles. Fig.2 shows microphotographs of the SPION samples. We carried out TEM for PLGA-PEG-Cipro SPIONs dissolved and precipitated from acetone and PLGA-PEG-Cipro SPIONs dissolved and precipitated from DMSO. DMSO was used for TEM sample preparation to achieve uniform dispersion of nanoparticles before imaging. It also enhances particle stability and avoids aggregation. A suitable contrast was obtained by using uranyl acetate as a negative stain. According to TEM analysis, these results are in contrast with the measurements obtained from DLS, showing the development of SPIONs having uniform clusters, well dispersed, and around a well-shaped shell and core structure. The average size of these SPIONs, as observed by TEM, is 6.5 ± 0.5 nm. Research shows that PLGA polymeric nanoparticles are functional as drug carriers if they are homogeneous and well-dispersed. Hence, our synthesized SPIONs are suitable for further applications and studies in the drug and medical industries, and they remain stable in terms of shape and size.

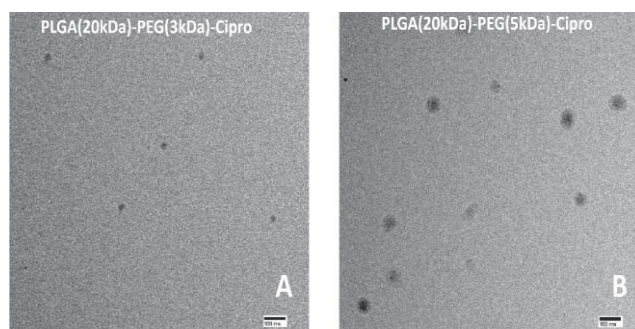


Fig.3. TEM microphotographs of Cipro-coated PLGA-PEG SPIONs, precipitated and dissolved in solvents, Acetone (A) and DMSO (B).

3.3 Particle Size and Zeta Potential

Hydrodynamic diameter, size distribution profile, polydispersity index (PDI), and zeta potential of synthesized PLGA-PEG SPIONs and PLGA-PEG-Cipro coated SPIONs were studied by performing the dynamic light scattering (DLS) method.

The average hydrodynamic diameter of PLGA-PEG SPIONs is observed to be 18.1 ± 2.2 nm. While PLGA-PEG-Cipro coated SPIONs are 20.2 ± 2.4 nm. The observed size of the same PLGA-PEG-Cipro coated SPIONs according to TEM is 6.5 ± 0.5 nm with a PDI of 0.18 ± 0.01 nm. The results also show that a homogeneous population with a restricted size distribution was present in all nanoparticles generated for this study, as evidenced by their low polydispersity of less than 0.20. A negative zeta potential larger than -21 mV was observed and verified by several sample runs. Hence, based on DLS measurement and zeta potential, we can conclude that these SPIONs have a narrow size distribution, which makes them eligible for antibacterial drug delivery as reported in previous research. Previous research also shows that the zeta potential of PLGA-PEG Cipro SPIONs has an important role in application in antimicrobial drug delivery in vivo, particularly the zeta potential of such SPIONs should be between -20 to -35 mV. This value is suitable for biological applications because such SPIONs have high stability [33] and prevent aggregation in biological fluids; also interaction of such SPIONs with positively charged antimicrobial peptides or proteins is higher [34,35]. Similarly, the particle size of PLGA-PEG Cipro SPIONs also has an important role in vivo study. SPIONs with a size range between 5 to 20 nm show efficient performance, reduce toxicity, and improve biocompatibility [36]. However, the PLGA-PEG Cipro SPIONs do not need a carrier protein for drug delivery in vivo. We can assume that our synthesized SPIONs have a suitable zeta potential and size for in vivo study. And these SPIONs can target specific infected sites in vivo, and the main targets could be colonies of bacteria and inflamed tissues.

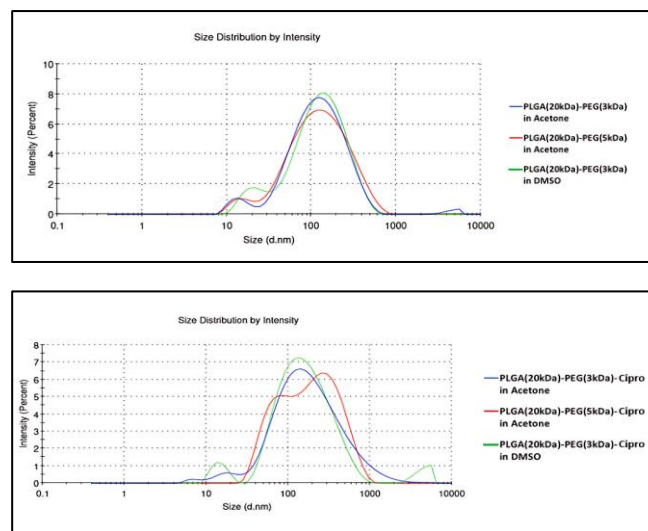


Fig.4. Size Distribution taken by DLS for PLGA-PEG (A) and PLGA-PEG-Cipro (B), Acetone and DMSO dissolved and precipitated SPIONs.

3.4 Thermogravimetric Analysis (TGA)

The thermal stability of PLGA-PEG-Cipro SPIONs was studied to understand multiple stages of mass loss corresponding to the decomposition of the organic components present in SPIONs. The thermogram shows several weight loss steps, the initial weight loss observed at lower temperatures (~ 50 - 150°C), which is attributed to the evaporation of adsorbed or residual moisture and volatile impurities. Subsequent weight loss in the range of 200 - 400°C corresponds to the degradation of the polymer chains (PLGA and PEG) and any organic functional groups attached to the nanoparticle surface. The TGA result confirmed the characteristic thermal decomposition of Cipro-coated PLGA-PEG SPIONs in comparison to other SPIONs discussed in previous research. As our synthesized SPIONs are covered with polymers, high energy is required to break the bond before the degradation of cipro. After the complete degradation of Cipro, the residue is composed mostly of bare SPIONs. After studying TGA, we can also assume that if we increase the amount of Cipro during the synthesis of PLGA-PEG Cipro-coated SPIONs, then the synthesized SPIONs will be more tangled, and it will take more time to degrade.

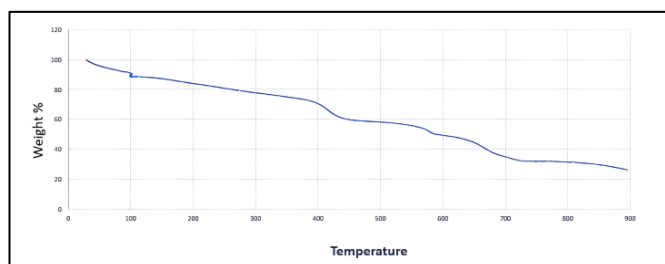


Fig.5. TGA of PLGA-PEG-Cipro-SPIONs showing decomposition patterns and weight loss of organic groups, polymers, and volatile impurities.

3.5 Fourier transform infrared (FT-IR) spectra

FTIR spectra of PLGA and PEG revealed characteristic absorption peaks corresponding to functional groups present in these polymers. For PLGA-PEG SPIONs, we observed C=O stretching vibration ($\sim 1750\text{ cm}^{-1}$) of the ester groups, and the N-H stretching vibration (~ 3264 and 3509 cm^{-1}) of the methylene groups is observed, while N-H bending is observed around 812 cm^{-1} . A smooth, wide band is also observed around 3500 cm^{-1} , which represents the oxygen atom of PLGA and PEG, and a small doublet is also present around 3000 cm^{-1} in the PLGA-PEG FTIR Spectrum. Also, if we look at the spectrum for PLGA-PEG SPIONs, the peaks related to the ether linkage (C-O-C) at around 950 - 840 cm^{-1} , and the C-H stretching vibrations are observed around 2888 cm^{-1} .

The FTIR spectrum of PLGA-PEG-coated SPIONs showed additional peaks and shifts compared to the spectra of the individual polymers, indicating chemical modifications on the nanoparticle surface. After the conjugation of SPIONs with ciprofloxacin, there is a clear difference between the PLGA-PEG SPIONs and the PLGA-PEG Cipro SPIONs spectra. For example, the appearance of new peaks or changes in peak intensities in the fingerprint region (1500 - 500 cm^{-1}) suggests the formation of bonds between the polymer chains and the SPION surface through functionalization or coating of ciprofloxacin. However, there is a new peak in the region of 2500 cm^{-1} . The C-H stretching vibrations are not observed around 2888 cm^{-1} , and the band around 3500 cm^{-1} , which is related to the oxygen atom, is shifted. The peaks related to the ether linkage (C-O-C) at around 950 - 840 cm^{-1} and the C-H stretching vibrations are also not seen in cipro-coated PLGA-PEG SPIONs.

3.5.1 Assessment of Nanoparticle Stability

Changes in the FTIR spectrum of PLGA-PEG-coated SPIONs before and after exposure to various environmental conditions (e.g., temperature, pH, solvent) provided insights into the stability of the nanoparticle formulation. Observed alterations in the polymer peaks and the appearance of different peaks indicated structural changes and interactions between the nanoparticles and ciprofloxacin with PLGA-PEG SPIONs.

3.5.2 Validation of Surface Chemistry

FTIR analysis confirmed the successful conjugation of targeting Ciprofloxacin drugs onto the surface of PLGA-PEG-coated SPIONs. Specific peaks corresponding to the functional groups present in the ligands or drugs can be identified in the FTIR spectrum, providing evidence of their presence on the nanoparticle surface. These are further compared in the following table with reference to Fig. 5.

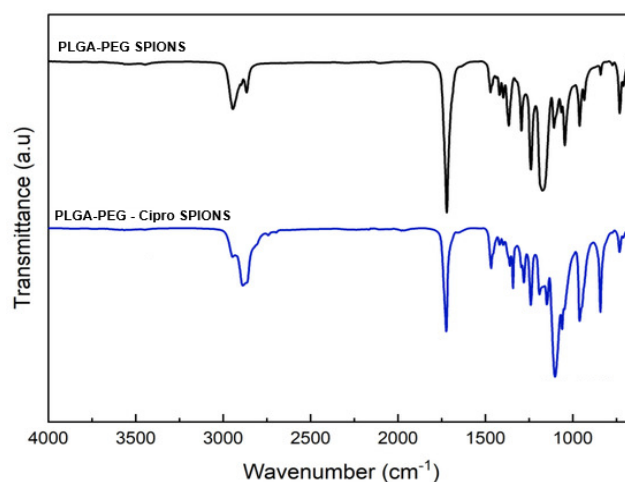


Fig.6. FTIR spectra of PLGA-PEG SPIONs and PLGA-PEG Cipro SPIONs

Table 1.

Comparing the FTIR Spectrum of PLGA-PEG SPIONs and PLGA-PEG Cipro SPIONs

<i>PLGA-PEG SPIONs Spectrum</i>	<i>PLGA-PEG Cipro SPIONs Spectrum</i>
C=O stretching ~1750 cm ⁻¹	No C=O stretching
Smooth wide band around 3500 cm ⁻¹	Smooth, wide band is shifted.
Ether linkage (C-O-C) at 950-840 cm ⁻¹	No Ether linkage
N-H bending at 812 cm ⁻¹	No N-H bending around 812 cm ⁻¹
No peak in the fingerprint region of the spectrum	The appearance of new peaks in the fingerprint region 1500-500 cm ⁻¹
No new peak in region 2500 cm ⁻¹	A new peak in region 2500 cm ⁻¹

4. Conclusion

In this research, we have shown how Ciprofloxacin, used as a coating material for SPIONs, may stabilize the antimicrobial drug delivery and transport it to an in vivo study. These SPIONs had a modest size (about 6 nm), good solubility in aqueous environments, and a magnetic property appropriate for in vivo magnetic resonance imaging. The shape and size of SPIONs were approximately spherical; these SPIONs are supposed to be around 6.5 ± 0.5 nm. DLS images showed a uniform spherical shell and core structure of the nanoparticles. Data showed a uniform population of SPIONs with negative zeta potential, i.e., more than -21 mV, and low polydispersity, i.e., less than 0.20. In the future, we aim to further study and characterize the in vivo study of these SPIONs and try to target infected, inflamed tissues and bacterial colonies. Although Ciprofloxacin was used as a model drug, this approach can be adapted for other antibiotics with similar functional groups. Future studies could explore broad-spectrum antibiotics or combination therapies using the same strategy.

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