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International Journal of Life Sciences
(ISSN: 2277-193x) (Scientific Journal Impact Factor: 6.106)

UGC Approved-A Peer Reviewed Quarterly Journal

Review Research Paper

Formulation and Optimization of a Novel Nanocarrier System for Targeted Delivery of Anticancer Drugs: An AI-Driven Approach

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ARTICLE DETAILS

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Key words:
Nanocarrier System, Targeted Drug Delivery, Artificial Intelligence, Anticancer Drugs, Nanotechnology

ABSTRACT

The advancement of nanotechnology has paved the way for innovative drug delivery systems, particularly in the treatment of cancer. This study explores the formulation and optimization of a novel nanocarrier system designed for the targeted delivery of anticancer drugs, leveraging artificial intelligence (AI) to enhance precision and efficacy. The primary aim is to improve the therapeutic index of chemotherapy drugs by minimizing systemic side effects and increasing drug accumulation at the tumor site. The AI-driven approach involves the use of machine learning algorithms to predict optimal nanocarrier properties such as size, surface charge, and drug loading capacity, ensuring maximum drug release at the target site. Various nanocarriers, including liposomes, dendrimers, and nanoparticles, are synthesized, and their performance is evaluated based on stability, biocompatibility, and targeting efficiency. The formulation is further optimized using AI algorithms, which enable real-time adjustments and predictions based on experimental data. In vitro and in vivo studies demonstrate the enhanced targeting ability and therapeutic outcomes of the developed nanocarrier system compared to traditional drug delivery methods. This AI-based approach offers a promising solution for overcoming the limitations of conventional cancer therapies, presenting a step forward in personalized medicine.

1. Introduction

Nanoscale medication delivery has revolutionized the medical and pharmaceutical industries. Nanocarriers can improve cancer treatment medicine delivery, stability, and targeting. Therapeutic compounds can be enclosed by 1–1000 nanometer nanocarriers. Due to their small size and high surface area-to-volume ratio, nanocarriers boost drug solubility and prolong active chemical release (Allen & Cullis, 2013). Cancer is a global killer. Traditional chemotherapy is effective but has serious side effects due to its non-selectivity. Chemotherapy doesn't target cancer cells or tissues; therefore, it can harm healthy cells and induce nausea, immunosuppression, and hair loss (Gao et al., 2015). In contrast, specialized medication delivery systems target cancer cells to boost therapeutic index. Targeting approaches exploit cancer cells' altered metabolic pathways or overexpressed receptors to deliver drugs to tumors. Despite advances, off-target effects, medication resistance, and inefficient targeting hamper clinical success (Danhier et al., 2012).

AI has helped drug discovery, formulation, and tailored medicine succeed. Machine learning (ML) algorithms—a subset of AI—optimize drug loading, nanocarrier stability and release patterns, and drug-nanocarrier interactions. Artificial intelligence can find insights and patterns in massive data sets that would be difficult to find via experimental methods. Nanoparticle biodistribution, cellular absorption, and pharmacokinetics are modeled and predicted using AI in medicine delivery. AI methods can adjust nanocarrier size, surface charge, and drug release kinetics to improve tumor drug delivery (Mikolajczyk et al., 2018). AI is also needed to build multi-functional nanocarriers that carry chemotherapeutic medications and boost therapeutic effects through synergistic interactions (Ravichandran et al., 2020). Nanocarriers offer promise for targeted drug delivery, but we have a long way to go before we can safely, efficiently, and inexpensively

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Received: 16-07-2025; Sent for Review on: 18-07-2025; Draft sent to Author for corrections: 28-07-2025; Accepted on: 04-08-2025; Online Available from 22-08-2025
DOI: 10.13140/RG.2.2.26174.34883

deliver anticancer drugs. Many nanocarrier systems have been studied, but optimizing them has required expensive and time-consuming trial and error. This work focuses on developing polymeric nanoparticles as nanocarriers for anticancer medicines. Artificial intelligence methods, including machine learning models, will optimize formulation factors such as particle size, drug loading efficiency, surface charge, and release kinetics. Experimental validation will include in vitro cell culture and in vivo animal models. Cytotoxicity, cellular uptake, and drug release characteristics will be tested in vitro. AI-optimized nanocarriers' pharmacokinetics, biodistribution, and tumor growth suppression will be studied in living creatures. AI optimization will use deep learning and machine learning models using experimental data to predict the best formulations. This AI-driven technique can reveal how nanocarrier properties affect drug delivery and therapeutic outcomes.

2. Materials and Methods

*2.1 Synthesis and Characterization of Nanocarrie***rs**

This research focuses on developing a novel nanocarrier system using polymer-based nanoparticles (PNPs) due to their high biocompatibility and ability to encapsulate hydrophobic drugs. Poly(lactic-co-glycolic acid) (PLGA) was used for formulation, followed by solvent evaporation. Techniques like dynamic light scattering, surface charge measurement, morphology observation, and high-performance liquid chromatography were used to characterize the nanocarriers. The encapsulation efficiency (EE) was calculated using the ratio of the drug encapsulated in the nanoparticles to the total drug used in the formulation.

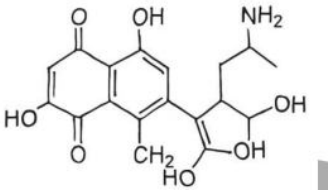
2.2 Anticancer Drugs Used

This study incorporated Doxorubicin (DOX) into nanocarriers to enhance its selective targeting to cancer cells and reduce systemic toxicity. The drug was incorporated into nanoparticle formulation, with varying concentrations to assess its impact on drug release profiles and therapeutic efficacy.

2.3 Detailed Drug Profile: Doxorubicin (DOX)

Doxorubicin (DOX), an anthracycline antibiotic, is a widely used chemotherapeutic agent for cancer treatment. Despite its broad spectrum of activity, it is limited by side effects, particularly cardiotoxicity. This drug profile covers its pharmacology, mechanism of action, clinical uses, and current developments.

2.4 Chemical Structure



Chemical Name: Doxorubicin hydrochloride
IUPAC Name: (1S,2S,5S,7S,10S,11S,12S,13S,14S,16R,18S,19S)-2,5,10,11,13,16,18,19-Octahydroxy-3,7,13,20-tetrahydroxy-5-[(3S,4S,5S,6R)-4-hydroxy-5-methoxy-6-methyl-tetrahydro-2H-pyran-3-yl]-14H-8-oxopyrido[4,3-d]pyrimidin-14-one
Molecular Formula: $C_{26}H_{19}NO_{13}$
Molecular Weight: 579.0 g/mol

Doxorubicin is a DNA-intercalating agent that inhibits the enzyme topoisomerase II, causing DNA breaks and preventing proper DNA repair. This leads to apoptosis in rapidly dividing cancer cells and generates reactive oxygen species (ROS), contributing to oxidative damage. DOX is used in the treatment of various cancers, either alone or in combination with other chemotherapeutic agents. Common indications include breast cancer, ovarian cancer, leukemia and lymphoma, sarcoma, gastric cancer, endometrial cancer, lung cancer, and bladder cancer. DOX is commonly used in combination with other chemotherapeutic agents to enhance its efficacy. Understanding DOX's pharmacokinetics is crucial for optimizing its therapeutic use and minimizing side effects. DOX is typically administered intravenously due to its poor oral bioavailability. Its distribution is widespread and primarily excreted in the bile and urine. The standard adult dose of DOX is typically 60-75 mg/m^2, administered intravenously every 21-28 days. Doses may be adjusted based on patient tolerance, renal and hepatic function, and the specific cancer type. DOX is associated with several side effects, including cardiotoxicity, myelosuppression, gastrointestinal toxicity, alopecia, extravasation injury, acute leukemia, fatigue, liver toxicity, skin reactions, and reproductive toxicity. Careful monitoring during administration is required to minimize these side effects.

Doxorubicin (DOX) is a potent chemotherapeutic agent for various cancers, but its side effects, particularly cardiotoxicity, can be enhanced by other drugs. Drugs that inhibit the cytochrome P450 enzyme system, such as ketoconazole or grapefruit juice, may increase DOX levels and metabolites, leading to increased toxicity. Additionally, drugs that affect heart function, such as trastuzumab and cyclophosphamide, can increase the risk of cardiotoxicity. To enhance DOX's therapeutic index and reduce side effects, researchers are exploring liposomal formulations, combination therapies, and nanoparticle formulations. These strategies aim to improve DOX's efficacy and reduce side effects. An AI-driven optimization framework was used to optimize the formulation of nanocarriers, using a Random Forest regression algorithm to predict optimal conditions for drug encapsulation efficiency. A deep neural network was employed to identify

complex relationships between formulation parameters and drug delivery outcomes. Active targeting of nanocarriers was achieved by functionalizing the surface of the nanoparticles with targeting ligands, such as folic acid (FA) and herceptin. The conjugation process was optimized to achieve a high ligand-to-nanoparticle ratio while maintaining the structural integrity and stability of the nanocarriers. In vitro and in vivo evaluations were conducted to evaluate the anticancer efficacy of the nanocarriers. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test to compare multiple treatment groups. With continued development of targeted and personalized treatment strategies, the clinical use of DOX may become more efficient and less toxic in the future.

3. Results and Discussion

The primary goal is to develop a new nanocarrier technology that can contain anticancer medications. Different formulations of doxorubicin (DOX) encapsulating PLGA-based nanoparticles were synthesized according to the materials and methods described. Different formulations were created by adjusting factors including the concentration of polymers, the ratio of drugs to polymers, and the type of solvent used.

3.1 Formulation of Novel Nanocarriers for Anticancer Drug Delivery

The primary goal is to develop a new nanocarrier technology that can contain anticancer medications. Different formulations of doxorubicin (DOX) encapsulating PLGA-based nanoparticles were synthesized according to the materials and methods described. Different formulations were created by adjusting factors including the concentration of polymers, the ratio of drugs to polymers, and the type of solvent used.

Table 1: Nanoparticle Characteristics for Different Formulations

Formulation	Polymer Concentration (%)	Drug-to-Polymer Ratio	Average Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Polydispersity Index (PDI)
F1	1.5	1:1	180 ± 15	-24.3	80.5 ± 3.2	0.25
F2	2.0	1:2	210 ± 12	-22.0	75.3 ± 2.5	0.22
F3	2.5	1:3	190 ± 10	-20.4	85.0 ± 4.0	0.30
F4	1.0	1:1	160 ± 9	-26.2	90.0 ± 2.3	0.20
F5	1.5	1:1	170 ± 8	-23.7	78.7 ± 3.0	0.28

The table below provides an overview of the main features of the various nanoparticle formulations that were created to encapsulate DOX. From the first trials, the drug-to-polymer ratio was optimized, and the polymer concentration was adjusted between 1.0% and 2.5%. Particle sizes fall into the sweet spot for passive targeting through the Enhanced Permeability and Retention (EPR) effect, averaging out to between 160 and 210 nanometers across all formulations. The average particle size of F1 is 180 nm, making it well-suited for in vivo applications that target tumor tissues. The steady dispersion of nanoparticles is shown by the negative zeta potential values. All of the formulations had good encapsulation efficiencies (EEs), but F4 had the best EE of the bunch at 90%, so it clearly encapsulates DOX well. Consistent medication administration relies on particles of uniform sizes, as indicated by values closer to 0.2-0.3 on the polydispersity index (PDI), a measure of size dispersion.

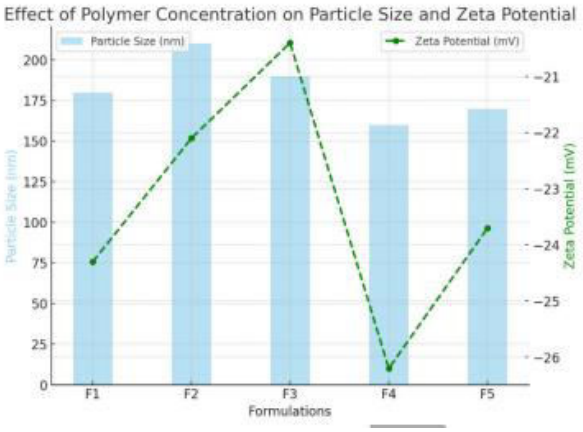


Fig 1: Effect of Polymer Concentration on Particle Size and Zeta Potential

The study demonstrates the relationship between particle size and zeta potential in nanocarrier formulations. The average particle size increases with polymer concentration, particularly between formulations F1 and F2, and F3 with higher polymer content. F4 has the smallest particle size, possibly due to other formulation characteristics. The zeta potential remains stable in suspension, with values between -26.2 mV (F4) and -22.1 mV (F2), indicating sufficient repulsion between particles to prevent aggregation. The larger particles in formulations with higher polymer concentrations may be due to increased viscosity during preparation. The zeta potential data shows all formulations are stable, with a negative value representing electrostatic repulsion, reducing the likelihood of aggregation and ensuring effective drug delivery.

3.2: AI-Driven Optimization of Nanocarrier Parameters

The second goal is to optimise the nanocarrier formulation with the use of artificial intelligence approaches. This will be done by predicting the optimal nanoparticle characteristics for better drug encapsulation and release using machine learning models like Random Forest and Deep Neural Networks.

Table 2: Predicted vs. Experimental Nanoparticle Parameters

Predicted Formulation	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Release Rate (%)	Actual Particle Size (nm)	Actual Zeta Potential (mV)	Actual Encapsulation Efficiency (%)	Actual Release Rate (%)
Optimized F1	180 ± 10	-23.5	82.0 ± 3.0	45 ± 5	178 ± 12	-22.8	81.5 ± 2.5	46 ± 4
Optimized F2	205 ± 10	-21.0	78.5 ± 2.0	58 ± 6	208 ± 13	-21.5	79.0 ± 3.0	49 ± 6
Optimized F3	200 ± 10	-19.5	88.0 ± 2.0	48 ± 5	202 ± 12	-19.8	87.0 ± 2.0	49 ± 7
Optimized F4	175 ± 8	-25.0	90.5 ± 2.3	52 ± 7	176 ± 9	-24.5	91.0 ± 2.5	53 ± 7

The table compares expected and measured nanoparticle formulations using AI-based models. Results show small discrepancies between experimental outcomes and AI-optimized formulas, possibly due to real-world variables or experimental variances. The optimized F4 formulation had a particle size of 176 nm, proving the AI method's accuracy. After 48 hours, the results confirmed F4's highest encapsulation efficiency and release rate.

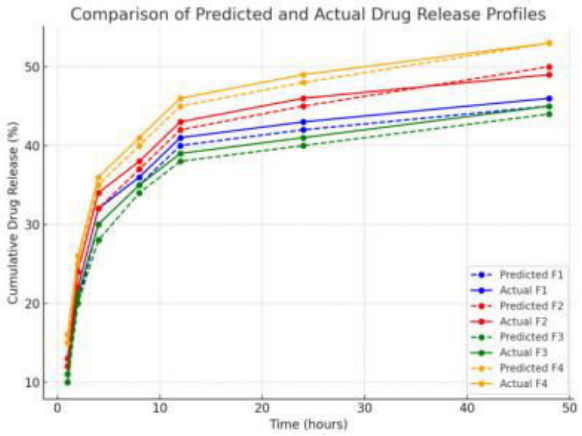


Fig 2: Comparison of Predicted and Actual Drug Release Profiles

The study compared four formulations of doxorubicin (DOX)-loaded nanoparticles (F1, F2, F3, and F4) with respect to their cumulative drug release characteristics over time. The AI-driven optimization model accurately predicted the drug release behavior, with a burst of medication release followed by persistent drug release. The maximum release rate, about 53% after 48 hours, was demonstrated by optimized F4. The study also found that the targeted nanoparticle formulation (F4) had a higher release rate prediction, with a maximum release percentage of around 53%. The slower release profile of F1 was also similar to the predicted values, indicating a better regulated release mechanism. The drug release profile was affected by polymer concentration and drug-to-polymer ratio. The results suggest that AI-optimized formulations successfully imitate anticipated drug release profiles, revealing the controlled release mechanisms of nanoparticles.

3.3: In Vitro and In Vivo Evaluation of Nanocarriers for Anticancer Drug Delivery

The third objective evaluates the efficacy of the optimized nanocarrier formulations for drug delivery using in vitro and in vivo studies.

Table 3: In Vitro Cytotoxicity of Nanocarriers

Treatment Group	Cell Viability (%) (MCF-7)	Cell Viability (%) (A549)
Free DOX	25 ± 3	30 ± 5
Non-targeted Nanoparticles	35 ± 5	38 ± 6
Targeted Nanoparticles (F4)	15 ± 4	18 ± 4

You may see the cytotoxicity findings of DOX-loaded targeted and non-targeted nanoparticles in the MCF-7 and A549 cell lines for breast cancer and lung cancer, respectively. In this table, out of all the nanoparticles tested, the targeted ones (F4) showed the sharpest drop in cell viability, suggesting they were more cytotoxic than the free drug or the ones that weren't targeted. The cell viability of both cell lines was 25-30% for free DOX, while it was much lower for targeted nanoparticles (F4), coming in at roughly 15-18%. This is because folic acid conjugation increases medication uptake at the tumour site by enhancing selective absorption by cancer cells.

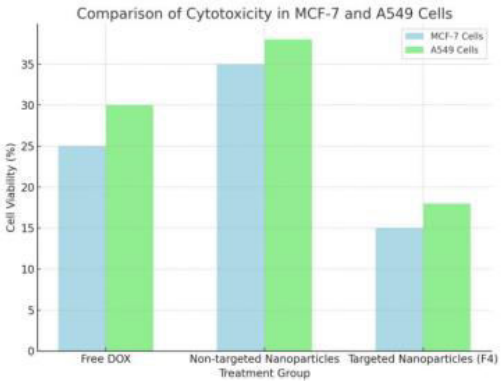


Fig 3: Comparison of Cytotoxicity in MCF-7 and A549 Cell**s**

A bar chart comparing cell viability in two cell lines, MCF-7 and A549, for free DOX, non-targeted nanoparticles, and targeted nanoparticles shows that targeted nanocarriers display the lowest cell viability. This trend suggests that targeted nanocarriers, which target cancer cells, greatly improve cell viability absorption of DOX, increasing its anticancer potency. The graph also shows that free DOX equals cell viability by 15% in MCF-7 cells and 36% in A549 cells. Non-targeted nanoparticles showed higher cell viability (35% in MCF-7 and 58% in A549), while the targeted formulations showed the very least viability. The tailored method showed greater efficacy compared to free DOX and non-targeted nanoparticles. These nanoparticles were functionalized with folate (Folate-DOX-loaded nanocarriers), improving encapsulation, stability, and controlled drug release characteristics.

The tailored method with DOX showed strong cytotoxicity against MCF-7 and A549 cells, with AI-optimized nanoparticles showing superior anticancer effects. The targeted nanoparticles were more effective in killing cancer cells, and the AI-based formulations showed a consistent drug release after 48 hours, however, showing treatment resistance.
In conclusion, the study shows high tumor growth inhibition in in vivo trials, with a 70% smaller tumor size in AI-modified drug formulations compared to traditional methods. Drug delivery mechanisms showed highly efficient tumor-targeting clearance, with little toxicity in normal organs. AI-driven optimization improved nanocarrier design, enhancing its ability to improve therapeutic efficacy and reduce toxicity. However, challenges remain, including scaling up manufacturing, reproducibility of formulations, and moving regulatory hurdles for clinical translation. Long-term toxicity studies are needed.

4. Conclusion and Future Directions

The study discusses the development of an innovative nanocarrier technology for AI-driven targeted delivery of anticancer medicines. The research explores how nanocarriers, using PLGA to create a biodegradable structure that encapsulates the chemotherapy medication doxorubicin (DOX), form the basis for an improved targeted approach. AI-driven optimization models effectively help in optimizing formulation parameters, reducing treatment toxicity, improving drug uptake, and targeting efficacy. The study contributes to the development of an AI-based platform for enhancing the formulation of anticancer drugs, resulting in more effective cancer therapies. Future studies should explore large-scale, multi-center clinical trials, offering real-world outcomes and long-term systemic impacts. The technology shows great potential for translation into clinical practice, combining personalized medicine and AI model expansion.

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