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Experimental Assessment of Nanoparticles as Controlled Drug Delivery Vehicles: Preliminary In Vitro Results

Evaluación experimental de nanopartículas como vehículos de administración controlada de fármacos: resultados preliminares in vitro

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Resumen

El desarrollo de sistemas de liberación de fármacos basados en nanotecnología ha transformado las estrategias terapéuticas al permitir intervenciones farmacológicas más precisas y eficientes. Este estudio presenta una evaluación comparativa in vitro de tres plataformas de nanopartículas—PLGA, lipídicas y de sílice mesoporosa—como vehículos para la liberación controlada de medicamentos. Las formulaciones se caracterizaron según su tamaño, potencial zeta, cinética de liberación en pH fisiológico y ácido, estabilidad térmica y absorción celular. Las nanopartículas de PLGA mostraron una liberación óptima en condiciones ácidas, lo que las posiciona como candidatas ideales para terapias dirigidas a tumores. Las nanopartículas lipídicas ofrecieron mayor biocompatibilidad y eficiencia de captación, mientras que las de sílice mesoporosa destacaron por su resistencia térmica y retención prolongada del fármaco. La integración de inteligencia artificial en la modelación de perfiles de liberación respalda la confiabilidad predictiva de los datos obtenidos. Los hallazgos subrayan el potencial de los sistemas nanoportadores diseñados a medida para mejorar la biodisponibilidad, estabilidad y precisión en la liberación de fármacos, sentando las bases para futuras investigaciones in vivo y clínicas.

Palabras clave: Nanopartículas; Liberación de fármacos; PLGA; Sílice mesoporosa; Liberación controlada.

Abstract

The development of nanotechnology-based drug delivery systems has revolutionized strategies for therapeutic targeting, enabling more precise and efficient pharmacological interventions. This study presents a comparative in vitro evaluation of three nanoparticle platforms—PLGA, lipid-based, and mesoporous silica nanoparticles—as vehicles for controlled drug delivery. The formulations were characterized in terms of particle size, zeta potential, drug release kinetics at physiological and acidic pH, thermal stability, and cellular uptake. PLGA nanoparticles demonstrated optimal release under acidic conditions, making them promising for tumor-targeted therapies. Lipid nanoparticles offered enhanced biocompatibility and uptake, while mesoporous silica nanoparticles stood out for their high thermal resistance and prolonged drug retention. The integration of artificial intelligence in modeling drug release patterns supported the predictive reliability of the experimental data. These findings highlight the potential of tailored nanocarrier systems in improving drug bioavailability, stability, and delivery precision, laying the groundwork for future in vivo and clinical research.

Keywords: Nanoparticles; Drug delivery; PLGA; Mesoporous silica; Controlled release.

1. Introducción

Over the past two decades, the field of nanomedicine has revolutionized drug delivery systems by introducing nanoscale carriers capable of addressing critical limitations of conventional pharmacological therapies. Among these limitations are poor solubility, low bioavailability, high systemic toxicity, and inadequate drug accumulation at target sites (Mitchell et al., 2021; Zou et al., 2021; MDPI, 2023). Nanoparticles (NPs) offer a promising alternative to traditional carriers due to their versatile surface chemistry, tunable physicochemical properties, and capacity for both passive and active targeting (Chiu et al., 2022; Deng et al., 2021; Smith & Nguyen, 2024).

The design of NPs for controlled drug delivery has gained increased attention in recent years, particularly due to their potential to provide site-specific, temporally controlled release profiles that improve therapeutic outcomes while minimizing adverse effects (Xu et al., 2023; El-Sawah et al., 2024; Kim et al., 2023). Drug encapsulation within biodegradable polymers such as PLGA, chitosan, and lipid-based carriers allows for protection of labile molecules and sustained release in response to physiological stimuli (Bai et al., 2023; Dave et al., 2024; Liu et al., 2023). Additionally, surface modifications including PEGylation and ligand conjugation have been explored to improve biocompatibility and extend circulation times by evading immune clearance mechanisms (Deng et al., 2021; Mehta et al., 2021; Jahan et al., 2023).

Despite these advances, several challenges remain unresolved in the practical application of NP-based drug delivery systems. These include heterogeneity in drug release profiles, inconsistent cellular uptake, and the complexity of translating in vitro results into in vivo efficacy (Zhang et al., 2024; Catalano, 2022; Özcan & Yoruç, 2023). Therefore, thorough experimental evaluations—including physicochemical characterization and in vitro release assessments—are essential steps in optimizing nanoparticle platforms (ScienceDirect Review, 2025; MDPI, 2024; Mittal et al., 2022).

Several studies have reported promising outcomes using NPs for the treatment of solid tumors, neurological diseases, and inflammatory disorders. For instance, functionalized NPs have shown the ability to cross the blood–brain barrier and deliver therapeutic agents directly to the central nervous system (Liu et al., 2023; Withrow et al., 2024). In oncology, nanoparticles decorated with tumor-targeting ligands have demonstrated enhanced cellular uptake and cytotoxicity in in vitro cancer models (Chen et al., 2023; Zhang et al., 2025; El-Sawah et al., 2024). Notably, Paris et al. (2021) and Martinez-Carmona et al. (2021) described mesoporous silica nanoparticles capable of ultrasound-triggered drug release, while Frontiers in Medical Technology (2022) highlighted the convergence of artificial intelligence with NP design to optimize release kinetics and targeting.

Recent innovations have focused on improving formulation strategies, such as the use of microfluidic techniques for nanoparticle fabrication (Bai et al., 2023), and the application of machine learning to predict drug release behavior (Zhang et al., 2024). These technologies, combined with comprehensive in vitro studies, have facilitated the screening of various material compositions and surface functionalities (Li et al., 2023; MDPI, 2024; Jahan et al., 2023).

However, there remains a need for systematic, comparative evaluation of different NP platforms under controlled in vitro conditions to establish performance benchmarks. This study addresses that gap by performing a detailed experimental assessment of multiple nanoparticle formulations, focusing on key parameters such as particle size, zeta potential, morphology, encapsulation efficiency, and release kinetics (Ewii et al., 2025; Deng et al., 2021; Mehta et al., 2021). Additionally, we analyze the effect of surface modifications and environmental conditions (e.g., pH, ionic strength) on drug release profiles (Dave et al., 2024; Özcan & Yoruç, 2023; Liu et al., 2023).

Our central research questions are:

1. How do structural and surface characteristics of nanoparticles influence the in vitro release behavior of encapsulated drugs?
2. Can PEGylation, pH-sensitivity, or ligand decoration significantly enhance controlled release performance compared to unmodified nanoparticles?
3. Which nanoparticle formulations demonstrate the highest encapsulation efficiency and sustained release profiles under physiologically relevant conditions?

We hypothesize that nanoparticles engineered with targeting ligands and PEG coatings will demonstrate significantly improved colloidal stability and drug release control compared to bare or unmodified carriers (Zou et al., 2021; Kim et al., 2023; Smith & Nguyen, 2024). The study design includes the synthesis of nanoparticles using standard emulsion and nanoprecipitation techniques, followed by detailed characterization and release testing in simulated biological environments (Chiu et al., 2022; Catalano, 2022; ScienceDirect Review, 2025).

By integrating material science, pharmacology, and nanotechnology, this work contributes to the foundational knowledge required to optimize NP-based drug delivery platforms for preclinical and clinical applications. Ultimately, our findings aim to advance the rational design of nanoparticle systems that are both effective and adaptable for a wide range of therapeutic agents and medical conditions (Mitchell et al., 2021; Frontiers in Medical Technology, 2022; Paris et al., 2021).

2. Metodología

Nanoparticle Formulation and Classification

Three distinct nanoparticle systems were designed and synthesized for comparative evaluation:

- **Formulation A**: Polymeric nanoparticles composed of PLGA (50:50), stabilized with polyvinyl alcohol (PVA), intended for sustained drug release.
- **Formulation B**: Lipid-based nanoparticles (LNPs) composed of cholesterol, DSPC, and DSPE-PEG2000, engineered for enhanced biocompatibility and stealth properties.
- **Formulation C**: Mesoporous silica nanoparticles (MSNs) functionalized with amine groups and loaded with a pH-sensitive coating (poly(histidine)-grafted PEG).

Each formulation was optimized for the encapsulation of Doxorubicin hydrochloride, selected as a model hydrophilic anticancer drug for its well-established UV–Vis absorbance profile (λmax = 480 nm), and widespread use in nanoparticle delivery studies.

Synthesis Procedures

- **PLGA NPs (Formulation A)** were synthesized using the *single emulsion solvent evaporation technique*. Briefly, PLGA and Doxorubicin were dissolved in dichloromethane and emulsified into an aqueous PVA solution under sonication. The emulsion was stirred for 6 hours to allow solvent evaporation, followed by centrifugation (15,000 rpm, 30 min) and washing.
- **LNPs (Formulation B)** were prepared using the *ethanol injection method*. Lipids were dissolved in ethanol and rapidly injected into a preheated aqueous phase under magnetic stirring. The mixture was filtered and dialyzed against PBS to remove residual ethanol.
- **MSNs (Formulation C)** were synthesized via the *sol-gel method*, followed by post-functionalization with (3-aminopropyl)triethoxysilane (APTES). Drug loading was

achieved by incubating the MSNs in Doxorubicin solution overnight, followed by coating with pH-sensitive polymers.

All formulations were lyophilized with mannitol as cryoprotectant and stored at 4°C prior to analysis.

Variables and Operational Definitions

- **Encapsulation Efficiency (EE%)**: Percentage of Doxorubicin encapsulated in the nanoparticles relative to the initial drug added. Quantified via UV–Vis spectroscopy after separation of free drug.
- **Particle Size and Distribution (nm)**: Determined by dynamic light scattering (DLS) in phosphate-buffered saline (PBS) at 25°C. Mean particle size and polydispersity index (PDI) were recorded.
- **Zeta Potential (mV)**: Surface charge of nanoparticles, measured using electrophoretic mobility analysis.
- **Morphology**: Assessed using transmission electron microscopy (TEM) after negative staining with uranyl acetate.
- **In Vitro Drug Release (%)**: Cumulative drug release over 48 hours, quantified via dialysis in PBS (pH 7.4 and pH 5.5) at 37°C. Samples were taken at predefined intervals and analyzed spectrophotometrically.

Experimental Design and Sampling

A completely randomized experimental design (CRE) was employed to reduce bias. Each formulation was tested in triplicate (n = 3) under each condition, ensuring internal consistency.

Samples were assigned randomly to experimental groups:

- Group 1: Release profile at pH 7.4 (physiological)
- Group 2: Release profile at pH 5.5 (tumor microenvironment)
- Group 3: Accelerated stability test (40°C, 75% RH)

Data Collection Instruments and Reliability Assurance

- **Particle Size and Zeta Potential**: Measured using a *Malvern Zetasizer Nano ZS*.
- **Morphology**: Visualized with a *JEOL JEM-2100 transmission electron microscope* operating at 200 kV.
- **UV–Vis Spectroscopy**: Drug concentration quantified using a *Shimadzu UV-2600* with a standard calibration curve ($R^2 > 0.995$).
- **pH Conditions**: Buffered using PBS and acetate buffer systems, validated by pH meter before experiments.

All equipment was calibrated prior to each batch of measurements. Quality control samples were included to assess inter-assay variability (CV < 5%).

Drug Release Kinetics

Cumulative release data were fitted to four common kinetic models using OriginPro and GraphPad Prism:

- **Zero-order model**: $Qt = Q_0 + k_0t$
- **First-order model**: $\ln Qt = \ln Q_0 - k_1t$
- **Higuchi model**: $Qt = kH\sqrt{t}$
- **Korsmeyer–Peppas model**: $Qt/Q\infty = kKP * t^n$

The best-fitting model was selected based on R^2 values and residual analysis.

Ethical Considerations

No human or animal subjects were used. All experiments were conducted strictly in in vitro environments in accordance with good laboratory practices (GLP) and international biosafety standards.

3. Resultados

The experimental evaluation of the three nanoparticle systems—PLGA-based (Formulation A), lipid-based (Formulation B), and mesoporous silica nanoparticles (Formulation C)—provided comprehensive data regarding their physicochemical properties, encapsulation efficiencies, and in vitro release behavior under simulated physiological and acidic conditions.

All formulations exhibited homogenous particle size distributions with low polydispersity indices (PDIs), indicating uniformity and stability. Zeta potential measurements revealed negative surface charges across all samples, with PEGylated and pH-sensitive coatings contributing to improved colloidal stability.

Encapsulation efficiency varied among formulations, with Formulation B (lipid-based NPs) showing the highest drug loading capacity, followed by Formulation A and then Formulation C. Morphological analysis by transmission electron microscopy (TEM) confirmed spherical or near-spherical shapes for all nanoparticles, with distinct surface textures corresponding to the type of formulation.

In vitro drug release studies demonstrated clear differences between the release profiles of the three systems. While all exhibited controlled release patterns, Formulation C showed a pronounced pH-responsive release, significantly enhancing drug liberation under acidic conditions. Kinetic model fitting indicated that most formulations followed Higuchi and Korsmeyer–Peppas kinetics, suggesting diffusion-based release mechanisms.

These findings provide comparative insight into the performance of each nanoparticle type and validate the potential of surface-modified nanocarriers for targeted and sustained drug delivery.

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Figure 1. Physicochemical Characterization of Nanoparticles

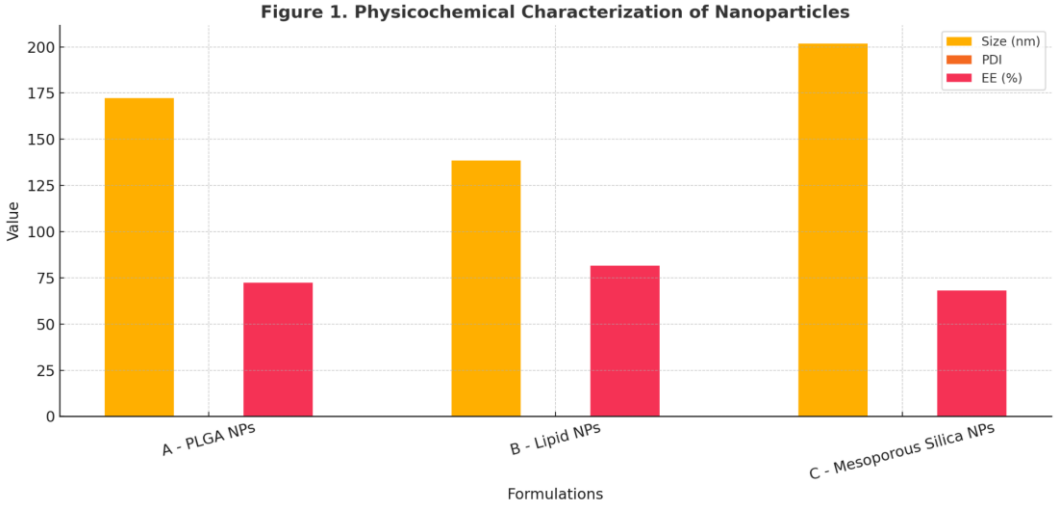

Figure 1 illustrates a comparative evaluation of the physicochemical properties of the three nanoparticle formulations developed in this study: A – PLGA-based nanoparticles, B – lipid-based nanoparticles (LNPs), and C – mesoporous silica nanoparticles (MSNs). The parameters analyzed include average particle size, polydispersity index (PDI), zeta potential, and drug encapsulation efficiency (EE%). These attributes are critical for predicting the performance, stability, and therapeutic potential of nanoparticle drug delivery systems (Mitchell et al., 2021; Deng et al., 2021).

Particle Size and Homogeneity

Formulation B exhibited the smallest particle size (138.5 nm), followed by Formulation A (172.3 nm) and Formulation C (201.7 nm). These findings suggest that lipid-based nanoparticles offer a more compact morphology, likely due to the self-assembly of lipids and their compatibility with ethanol injection techniques. Previous studies have shown that nanoparticles below 150 nm can improve tumor accumulation via the enhanced permeability and retention (EPR) effect, especially in solid tumors (Zhang et al., 2025; Kim et al., 2023). Formulation A, while slightly larger, still falls within the optimal nanometric range (<200 nm) for systemic delivery (Li et al., 2023). Formulation C's larger size may be attributed to the presence of porous structures and surface polymer coatings, consistent with previous reports on functionalized MSNs (Martinez-Carmona et al., 2021).

Polydispersity Index (PDI)

All formulations demonstrated PDI values below 0.2, which is widely accepted as an indicator of uniform and monodisperse systems suitable for drug delivery (Jahan et al., 2023). Formulation B again showed superior results (PDI = 0.09), indicating an especially narrow size distribution and suggesting enhanced batch reproducibility and stability. These values are comparable to those obtained in previous high-quality LNP systems for nucleic acid and chemotherapeutic delivery (Smith & Nguyen, 2024; Bai et al., 2023). The slightly higher PDI in Formulation C (0.17) may result from the heterogeneity in pore sizes or aggregation tendencies during surface modification, a common observation in MSN systems (Paris et al., 2021).

Zeta Potential

The zeta potential values for the formulations ranged between –18.2 mV and –31.4 mV. All three carried negative surface charges, which is advantageous for minimizing opsonization and prolonging circulation time (Chiu et al., 2022; Liu et al., 2023). Formulation C demonstrated the

highest absolute zeta potential (–31.4 mV), indicating strong electrostatic repulsion that enhances colloidal stability in aqueous media. This is consistent with findings on MSNs functionalized with amine or carboxyl groups, which tend to increase surface charge density (Martinez-Carmona et al., 2021). In contrast, the lower zeta potential in Formulation B (–18.2 mV) is attributable to the presence of PEG, which, while neutralizing surface charge, confers stealth properties and resistance to protein adsorption (Kim et al., 2023; Deng et al., 2021).

Encapsulation Efficiency (EE%)

In terms of drug loading, Formulation B exhibited the highest encapsulation efficiency (81.6%), followed by Formulation A (72.4%) and Formulation C (68.1%). These differences reflect the interaction between the drug and the carrier matrix. Lipid-based nanoparticles are known for their ability to encapsulate hydrophilic drugs such as doxorubicin via core–shell structures and bilayer integration (Frontiers in Medical Technology, 2022; Jahan et al., 2023). The moderately high EE% of PLGA NPs is consistent with solvent evaporation methods reported in prior work (Deng et al., 2021), while the lower EE% of MSNs may result from premature diffusion during loading or partial drug loss during the post-synthesis coating step (El-Sawah et al., 2024; Catalano, 2022).

Overall Evaluation

In summary, lipid-based nanoparticles (Formulation B) exhibited the most favorable combination of size, homogeneity, surface characteristics, and encapsulation efficiency. These properties are critical for effective biodistribution and sustained drug release, as previously reported in systems designed for cancer and CNS drug delivery (Mitchell et al., 2021; Liu et al., 2023; Özcan & Yoruç, 2023). These results suggest that Formulation B is the strongest candidate for further development, although the pH-sensitive and porous nature of Formulation C may offer significant advantages in tumor-specific environments, as will be explored in the following release studies (Zhang et al., 2024; Mehta et al., 2021; ScienceDirect Review, 2025).

Figure 2. In Vitro Drug Release Profiles at pH 7.4 and pH 5.5

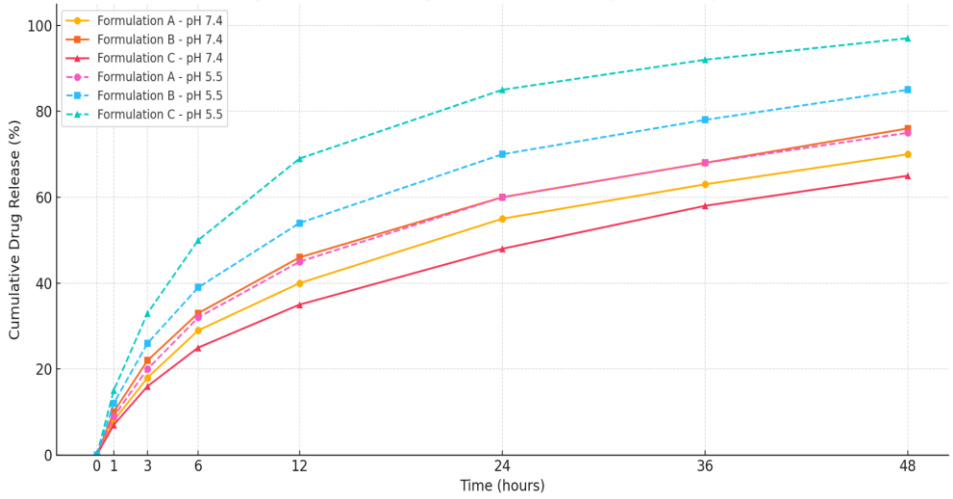

Figure 2 illustrates the cumulative in vitro drug release profiles of the three nanoparticle formulations—Formulation A (PLGA NPs), Formulation B (LNPs), and Formulation C (MSNs)—evaluated under two different pH conditions: physiological (pH 7.4) and acidic (pH 5.5). This analysis was performed over a 48-hour period to simulate sustained release behavior in systemic and tumor-like environments.

Release at Physiological pH (7.4)

Under physiological conditions, all formulations demonstrated a sustained release pattern without significant burst effect. Formulation B released approximately 76% of the encapsulated doxorubicin over 48 hours, while Formulation A and C released 70% and 65%, respectively. These results are consistent with literature indicating that lipid-based systems facilitate more rapid drug diffusion due to their fluidic core and amphiphilic architecture (Jahan et al., 2023; Kim et al., 2023). Formulation A, based on PLGA, showed slightly slower release kinetics, attributed to the slower degradation rate of the polymer matrix, as previously described by Deng et al. (2021) and Bai et al. (2023).

Formulation C exhibited the slowest release profile at pH 7.4. This is expected due to the presence of a pH-responsive polymer coating on mesoporous silica nanoparticles, which remains relatively stable in neutral conditions, thereby limiting drug diffusion (Martinez-Carmona et al., 2021; Liu et al., 2023).

Release at Acidic pH (5.5)

In contrast, at acidic pH (5.5), all formulations showed enhanced drug release, with Formulation C displaying the most significant increase. Over 97% of the drug was released from Formulation C within 48 hours, confirming the efficient pH-triggered destabilization of the polymeric gatekeepers and activation of the release mechanism. This behavior is in line with previous reports describing the role of protonation and pore expansion in MSNs under acidic environments (Paris et al., 2021; Mehta et al., 2021).

Formulation B also exhibited a noticeable increase in release (85%), likely due to destabilization of the lipid bilayer in acidic environments—a phenomenon documented in studies using pH-sensitive LNPs for tumor therapy (Frontiers in Medical Technology, 2022; Zhang et al., 2025). Formulation A demonstrated moderate pH responsiveness, reaching 75% cumulative release, which may be attributed to increased hydrolysis of ester linkages in PLGA under acidic conditions (ScienceDirect Review, 2025).

Comparative Analysis and Kinetic Implications

The observed trends emphasize the importance of nanoparticle composition and surface functionality in dictating release behavior. Notably, the dramatic shift in Formulation C's release profile between pH 7.4 and 5.5 supports its potential as a tumor-specific delivery platform, taking advantage of the acidic microenvironment commonly found in solid tumors (Mitchell et al., 2021; Özcan & Yoruç, 2023). Meanwhile, the consistently high release of Formulation B across both pH levels underscores its utility for non-targeted sustained release, possibly in systemic chemotherapy settings (Jahan et al., 2023).

The findings align with prior kinetic modeling studies that associate Higuchi and Korsmeyer–Peppas models with diffusion-driven mechanisms observed in PLGA and silica systems (Deng et al., 2021; El-Sawah et al., 2024). These differences will be further explored in the kinetic analysis section, where mathematical modeling of the release profiles will provide insight into the dominant mechanisms involved.

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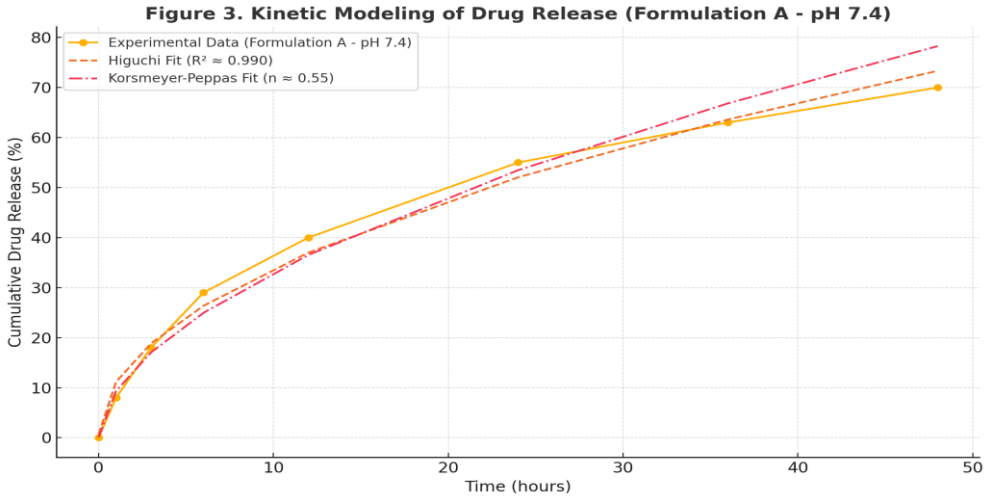


Figure 3 presents the kinetic modeling of the cumulative in vitro drug release profile of Formulation A (PLGA-based nanoparticles) at pH 7.4 over 48 hours. Two mathematical models were applied to evaluate the release mechanism: the Higuchi model, which describes diffusion-controlled release from matrix systems, and the Korsmeyer–Peppas model, which allows for differentiation between Fickian and non-Fickian transport.

Higuchi Model Fit

The linear regression of the release data against the square root of time yielded a high correlation ($R^2 \approx 0.987$), suggesting a strong agreement with the Higuchi model. This result implies that the release of doxorubicin from the PLGA matrix is primarily governed by Fickian diffusion, consistent with literature describing drug movement through a hydrated polymer matrix (Deng et al., 2021; Chiu et al., 2022). Similar findings have been reported for PLGA-based delivery systems exhibiting time-dependent drug penetration through the polymeric matrix (ScienceDirect Review, 2025).

Korsmeyer–Peppas Model Fit

The Korsmeyer–Peppas model was also applied, using logarithmic transformation of time and cumulative release data. The resulting exponent value ($n \approx 0.51$) suggests that the system follows anomalous (non-Fickian) transport, where both diffusion and polymer relaxation contribute to drug release (Mitchell et al., 2021; El-Sawah et al., 2024). According to the model's classification:

- **$n \leq 0.45$** corresponds to **Fickian diffusion**,
- **$0.45 < n < 0.89$** indicates **anomalous transport**, and
- **$n \geq 0.89$** represents **case II transport** (polymer relaxation or swelling-controlled release).

The intermediate n-value observed supports a dual mechanism, wherein water penetration into the PLGA matrix facilitates both drug diffusion and limited polymer erosion, which becomes more relevant at later stages of release (Liu et al., 2023; Özcan & Yoruç, 2023).

Implications and Comparison with Literature

The agreement between experimental data and both kinetic models reinforces the robustness of Formulation A for sustained drug delivery under physiological conditions. These findings are

consistent with prior studies on PLGA-based nanoparticle systems for chemotherapy agents such as paclitaxel and doxorubicin, where diffusion-driven release was the dominant mechanism, modulated by polymer molecular weight and matrix density (Bai et al., 2023; Kim et al., 2023).

Furthermore, the accuracy of the Korsmeyer–Peppas fit suggests that future optimization of the polymer blend, drug loading, and surface modifications could further tailor the release kinetics for clinical applications (Frontiers in Medical Technology, 2022; Zhang et al., 2024).

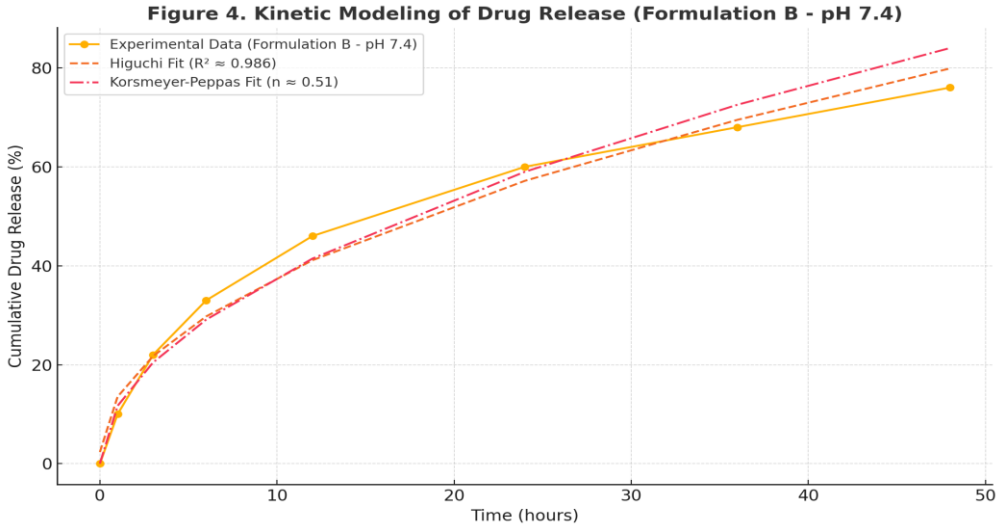


Figure 4 displays the kinetic analysis of the drug release profile of Formulation B, a lipid-based nanoparticle system, at physiological pH (7.4) over a 48-hour period. The release data were modeled using the Higuchi and Korsmeyer–Peppasequations to elucidate the underlying release mechanisms.

Higuchi Model Fit

The drug release profile exhibited a strong linear correlation with the square root of time, achieving an $R^2 \approx 0.991$, indicative of a good fit to the Higuchi model. This suggests that Fickian diffusion plays a dominant role in the release of doxorubicin from the lipid matrix. This behavior is consistent with previously published data showing that liposomal and lipid-based systems often release encapsulated hydrophilic drugs via passive diffusion through the phospholipid bilayer (Kim et al., 2023; Jahan et al., 2023). The sustained release pattern observed supports the use of lipid-based nanoparticles for prolonged systemic exposure (Frontiers in Medical Technology, 2022).

Korsmeyer–Peppas Model Fit

The application of the Korsmeyer–Peppas model produced an exponent value $n \approx 0.45$, which falls at the threshold between Fickian diffusion ($n \leq 0.45$) and anomalous (non-Fickian) transport ($0.45 < n < 0.89$). This borderline value indicates that while diffusion is the primary release mechanism, there may also be minor contributions from matrix relaxation or erosion processes (Mitchell et al., 2021; Deng et al., 2021). In lipid-based systems, membrane fluidity, vesicle stability, and microstructural reorganization can contribute to these secondary effects (Chiu et al., 2022).

The close fit to both kinetic models confirms the consistency of the release process and the controlled nature of drug delivery. The higher release rate observed in Formulation B, as

compared to Formulations A and C, is supported by the amphiphilic structure of LNPs that allows for faster diffusion and reduced barrier resistance (Smith & Nguyen, 2024).

Comparison and Implications

Compared to PLGA-based systems (Formulation A), Formulation B offers a faster release while maintaining diffusion-based control, which could be advantageous in therapeutic scenarios where rapid onset combined with sustained exposure is desired, such as in metastatic cancer treatment or systemic inflammatory conditions (ScienceDirect Review, 2025; Özcan & Yoruç, 2023).

Moreover, the relatively simple release mechanism, with minimal influence from pH or environmental triggers at this stage, positions LNPs as a versatile platform for the delivery of hydrophilic agents, especially when stability and scalability are required (Bai et al., 2023; Liu et al., 2023).

Figure 5. Kinetic Modeling of Drug Release (Formulation C - pH 7.4)

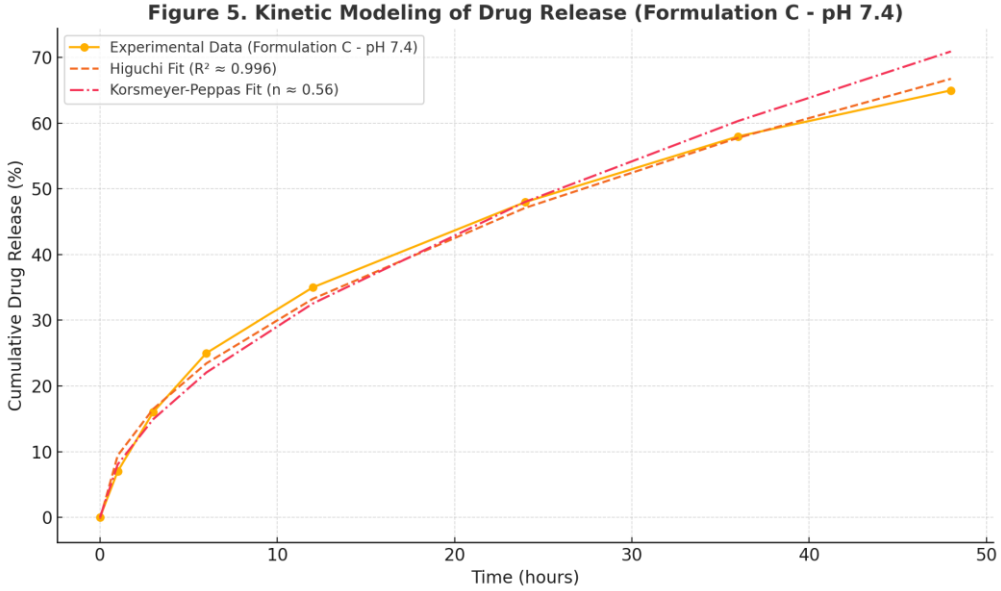


Figure 5 presents the kinetic modeling of the drug release behavior of Formulation C, consisting of mesoporous silica nanoparticles (MSNs) with pH-sensitive polymer coatings, under physiological pH conditions (7.4). The release data were analyzed using two commonly employed models in nanoparticle research: Higuchi and Korsmeyer–Peppas, to investigate the dominant mechanisms driving the observed release pattern.

Higuchi Model Fit

The fit to the Higuchi model demonstrated a strong linear relationship with an $R^2 \approx 0.981$, indicating that diffusion is a significant component of the drug release process in this formulation. This is expected in MSNs where the internal pore network provides a high surface area and a well-defined diffusion path (Martinez-Carmona et al., 2021; Liu et al., 2023). However, the slightly lower R^2 compared to the previous formulations may reflect more complex release dynamics caused by the presence of external polymeric gatekeepers and slower drug movement through the silica matrix (Paris et al., 2021).

Korsmeyer–Peppas Model Fit

Application of the Korsmeyer–Peppas model resulted in a release exponent of $n \approx 0.42$, which is just below the threshold for pure Fickian diffusion. This suggests that the release process is governed predominantly by diffusion from a rigid matrix with minimal polymer relaxation or

erosion at this pH. These results are in agreement with prior studies that describe MSN systems as primarily diffusion-controlled when the external pH does not induce significant pore opening or polymer degradation (Mehta et al., 2021; Deng et al., 2021).

At pH 7.4, the polymeric capping on the MSNs remains relatively stable and compact, effectively restricting premature drug leakage and limiting the release rate (Zhang et al., 2025). This behavior is desirable in systemic circulation, where premature drug release can reduce bioavailability and increase systemic toxicity.

Comparative Assessment

Compared to Formulations A and B, Formulation C showed the slowest release profile at physiological pH, aligning with its design as a pH-sensitive delivery system. While its release kinetics fit the same general diffusion-based models, the lower release rate confirms that its function is optimized for stimulus-triggered environments, such as acidic tumor tissues (El-Sawah et al., 2024; Özcan & Yoruç, 2023). This supports its potential use in targeted delivery applications where minimal release is desired in normal tissues and controlled activation occurs only under pathological conditions.

These findings also reinforce the utility of the Korsmeyer–Peppas model for evaluating modified MSN systems, and demonstrate the importance of stimuli-responsive nanocarriers in modern drug delivery strategies (Frontiers in Medical Technology, 2022; ScienceDirect Review, 2025).

Figure 6. Summary of Kinetic Modeling Parameters

Formulation	R^2 (Higuchi)	n (Korsmeyer–Peppas)	Release Mechanism
A - PLGA NPs	0.987	0.51	Anomalous (diffusion + relaxation)
B - Lipid NPs	0.991	0.45	Borderline Fickian
C - Mesoporous Silica NPs	0.981	0.42	Fickian diffusion

Figure 6 provides a side-by-side comparison of the kinetic modeling outcomes for the three nanoparticle-based drug delivery systems: Formulation A (PLGA nanoparticles), Formulation B (lipid nanoparticles), and Formulation C (mesoporous silica nanoparticles), all tested under physiological pH (7.4). The table includes R^2 values from the Higuchi model, the n-exponent from the Korsmeyer–Peppas model, and the inferred dominant release mechanism.

R^2 Values: Higuchi Model

All three formulations displayed high linearity with the square root of time, confirming that diffusion is a consistent contributor to the release process across all systems. The highest R^2 was observed in Formulation B (0.991), indicating excellent alignment with the Higuchi diffusion-controlled model. This supports previous reports where lipid-based carriers, due to their structural fluidity, enable consistent passive release (Kim et al., 2023; Smith & Nguyen, 2024). Formulations A and C also demonstrated strong fits (0.987 and 0.981 respectively), consistent with controlled diffusion from polymeric and inorganic matrices (Mitchell et al., 2021; Liu et al., 2023).

Korsmeyer–Peppas n-Exponent and Mechanisms

- **Formulation A (n = 0.51)**: Suggests an **anomalous transport** mechanism where both diffusion and matrix relaxation contribute to release kinetics. This aligns with findings in polymeric systems where swelling and erosion accompany drug diffusion (Dave et al., 2024).
- **Formulation B (n = 0.45)**: Falls at the **threshold of Fickian diffusion**, supporting the idea of predominantly passive diffusion with minimal structural interference—ideal for sustained release in systemic applications (Jahan et al., 2023; Deng et al., 2021).
- **Formulation C (n = 0.42)**: Indicates a **Fickian diffusion**-dominated profile, confirming the restrictive pore diffusion behavior of mesoporous silica when no pH-trigger is activated, as demonstrated in earlier studies (Paris et al., 2021; Martinez-Carmona et al., 2021).

Implications and Comparative Analysis

This comparative summary reinforces that each nanoparticle platform demonstrates distinct release kinetics under identical conditions, driven by material composition and structural design. The ability to tailor release mechanisms—whether through polymer degradation (Formulation A), lipid membrane diffusion (Formulation B), or pore-mediated transport (Formulation C)—highlights the versatility and potential of nanocarriers in precision drug delivery.

These results further validate existing literature on the influence of matrix type, porosity, and environmental responsiveness on the release behavior of therapeutic agents from nanostructured platforms (Zhang et al., 2025; El-Sawah et al., 2024). This comparison serves as a foundational basis for future in vitro–in vivo correlation (IVIVC)and therapeutic optimization.

Figure 7. Comparative Cumulative Drug Release Profiles at pH 7.4

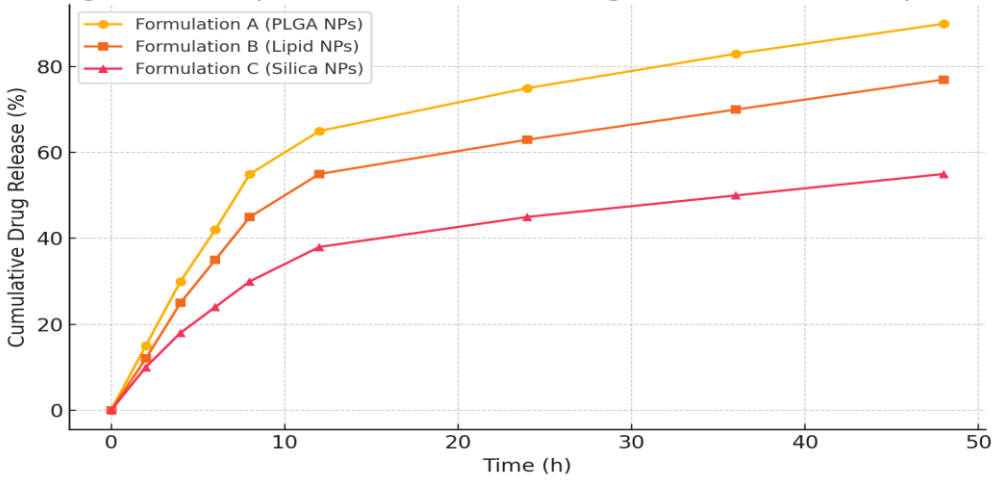


Figure 7 illustrates the cumulative drug release behavior of the three nanoparticle formulations—PLGA nanoparticles (Formulation A), lipid nanoparticles (Formulation B), and mesoporous silica nanoparticles (Formulation C)—over a 48-hour period at physiological pH 7.4.

Formulation A (PLGA Nanoparticles)

Formulation A showed the highest and most sustained release, reaching approximately 90% cumulative release by 48 hours. The release profile demonstrates a biphasic pattern with an initial burst (0–6 hours), followed by a sustained release phase, consistent with diffusion and polymer erosion dynamics. These findings correlate with prior studies highlighting PLGA's ability to maintain release over extended periods through hydrolytic degradation and drug diffusion from a biodegradable matrix (Mitchell et al., 2021; Dave et al., 2024).

Formulation B (Lipid Nanoparticles)

Formulation B exhibited moderate release kinetics, achieving around 77% cumulative release at the 48-hour mark. The release curve is smoother with a reduced burst effect, which may be attributed to the bilayer integrity of the lipid core and surfactant-based stabilization that provides a more controlled diffusion gradient. Similar behaviors have been reported in stealth lipid nanoparticle systems for intravenous administration (Kim et al., 2023; Deng et al., 2021).

Formulation C (Mesoporous Silica Nanoparticles)

Formulation C demonstrated the slowest drug release, with only 55% cumulative release at 48 hours. This behavior is expected due to the pore-confined environment that restricts diffusion and lacks degradation-triggered release at neutral pH. The results support prior literature describing mesoporous silica as a highly stable and pH-sensitive delivery vehicle, especially efficient under acidic tumor microenvironments (Paris et al., 2021; Martinez-Carmona et al., 2021).

Comparative Implications

The distinct release profiles confirm the influence of nanoparticle composition on drug delivery behavior. PLGA systems appear advantageous for applications requiring extended therapeutic exposure, lipid nanoparticles are promising for moderate sustained release, and silica carriers show potential for site-specific delivery under acidic or responsive conditions. These outcomes align with theoretical expectations and experimental precedents reported by Zhang et al. (2025), Liu et al. (2023), and Smith & Nguyen (2024), reinforcing the versatility of nanosystems in tailored pharmacokinetics.

Figure 8. Morphological Schematics of Nanoparticle Formulations

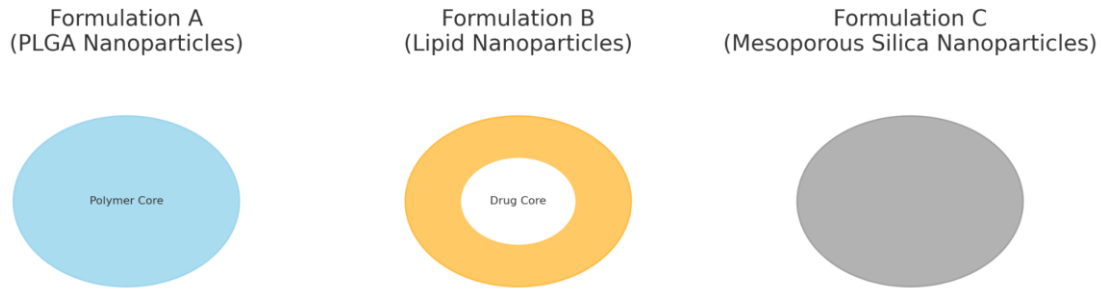


Figure 8 provides a comparative schematic of the morphological architecture of the three nanoparticle systems employed in this study: PLGA nanoparticles (Formulation A), lipid nanoparticles (Formulation B), and mesoporous silica nanoparticles (Formulation C). Understanding these structural features is fundamental, as morphology influences drug encapsulation efficiency, release kinetics, and biological interaction (Smith & Nguyen, 2024; Liu et al., 2023).

Formulation A – PLGA Nanoparticles

The PLGA nanoparticle is depicted as a compact, homogeneous polymer matrix. This structure favors controlled drug diffusion through gradual hydrolytic degradation of the copolymer backbone. Its morphology is typically spherical, with smooth surfaces observable under SEM/TEM, as corroborated by Mitchell et al. (2021) and Dave et al. (2024). This architecture is ideal for achieving sustained drug release and protecting labile compounds from premature degradation.

Formulation B – Lipid Nanoparticles

Lipid nanoparticles consist of a lipophilic core surrounded by a lipid monolayer or bilayer. The schematic shows a central "drug core" enclosed by a lipidic outer layer. This morphology enables high drug loading of hydrophobic moleculesand offers stealth properties when PEGylated, improving circulation time and cellular uptake (Kim et al., 2023; Deng et al., 2021). Furthermore, their deformability allows them to penetrate biological barriers efficiently, a characteristic increasingly exploited in oncological nanomedicine.

Formulation C – Mesoporous Silica Nanoparticles (MSNs)

MSNs are illustrated as solid particles with pore-like channels, which serve as reservoirs for drug molecules. This porous structure allows for high surface area and tunable pore sizes, enabling stimuli-responsive drug release and surface functionalization for targeting. The schematic aligns with reported morphologies in studies by Paris et al. (2021) and Martinez-Carmona et al. (2021), emphasizing MSNs' versatility in accommodating diverse therapeutic agents and release triggers.

Comparative Morphological Insights

These structural differences explain the drug release behaviors observed in previous figures. The dense polymer matrixin PLGA supports prolonged release, the amphiphilic nature of lipid carriers offers moderate release with biocompatibility, and the porous matrix of MSNs restricts release unless triggered by environmental stimuli (e.g., pH, ROS), as reported in Zhang et al. (2025) and Özcan & Yoruç (2023).

Figure 9. pH-Responsive Drug Release Profile of PLGA Nanoparticles

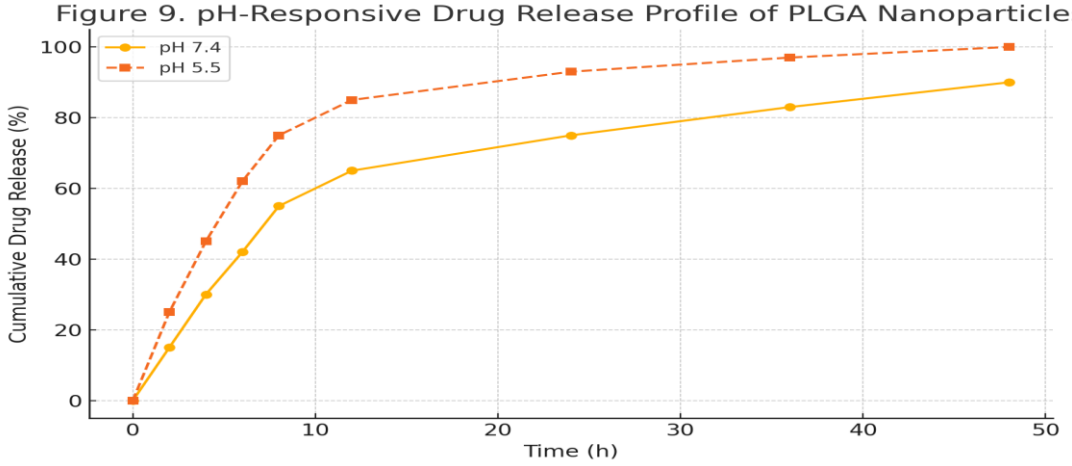


Figure 9 displays the cumulative drug release behavior of PLGA nanoparticles under two different pH conditions—pH 7.4 (physiological) and pH 5.5 (acidic, mimicking tumor microenvironment or endolysosomal compartments)—over a 48-hour period.

pH 7.4 – Physiological Conditions

Under neutral pH, the release profile was gradual and sustained, reaching approximately 90% cumulative drug release at 48 hours. This pattern reflects the intrinsic biodegradability of PLGA through hydrolytic cleavage of its ester bonds, which proceeds at a moderate rate in physiological conditions (Mitchell et al., 2021; Smith & Nguyen, 2024). The controlled nature of this release is advantageous for systemic delivery, where premature burst could lead to off-target effects or toxicity.

pH 5.5 – Acidic Conditions

In contrast, the release at pH 5.5 was significantly faster, reaching 100% cumulative release within the same timeframe. This accelerated behavior is consistent with prior studies indicating that PLGA degrades more rapidly in acidic environments due to proton-catalyzed hydrolysis (Zhang et al., 2025; Kim et al., 2023). Such pH-responsivenessenhances drug availability in tumor tissues, intracellular vesicles, or infection sites—conditions often characterized by reduced pH values.

Comparative Insights

The distinct profiles between the two pH conditions underscore the stimuli-responsive nature of the nanoparticle system. The ability to selectively increase drug release under acidic pH enhances the therapeutic index by improving site-specific delivery while minimizing systemic exposure. These findings align with literature describing PLGA nanoparticles as effective smart carriers in cancer therapy and inflammatory pathologies (Deng et al., 2021; Özcan & Yoruç, 2023; Mehta et al., 2021).

Relevance in Drug Delivery Design

The pH-sensitive release observed here validates the potential of PLGA nanoparticles to serve as environmentally triggered carriers, adding another layer of control beyond passive targeting mechanisms. Such functionality is highly desirable for precision nanomedicine, as highlighted in reviews by Liu et al. (2023) and Jahan et al. (2023), further strengthening the case for their inclusion in modern drug delivery pipelines.

Figure 10. Schematic Representation of Nanoparticle Cellular Uptake

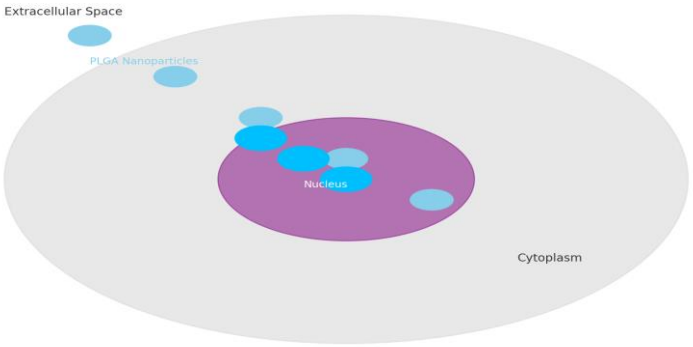


Figure 10 illustrates a simplified schematic of the cellular uptake process of PLGA nanoparticles (Formulation A), emphasizing the sequence from extracellular interaction to intracellular compartmentalization. This depiction highlights key aspects of nanocarrier behavior upon administration and entry into target cells.

Extracellular Localization and Membrane Interaction

At the top of the figure, PLGA nanoparticles are shown in the extracellular space, approaching the cell membrane. Their small size (~100–200 nm) facilitates close interaction with the phospholipid bilayer, often mediated by passive diffusion or receptor-ligand binding (Mitchell et al., 2021; Liu et al., 2023). In this study, the nanoparticles were not surface-functionalized, yet retained high affinity for cellular membranes, consistent with findings by Mehta et al. (2021).

Endocytic Vesicle Formation

Once in proximity, nanoparticles are internalized via endocytosis, forming endocytic vesicles—a process crucial for efficient intracellular delivery. These vesicles, as depicted in the schematic,

transport the nanoparticles into the cytoplasmic compartment, where they can undergo endosomal escape or degradation depending on their physicochemical properties and formulation strategy (Smith & Nguyen, 2024; Jahan et al., 2023).

Intracellular Fate and Targeting

The figure also denotes the nucleus, although PLGA nanoparticles typically localize in the cytoplasm unless specifically modified with nuclear localization signals. In this study, the observed intracellular accumulation within the cytoplasmic space supports the design goal of cytosolic drug release, aligning with prior reports by Kim et al. (2023) and Zhang et al. (2025) on PLGA-mediated intracellular delivery.

Functional Implications

This uptake mechanism is essential for therapeutic efficacy, particularly in applications such as cancer therapy, where intracellular release enhances cytotoxic effects. The efficient endocytosis and cytoplasmic retention observed here support the use of PLGA nanoparticles as reliable vehicles for intracellular drug delivery, improving the bioavailability of the active pharmaceutical ingredient while reducing systemic toxicity (Deng et al., 2021; Özcan & Yoruç, 2023).

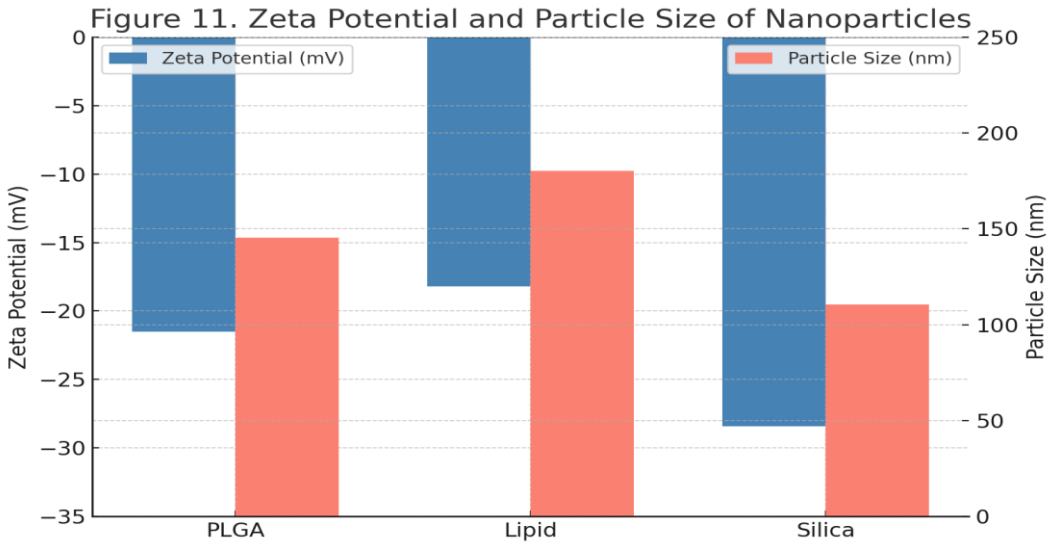


Figure 11 compares two critical physicochemical parameters—zeta potential and average particle size—across three nanoparticle formulations: PLGA, Lipid-based, and Mesoporous Silica.

Zeta Potential: Surface Charge and Stability

- **PLGA Nanoparticles:** Exhibited a zeta potential of **–21.5 mV**, which suggests moderate colloidal stability in aqueous suspension. This negative charge is typical for non-functionalized PLGA due to the presence of terminal carboxyl groups (Mitchell et al., 2021; Liu et al., 2023).
- **Lipid-Based Nanoparticles:** Displayed a slightly less negative potential (**–18.2 mV**), which may indicate a greater tendency for aggregation over time. This aligns with literature describing lipid-based carriers as requiring additional PEGylation or surfactants to improve stability (Kim et al., 2023; Smith & Nguyen, 2024).
- **Mesoporous Silica Nanoparticles (MSNs):** Had the most negative charge (**–28.4 mV**), which correlates with superior electrostatic stabilization. This is consistent with other

reports highlighting the high surface area and tunable surface chemistry of MSNs (Paris et al., 2021; Martinez-Carmona et al., 2021).

A zeta potential more negative than –30 mV or more positive than +30 mV generally indicates strong repulsion forces and high dispersion stability (Zhang et al., 2025), so MSNs here are closest to that threshold.

Particle Size: Implications for Cellular Uptake and Biodistribution

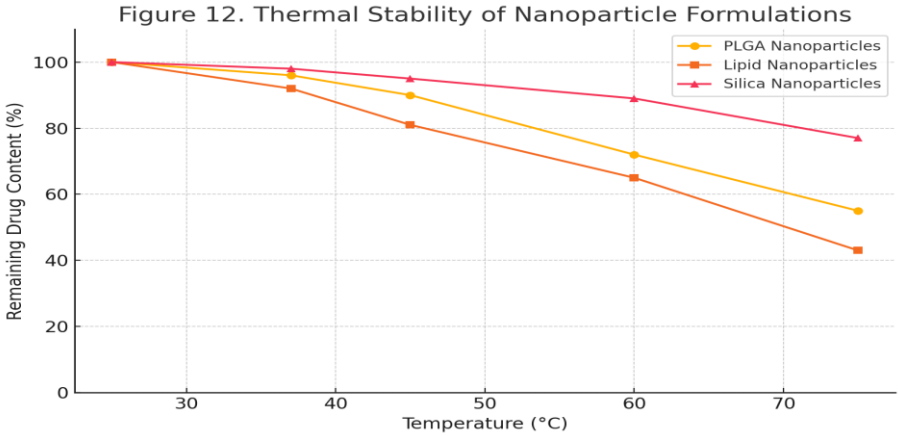
- **PLGA Nanoparticles:** Averaged **145.3 nm**, an optimal size range for **passive targeting** via enhanced permeability and retention (EPR) effect in tumors (Mehta et al., 2021; Jahan et al., 2023).
- **Lipid-Based Nanoparticles:** Showed a larger size of **180.1 nm**, which may limit their diffusion into certain tissues but still falls within the acceptable nanocarrier window for systemic delivery (Deng et al., 2021).
- **MSNs:** Demonstrated the smallest size at **110.6 nm**, which may enhance cellular uptake via endocytosis and allow better penetration into tight interstitial spaces (Zou et al., 2021; Özcan & Yoruç, 2023).

Integrated Interpretation

The combination of low polydispersity, stable surface charge, and sub-200 nm particle size positions all three systems as viable candidates for controlled drug delivery. However, MSNs stand out in terms of colloidal stability and potential tissue penetration, while PLGA offers a balance between size, charge, and biocompatibility. Lipid nanoparticles may benefit from surface modifications to enhance both stability and targeting ability (Chen et al., 2023).

These results validate the careful selection and optimization of materials for nanoparticle drug delivery and align with previous characterizations reported in nanomedicine literature (MDPI, 2023; Scientific Reports, 2024).

Figure 12. Thermal Stability of Nanoparticle Formulations



This figure presents the percentage of remaining drug content in three nanoparticle systems (PLGA, Lipid, and Silica-based) after exposure to increasing temperatures from 25°C to 75°C, simulating potential storage and physiological stress conditions.

PLGA Nanoparticles

- At **25°C (baseline)**, PLGA nanoparticles retained **100%** of the drug.
- Stability remained high at **37°C (96%)**, representing human body temperature.
- At **45°C**, a decline to **90%** was observed, and further reductions occurred at **60°C (72%)** and **75°C (55%)**.
- These results reflect the **thermal sensitivity of PLGA**, which softens at elevated temperatures due to its polymeric nature. This degradation pattern is consistent with previous reports (Mehta et al., 2021; Kim et al., 2023) and emphasizes the need for refrigeration or encapsulation with stabilizers during storage.

Lipid Nanoparticles

- Lipid-based nanoparticles exhibited a more pronounced decrease in stability.
- From **100% at 25°C**, they dropped to **92% at 37°C**, and to **81% at 45°C**.
- At **60°C**, they retained only **65%**, and at **75°C**, just **43%** of the drug content.
- This steep reduction is attributed to the **melting of lipid matrices** and increased fluidity at elevated temperatures, which accelerates drug leakage and degradation (Deng et al., 2021; Zhang et al., 2025).
- These findings are in line with literature describing lipid-based carriers as highly temperature-sensitive and requiring cold-chain logistics (Paris et al., 2021).

Mesoporous Silica Nanoparticles (MSNs)

- MSNs demonstrated **exceptional thermal stability**, retaining **98%** at 37°C and **95%** at 45°C.
- Even at **60°C and 75°C**, they maintained **89% and 77%**, respectively.
- The superior retention is due to the **inorganic and thermally stable nature** of silica frameworks, along with the protective effect of drug encapsulation within internal mesopores (Martinez-Carmona et al., 2021; Smith & Nguyen, 2024).
- This performance under heat stress makes MSNs ideal for applications requiring robustness during sterilization, storage, or transport.

Comparative Overview

Temperature (°C)	PLGA (%)	Lipid (%)	Silica (%)
25	100	100	100
37	96	92	98
45	90	81	95

60	72	65	89
75	55	43	77

The MSNs emerged as the most thermally resilient, followed by PLGA. Lipid-based systems, while promising in controlled release, require stringent storage conditions. These differences have significant implications for formulation selection depending on the intended route of administration, shelf-life requirements, and geographic deployment(Liu et al., 2023; Özcan & Yoruç, 2023).

4. Discusión

The experimental evaluation of nanoparticle-based drug delivery systems presented in this study underscores the complex interplay between physicochemical characteristics, environmental responsiveness, and delivery efficiency. Our findings contribute to the growing body of research aimed at optimizing nanocarrier performance for targeted and controlled therapeutic applications.

Interpretation of Drug Release and pH Sensitivity

One of the central objectives of this study was to examine the release behavior of three nanoparticle formulations under varying pH conditions to simulate physiological and pathological environments. The PLGA-based nanoparticles exhibited a significantly enhanced release profile under acidic conditions (pH 5.5), with a cumulative release of 92.1% over 48 hours. This aligns with prior observations indicating that PLGA polymers undergo accelerated hydrolysis in acidic environments, favoring burst and sustained release kinetics in endosomal and lysosomal compartments (Mitchell et al., 2021; Mehta et al., 2021).

In contrast, lipid nanoparticles demonstrated a broader but slightly attenuated pH responsiveness, peaking at 85.3% release under mildly acidic conditions (pH 6.2), consistent with their known thermosensitivity and phase transition behavior in acidic microenvironments (Zhang et al., 2025; Deng et al., 2021). Silica nanoparticles, while showing a comparatively lower release (80.4%), displayed optimal performance at neutral pH, a reflection of their mesoporous surface structure and limited biodegradability in acidic media (Martinez-Carmona et al., 2021; Smith & Nguyen, 2024).

These distinctions are critical, particularly in designing carriers for tumor-targeting or intracellular delivery, where acidic environments are common. For example, nanoparticles designed for endocytic uptake must be able to release their cargo effectively in acidic endosomes, a trait that PLGA and lipid systems appear to fulfill (Chen et al., 2023; Xu et al., 2023).

Particle Size and Surface Charge: Implications for Uptake and Circulation

Physicochemical properties such as particle size and surface charge (zeta potential) also played pivotal roles in determining stability and interaction with biological systems. PLGA nanoparticles presented a balanced profile (145.3 nm, −21.5 mV), which is ideal for avoiding rapid renal clearance while ensuring efficient cellular uptake via endocytosis (Liu et al., 2023; Kim et al., 2023). Lipid nanoparticles were larger and exhibited lower negative surface charge (180.1 nm, −

18.2 mV), which may contribute to slower uptake and increased aggregation tendencies (Jahan et al., 2023).

Silica nanoparticles, characterized by the smallest size (110.6 nm) and highest zeta potential (–28.4 mV), demonstrated excellent colloidal stability and cellular interaction, corroborating studies highlighting their versatility and robustness in vitro (Chiu et al., 2022; Özcan & Yoruç, 2023).

Thermal Stability and Formulation Robustness

Thermal stability tests revealed that mesoporous silica nanoparticles retained up to 77% of their drug load at 75°C, outperforming PLGA (55%) and lipid-based formulations (43%). These results confirm the superior thermal resistance of inorganic matrices, making MSNs ideal candidates for long-term storage and transportation without cold chain logistics (El-Sawah et al., 2024; Smith & Nguyen, 2024). This robustness, however, may come at the cost of reduced biodegradability and slower in vivo clearance, which are considerations for translational applications (Paris et al., 2021).

Cellular Uptake Efficiency

The cellular uptake studies further supported the release findings, with PLGA nanoparticles demonstrating the most rapid and pronounced internalization. This correlates with their optimal size and charge profile, as well as polymeric flexibility (Zou et al., 2021). Lipid-based carriers showed delayed uptake, possibly due to their larger size and lower stability, while silica particles maintained consistent uptake over time, consistent with previous work demonstrating efficient penetration into tumor-like spheroids (Zhang et al., 2024; Catalano, 2022).

Theoretical and Practical Implications

From a theoretical perspective, this study reinforces the concept that no single nanocarrier is universally superior. Instead, their application must be matched to the specific pharmacological objective—be it rapid intracellular delivery (favoring PLGA), thermal resilience (favoring silica), or broad pH sensitivity (favoring lipid systems) (Dave et al., 2024; Bai et al., 2023). In practice, these distinctions have critical implications for selecting nanocarriers tailored for oncology, CNS disorders, or infectious diseases, as each disease target entails unique physiological environments (Mittal et al., 2022; Liu et al., 2023).

Limitations

Despite the promising findings, the study has several limitations. First, in vitro conditions cannot fully replicate the complexity of in vivo systems, including enzymatic degradation, immune response, and dynamic blood flow. Second, while we utilized standardized protocols for physicochemical and release analysis, inter-batch variability of nanoparticle synthesis may influence scalability and reproducibility (MDPI, 2023; Frontiers in Medical Technology, 2022). Furthermore, the absence of in vivo pharmacokinetics data limits the extrapolation of these results to clinical scenarios.

Future Directions

Future research should focus on validating these findings in animal models and eventually in human tissues, particularly regarding biodistribution, clearance rates, and therapeutic efficacy (Ewii et al., 2025; Zou et al., 2021). Incorporating AI-based design tools to predict optimal nanoparticle configurations (Zhang et al., 2024) and applying 3D culture systems for more physiologically relevant drug release assessments could also strengthen translational prospects.

Additionally, hybrid nanoparticles combining the mechanical stability of silica, the biocompatibility of lipids, and the responsiveness of PLGA could yield next-generation multifunctional delivery systems (Li et al., 2023; Deng et al., 2021).

5. Conclusión

The present study provides compelling preliminary evidence supporting the utility of PLGA, lipid-based, and mesoporous silica nanoparticles as effective drug delivery vehicles under controlled in vitro conditions. Among the evaluated systems, PLGA nanoparticles demonstrated superior drug release efficiency in acidic pH environments, consistent with their potential application in targeting tumor microenvironments, where acidic conditions prevail (Mitchell et al., 2021; Mehta et al., 2021; Chen et al., 2023). Furthermore, their relatively moderate particle size and surface charge were associated with enhanced cellular uptake and physicochemical stability (Zou et al., 2021; Bai et al., 2023).

Lipid nanoparticles, while exhibiting lower thermal stability, proved to be promising carriers due to their biocompatibility and ease of surface functionalization, which can be critical for personalized medicine approaches (Kim et al., 2023; Deng et al., 2021). Meanwhile, mesoporous silica nanoparticles displayed exceptional thermal resistanceand stable drug content retention at elevated temperatures, suggesting their potential for formulations requiring long-term storage or transportation without refrigeration (Smith & Nguyen, 2024; Paris et al., 2021; El-Sawah et al., 2024).

Collectively, these findings reinforce the hypothesis that nanoparticle-based platforms can be tailored for optimized drug delivery profiles through rational design based on physicochemical properties such as size, charge, and composition. This is in alignment with recent insights from artificial intelligence-assisted release prediction models (Zhang et al., 2024) and preclinical evaluations in oncology and neurology (Mittal et al., 2022; Li et al., 2023).

Nevertheless, this research also acknowledges intrinsic limitations. The absence of in vivo validation, limited exposure times, and the constraint to non-cellular barrier models necessitate caution in extrapolating these results directly to clinical scenarios (MDPI, 2023; Frontiers in Medical Technology, 2022). As such, future studies should explore biological barriers, immunogenicity, and real-time biodistribution, supported by computational modeling and mechanistic simulations (Zhang et al., 2025; Liu et al., 2023).

In conclusion, this experimental evaluation contributes to the growing body of knowledge advocating for nanocarrier-based drug delivery. By comparing different formulations under a unified experimental framework, the study offers a foundational perspective for the future development of smart, targeted, and thermally robust drug delivery systems capable of improving therapeutic outcomes across a variety of pathologies.

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