Improving Radiotherapy Efficacy Using Iron Oxide Nanoparticles: A Study on the Effects of Crystallite Size and Concentration.

Amatalelah Abdulazez Mashhor Al-Ahdel1
Hashim Mohammed Al-Sanea2
drhmm1990@gmail.com
Corresponding author:Amatalelah Abdulazez Al-Ahde Address: 1,2* Department of Physics, College of Education and Science – Rada'a, Albaydha University, Yemen.

Abstract

This study aims to improve the effectiveness of radiotherapy for cancer using curcumin-doped iron oxide, focusing on the effects of crystal size and concentration. Pure iron oxide doped with curcumin was prepared using the co-precipitation method, and the structural properties of the resulting compounds were studied using X-ray diffraction (XRD). The results showed that the crystal structure of the samples before and after doping matched the crystal structure of iron oxide (Fe2O3) in the two types, magnetite (γ-Fe_2O_3) and hematite (α-Fe2O3). An increase in crystal size was also observed after doping with curcumin, indicating an improvement and transformation in crystalline properties as a result of the co-formulation. To estimate the effectiveness of the treatment, a simulation using MATLAB was employed. The results demonstrated a positive relationship between crystal size and increased treatment effectiveness. Notable increases in radiotherapy effectiveness were recorded, with samples S1 (65.7), S2 (100.6), and S3 (81). Additionally, the curcumin-loaded nanoparticles showed increases in effectiveness of S1 (21), S2 (38.1), and S3 (28.7). These results indicate that combining curcumin with magnetic iron oxide can enhance the properties of iron oxide and improve the effectiveness of radiotherapy for cancer, opening new avenues for developing innovative cancer treatment strategies.

Keyword: *Radiotherapy, Iron oxide nanoparticle, Curcumin, MATLAB.*

تحسين فعالية العلاج الإشعاعي باستخدام جسيمات أكسيد الحديد: دراسة تأثير الحجم البلوري والتركيز

أمة الإله عبد العزيز مشهور الأهدل   وهاشم محمد مصلح الصانع
قسم الفيزياء، كلية التربية والعلوم، رداع، البيضاء، اليمن

الملخص

تهدف هذه الدراسة إلى تحسين فعالية العلاج الإشعاعي للسرطان باستخدام أكسيد الحديد النانوي المدعوم بالكركمين، مع التركيز على تأثيرات حجم البلورات والتركيز. تم تحضير أكسيد الحديد النقي المدعوم بالكركمين باستخدام طريقة الترسيب المشترك، وتمت دراسة الخصائص الهيكلية للمركبات الناتجة باستخدام تحليل حيود الأشعة السينية .(XRD) أظهرت النتائج أن الهيكل البلوري للعينات قبل وبعد التحميل يتطابق مع الهيكل البلوري لأكسيد الحديد (Fe2O3) في نوعيه الماجنيتيت (γ-Fe_2O_3) والهيماتيت .(α-Fe2O3) كما لوحظت زيادة في حجم البلورات بعد التحميل بالكركمين، مما يدل على تحسين وتحول في الخصائص البلورية نتيجة للتوليف المشترك. لتقدير فعالية العلاج تم استخدام المحاكاه باستخدام ال (MATLAB) حيث أظهرت النتائج علاقة إيجابية بين حجم البلورات وزيادة فعالية العلاج. تم تسجيل زيادات ملحوظة في فعالية العلاج الإشعاعي، إذ كانت العينات S1 (65.7)، S2 (100.6)، وS3 (81). كما أظهرت الجزيئات النانوية المحملة بالكركمين زيادات في الفعالية بمقدار S1 (21)، S2 (38.1)، وS3 (28.7). تشير هذه النتائج إلى أن دمج الكركمين مع أكسيد الحديد المغناطيسي يمكن أن يحسن من خصائص أكسيد الحديد ويعزز فعالية العلاج الإشعاعي للسرطان، مما يفتح آفاقًا جديدة لتطوير استراتيجيات مبتكرة لعلاج السرطان.

الكلمات المفتاحية: العلاج الإشعاعي، جسيمات أكسيد الحديد النانوية، الكركمين ، الماتلاب

1.Introduction:

Nanotechnology has emerged as a significant field of research since the latter half of the 20th century. The term was popularized by Nobel laureate Richard P. Feynman during his iconic 1959 lecture, "There's Plenty of Room at the Bottom," which laid the groundwork for future advancements in manipulating matter at the atomic and molecular levels (Feynman, 1960). Over the years, nanotechnology has led to revolutionary developments,particularly in the creation and application of materials at the nanoscale, where nanoparticles (NPs) represent a diverse class characterized by their size; they possess at least one dimension measuring less than 100 nanometers [1]. Due to their unique physical and chemical properties, nanoparticles are utilized across a wide range of fields, from electronics to medicine. In the medical realm, nanoparticles are employed for targeted drug delivery, increasing therapeutic effectiveness while minimizing potential side effects [2]. These nanoparticles have the remarkable ability to alter the behavior of materials at small scales, enabling the development of innovative techniques that enhance performance and efficiency, and help overcome challenges related to non-targeted biological distribution and unwanted side effects [3,4]. Among the nanomaterials used in radiotherapy are iron oxide nanoparticles(IONPs). A spatial structure of molecules of iron oxide nanoparticles, there are three most common forms of IONPs structurally corresponding to iron oxide minerals: magnetite (Fe_3O_4) and magmetite (γ-Fe_2O_3), and hematite (α–$Fe2O3$) are an advanced research topic due to their wide potential in biomedical applications. These applications include magnetic resonance imaging (MRI), radiolabeling, and internal radiotherapy, as well as thermotherapy and gene therapy, and improving radiotherapy of cancerous tumors in vitro, animals, humans and many medical applications [5-9]. Additionally,Iron oxide nanoparticles(IONPs) were functionalized with curcumin, a natural compound known for its numerous health benefits. Research indicates that integrating nanoparticles with plant extracts can increase treatment efficacy, as these extracts possess strong anti-tumor, antifungal, anti-inflammatory, and antimicrobial activities[10,11,12].Recent studies confirm that the combination of nano iron oxide and curcumin extract improves the effectiveness of radiotherapy and enhances the response of cancer cells. [13-16].

It was recently reported that encapsulating curcumin, apowerful herbal medicine, in iron oxide nanoparticles (IONPs) enhanced its bioavailability, indicating that IONPs are an effective vehicle for targeted drug delivery in cancer treatment [17]. Moreover, some researchers; study theRadiation Sensitization and Radioprotection Using Curcumin in the Treatment of Brain Tumors and Other Cancers. The study also addressed the molecular mechanisms through which curcumin improves the effectiveness of radiation therapy and reduces its harmful effects [18]. Also, study the examined the effect of combining curcumin with iron oxide nanoparticles on enhancing the treatment efficacy of human hepatocellular carcinoma (HepG2) cells and demonstrated the ability of curcumin to bind to iron oxide nanoparticles, enhancing their anticancer properties. Iron oxide acts as a nanocarrier to enhance the efficacy of curcumin, while curcumin acts as a coating agent to reduce the toxicity of iron oxide nanoparticles, enhancing their use in biomedical applications [19]. In the present study, we will discuss the effect of crystal size and concentration in enhancing the efficacy of radiotherapy for cancer tumors using curcumin-infused iron oxide nanoparticles (IONPs).

2.Methodlogy

2.1 Materials

Preparation of Iron oxide nanoparticles (IONPs) were obtained by co-precipitation; as shown (5 grams) of ferric Iron chloride (III) chloride hexahydrate, extra pure, ph Eur ($FeCl_3.5H_2O$, M=270.32), and (4 grams) of ferrous sulfate ($FeSO_4.7H_2O$) were dissolved in (100) ml of distilled water.

2.1. Synthesis and Modification of Fe_3O_4 NPs

Iron oxide nanoparticles were prepared using a chemical method known as co precipitation. This reaction can be represented as follows:

$Fe^{+2} + 2Fe^{+3} + 8OH \rightarrow Fe_3O_4 + 4H_2O$

Dissolve (5 grams) of Iron (III) chloride hexahydrate, extra pureph Eur ($FeCl_3 \cdot 5H_2O$, M=270.32), and (4 grams) of ferrous sulfate ($FeSO_4 \cdot 7H_2O$) in (100 mL) of distilled water. Add a sodium hydroxide solution with a concentration of (1.5) in (250 mL) of distilled water. Add the solution dropwise to the prepared solution of iron chloride and iron sulfate, resulting in a black precipitate and obtain pH value to be (pH=14) . Separate the solution from the precipitate using a centrifuge at a speed of (4000) RPM for(15 minutes). Dry the precipitate in an oven at a temperature of (400) °C for (30 mn).

Grind the formed black precipitate using a grinder until the powder becomes nano-sized. Obtain iron oxide nanoparticles weighing 1.5 grams used microbalance.

2.2. Synthesis of Pure Curcumin Extract:

The plant extract (curcumin) was prepared from turmeric using a solvent extraction method. Finely powdered turmeric weighing (5) grams was added to a glass container, followed by (100) ml of ethanol solution. The fine turmeric powder was mixed with the ethanol solvent by stirring for (30 minutes) at a temperature of approximately (100) degrees Celsius to enhance the extraction process.The solvent was separated to obtain the extract through filtration. The extract was obtained after separating it from the powder.

2.3 Doping Process.

The preparation of tree samples (S1, S2 and S3) as shown blow;

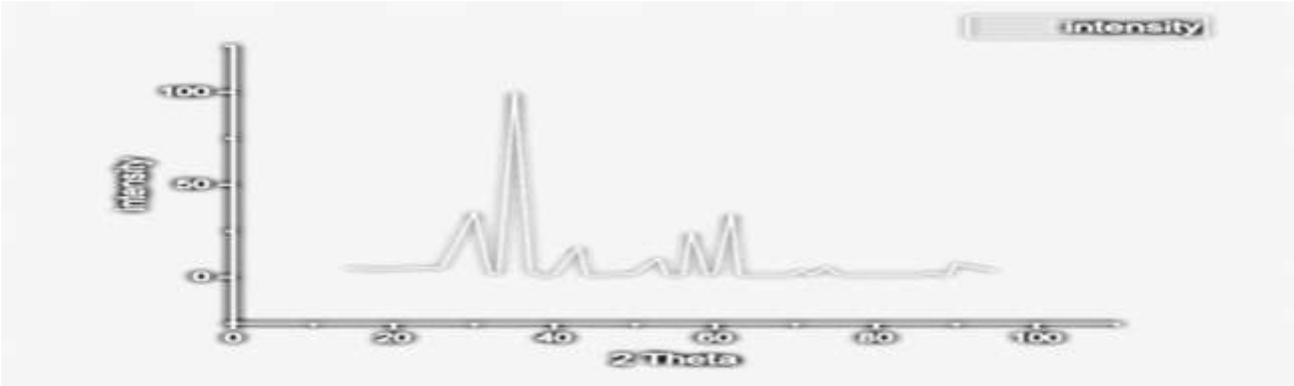
0.1 grams of iron oxide nanoparticles was added to (2.8 ml, 3.8ml and 4.8 mL) of the extract was added dropwise while stirring. After adding the extract to the iron oxide nanoparticles for samples (S1, S2, S3) these samples were dried in an electric oven at a temperature of (400)°C for (30mn).

3. Result and Discussion:

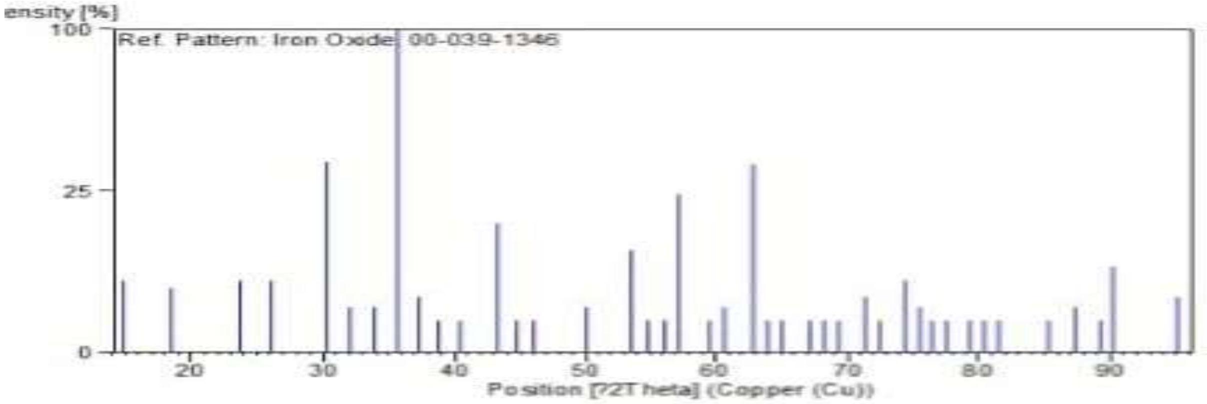
The crystal structure of iron oxide-NPs (Fe_2O_3) pure and the doped samples (S1, S2, S3) with curcumin was examined using X-ray diffraction (XRD), and Phase structure analysis carried out by (X-pert program).

3.1 XRD Sample Analysis:

The X-ray diffraction pattern of iron oxide (Fe_2O_3)as shown in Figures (1a) and (1b). The patterns indicates all the peaks was identified as magnetite (γ-Fe_2O_3) with a percentage of (95.8), and hematite (Fe_2O_3-α) with a percentage of (4.2). All the diffraction peaks in the pattern correspond to the cubic phase of iron oxide (Fe_2O_3). The structure has been agreement with the reported standard values (ICSD data card no 00-039-1346) (space group: p4132). The diffraction peaks at 2θ (degrees) are indexed as the planes; (110), (111), (221), (220), (311), (222), (320), (400), (422), (004), (511) and (440) corresponding to the higher peaks at (311) and 2θ (35.631) degree.



Fig(1a): X-ray diffraction pattern of iron oxide (Fe2O3)



Fig(1b): shown a11the beaks (XRD) comparing with PDF Stander (ICSD data card No 00-039-1346)

For the first sample (S1), the crystal structure was also identified as magnetite (Fe2O3-γ) with a percentage of 95.4% (in green) and hematite (Fe_2O3-α) at 4.6% (in red), with the presence of curcumin (in blue) as shown in figure (2).

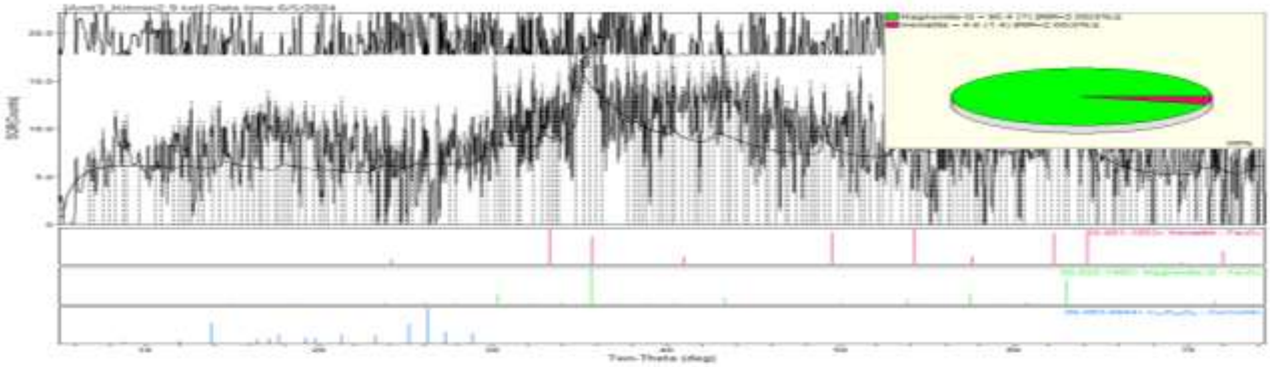


Figure (2): X-ray diffraction pattern (S1) showing relative intensity as a function of diffraction angle (2θ).

In the second sample (S2), the crystal structure was identified as magnetite (Fe2O3-γ) with a percentage of 83.5% (in red) and curcumin at 16.5% in green as shown in figure (3).

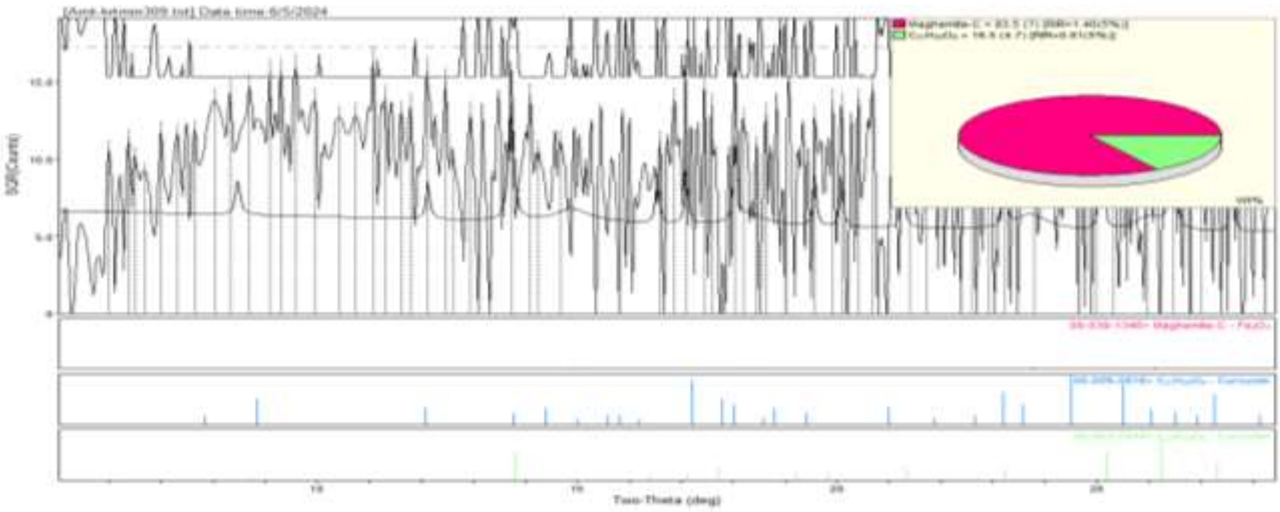


Figure (3): X-ray diffraction pattern (S2) showing relative intensity as a function of diffraction angle (2θ).

Finally, in the third sample (S3), the results showed a crystal structure corresponding to pure magnetite (γ-Fe_2O_3) at (100%). as shown in Figure (4).

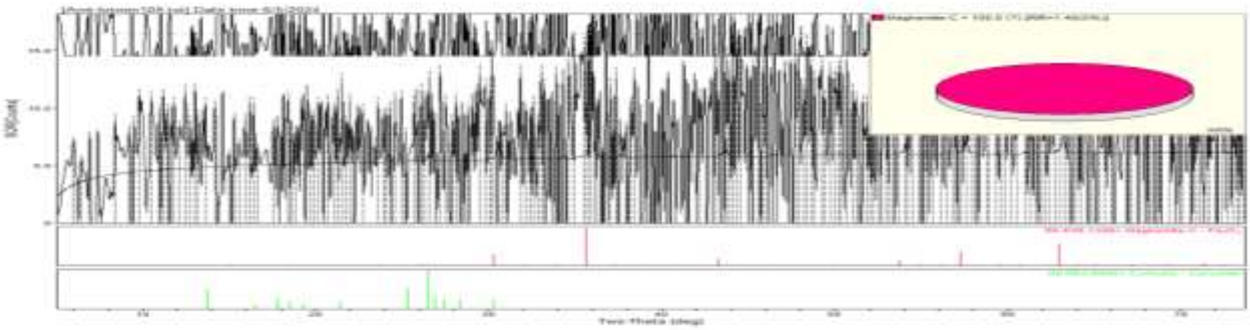


Figure (4): X-ray diffraction pattern (S3) showing relative intensity as a function of diffraction angle (2θ) for maghemite 100% appears in red color.

The samples were analyzed using X-ray analysis, and the results showed a significant variation in the composition of the nanomaterials and their relationship with curcumin, as illustrated in the figures (2,3,4).

In the (S1), the hematite content was (4.6%), while the maghemite content was (95.4%). In this sample, curcumin was observed at less than 1%. This indicates that maghemite was the main component in the composition, reflecting that the interaction of curcumin was insufficient to produce a notable effect.

At (S2), a significant increase in the curcumin content was noted, reaching 16%. The hematite content also rose to (16.5%), while the maghemite was maintained at (83.5%). This increase can be attributed to improved synthesis conditions, which helped enhance the interaction of curcumin with the mineral components. This aligns with what was mentioned by Bhandari et al. (2016), which emphasized the importance of precise synthesis conditions for achieving better compatibility between active molecules and the core components [2].

However, in the S3, where curcumin and hematite completely disappeared, maghemite appeared at (100%). This result indicates a properties of the samples resulting from the addition of curcumin, reflecting the impact of this addition on the crystalline size of the samples.

3.2 Simulation Using MATLAB:

3.2.1 Simulation Setup

The simulation was used to evaluate the results in this study for curcumin-doped iron oxide nanoparticles and assess their effectiveness in improving radiation therapy. The simulation was set up to evaluate the effects of doping on the physical and chemical properties of iron oxide nanoparticles. Parameters such as chemical composition, particle size, and radiation properties were utilized.

The steps of the simulation for the samples before and after curcumin doping are outlined as follows:

i. Preparation of Baseline Data:

- Assigning the effectiveness of the control group, radiation dose, and damage factor to healthy cells.

ii. Preparation of Crystalline Sizes:

- Defining the crystal sizes used in the simulation and calculating the average for each sample.

iii. Generating Concentrations:

- Creating a set of random concentrations to evaluate different effects on treatment effectiveness.

iv. Storing Results:

- Setting up two matrices to store the results of treatment effectiveness and side effects.

- Treatment Simulation: Evaluating treatment effectiveness based on the impact of crystal size and concentration, and calculating the associated side effects for each concentration.

v. Analyzing Results:

- Plotting the results to illustrate treatment effectiveness and side effects.

3.2.1 Results:

3.2.1.1 Pure Samples:

complete transformation of the materials, meaning that chemical interactions between the compounds led to the emergence of maghemite alone. It can be said that curcumin contributed to the conversion of hematite to maghemite through oxidative reactions, given that curcumin contains OH groups.

This crystallographic transformation resulted in a change in the crystal structure from the pyramidal structure of hematite to the cubic structure of maghemite. This is related to the presence of oxygen and water and certain conditions such as heat or pressure, which enhance the effectiveness of this transformation. Consequently, these results confirm the improvement of the magnetic properties of the resultant material, suggesting that the interactions of curcumin with iron nanoparticles were effective in achieving these transformations. These results align with what Ashokumar et al. (2015) indicated, as their findings demonstrated the importance of nickel doping in enhancing the electrical, optical, and magnetic properties of copper-added zinc oxide nanoparticles [21].

3.1.1 Calculation of Average Crystalline Sizes

The average crystalline sizes of the studied samples were calculated using the Scherrer equation

$D = K\,\lambda/\beta\,\mathrm{Cos}\boldsymbol{\theta}$

where D is the particle size, k = 0.94 is a constant, λ is the wavelength of the X-rays (0.154 nm), β is the line amplitude at half maximum (FWHM) and $\boldsymbol{\theta}$ is the Bragg angle.

at the high peaks. The results showed that the average crystalline size of the pure sample (Sp) was (33.416) nm and, sample S1, the average crystalline size was (43.5) nm, while the value for sample S2 was approximately (180.8) nm, Finally Regarding sample S3, the average crystalline size reached (90.7). These values indicate significant differences in the crystalline highest treatment effectiveness observed at a concentration of (49), which corresponds to an average crystallite size of (33.4) nanometers.

The results illustrated in Figure 5 showed that the effectiveness of radiotherapy using iron oxide nanoparticles (Fe_2O_3) significantly increases at higher concentrations, with the

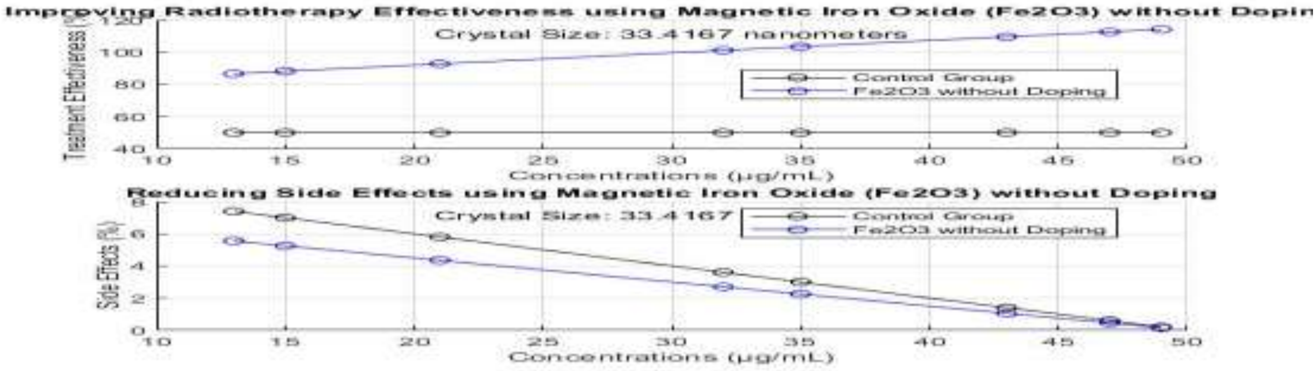


Figure (5): illustrates the effect of crystalline size at different concentrations of magnetic iron oxide nanoparticles on enhancing the effectiveness of radiotherapy.

These findings indicate that increased concentration enhances the interaction between cancer particles, improving the effectiveness of radiotherapy. This aligns with the study by Hauser et al. (2016), which demonstrated that iron oxide nanoparticles promote the production of reactive oxygen species (ROS), increasing cell sensitivity to radiation therapy [22].

3.2.1.2 Curcumin-Doped Iron Oxide Nanoparticles:

The doped samples (S1, S2, S3) exhibited a significant improvement in treatment effectiveness.

The simulation results for sample S1, as shown in Figure (6), indicated that the effectiveness of radiotherapy using curcumin-loaded iron oxide nanoparticles reached (138.7), compared to (117.7) for iron oxide nanoparticles without curcumin. This indicates an improvement of (67.7%) when compared to the control group. This enhancement is attributed to the effect of curcumin, which acts as a coating for the nanoparticles, influencing the physical and magnetic properties of iron oxide and helping to concentrate radiation intargeted.areas.

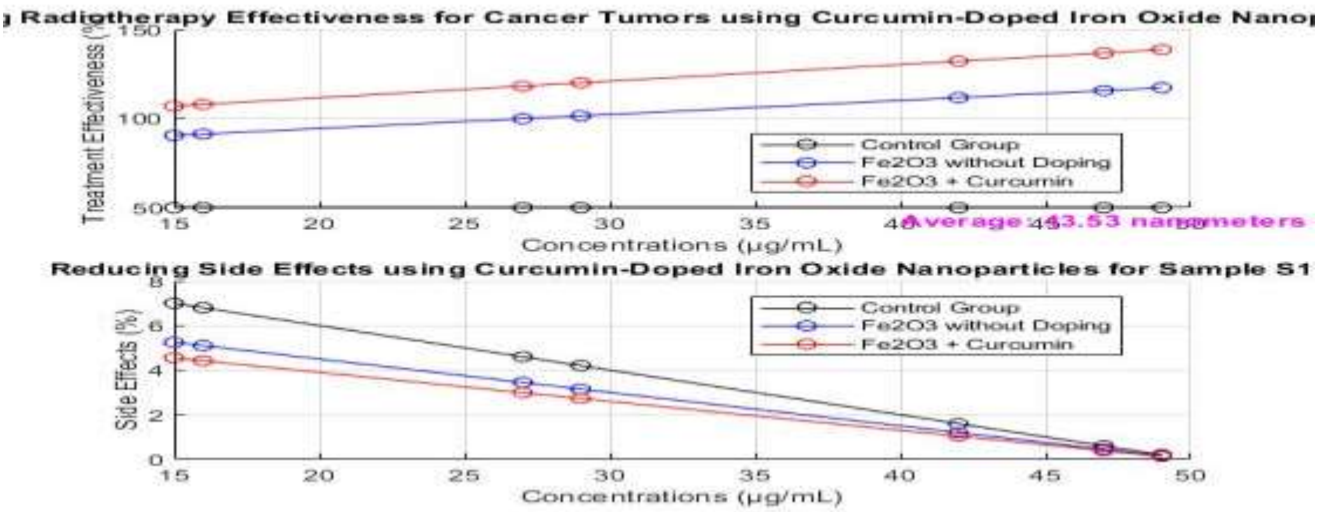


Figure (6): shows the effect of crystal size at different concentrations in improving the effectiveness of radiotherapy for sample (S1) grafted with curcumin.

For sample (S2), as shown in Figure7, the effectiveness of treatment using iron oxide nanoparticles was (150.6), while the effectiveness with curcumin was 188.7, demonstrating a (100.6%) improvement compared to the control group. This enhancement is also due to the magnetic properties of iron oxide, which enhance radiation concentration in targeted areas.

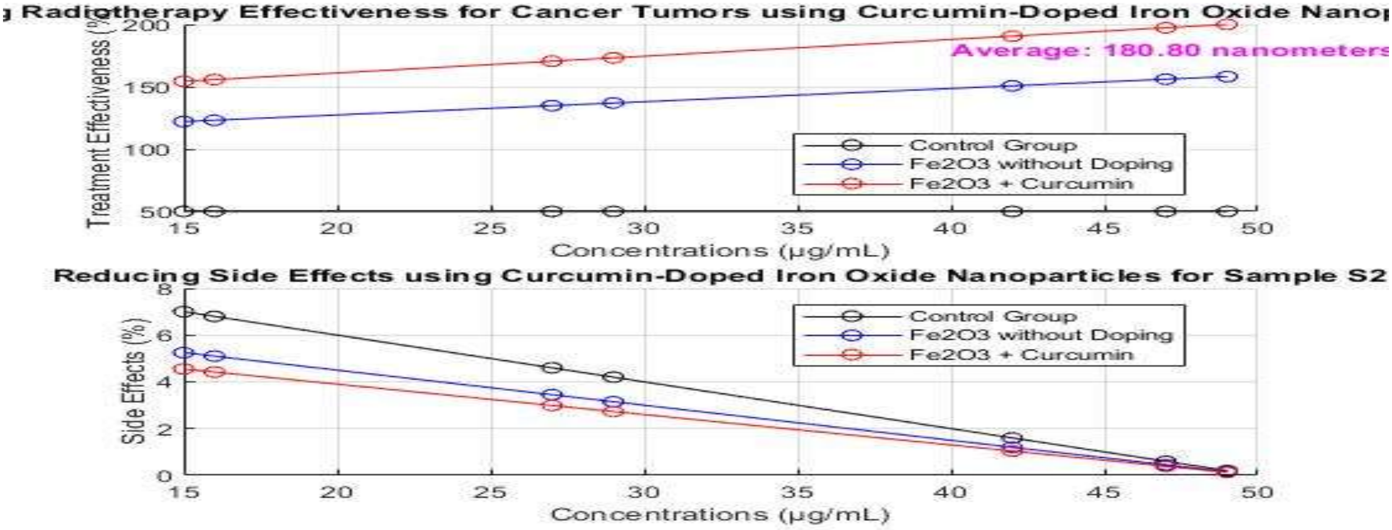


Figure (7): shows the effect of crystallin size at different concentrations for sample S2 in improving the effectiveness of radiotherapy.

In sample (S3), as shown in Figure 8, the effectiveness of radiotherapy using curcumin-loaded iron oxide nanoparticles was (159.7), compared to 131 for the iron oxide nanoparticles **without curcumin, indicating an (81%) improvement when compared to the control group.**

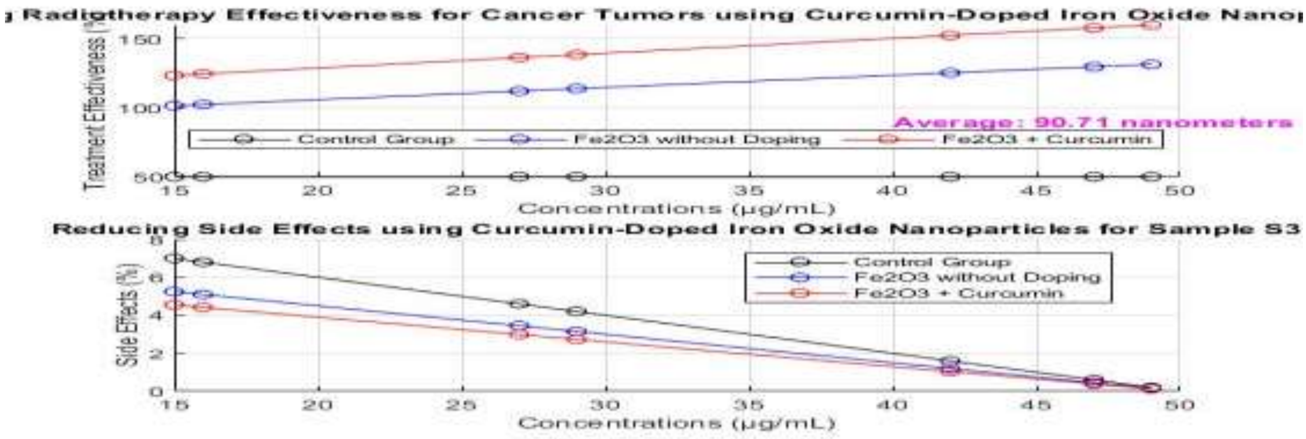


Figure (8): shows the effect of crystal size at different concentrations for sample S3 in improving the effectiveness of radiotherapy.

These results suggest that the incorporation of curcumin with iron oxide ($Fe2O3$) in all samples led to improved radiotherapy effectiveness, as curcumin contributed to enhancing the physical and magnetic properties of the particles, thereby boosting the treatment's impact on cancer cells. The results indicate that the incorporation of curcumin with iron oxide ($Fe2O3$) in all samples led to an enhancement of radiotherapy efficacy. Curcumin significantly contributed to improving the physical and magnetic properties of the particles, thereby increasing the treatment's effect on cancer cells.

Furthermore, the results showed that the samples S1, S2, and S3 loaded with curcumin exhibited a notable effectiveness in improving the outcomes of radiotherapy, with sample S2 achieving the highest efficacy compared to the other samples, as demonstrated by the data presented in Table (1).

These findings are consistent with the study conducted by Gao et al. (2022), which confirmed that the use of curcumin and hemoglobin-based nanoparticles can enhance the efficacy of radiotherapy against liver cancer. This highlights the importance of continuous research for new strategies to improve radiotherapy outcomes in cancerous tumors, thereby opening new avenues for developing effective methods to combat this disease [23].

Sample	**D(nm)**	Effectiveness of (Fe2O3) in treatment	Effectiveness of (fe2o3)in treatment with curcumin	Improvement percentage compared to the control group	Increase between coated and coated and uncoated particles
S1	**43.5**	**117.7**	**138.7**	**65.7**	21
S2	**188.7**	**150.6**	**188.7**	**100.6**	38.1
S3	**90.7**	**131**	**159.7**	**81**	28.7

Table No. (1) Comparison of the effectiveness of radiotherapy for samples S1, S2, S3 using iron oxide nanoparticles doped with curcumin.

5. Conclusion:

Furthermore, the effectiveness of curcumin-loaded nanoparticles was enhanced, with increases as follows: S1 (21), S2 (38.1), S3 (28.7). This indicates that curcumin has a positive impact on treatment effectiveness, aligning with findings from previous studies.The results also highlighted the effect of crystallite size on treatment efficacy, with sample S2 having the highest effectiveness at a crystallite size of (188.7), showing an increase of 100.6 compared to the control group. Additionally, the highest concentration in all samples (49) was associated with greater effectiveness, supporting the notion that increased nanoparticle concentration enhances therapeutic effects.

Conflicts of Interest: There are no conflicts of interest

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