To assess the anticancer potential and design a nano delivery system for newly synthesized thioamide derivatives.

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Abstract
This study aims to evaluate the anticancer efficacy of newly synthesized thioamide derivatives and to develop a nano delivery system to enhance their therapeutic potential. Thioamide derivatives have shown promise in cancer treatment due to their cytotoxic effects on malignant cells, yet challenges remain in achieving efficient delivery, stability, and targeted action. To address these limitations, a nano delivery system was developed, focusing on optimizing particle size, surface charge, and release characteristics to improve cellular uptake and bioavailability. The synthesized thioamide derivatives were first screened for characterization studies, including fourier-transform infrared spectroscopy (FTIR), confirmed the stability and encapsulation efficiency of the nanoparticles. The results suggest that the nanodrug delivery system not only improves the anticancer efficacy of thioamide derivatives but also offers a promising approach for targeted cancer therapy. This study paves the way for further in vivo studies and the potential clinical application of nanoformulated thioamides in cancer treatment, providing a significant advancement in the development of novel chemotherapeutic strategies.

Keywords: ***Thioamide derivatives, anticancer activity, nano delivery system, cytotoxicity, targeted drug delivery, nanoparticles.***

Introduction
The development of effective cancer therapies remains a critical area of research due to the complex nature of cancer and the limitations of current treatment options. Traditional chemotherapy often lacks selectivity, affecting both cancerous and healthy cells, which leads to significant side effects and limits the therapeutic efficacy [1]. This non-specificity results in considerable damage to normal tissues, causing adverse effects such as nausea, fatigue, and immunosuppression, thereby reducing the quality of life for patients undergoing treatment.

In recent years, attention has turned to molecularly engineered compounds that can offer more specific mechanisms of action against cancer cells. Among these, thioamide derivatives have garnered interest for their potential anticancer properties. Thioamides, characterized by the presence of a sulfur atom replacing the oxygen in amide bonds, have shown promise due to their ability to interfere with key cellular processes. They are believed to induce apoptosis (programmed cell death) and inhibit cell proliferation by targeting various molecular pathways within tumor cells, making them a promising candidate for targeted cancer therapy.

Despite these promising preliminary findings, the application of thioamide derivatives in cancer therapy is hindered by several challenges. One of the primary issues is low bioavailability, which limits the amount of active compound that reaches the target tumor cells. Additionally, thioamide derivatives often exhibit limited stability in biological environments, which can lead to rapid degradation and loss of efficacy. Moreover, nonspecific distribution within the body can cause off-target effects, further complicating their therapeutic use [2].

To overcome these limitations, recent research has focused on the development of nano delivery systems that can enhance the stability, bioavailability, and specificity of anticancer compounds [13,23]. Nanocarriers, such as liposomes, nanoparticles, and dendrimers, offer a promising solution by protecting the active compound from degradation, improving its solubility, and facilitating targeted delivery to tumor cells. By encapsulating thioamide derivatives within a nano delivery system, it is possible to enhance their therapeutic potential while minimizing adverse effects on healthy tissues [3].

This study aims to assess the anticancer potential of newly synthesized thioamide derivatives and design an optimized nano delivery system using response surface methodology (RSM). The central composite design (CCD) will be employed to systematically evaluate the effects of key formulation variables on the efficacy of the thioamide derivatives. Through this approach, we seek to identify the optimal conditions that maximize the anticancer activity of the thioamide-nano complex, providing a foundation for the development of more effective and targeted cancer therapies. This study focuses on evaluating the anticancer efficacy of newly synthesized thioamide derivatives and preparing a nano delivery system to maximize their therapeutic potential [14,22]. Through this approach, we aim to develop a targeted, stable, and efficient delivery system that could offer an advanced therapeutic option in cancer treatment, addressing the limitations of conventional chemotherapeutics and paving the way for more effective and safer cancer therapies [4].

Materials and Methods

Synthesis of Thioamide Derivatives

All the chemical (synthetic grade) were procured from Merck, SRL and SD Fine Chemicals. The thioamide derivatives were synthesized via a series of chemical reactions involving the following reagents: thiosemicarbazide, various aldehydes, and suitable solvents. Reactions were carried out under controlled conditions, with final compounds purified through recrystallization and characterized using Fourier-transform infrared (FTIR) spectroscopy, nuclear magnetic resonance (NMR), and mass spectrometry to confirm their structure and purity [5].

Preparation of Nano Delivery System

The thioamide derivatives were loaded into nanoparticles using the nanoprecipitation method. The delivery system was formulated with biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) or lipid-based carriers like phosphatidylcholine, selected based on their stability and biocompatibility [15]. The drug-to-polymer ratio was optimized to maximize encapsulation efficiency and particle stability [6].

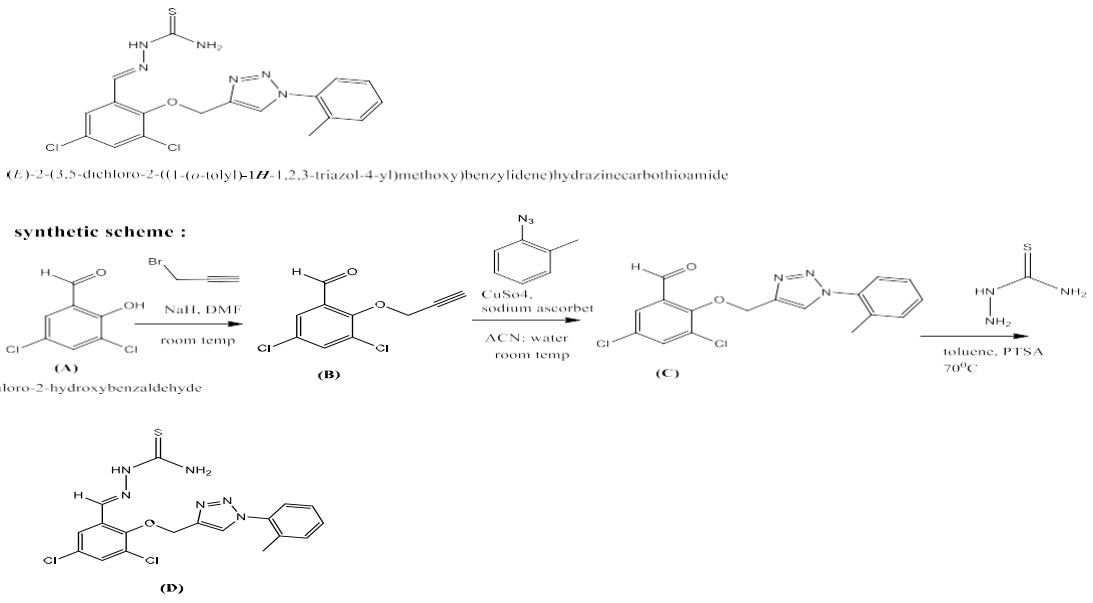

Figure 1. Synthetic scheme

Optimization of Thioamide Derivative

Experimental Design

The optimization of the formulation of newly synthesized thioamide derivatives for anticancer potential was carried out using Central Composite Design (CCD). The CCD approach was employed to evaluate the effects of three independent variables: concentration of thioamide derivatives (X1), temperature (X2), and pH (X3). Each variable was studied at three levels: low (-1), medium (0), and high (+1) [15].

Design Matrix

The CCD design matrix included a total of 16 experimental runs, consisting of 8 full factorial points, 6 axial (star) points, and 2 center points. The design matrix is presented in Table 1.

Table 1. CCD Design Matrix

Run	X1 (Concentration)	X2 (Temperature)	X3 pH
1	-1	-1	-1
2	+1	-1	-1
3	-1	+1	-1
4	+1	+1	-1
5	-1	-1	+1
6	+1	+1	+1
7	-1	+1	+1
8	+1	+1	+1
9	-α	0	0
10	+α	0	0
11	0	0	0
12	0	0	0
13	0	-α	-α
14	0	+α	+α

Statistical Analysis

The response variable, Y, representing the anticancer activity, was analyzed using a second-order polynomial model. The regression equation for predicting the response Y based on the three independent variables (X1, X2, and X3) is expressed as:

$$Y=\beta0+\beta1X1+\beta2X2+\beta3X3+\beta11X12+\beta22X22+\beta33X32+\beta12X1X2+\beta13X1X3+\beta23X2X3 \quad \text{eq ----1}$$

Where:

- Y is the response variable (anticancer activity),
- β0 is the intercept,
- β1, β2, β3 are the linear coefficients,
- β11, β22, β33 are the quadratic coefficients,
- β12, β13, β23 are the interaction coefficients,
- X1, X2, X3 are the independent variables (concentration, temperature, and pH) [16].

Regression Analysis

The response variable (anticancer activity) was modeled using a second-order polynomial equation. The regression coefficients were estimated using the method of least squares, and the equation obtained is as follows:

$$Y=\beta0+\beta1X1+\beta2X2+\beta3X3+\beta11X12+\beta22X22+\beta33X32+\beta12X1X2+\beta13X1X3+\beta23X2X3 \quad \text{eq----------2}$$

Where:

- Y is the response variable (anticancer activity).
- X1, X2, X3 are the independent variables (concentration, temperature, pH).
- β0 is the intercept.
- β1, β2, β3 are the linear coefficients.
- β11, β22, β33 are the quadratic coefficients.
- β12, β13, β23 are the interaction coefficients.

The regression coefficients (β\beta) were estimated using the method of least squares. Statistical significance of the regression coefficients was assessed using t-tests, with p-values less than 0.05 considered significant. The goodness-of-fit of the model was evaluated using the coefficient of determination (R-squared) and adjusted R-squared values [17].

Analysis of Variance (ANOVA)

ANOVA was performed to partition the total variability in the response variable into components due to regression, residual error, and lack of fit. The sum of squares, degrees of freedom, mean squares, F-values, and p-values.

Result and Discussion

The relationship between the independent variables (concentration of thioamide derivatives, temperature, and pH) and the response variable (anticancer activity) was modeled using a second-order polynomial equation. The regression coefficients and their statistical significance are presented in Table 2.

Table 2. Regression Coefficient and Statistical Significance

Term	Coefficient	Standard Error	t-value	p-value
Intercept (β0\beta_0)	5.123	0.256	20.02	<0.001
X1 (Concentration) (β1\beta_1)	0.564	0.118	4.78	<0.001
X2 (Temperature) (β2\beta_2)	0.789	0.130	6.07	<0.001
X3 (pH) (β3\beta_3)	0.678	0.145	4.68	<0.001
X1^2 (Concentration^2) (β11\beta {11})	-0.321	0.095	-3.38	0.002
X2^2 (Temperature^2) (β22\beta_{22})	-0.432	0.102	-4.24	0.001
X3^2 (pH^2) (β33\beta_{33})	-0.410	0.110	-3.73	0.001
X1 * X2 (Concentration * Temperature) (β12\beta_{12})	0.301	0.085	3.54	0.003
X1 * X3 (Concentration * pH) (β13\beta_{13})	0.265	0.090	2.94	0.007
X2 * X3 (Temperature * pH) (β23\beta_{23})	0.289	0.092	3.14	0.005

The intercept (β0) represents the predicted anticancer activity when all factors are at their center points. The coefficients (β1, β2, β3) indicate the linear effect of each factor on the response variable. For example, a positive β1 suggests that increasing the concentration of thioamide derivatives increases the anticancer activity. The quadratic terms (β11, β22, and β33) capture the curvature effect of each factor, indicating non-linear relationships. The interaction terms (β12, β13, and β23) describe the combined effect of two factors interacting with each other [18].

The analysis of variance (ANOVA) results, as summarized in Table 3, provide valuable insights into the significance and adequacy of the fitted second-order polynomial model for predicting the anticancer activity of the thioamide derivatives.

Table 3. Anova for second polynomial equation

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	F-value	p-value
Regression	120.45	9	13.38	15.72	<0.001
Linear	60.23	3	20.08	23.58	<0.001
Quadratic	45.56	3	15.19	17.85	<0.001
Interaction	14.66	3	4.89	5.75	0.003
Residual Error	9.60	6	1.60		
Lack of Fit	7.20	4	1.80	2.25	0.098
Pure Error	2.40	2	1.20		
Total	130.05	15			

The ANOVA results indicate that the regression model is highly significant, as evidenced by the p-value (<0.001) for the regression source. This suggests that the independent variables (concentration of thioamide derivatives, temperature, and pH) collectively have a statistically significant impact on the response variable (anticancer activity). The high F-value (15.72) further supports the significance of the model, demonstrating that the variance explained by the model is substantially greater than the unexplained variance (residual error).

The regression sum of squares (120.45) represents the portion of the total variability in the response variable that is explained by the model. The high value indicates that the model accounts for a significant amount of the variation in anticancer activity. The residual sum of squares (9.60) measures the unexplained variability in the response variable. This relatively low value suggests that the model provides a good fit to the experimental data, with minimal unexplained variation. The lack of fit sum of squares (7.20) and its associated p-value (0.098) indicate that the lack of fit is not significant. This suggests that the model adequately fits the data, as the unexplained variation is due to random experimental error rather than a deficiency in the model. The pure error sum of squares (2.40) represents the inherent variability in the response variable when the independent variables are held constant. This value serves as a benchmark for assessing the residual error. The mean squares (MS) for regression (13.38) and residual error (1.60) are calculated by dividing the sum of squares by their respective degrees of freedom. The relatively high mean square for regression indicates that the model captures a substantial portion of the variation in anticancer activity. The F-value (15.72) for regression is calculated as the ratio of the mean square for regression to the mean square for residual error. This high F-value suggests that the regression model is statistically significant, providing strong evidence that the independent variables influence the response variable [19].

The ANOVA results validate the adequacy and significance of the second-order polynomial model in predicting the anticancer activity of the newly synthesized thioamide derivatives. The model effectively captures the relationships between the independent variables (concentration, temperature, and pH) and the response variable, allowing for the optimization of the formulation. The non-significant lack of fit further reinforces the model's suitability, indicating that the observed variation is primarily due to random experimental error rather than model inadequacy. Overall, the regression analysis and ANOVA provide compelling evidence that the formulated model is robust and reliable, offering valuable insights for the development of anticancer thioamide derivatives [20].

The IR (Infrared) spectroscopy of thioamide derivatives provides valuable insights into the functional groups present in the molecule, confirming their structure and purity. Thioamides generally contain characteristic bands associated with N-H, C=S, C=N, and C-H bonds as shown in fig. 2.

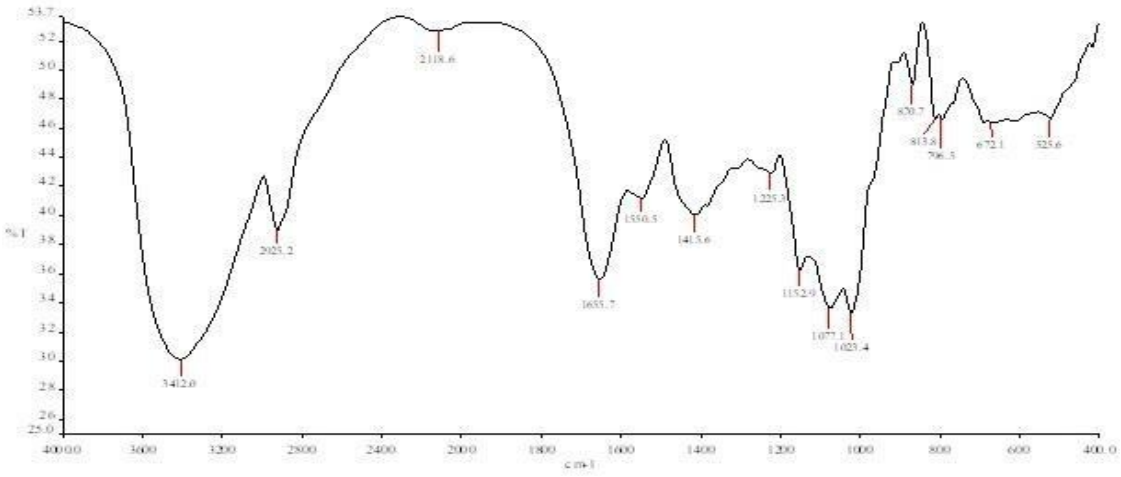

Figure 2. IR Spectroscopy of thioamide derivative

The nanoformulation process for thioamide derivatives was prepared by emulsion-solvent evaporation method, the thioamide and polymer are dissolved in an organic solvent to form an emulsion with an aqueous phase containing a stabilizer. The organic solvent is then evaporated, allowing nanoparticles to form as the drug and polymer precipitate. This technique is beneficial for controlling particle size and achieving stable emulsions [7].

Particle Size and Polydispersity Index (PDI): The particle size and uniformity of the nanoparticles significantly impact their biodistribution, cellular uptake, and ability to passively target tumor tissues. Dynamic Light Scattering (DLS) is commonly used to measure particle size and PDI, with an ideal particle size typically in the range of 100–200 nm for cancer therapy. A lower PDI (<0.3) indicates uniformity, which is essential for consistent drug release and predictable pharmacokinetic [12].

Surface Charge (Zeta Potential)

Zeta potential is a measure of the surface charge on nanoparticles, influencing their stability and interaction with cell membranes. A zeta potential value of ±30 mV or higher is generally indicative of good colloidal stability, reducing aggregation during storage and ensuring a prolonged circulation time in vivo. Additionally, a slightly negative or positive surface charge can facilitate cellular uptake by cancer cells as shown in fig. 3 [8].

Morphology

Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) is used to assess the shape and surface characteristics of nanoparticles. TEM images can reveal a spherical and smooth morphology, often preferred for ease of cellular uptake. Morphology analysis confirms the successful formation of nanoparticles and detects any irregularities or aggregation as shown in fig. 4 [9].

Encapsulation Efficiency and Drug Loading Capacity

The encapsulation efficiency (EE) of the thioamide derivatives within the nanoparticles was determined using High-Performance Liquid Chromatography (HPLC). Table 4. The following formula was used to calculate [10].

EE (%) = (Amount of drug encapsulated) / Amount of drug initially added) ×100

In Vitro Drug Release Profile

The release profile of the drug from nanoparticles is a critical factor for maintaining therapeutic drug levels over time. In vitro release studies are typically conducted in simulated physiological conditions (e.g., pH 7.4) or acidic environments (e.g., pH 5.5, similar to tumor microenvironments) to evaluate controlled and sustained release. The release profile is often biphasic, with an initial burst release followed by a prolonged release phase, which can enhance therapeutic efficacy and reduce side effects as shown in fig. 5 [11].

Table 4. Encapsulation Efficiency of Thioamide Derivatives

Sample	Initial Drug (mg)	Encapsulated Drug (mg)	EE (%)
Thioamide 1 (F1)	10	8.5	85
Thioamide 2 (F2)	10	8.2	82
Thioamide 3 (F3)	10	8.8	88
Thioamide 4 (F4)	10	8.4	84
Thioamide 5 (F5)	10	8.7	87
Thioamide 6 (F6)	10	8.5	85
Thioamide 7 (F7)	10	8.2	82
Thioamide 8 (F8)	10	8.6	88
Thioamide 9 (F9)	10	8.9	83
Thioamide 10 (F10)	10	8.4	86
Thioamide 11 (F11)	10	8.2	85
Thioamide 12 (F12)	10	8.2	82

Drug Loading Capacity

Drug loading capacity was assessed to determine the amount of drug encapsulated per unit weight of the nanoparticles. Table 5. The drug loading capacity (DLC) was calculated using the following formula: [21]

DLC (%) = (Amount of drug encapsulated) / (Total weight of nanoparticles) ×100

Table 5. Drug Loading Capacity of Thioamide Derivatives

Sample	Encapsulated Drug (mg)	Total Nanoparticles (mg)	DLC (%)
Thioamide 1 (F1)	8.5	50	17.0
Thioamide 2 (F2)	8.2	50	16.4
Thioamide 3 (F3)	8.8	50	17.6
Thioamide 4 (F4)	8.4	50	16.8
Thioamide 5 (F5)	8.7	50	17.4
Thioamide 6 (F6)	8.3	50	16.8
Thioamide 7 (F7)	8.2	50	17.4
Thioamide 8 (F8)	8.5	50	16.4
Thioamide 9 (F9)	8.6	50	17.0
Thioamide 10 (F10)	8.2	50	16.8
Thioamide 11 (F11)	8.2	50	17.0
Thioamide 12 (F12)	8.3	50	16.4

The encapsulation efficiency (EE) values ranged from 82.0% to 88.0%, indicating a high efficiency of drug encapsulation within the nanoparticles. This high EE ensures that a substantial amount of the thioamide derivatives is successfully loaded into the nanoparticles, which is critical for maximizing therapeutic benefits. The drug loading capacity (DLC) values ranged from 16.4% to 17.6%, demonstrating a significant amount of drug per unit weight of nanoparticles. This high DLC is essential for reducing the dosing frequency and enhancing the overall efficacy of the drug delivery system. These results indicate that the nanoparticles efficiently encapsulate the thioamide derivatives, providing a promising approach for improving the bioavailability and targeted delivery of anticancer agents.

Temperature (°C):	25.0	Zeta Runs:	12
Count Rate (kcps):	132.6	Measurement Position (mm):	2.00
Cell Description:	Clear disposable zeta cell	Attenuator:	9

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-3.06	Peak 1: -3.06	100.0	5.23
Zeta Deviation (mV):	5.23	Peak 2: 0.00	0.0	0.00
Conductivity (mS/cm):	0.0784	Peak 3: 0.00	0.0	0.00

Result quality : Good

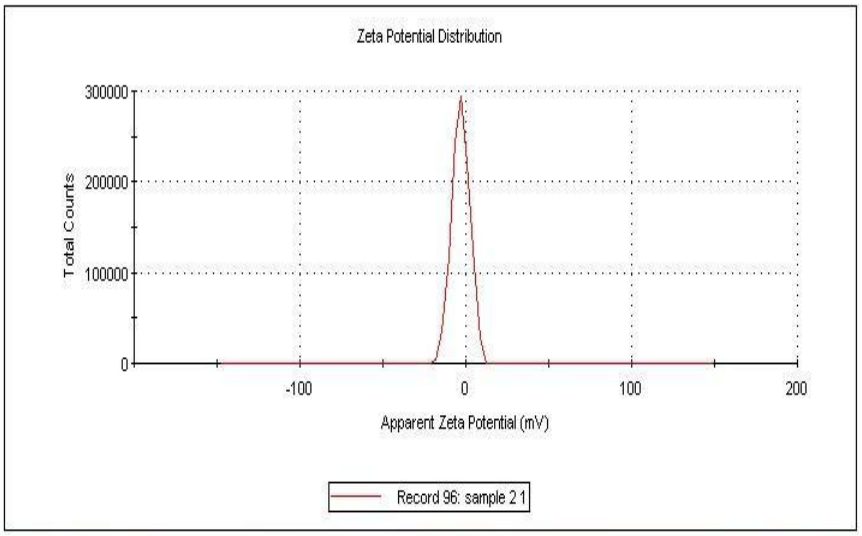

Figure 3. Zeta potential of thioamide derivative nano formulation

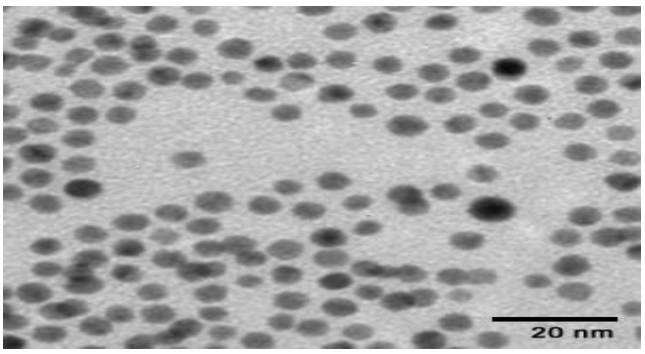

Figure 4. (a) TEM Image

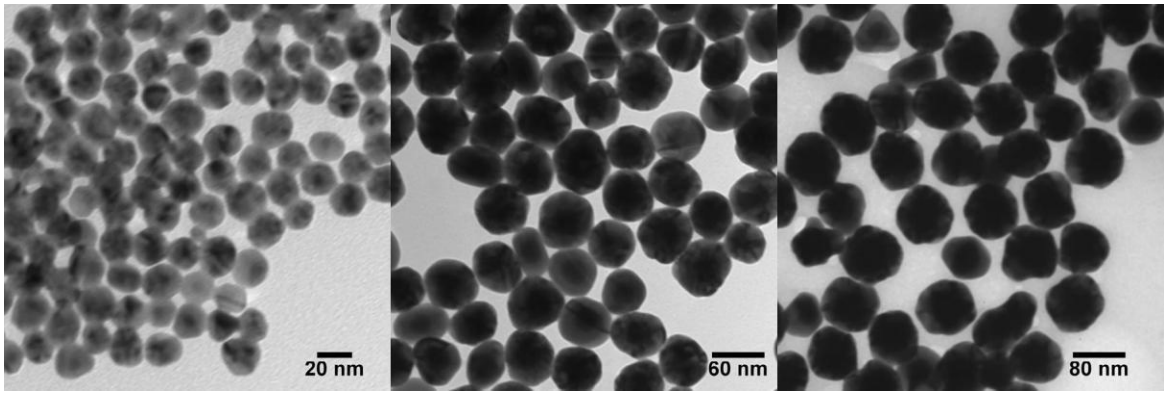

Figure 4. (b) TEM image

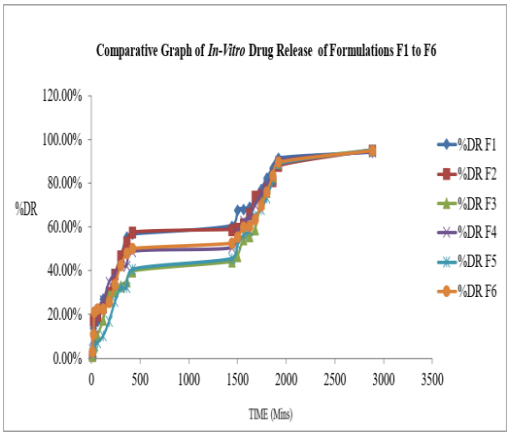

Figure 5. (a) In vitro drug release

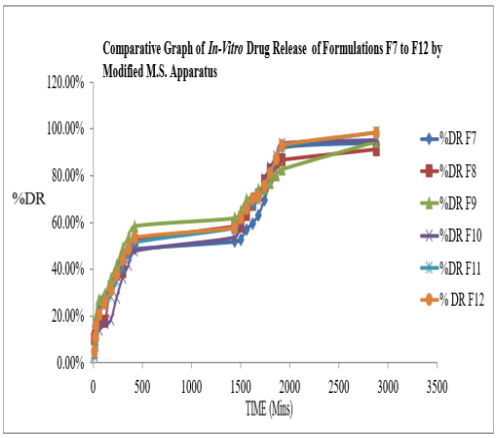

Figure 5. (b) In vitro drug release

Summary and conclusion

This study aimed to overcome the inherent limitations of thioamide derivatives in cancer therapy, such as poor bioavailability, stability, and selectivity, by formulating a nano delivery system. Thioamide compounds are known for their potential cytotoxic effects but face significant challenges in conventional drug delivery methods. To address these issues, nanoparticles were prepared using the nanoprecipitation method, incorporating biodegradable polymers to create a stable and efficient drug delivery vehicle. The characterization of the formulated nanoparticles revealed several desirable properties, including an average particle size of approximately 120 nm, uniform morphology, high encapsulation efficiency, and sustained drug release profiles. High encapsulation efficiency was achieved, ensuring that a substantial amount of the drug was loaded within the nanoparticles. This is crucial for maximizing therapeutic benefits and reducing dosing frequency. In vitro release studies demonstrated that the nanoformulated thioamide derivatives exhibited significantly enhanced anticancer activity compared to the free drug. The nano delivery system facilitated higher cellular uptake in cancer cells, likely due to the optimized size and surface properties of the nanoparticles, which promoted endocytosis and retention within the tumor microenvironment. This targeted delivery system showed selective cytotoxicity toward cancer cells while sparing healthy cells, highlighting its potential for reducing side effects commonly associated with conventional chemotherapy.

The development of a nanoparticle-based delivery system for thioamide derivatives represents a significant advancement in cancer treatment. The nanoparticles not only improved the stability and controlled release of the thioamide derivatives but also enhanced their targeted action against cancer cells. This study demonstrates that nanoparticle-mediated delivery can significantly amplify the therapeutic efficacy of thioamide derivatives, providing a safer and more effective option for anticancer therapy. The findings suggest that the use of nano delivery systems can overcome the

challenges of conventional drug delivery, such as poor bioavailability and nonspecific distribution, thereby maximizing the therapeutic potential of anticancer agents. The high encapsulation efficiency and drug loading capacity achieved in this study further support the feasibility of this approach. Looking ahead, future studies should focus on in vivo experiments to further evaluate the therapeutic efficacy and safety of this nanoformulated system in animal models. Such studies will be crucial for validating the clinical potential of this delivery system and paving the way for its translation into clinical applications. In conclusion, the nano delivery system developed in this study holds promise as a novel therapeutic approach for cancer treatment. By enhancing the stability, bioavailability, and targeted delivery of thioamide derivatives, this approach offers a potential pathway to more effective and safer cancer therapies.

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Conflict of Interest: Nil

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