



Anastrozole loading onto the magnetic core-shell material composed of $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{p}(\text{acrylonitrile-co-acrylic acid})$

Yousaf Ali¹, Muhammad Ilyas¹, Mohsin Alam¹, Nizam ali khan¹, Khalilullah^{2*}, Hammad Ali¹, Muhammad Ahsan^{1*}

¹Department of chemistry Abdul Wali Khan University, Mardan 23200, KPK, Pakistan

²Federal University of arts, science and technology, Karachi, Pakistan.

*Corresponding Author

Khalilullah* and Muhammad Ahsan*

Department of chemistry
Abdul Wali Khan
University, Mardan 23200,
KPK, Pakistan.

Article History

Received: 19.08.2024

Accepted: 09.09.2024

Published: 26.10.2024

Abstract: Anastrozole is a prescribed medication utilized for the treatment of hormone-dependent breast cancer, primarily in postmenopausal women. Administered orally once daily. Anastrozole inhibits the enzyme aromatase, which converts androgens into oestrogens. However, the administration of the medicine frequently results in adverse effects that vary based on dosage, including fatigue, diarrhea, hot flushes, nausea, headaches, and musculoskeletal discomfort. Anastrozole has been associated with additional adverse effects and increased bone loss. To mitigate the negative effects of anastrozole and ensure its effective distribution, it must be adhered to surfaces that are biocompatible and stable within the human body. The co-precipitation approach was employed to synthesized iron oxide nanoparticles, subsequently coated with silica by the Stober process. The synthesised $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanocomposite was then coated with copolymer of acrylonitrile and acrylic acid (AN-co-AA) using microwave assisted polymerization. The $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{p}(\text{AN-co-AA})$ was analyzed using FTIR, EDX, and SEM techniques. The investigation examined how contact time, pH, drug quantity, and nanocomposite quantity influenced drug loading. The optimal adsorption (96.1%) occurred with 16 hour reaction duration, a pH of 4, anastrozole concentration of 20 $\mu\text{g/mL}$, and an adsorbent dosage of 10 mg.

Keywords: Fe_3O_4 , $\text{Fe}_3\text{O}_4@\text{SiO}_2$, $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{p}(\text{AN-co-AA})$, Anastrozole Loading.

Cite this article:

Ali, Y., Khan, I., Mohsin., Khan, N. A., Khalilullah., Ali, H, Ahsan, M., (2024). Anastrozole loading onto the magnetic core-shell material composed of $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{p}(\text{acrylonitrile-co-acrylic acid})$. ISAR Journal of Multidisciplinary Research and Studies, 2(10), 1-5.

1. Introduction

Anastrozole is a prescription drug that is mostly used on women who have gone through menopause to treat hormone-dependent breast cancer. It is swallowed once a day. Anastrozole stops an enzyme known as aromatase from doing its job. Aromatase changes androgens into oestrogens. But the drug often has side effects that depend on how much you take. These can include feeling tired, having diarrhea, having hot flashes, feeling sick, getting headaches, having muscle and joint pain, and more. Anastrozole has been linked to more bone loss and other side effects as well. To get around anastrozole side effects and make sure it works properly, it needs to be loaded on surfaces that are biocompatible with and safe around the human body [1]. Recent years have seen a lot of interest in the use of magnetic iron oxide nanoparticles (IONPs) in different areas of medicine, such as MRI, biomolecule isolation, focused drug delivery, and more [2]. One important thing about IONPs is that an outside magnetic field can be used to move them to a certain place and target living things. Furthermore, magnetic nanoparticles can produce heat when they come into contact with an outside AC magnetic field. This can cause the tissue temperature to rise to 45–47 °C due to hysteresis caused by Brownian and/or Neel relaxation [3]. The heat that is made, which can reach a lethal level, is used to kill tumor or even

bacteria cells through hyperthermia [4]. However, one of the biggest problems with using these nanoparticles in medicine is that they tend to stick together in water. Researchers have looked into adding different coatings to IONP nanoparticles to keep them from sticking together and make them more stable in liquids. Some studies looked at a lot of different organic and inorganic substances that include minerals, biomolecules, carbohydrates, and natural compounds. Recently, some research has looked at silica as a good way to coat metal oxide nanoparticles because it is chemically neutral, non-toxic, thermally stable, biocompatible, and doesn't break down in living things. The easy sol-gel method is a good way to protect metal oxide nanoparticles, but the thick silica layer it creates can stop the outer molecules from interacting properly with the core molecules. [2]. Although magnetic nanoparticles could be useful, they can't be used as much as they could because they agglomerate, which means they don't stay stable in dispersion media, don't stick to proteins, and iron leaches out [5]. So, to get around these issues and make IONPs work better in a certain situation, they are changed with ligands or put into a matrix like polymer or silica [6]. A lot of interest has been shown in using silica, which is made by breaking down tetraethyl orthosilicate (TEOS), as a covering for IONPs because it is biocompatible, stable, and non-toxic [7,8]. Silica is usually not reactive and stays stable at high temperatures. It is also very stable in colloidal form

because it has a low isoelectric point and a low van der Waals force compared to other metal oxides [9]. In addition, the silica shell on IONPs makes it possible for them to attach to more functional groups and connect with bio targets for use [10]. For instance, silica was put on top of iron oxide nanoparticles to make core-shell nanocomposites that could catch nucleic acids [11,12]. Recently, a nanoscale platform was made by encapsulating Fe₃O₄ in silica and then functionalizing it with chitosan and photoluminescence GdOF: Ce³⁺, Tb³⁺ for testing its toxicity in living organisms [13]. The Stöber method and reverse micro emulsion are the two most common ways to cover IONPs with silica. The second technique has demonstrated potential for coating hydrophobic nanoparticles with silica, including oleic acid-coated iron oxide nanoparticles, to produce a precisely defined and tunable core-shell architecture of magnetic silica nanocomposites. Researchers have determined that the thickness of the silica shell may be modified by adjusting variables such as the quantity of TEOS, the nanoparticles, and ammonium hydroxide.

[14]. In an interesting twist, it was shown that the silica shell can only hold one nanoparticle as a core [15]. The silica-coated IONPs are often further modified with different stimuli-responsive polymers, such as pH-responsive poly (acrylic acid) (PAA) and thermosensitive PNIPAm. This makes the nanoparticles more dispersible in water and changes the physicochemical properties of the polymers in response to different stimuli [16]. Nanoparticles with polymers on them can stop grains from growing and clumping together and make it easier for other nanoparticles to stick to them. Different types of polymerization methods are used to make the polymer coating. The microwave assisted polymerization method is one of the best ways to polymerize. The microwave assisted polymerization technique has slowly become a popular synthetic tool because it has many benefits, including shorter reaction times, higher yields, fewer by-products, and the ability to be scaled up without any negative effects. This is because the microwave heating process, high temperatures, and short periods of high pressure make reactions happen faster than with traditional methods. The physical qualities of the polymer that is made this way have also been seen to improve. Microwave-assisted polymerization is very useful in polymer study because it has many benefits, such as direct heating, high temperature uniformity, a fast reaction rate, and lower energy use. As was already said, it also leads to big changes in yield, selectivity, and the physical and chemical properties of new material phases [17].

In the current study iron oxide was coated with silica and then further coated with copolymer of acrylonitrile and acrylic acid. The synthesized composite was used for the loading of anastrozole.

2. Materials and Methods

2.1 Chemicals

All the chemicals used were of analytical grade. Acrylonitrile (AN), Acrylic acid (AA), Azobisisobutyronitrile (AIBN), Ethylene glycol dimethacrylate (EGDMA) and Anastrozole anticancer drug were purchased from sigma Aldrich.

2.2 Preparation of iron oxide nanomaterials

Fe₃O₄ MNPs were synthesized by the chemical co-precipitation method as mentioned in our earlier publication [1].

2.3 Silica coating on Fe₃O₄

Silica coating on MNPs were done by the stober method as mentioned in our earlier publication [1].

2.4 Polymer coating over MNPs@SiO₂

To prepare polymeric nanocomposites of Silica coated MNPs and polymeric shell, 0.4 g of the synthesized MNPs@SiO₂ was reserved and added to the 80 mL mixture of acetonitrile and dist.H₂O (3:1 v/v) in a vessel and 40 min sonicated. After sonication 0.08 g of AN and 0.0606 mL of AA as organic linker, 8 mg of AIBN as initiator and 0.244 mL of EGDMA as a cross linker was added to the reaction mixture. Then the mixture was 10 min purged with N₂ and 40 min sonicated at 353.15K and then the reacting mixture was kept for 25 min in oven at 403.15 K and then for few min at 423.15 K till polymerization. The product was filtered, washed several times with methanol and deionized water. The product was dry for 2h in an oven at 373.15 K and grinded [18].

2.5 Characterization

A Shimadzu Corporation made FTIR spectrophotometer was used to identify the functional groups in polymeric nanocomposite. SEM analysis were done to know about the structures of polymeric nanocomposite and to know about the elemental analysis of the synthesized polymeric nanocomposite an Oxford EDX (Inca-200) was used.

2.6 Anastrozole adsorption for its potential loading

20 mL of 20 ppm anastrozole working solution was used for every adsorption study. Then the 20 mL solution was taken in a 100 mL beaker and placed at room temperature in a shaker with 120 rpm speed. Various adsorption analysis were done with different desired pH, adsorbent weight, drug concentration, and time interval. The adsorbent polymeric nanocomposite was removed via an external magnet after the adsorption of anastrozole. The reacting solutions were then compared with parent solution of 20 ppm at 206 nm by a spectrophotometer of double beam. The % adsorption of drug anastrozole via polymeric nanocomposites was evaluated by given formula.

$$\% \text{ Ads.} = \frac{C_i - C_f}{C_i} \times 100$$

Where C_i is the initial concentrations and C_f is the final concentration

3. Results and discussion

3.1 FTIR Analysis

Figure 1 displays the FTIR spectrum of the magnetite coated silica coated polymeric nanocomposite. The peak at 2950 cm⁻¹ showed that the CH₃ and CH₂ groups of AA, AN, and EGDMA were stretching vibrations. The peak at 2200 cm⁻¹ showed the C–N group of AN. The sharp rise in absorption seen at 1725 cm⁻¹ was caused by the C=O groups of AA and EGDMA. The peaks seen at 1400 and 1330 cm⁻¹ show that the bending vibration of CH₃ in the C-CH₃ of the EGDMA. The broad peak at 1158 cm⁻¹ is because the C-O is stretching. The results showed that the polymer changed the surface of the Fe₃O₄@SiO₂ nanocomposite.

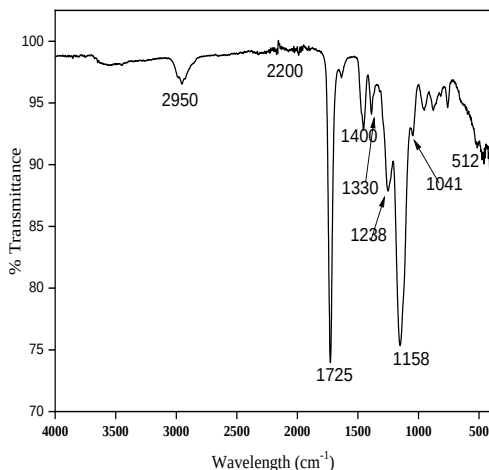


Figure 1. FTIR Analysis of polymeric nanocomposite

3.2 SEM Analysis

Figure 2 shows the SEM pictures of the polymeric nanocomposite. The image showed that the polymeric nanocomposite has rough surface morphology and not uniform distribution. It can be seen from the SEM image that the particles are bigger and their edges are brighter. Before, Javidi et al. (2015) used molecular imprinting to put a polymer layer on MNPs@SiO₂ and revealed that the polymer was shaped like a sphere and had a smooth surface [19].

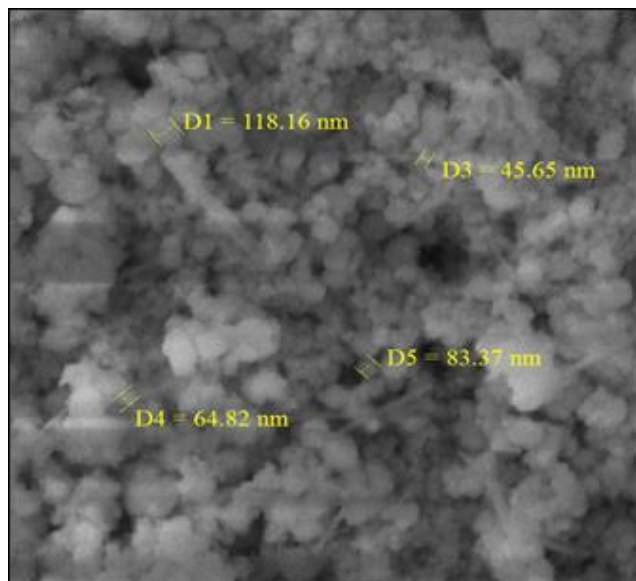


Figure 2. SEM image of polymeric nanocomposite

3.3 EDX spectrum

An EDX spectrum confirmed the elements that made up the synthesised polymeric nanocomposite. The EDX spectrum of the polymeric nanocomposite is shown in Figure 3. The fact that oxygen and carbon are present on the Fe₃O₄@SiO₂ shows that a polymer (AN-co-AA) is there. It was easy to see from the EDX spectrum that the polymeric shell surrounds the iron and silica elements. The results show that this simple, cheap, and quick method can be used to make multi-component core-shell hybrids.

Table 1. Elemental composition of polymeric nanocomposite

Element	Weight%	Atomic%
C	73.10	79.29
O	24.77	20.17
Si	0.26	0.10
Fe	1.87	0.44

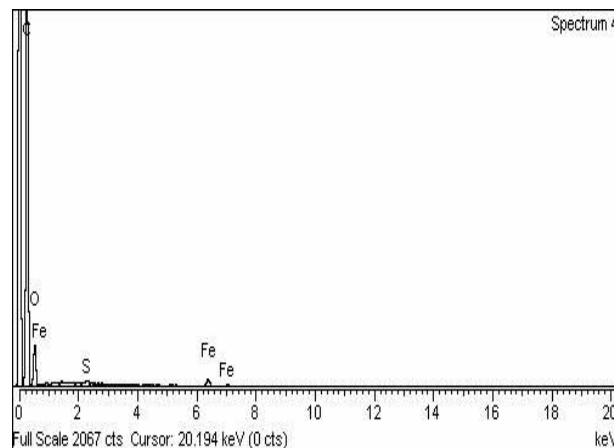


Figure 3. EDX spectrum of polymeric nanocomposite

3.4 Adsorption studies

3.4.1 Spectroscopic determination of anastrozole

Anastrozole was assessed for its maximum absorbance (max) at 358 nm by scanning a 20 µg/mL prepared drug solution with a double-beam UV/Visible spectrophotometer from 200 nm to 800 nm. To determine the impact of anastrozole concentration on absorbance value, the solutions absorbance with different concentrations (5.0, 10.0, 15.0, 20.0, 30.0 µg/mL) was calculated at 358 nm with a reference of 90% methanol (Figure 4). To find out the straight line equation absorbance versus concentration plot was used and the graph provide a linear lapse which facilitated us for concentration calculations in additional studies.

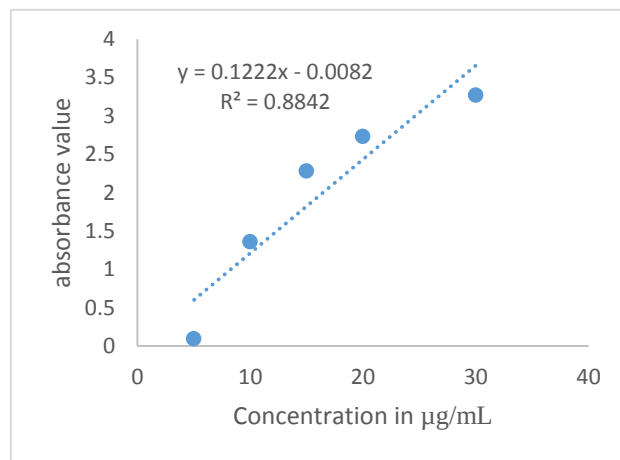


Figure 4. Anastrozole concentration effect on absorbance

As straight line equation is,

$$y = mx + c \dots \dots \dots \text{eq 1}$$

$$X=y-c / m \dots \dots \dots \text{eq 2}$$

$$X= y - 0.0082/0.1222 \dots \dots \text{eq 3}$$

3.4.2 Effect of polymeric nanocomposite on anastrozole adsorption

Utilizing 20 mL of working solutions with a range of concentrations from 05 to 40 mg, the anastrozole adsorption was carried out in a shaker incubator at 120 rpm speed and set time interval. The anastrozole adsorption values with reference to various concentrations of adsorbent dose plotted in figure 5. As the amount of adsorbent was raised from 05 to 10 mg, the adsorption of anastrozole increased. After that, a little rise was noticed, but it was not significant statistically. Therefore, optimum adsorbent dose of 10 mg was chosen maximum.

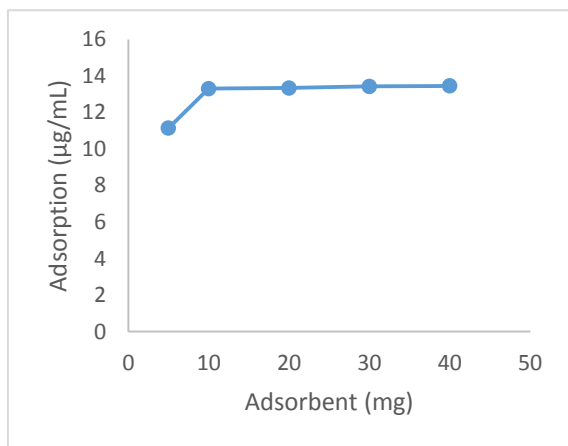


Figure 5. Anastrozole adsorption values with reference to various concentrations of adsorbent dose

3.4.3 Effect of Anastrozole concentration on adsorption

The impact of varied solution concentrations ranging from 05-30 µg/mL by using 20 mL working solutions and adsorbent dosage of 10 mg was studied in a shaker incubator at a speed of 120 rpm and constant duration of time. The anastrozole adsorption values with effect of anastrozole concentrations are plotted in figure 6. Anastrozole adsorption increased when anastrozole concentration rises from 5 to 20 µg/mL, and an additional rise to 30 µg/mL was not statistically significant. So optimum concentration of anastrozole was taken 20 µg/mL.

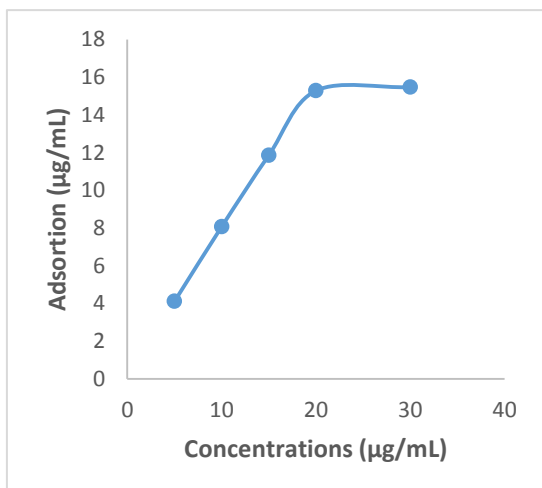


Figure 6: Effect of Anastrozole concentration on adsorption

3.4.3 Influence of time on anastrozole adsorption

Adsorption was carried out in a shaker incubator at 120 rpm. Adsorption was carried out in a shaker incubator at 120 rpm speed and at various interval of times, including 02.00 hours, 03.00 hours, 04.00 hours, 05.00 hours, 12.00 hours, and 16.00 hours, with constant conditions adsorbent dose (10mg) and concentration of drug (20µg/mL).with increase in time the adsorption also increased and the maximum adsorption was found in 18 hours. Therefore, the optimum time was selected 18 hours. Effect of time on anastrozole adsorption are plotted in figure 7.

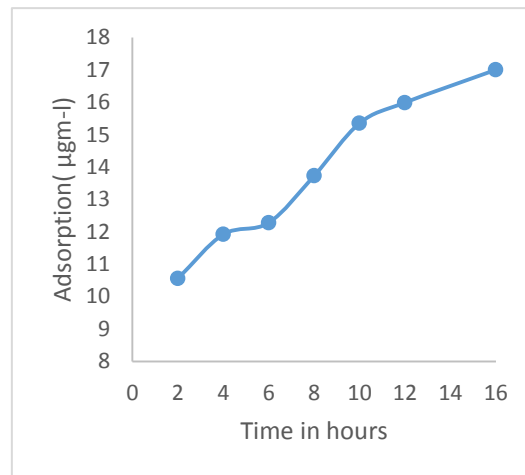


Figure 7. Time effect on anastrozole adsorption

3.4.4 Effect of pH on adsorption of anastrozole

Anastrozole adsorption was also done while examining how pH levels between 2 and 10 affected the process. Other reaction parameters, such as the amount of adsorbent (10 mg), the volume of Anastrozole solution (20 µg/mL), the adsorption period (16 hours), and the speed of shaking in the shaker incubator (120 rpm), were maintained constant. A UV-Visible double beam spectrophotometer was used to measure the results for each pH value. The results of adsorption are plotted in figure 8. The findings demonstrated that the produced adsorbent has the capacity to adsorb letrozole at all pH levels, but that it absorbs the most anastrozole (96.1%) at 4 pH. Therefore, the optimum pH was nominated as 4 for anastrozole adsorption. The final shape of the synthesised adsorbent, the fundamental structure of anastrozole, and the site of zero-charge are responsible for this (PZ-Ch). At the adsorbent surface, PZ-Ch has a positive (+ve) charge when the pH is less than 4, and a negative (-ve) charge when the pH is higher.

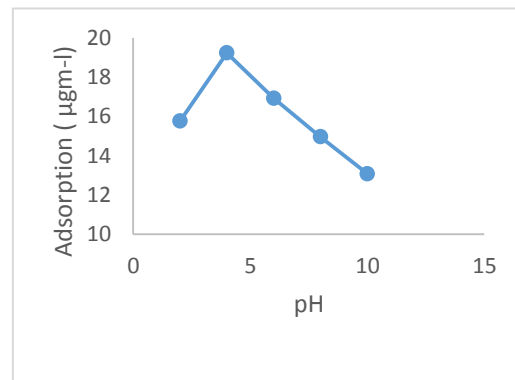


Figure.8 Effect of pH on adsorption of docetaxel

4 Conclusion

The co-precipitation approach was utilized to synthesized iron oxide nanoparticles, thereafter coated with silica via the Stober process. The magnetite coated silica were then covered with a polymer made of AN, and AA, through microwave assisted precipitation polymerization. We used FTIR, SEM and EDX to study the magnetite coated silica covered with a polymer that was made. We looked at how well the magnetite coated silica covered with a polymer nanocomposite loaded with anticancer drug, specifically anastrozole. The results showed that anastrozole was loaded onto the polymeric nanocomposite successfully.

References

1. Ahsan M, Qasim S, Shah A, Nawaz I, Kashif M. and Ahmad W. (2024). Loading of anticancer drug anastrozole using Fe₃O₄@ SiO₂. *Brazilian Journal of Science*. 3(2):93-101.
2. Kermanian M, Sadighian S, Naghibi M. and Khoshkam M. (2021). PVP Surface-protected silica coated iron oxide nanoparticles for MR imaging application. *Journal of Biomaterials Science, Polymer Edition*. 32(10):356-1369.
3. Guardia P, Di Corato R, Lartigue L, Wilhelm C, Espinosa A, Garcia-Hernandez M, Gazeau F, Manna L. and Pellegrino T. (2012). Water-soluble iron oxide nanocubes with high values of specific absorption rate for cancer cell hyperthermia treatment. *ACS nano*. 6(4):3080-3091.
4. Raval YS, Fellows BD, Murbach J, Cordeau Y, Mefford OT. and Tzeng TRJ. (2017). Multianchored Glycoconjugate-Functionalized Magnetic Nanoparticles: A Tool for Selective Killing of Targeted Bacteria via Alternating Magnetic Fields. *Advanced Functional Materials*. 27(26):1701473.
5. Sandler Sarah E, Benjamin Fellows and O. Thompson Mefford. (2019). Best practices for characterization of magnetic nanoparticles for biomedical applications.14159-14169.
6. Sanchez C, El Hajj Diab D, Connord V, Clerc P, Meunier E, Pipy B, Payre B, Tan RP, Gougeon M, Carrey J. and Gigoux V. (2014). Targeting a G-protein-coupled receptor overexpressed in endocrine tumors by magnetic nanoparticles to induce cell death. *ACS nano*. 8(2):1350-1363.
7. Chen F, Hableel G, Zhao ER. and Jokerst JV. (2018). Multifunctional nanomedicine with silica: Role of silica in nanoparticles for theranostic, imaging, and drug monitoring. *Journal of colloid and interface science*. 521:261-279.
8. Sahoo B, Devi KSP, Dutta S, Maiti TK, Pramanik P. and Dhara D. (2014). Biocompatible mesoporous silica-coated superparamagnetic manganese ferrite nanoparticles for targeted drug delivery and MR imaging applications. *Journal of colloid and interface science*. 431:31-41.
9. Metin CO, Lake LW, Miranda CR. and Nguyen QP. (2011). Stability of aqueous silica nanoparticle dispersions. *Journal of Nanoparticle Research*. 13:839-850.
10. Puddu M, Paunescu D, Stark WJ. and Grass RN. (2014). Magnetically recoverable, thermostable, hydrophobic DNA/silica encapsulates and their application as invisible oil tags. *ACS nano*. 8(3):2677-2685.
11. Li X, Zhang J. and Gu H. (2011). Adsorption and desorption behaviors of DNA with magnetic mesoporous silica nanoparticles. *Langmuir*. 27(10):6099-6106.
12. Kang K, Choi J, Nam JH, Lee SC, Kim KJ, Lee SW. and Chang JH. (2009). Preparation and characterization of chemically functionalized silica-coated magnetic nanoparticles as a DNA separator. *The Journal of Physical Chemistry B*. 113(2):536-543.
13. Khan LU, da Silva GH, de Medeiros, AM, Khan ZU, Gidlund M, Brito HF, Moscoso-Londono O, Muraca D, Knobel M, Perez CA. and Martinez DST. (2019). Fe₃O₄@ SiO₂ nanoparticles concurrently coated with chitosan and GdOF: Ce³⁺, Tb³⁺ luminophore for bioimaging: toxicity evaluation in the zebrafish model. *ACS Applied Nano Materials*. 2(6):3414-3425.
14. Yi DK, Selvan ST, Lee SS, Papaefthymiou GC, Kundaliya D. and Ying JY. (2005). Silica-coated nanocomposites of magnetic nanoparticles and quantum dots. *Journal of the American Chemical Society*. 127(14):4990-4991.
15. Ding HL, Zhang YX, Wang S, Xu JM, Xu SC. and Li GH. (2012). Fe₃O₄@ SiO₂ core/shell nanoparticles: the silica coating regulations with a single core for different core sizes and shell thicknesses. *Chemistry of Materials*. 24(23):4572-4580.
16. Nayeem J, Al-Bari MAA, Mahiuddin M, Rahman MA, Mefford OT, Ahmad H. and Rahman M.M. (2021). Silica coating of iron oxide magnetic nanoparticles by reverse microemulsion method and their functionalization with cationic polymer P (NIPAm-co-AMPTMA) for antibacterial vancomycin immobilization. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 611: 125857.
17. Bibi A, Shah A, Israr M, Rani S, Tariq N, Habib R, Ahsan M. and Khan MA. (2024). Docetaxel: Strategy to Enhance Their Efficiency Using Polymeric Nanocomposite. *Journal of Animal and Plant Research*. 1(2):7-12.
18. Javidi J, Esmailpour M. and Khansari MR. (2015). Synthesis, characterization and application of core-shell magnetic molecularly imprinted polymers for selective recognition of clozapine from human serum. *Rsc Advances*. 5(89):73268-73278.