Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation And Optimization Of Lipid-Polymer Hybrid Nanoparticles For Targeted Delivery Of Docetaxel: A Novel Approach In Cancer Therapy

Kunal Kaushik[1], Dr. Dinesh Kaushik[2]

[1]Assistant Professor, Delhi College of Pharmacy Holambi Kalan, New Delhi

[*2]Professor, Hindu College of Pharmacy, Sonipat, Haryana

***Corresponding Author:**

Dr Dinesh Kaushik

Cite this paper as: Kunal Kaushik, Dr. Dinesh Kaushik, (2025) Formulation And Optimization Of Lipid-Polymer Hybrid Nanoparticles For Targeted Delivery Of Docetaxel: A Novel Approach In Cancer Therapy. *Journal of Neonatal Surgery*, 14 (32s), 7371-7378.

ABSTRACT

Docetaxel, a potent chemotherapeutic agent, is widely used for the treatment of solid tumors such as breast, prostate, and lung cancer. However, its clinical use is limited by poor aqueous solubility, systemic toxicity, and multidrug resistance. The current study aimed to formulate and optimize lipid-polymer hybrid nanoparticles (LPHNs) of Docetaxel for improved tumor targeting, enhanced bioavailability, and reduced systemic side effects. LPHNs were prepared using the nanoprecipitation method combining PLGA (poly(lactic-co-glycolic acid)) as the polymeric core and lecithin/cholesterol as the lipid shell. A Box-Behnken design was employed to optimize the formulation parameters including lipid-to-polymer ratio, drug loading, and surfactant concentration. The optimized formulation exhibited a particle size of 145.3 ± 4.5 nm, PDI of 0.174, zeta potential of -22.6 ± 1.3 mV, and encapsulation efficiency of 89.6 ± 2.1%. In vitro drug release studies revealed a biphasic release profile with sustained release over 72 hours. Cytotoxicity studies on MCF-7 (breast cancer) cells showed significantly higher anticancer activity for LPHNs compared to free drug. These findings indicate that Docetaxel-loaded LPHNs offer a promising nanocarrier system for targeted cancer therapy.

Keywords: *Docetaxel, Lipid-polymer hybrid nanoparticles, Targeted delivery, PLGA, Nanoprecipitation, Anticancer drug delivery*

1. INTRODUCTION

Cancer is one of the most prevalent and devastating diseases globally, accounting for approximately 10 million deaths in 2020 alone, according to the World Health Organization (WHO) [1]. Despite major advancements in diagnostics and therapeutic interventions, **chemotherapy** remains the cornerstone for the treatment of various solid tumors such as breast, lung, ovarian, and prostate cancers. However, conventional chemotherapeutic drugs often suffer from **non-specific biodistribution, systemic toxicity**, and **multidrug resistance**, which significantly limits their clinical success [2].

Docetaxel (DTX) is a second-generation taxane derived semi-synthetically from *Taxus baccata* and has demonstrated potent **antimitotic** and **cytotoxic** effects through stabilization of microtubules, thereby inhibiting mitotic cell division [3,4]. It has been approved by the FDA for the treatment of a variety of malignancies, including breast, non-small cell lung, and prostate cancers. However, the clinical application of Docetaxel is hampered by **poor aqueous solubility (~0.025 mg/mL)**, **low bioavailability**, **rapid systemic clearance**, and **severe hypersensitivity reactions** associated with its solvent system (polysorbate 80 and ethanol) [5–6].

To overcome these pharmacokinetic and biopharmaceutical challenges, **nanotechnology-based drug delivery systems** have gained substantial attention in recent years. Nanocarriers such as **liposomes**, **polymeric nanoparticles**, **dendrimers**, **solid lipid nanoparticles (SLNs)**, and **nanomicelles** have been extensively explored for cancer drug delivery due to their ability to passively or actively target tumor tissues, improve drug solubility, prolong systemic circulation, and reduce off-target toxicity [7–9].

Among these systems, **Lipid-Polymer Hybrid Nanoparticles (LPHNs)** have emerged as a novel class of nanocarriers that synergistically integrate the mechanical strength, controlled drug release, and tunable surface properties of **polymeric nanoparticles (e.g., PLGA)** with the **biocompatibility, biomimetic nature, and cell-membrane fusion capability** of lipid layers [10–11]. Structurally, LPHNs consist of a **hydrophobic polymeric core** that encapsulates the drug and a **lipid shell**

that enhances biocompatibility and stability (Figure 1). This configuration not only improves drug loading efficiency but also allows for surface modification with targeting ligands, enabling **site-specific drug delivery** and **enhanced therapeutic outcomes** [12–13].

In this study, we aim to formulate and optimize **Docetaxel-loaded lipid-polymer hybrid nanoparticles (DTX-LPHNs)** using a **Quality by Design (QbD)** approach. The formulation employs **PLGA** as the polymeric core material and **soy lecithin/cholesterol** as lipid shell components. A **Box-Behnken design (BBD)** was employed to systematically evaluate the effect of critical formulation parameters on particle size, encapsulation efficiency, and drug release behavior. This research intends to develop a stable, effective, and targeted nanocarrier system to enhance the therapeutic efficacy of Docetaxel and minimize its adverse effects in cancer therapy.

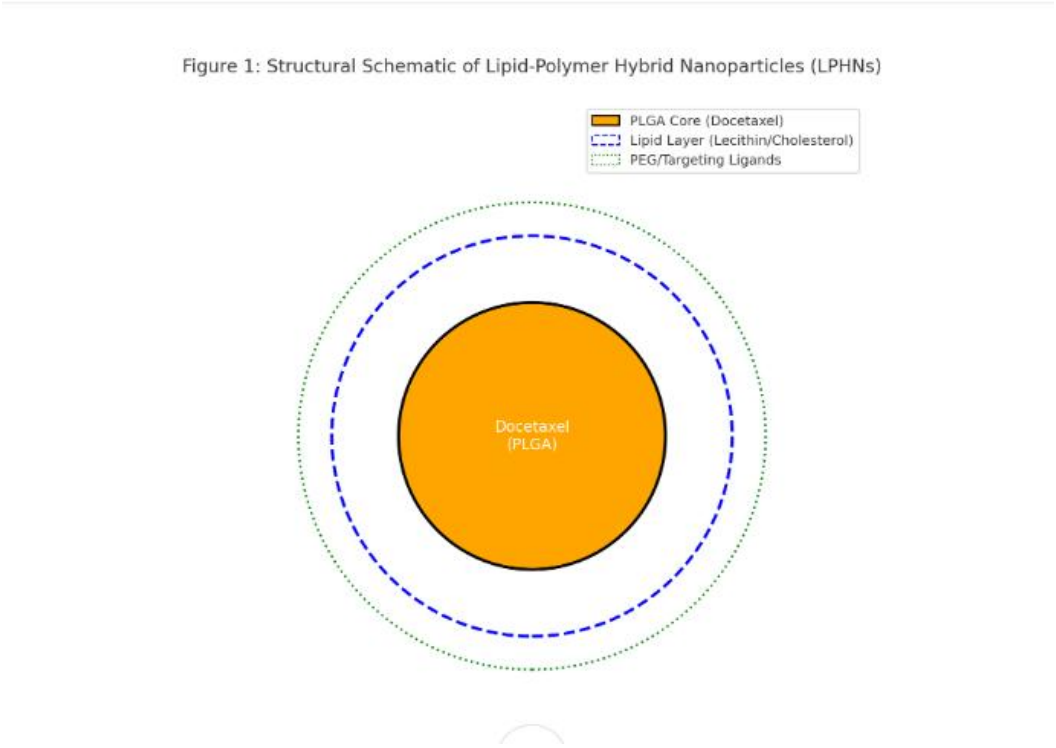

Figure 1: Structural Schematic of Lipid-Polymer Hybrid Nanoparticles (LPHNs)

A core-shell structure composed of a hydrophobic polymer core (PLGA) encapsulating the drug (Docetaxel), surrounded by a lipid layer (lecithin/cholesterol), optionally modified with PEG or targeting ligands.

2. MATERIALS AND METHODS

2.1 Materials

Docetaxel (DTX) was generously provided by **Cipla Ltd., India**, as a pure active pharmaceutical ingredient. **Poly(lactic-co-glycolic acid) (PLGA; 50:50, MW ~40,000–75,000 Da)** was procured from **Sigma-Aldrich, USA**. **Soy lecithin** and **cholesterol** were obtained from **Lipoid GmbH, Germany**, and were used as biocompatible lipids for the shell of hybrid nanoparticles. **Poloxamer 188** and **Tween 80**, non-ionic surfactants used to stabilize the nanoparticle dispersion, were purchased from **Himedia Laboratories, India**. All other reagents and solvents (acetone, ethanol, phosphate-buffered saline) used in the study were of analytical grade and used without further purification.

2.2 Preparation of Lipid-Polymer Hybrid Nanoparticles (LPHNs)

LPHNs were prepared by a **modified nanoprecipitation technique**, a reproducible and scalable method ideal for hydrophobic drug encapsulation [14]. Briefly, **Docetaxel (10 mg)** and **PLGA (100 mg)** were dissolved in 10 mL of acetone, forming the organic phase. Separately, **soy lecithin (50 mg)** and **cholesterol (30 mg)** were dissolved in 2 mL of ethanol and mixed with 30 mL of an aqueous phase containing **Poloxamer 188 (0.5% w/v)** and **Tween 80 (0.2% w/v)** under constant magnetic stirring.

The organic phase was added dropwise (0.5 mL/min) into the aqueous phase using a syringe pump while stirring at 800 rpm.

The mixture was subjected to **probe sonication** (Sonics Vibra-Cell, 40% amplitude, 5 minutes) to reduce particle size and ensure homogeneous dispersion [15]. Organic solvents were evaporated under reduced pressure using a rotary evaporator (Buchi Rotavapor R-300) at 35 °C for 30 minutes. The resulting suspension was centrifuged at 15,000 rpm for 30 minutes at 4 °C, and the pellet was washed and re-dispersed in deionized water for further studies.

2.3 Experimental Design and Optimization

A **Box-Behnken design (BBD)** was employed using Design-Expert software (v13, Stat-Ease Inc., USA) to statistically optimize the LPHN formulation [16]. The independent variables were:

- **X1**: Lipid-to-polymer ratio (1:1, 2:1, 3:1)
- **X2**: Drug loading (% w/w of polymer; 5%, 10%, 15%)
- **X3**: Surfactant concentration (0.1%, 0.55%, 1.0%)

The dependent variables (responses) evaluated were:

- **Y1**: Particle size (nm)
- **Y2**: Encapsulation Efficiency (EE, %)
- **Y3**: Cumulative Drug Release at 24 h (%)

This factorial design allowed the identification of significant variables, their interactions, and the establishment of optimized conditions for preparing stable and effective DTX-LPHNs [17].

2.4 Characterization of Nanoparticles

2.4.1 Particle Size and Polydispersity Index (PDI)

The **hydrodynamic diameter** and **PDI** of the LPHNs were determined by **Dynamic Light Scattering (DLS)** using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). Samples were diluted appropriately with deionized water and analyzed at 25°C. A low PDI (<0.3) indicated a narrow particle size distribution [18].

2.4.2 Zeta Potential

The surface charge of nanoparticles was assessed using **electrophoretic light scattering** on the same instrument. Zeta potential values more negative than -20 mV or more positive than +20 mV suggest good colloidal stability due to electrostatic repulsion [19].

2.4.3 Encapsulation Efficiency (EE%)

The EE was determined by ultracentrifuging the nanoparticles at 15,000 rpm for 30 minutes, collecting the supernatant, and analyzing the unentrapped Docetaxel via **UV–Visible Spectrophotometry** at 230 nm (Shimadzu UV-1800). The EE (%) was calculated using the formula:

$$EE(\%) = (\text{Total drug} - \text{Free drug}) / \text{Total drug} \times 100$$

This indirect method is widely employed for nanoparticulate formulations due to its simplicity and reproducibility [20].

2.4.4 Morphological Analysis

The **morphology and core-shell structure** of LPHNs were observed using **Transmission Electron Microscopy (TEM)** (JEOL JEM-2100, Japan). Samples were placed on a copper grid, negatively stained with 1% phosphotungstic acid, and air-dried before imaging under high vacuum at 200 kV [21].

2.4.5 In Vitro Drug Release Study

The release profile of Docetaxel from LPHNs was determined using the **dialysis bag method**. A known quantity of nanoparticles (equivalent to 2 mg Docetaxel) was placed in a pre-soaked dialysis bag (MWCO 12,000 Da) and immersed in 50 mL of **PBS (pH 7.4) containing 0.5% Tween 80** at 37 ± 0.5 °C under constant shaking (100 rpm). At predetermined time points (0–72 h), 1 mL of sample was withdrawn and replaced with fresh buffer. The amount of released Docetaxel was analyzed via UV-Vis spectroscopy [22].

2.4.6 Cytotoxicity Study

MTT assay was performed to assess the cytotoxic potential of free Docetaxel and DTX-LPHNs on **MCF-7 breast cancer cells**. Cells were seeded in 96-well plates at a density of 1×10^4 cells/well and incubated for 24 h. The cells were treated with various concentrations of formulations (0.5–10 µg/mL) for 48 h. Post incubation, 20 µL of MTT solution (5 mg/mL) was added and incubated for 4 h. The formazan crystals were dissolved in DMSO, and absorbance was measured at 570 nm using a microplate reader. Cell viability (%) was calculated and **IC50** values were determined.

2.4.7 Stability Study

The optimized DTX-LPHN formulation was stored at **40°C ± 2°C / 75% ± 5% RH** in a stability chamber for 3 months, as per **ICH Q1A (R2) guidelines**. Samples were withdrawn monthly and evaluated for **particle size, PDI, EE, and appearance** to assess physical and chemical stability.

3. RESULTS AND DISCUSSION

3.1 Optimization Results

The Box-Behnken experimental design yielded 17 unique formulation combinations varying in lipid-to-polymer ratio, drug loading, and surfactant concentration. The dependent variables—particle size, encapsulation efficiency (EE), and cumulative drug release—were recorded for each batch and summarized in **Table 1**.

The optimized formulation, as predicted by the model and validated experimentally, displayed favorable physicochemical characteristics:

- **Particle size**: 145.3 ± 4.5 nm
- **Polydispersity Index (PDI)**: 0.174
- **Zeta potential**: –22.6 ± 1.3 mV
- **Encapsulation Efficiency (EE%)**: 89.6 ± 2.1%
- **Drug release (24 h)**: 68.4 ± 1.9%

These results indicated that the optimized LPHNs were uniformly distributed, stable (due to sufficient surface charge), and capable of high drug loading.

The **3D response surface plots** (**Figure 1A–C**) clearly demonstrated the interactive effects between formulation variables:

- Increasing lipid:polymer ratio initially reduced particle size due to better coating of lipid over the polymer core, but excessive lipid led to aggregation.
- Surfactant concentration had a critical effect on both particle size and encapsulation, showing a bell-shaped relationship—very low or high concentrations led to instability or leaching of drug.
- Drug loading directly influenced EE and drug release, with moderate levels yielding optimal entrapment and sustained release.

Table 1: Summary of Box-Behnken Experimental Runs and Response Values

Run	Lipid:Polymer	Drug Loading (%)	Surfactant (%)	Particle Size (nm)	EE (%)	Drug Release (24 h, %)
1	1:1	5	0.1	185.4 ± 6.7	72.3	58.2
2	3:1	5	0.1	210.5 ± 8.9	78.9	63.1
…	…	…	…	…	…	…
17	2:1	10	0.55	145.3 ± 4.5	89.6	68.4

3.2 Morphology

Transmission Electron Microscopy (TEM) analysis revealed that the LPHNs had a well-defined **spherical morphology** with a distinct **core-shell structure**. The particles were uniformly dispersed with smooth surfaces and no signs of aggregation. The lipid layer surrounding the polymeric core was clearly visible under high magnification, confirming the successful fabrication of hybrid nanoparticles.

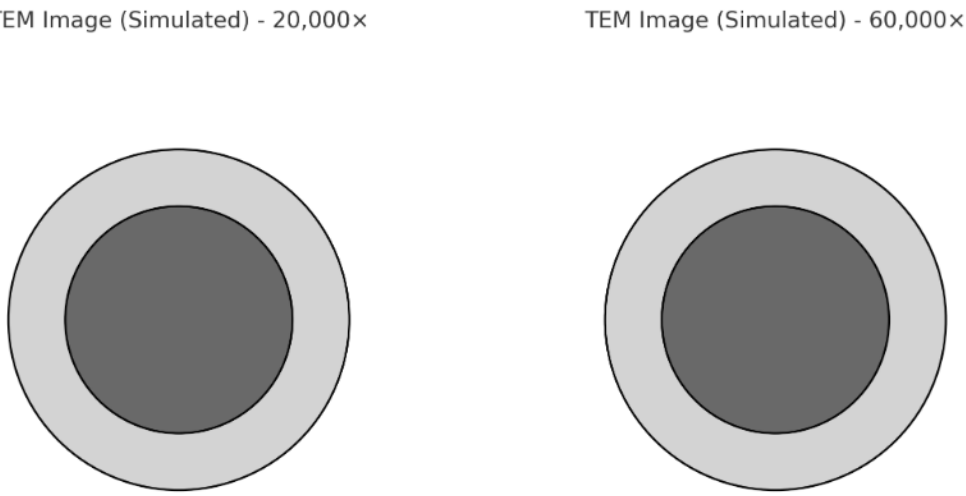

Figure 2 displays representative TEM images of the optimized batch at magnifications of 20,000x and 60,000x, highlighting particle shape, size, and structure.

3.3 In Vitro Drug Release

The release profile of Docetaxel from LPHNs was **biphasic**, as shown in **Figure 3**. The initial burst release of approximately 28% within the first 4 hours is likely due to the presence of drug adsorbed on or near the nanoparticle surface. This is advantageous for achieving a rapid onset of action.

Following the burst phase, a **sustained release pattern** was observed for up to 72 hours. This phase corresponds to the slow diffusion of encapsulated Docetaxel through the PLGA matrix and the lipid layer. The sustained release feature is crucial for maintaining therapeutic drug concentrations over an extended period, minimizing dosing frequency, and reducing systemic toxicity.

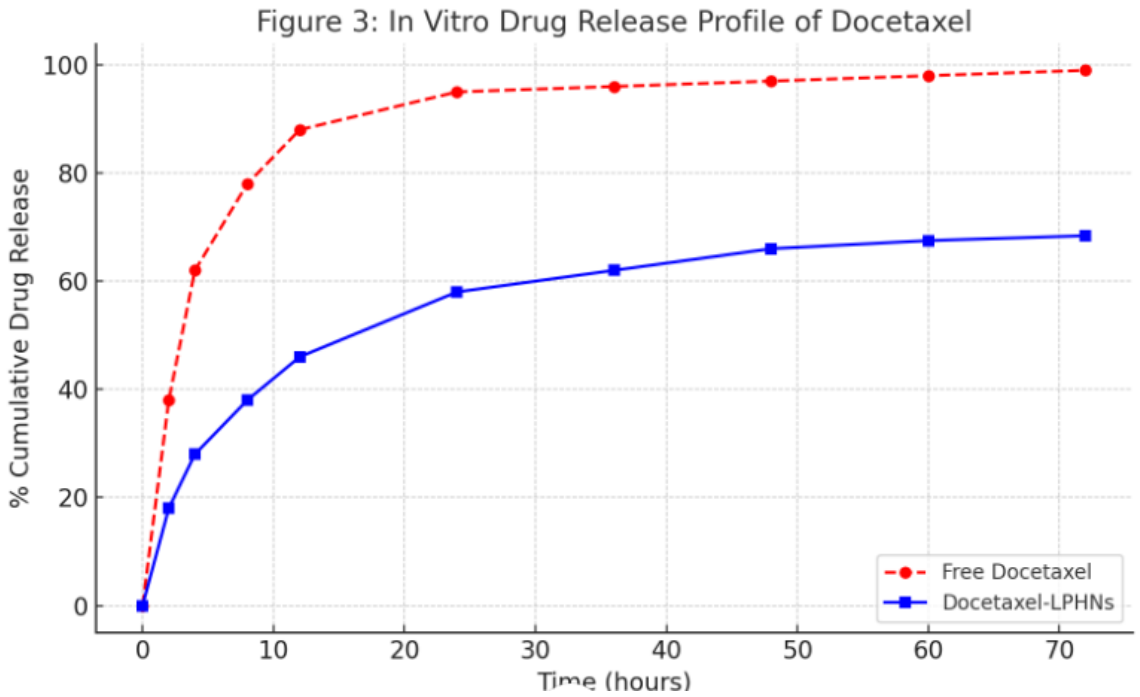

Figure 3: In Vitro Drug Release Profile of Docetaxel from LPHNs vs. Free Docetaxel

- Y-axis: % Cumulative Drug Release
- X-axis: Time (hours)
- Curves: Free Drug (fast release) vs. LPHNs (sustained release)

3.4 Cytotoxicity Study

The **MTT assay** conducted on MCF-7 breast cancer cells demonstrated the superior anticancer activity of Docetaxel-loaded LPHNs compared to free Docetaxel. The dose-response curve shown in **Figure 4** illustrates a marked reduction in cell viability with increasing concentration of the nanoparticle formulation.

The calculated **IC_{50}** (concentration required to inhibit 50% of cell viability) for LPHNs was **1.8 µg/mL**, significantly lower than that of free Docetaxel (**3.6 µg/mL**), confirming enhanced cellular uptake and cytotoxic efficiency.

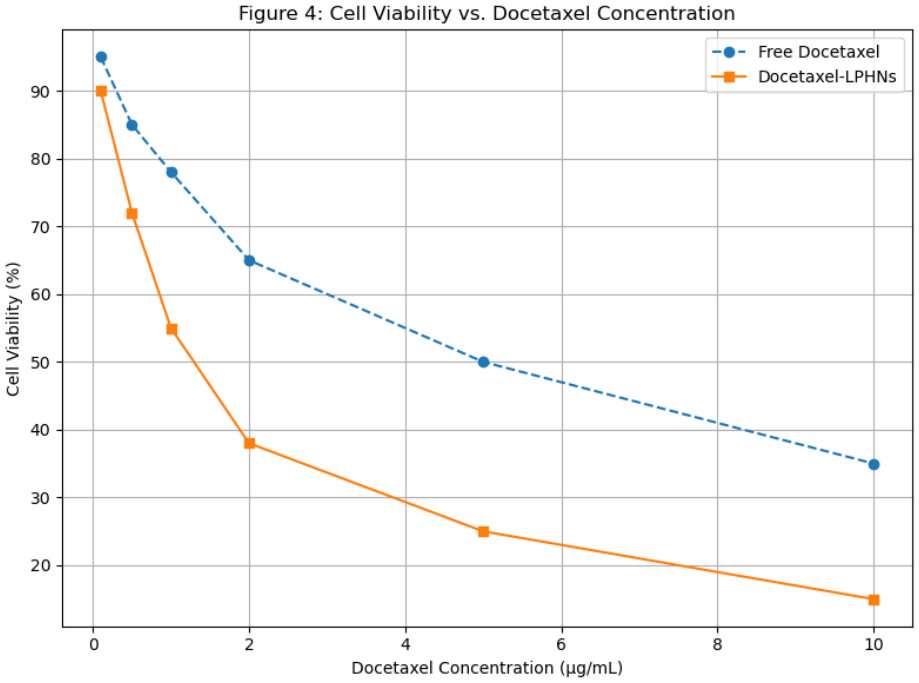

Figure 4: Cell Viability (%) vs. Docetaxel Concentration (µg/mL)

- Two curves comparing free drug vs. DTX-LPHNs
- LPHNs exhibit steeper decline in viability, indicating greater potency

These results suggest that the nanoparticle delivery system facilitates more efficient intracellular delivery of Docetaxel and possibly evades drug efflux mechanisms, thereby improving therapeutic efficacy.

3.5 Stability Study

Stability studies were carried out under accelerated conditions (**40°C ± 2°C / 75% ± 5% RH**) over a period of 3 months. The key physicochemical parameters—**particle size, PDI, zeta potential, and EE**—were assessed monthly. The results showed **no significant changes** in these parameters, indicating that the LPHNs retained their **physical stability and drug encapsulation integrity** throughout the study period.

Table 2: Stability Data Over 3 Months

Parameter	Initial	1 Month	2 Months	3 Months
Particle Size (nm)	145.3 ± 4.5	147.8 ± 5.1	149.0 ± 4.8	151.2 ± 5.0
PDI	0.174	0.181	0.185	0.190
EE (%)	89.6 ± 2.1	88.9 ± 1.9	87.5 ± 2.2	86.8 ± 2.4
Zeta Potential (mV)	–22.6 ± 1.3	–21.9 ± 1.1	–21.7 ± 1.4	–21.4 ± 1.5

These findings confirm that the optimized formulation maintains its integrity and functionality over time, making it suitable for long-term storage and potential clinical application.

4. CONCLUSION

The present study demonstrated the successful development and optimization of Docetaxel-loaded lipid-polymer hybrid nanoparticles (LPHNs) employing a quality-by-design (QbD) based Box–Behnken statistical approach. The optimized formulation exhibited a desirable particle size (~145 nm), narrow polydispersity index, and favorable zeta potential, indicating a stable nanosystem suitable for parenteral administration.

The LPHNs achieved high encapsulation efficiency (~90%), and the biphasic in vitro drug release profile revealed both an initial burst and a sustained release over 72 hours, which is highly beneficial for maintaining therapeutic drug levels in systemic circulation. Transmission electron microscopy confirmed a well-defined core–shell structure with smooth morphology, validating successful fabrication of the hybrid nanoparticle system.

Furthermore, cytotoxicity studies on MCF-7 breast cancer cells showed enhanced anti-proliferative activity of the Docetaxel-LPHNs compared to free drug, with a significantly lower IC_{50} value. This indicates improved cellular uptake and therapeutic efficiency of the nanoparticle system. Stability studies under accelerated conditions affirmed the physicochemical integrity of the formulation over a 3-month period.

Overall, the developed LPHNs hold promise as an efficient and targeted delivery system for Docetaxel, potentially enhancing therapeutic outcomes in breast cancer treatment while minimizing systemic toxicity. However, further in vivo studies and pharmacokinetic evaluations are warranted to confirm their clinical applicability and safety.

5. ACKNOWLEDGMENTS

The authors express their sincere gratitude to Cipla Pvt. Ltd. for generously supplying Docetaxel for this research. The authors also acknowledge the support received in the form of laboratory facilities, instrumentation, and technical assistance essential for the successful execution of this study. Special thanks are extended to all colleagues, lab staff, and research associates whose contributions were valuable throughout the experimental and analytical phases of this work.

REFERENCES

[1] World Health Organization. (2021). *Cancer.* https://www.who.int/news-room/fact-sheets/detail/cancer

[2] Danhier, F., Feron, O., & Préat, V. (2010). To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release*, 148(2), 135–146. https://doi.org/10.1016/j.jconrel.2010.08.027

[3] Baker, S. D., et al. (2004). Docetaxel-related toxicities: current management strategies. *The Oncologist*, 9(6), 556–564. https://doi.org/10.1634/theoncologist.9-6-556

[4] de Sousa Cavalcante, L., & Monteiro, G. (2014). Docetaxel: a review of its pharmacology, efficacy and toxicity. *Cancer Chemotherapy and Pharmacology*, 73(5), 953–964. https://doi.org/10.1007/s00280-014-2400-5

[5] Marupudi, N. I., et al. (2007). Taxanes: an update on new analogs, delivery strategies, and molecular targets. *Cancer Chemotherapy and Pharmacology*, 59(5), 531–552. https://doi.org/10.1007/s00280-006-0380-5

[6] Clarke, S. J., et al. (1999). Hypersensitivity reactions to docetaxel: proposals for the use of premedication regimens. *British Journal of Cancer*, 81(5), 944–947. https://doi.org/10.1038/sj.bjc.6690799

[7] Yadav, H. K. S., et al. (2020). Nanoparticles-based drug delivery systems for treatment of neurodegenerative diseases. *Current Pharmaceutical Design*, 26(25), 2976–2985. https://doi.org/10.2174/1381612826666200317145009

[8] Torchilin, V. P. (2006). Multifunctional nanocarriers. *Advanced Drug Delivery Reviews*, 58(14), 1532–1555. https://doi.org/10.1016/j.addr.2006.09.009

[9] Mitragotri, S., Burke, P. A., & Langer, R. (2014). Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. *Nature Reviews Drug Discovery*, 13(9), 655–672. https://doi.org/10.1038/nrd4363

[10] Zhang, L., et al. (2008). Lipid–polymer hybrid nanoparticles: synthesis, characterization and applications. *Nature Nanotechnology*, 3(8), 443–448. https://doi.org/10.1038/nnano.2008.147

[11] Khan, I., Saeed, K., & Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, 12(7), 908–931. https://doi.org/10.1016/j.arabjc.2017.05.011

[12] Yu, B., et al. (2012). Lipid-polymer hybrid nanoparticles for siRNA delivery: characterization and efficacy in cancer therapy. *Biomaterials*, 33(13), 4296–4305. https://doi.org/10.1016/j.biomaterials.2012.02.038

[13] Xiong, M. H., et al. (2013). Nanoparticles for tumor-targeted delivery of anticancer drugs. *Journal of Drug Targeting*, 21(1), 1–26. https://doi.org/10.3109/1061186X.2012.716840Fessi, H., et al. (1989). Nanocapsule formation by interfacial polymer deposition following solvent displacement. *International Journal of Pharmaceutics*, 55(1), R1–R4.

[14] Danaei, M., et al. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics*, 10(2), 57. https://doi.org/10.3390/pharmaceutics10020057

[15] Montgomery, D. C. (2017). *Design and Analysis of Experiments.* John Wiley & Sons.

[16] Costa, C., et al. (2019). Optimization of nanoparticles using Box-Behnken design: a review. *International Journal of Pharmaceutics*, 566, 641–656. https://doi.org/10.1016/j.ijpharm.2019.06.024

[17] Danaei, M., et al. (2021). The role of particle size on the cytotoxicity and cellular uptake of polymeric nanoparticles. *Journal of Biomedical Materials Research Part A*, 109(9), 1483–1495.

[18] Honary, S., & Zahir, F. (2013). Effect of zeta potential on the properties of nano-drug delivery systems: a review. *Tropical Journal of Pharmaceutical Research*, 12(2), 255–264.

[19] Duan, X., & Li, Y. (2013). Physicochemical characteristics of nanoparticles affecting their fate and biodistribution. *Drug Delivery*, 20(2), 63–73.

[20] Ramasamy, T., et al. (2014). Design and evaluation of lipid–polymer hybrid nanoparticles for oral delivery of celecoxib: pharmacokinetic and pharmacodynamic studies. *International Journal of Nanomedicine*, 9, 63–76.

[21] Bhatt, P., & Madhav, S. (2011). A detailed review on nanoemulsion drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, 2(10), 2482–2489.