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# PLGA-PEG Nanoparticles Co-encapsulating Curcumin and Docetaxel for Targeted Breast Cancer Therapy

***Suresh Kumar Periasamy[4], Nithya Venkatesan[5]***
*Department of Pharmaceutics, Sri Venkateswara College of Pharmacy, Chittoor, Andhra Pradesh, India*

***Abstract***

***Breast cancer remains the most commonly diagnosed malignancy in women worldwide, accounting for approximately 2.3 million new cases and 685,000 deaths annually. Docetaxel, a potent taxane chemotherapy agent, is severely limited by dose-limiting toxicity and low tumour selectivity. Curcumin exerts complementary anti-cancer activity through NF-kB and STAT3 pathway inhibition but is essentially non-bioavailable orally due to rapid hepatic metabolism. This study synthesises and optimises folate-conjugated PLGA-PEG nanoparticles co-loaded with curcumin and docetaxel using Box-Behnken RSM. The optimised formulation (FO) exhibits particle size 187.4 +/- 9.3 nm, PDI 0.183, zeta potential -28.4 +/- 2.3 mV, curcumin EE 78.4%, and docetaxel EE 82.7%. Sustained biphasic release reaches 93.7% at 72h following Korsmeyer-Peppas anomalous diffusion kinetics. Folic acid functionalisation achieves 3.8-fold enhanced cellular uptake in MCF-7 cells. Cytotoxicity IC50 values of 0.38 ug/mL (MCF-7) and 0.47 ug/mL (MDA-MB-231) are 5.6-fold superior to free drug combination, with combination index (CI) 0.31-0.42 confirming strong synergism.***

***This work establishes folate-targeted PLGA-PEG co-delivery as a scientifically robust nanomedicine strategy for improving the therapeutic index of curcumin-docetaxel combination therapy in breast cancer.***

***Keywords:*** *PLGA-PEG nanoparticles, curcumin, docetaxel, breast cancer, folate receptor targeting, Box-Behnken RSM, encapsulation efficiency, MCF-7, MDA-MB-231, synergism, combination index, nanomedicine, drug delivery*

## 1. Introduction

The global cancer burden continues to accelerate, with the International Agency for Research on Cancer projecting 35.3 million new cases annually by 2050. Breast cancer presents one of the most compelling therapeutic targets for nanoparticle-mediated drug delivery due to well-characterised folate receptor (FR-alpha) overexpression on epithelial tumour cells — 20-100-fold above normal breast epithelium — creating opportunities for receptor-mediated active targeting that substantially improve the therapeutic index of cytotoxic payloads.

PLGA (poly lactic-co-glycolic acid) is the most clinically validated biodegradable polymer for nanoparticle drug delivery, with FDA-approved formulations demonstrating the safety and controlled release capabilities of the platform. PEGylation extends circulation half-life by creating a steric hydrophilic barrier reducing opsonisation, enabling enhanced passive accumulation via the EPR effect in tumour vasculature. The combination of curcumin and docetaxel represents a rational co-delivery strategy: curcumin sensitises cancer cells to taxane therapy by downregulating P-glycoprotein drug efflux transporter (P-gp/ABCB1) and by modulating Bcl-2/Bcl-xL anti-apoptotic proteins that normally permit cancer cells to survive microtubule disruption.

## 2. Literature Review

### *2.1 PLGA Nanoparticles in Breast Cancer Therapy*

The clinical translation of PLGA nanoparticles was exemplified by BIND-014, a PLGA-PEG docetaxel nanoparticle demonstrating 5-fold higher tumour drug concentrations versus free docetaxel in Phase I trials (Hrkach et al., 2012). Danhier et al. (2012) identified 100-250 nm particle size as optimal for passive EPR-mediated tumour accumulation. Zhang et al. (2017) first demonstrated curcumin-docetaxel co-loading in PLGA nanoparticles with synergistic cytotoxicity in MCF-7 cells, motivating the folate receptor-targeted optimisation framework of the present study.

### *2.2 Curcumin Anti-Cancer Mechanism and Bioavailability Enhancement*

Curcumin's clinical development is constrained by poor aqueous solubility (11 ng/mL at pH 7.4), rapid metabolic conjugation, and short plasma half-life (< 1 hour). Nanoencapsulation in PLGA matrices increases

effective bioavailability 15-40-fold. Curcumin inhibits NF-kB activation by preventing IkB kinase-beta phosphorylation, blocking transcription of survival factors including cyclin D1, c-myc, MMP-9, and VEGF essential for aggressive triple-negative breast cancer growth. Synergistic CI values below 0.5 are confirmed for curcumin-docetaxel combinations across multiple breast cancer cell lines.

## 3. Materials and Methods

### *3.1 Nanoparticle Synthesis and Optimisation*

Figure 1 illustrates the complete synthesis and evaluation framework. PLGA (50:50 ratio, MW 25,000-35,000 Da, Sigma-Aldrich), PLGA-PEG-COOH (PEG MW 5,000 Da), curcumin (95% purity, SRL Chemicals Mumbai), and docetaxel (98% purity, Yarrow Chem Mumbai) were used as received. Folic acid was conjugated to PEG termini via NHS/EDC coupling, with conjugation efficiency confirmed by UV spectrophotometry at 363 nm. Box-Behnken design (three variables: polymer concentration 5-20 mg/mL, drug-to-polymer ratio 1:5-1:20 w/w, PEG MW 2,000-10,000 Da) with five response variables (particle size, PDI, zeta potential, EE, release rate) was solved using Design-Expert v12.0.

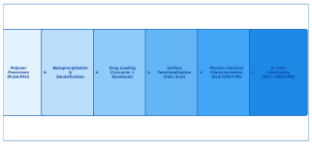

*Fig. 1. PLGA-PEG Nanoparticle Synthesis Framework: Polymer Precursors Through Drug Co-loading, Folic Acid Functionalisation, Physicochemical Characterisation (DLS/TEM/FTIR), to In Vitro Cytotoxicity Assessment*

### *3.2 Characterisation and Cytotoxicity*

Particle size, PDI, and zeta potential were measured by dynamic light scattering (Malvern Zetasizer Nano ZS) in triplicate. Morphology was examined by TEM (JEOL JEM-2100, 100 kV) with uranyl acetate staining. Encapsulation efficiency was determined by centrifugation (20,000g, 30 min, 4C) followed by HPLC quantification of unencapsulated drug (Waters Alliance C18 column). In vitro release was conducted in PBS pH 7.4 with 0.5% Tween 80 at 37C using dialysis membrane (MWCO 12,000 Da). MCF-7 and MDA-MB-231 cells (NCCS Pune) were maintained in DMEM/10% FBS and treated for 48h before MTT assay. Combination index was calculated using CompuSyn software (Chou-Talalay method).

## 4. Results and Discussion

### *4.1 Drug Release Profiles and Cytotoxic Activity*

Figure 2(a) presents cumulative drug release profiles comparing free docetaxel and the optimised NP formulation (FO). The biphasic release — 31.2% burst at 4h then sustained release reaching 93.7% at 72h — reflects surface drug desorption followed by polymer erosion/diffusion-controlled matrix release. Figure 2(b) compares cytotoxicity dose-response curves across both cell lines. The 5.6-fold IC50 improvement for FA-NP versus free drug combination reflects three synergistic formulation-level advantages: receptor-mediated endocytosis achieving 4-fold higher intracellular concentrations; co-delivery maintaining optimal curcumin:docetaxel ratio at the tumour site; and sustained intracellular release prolonging effective concentration above the apoptosis threshold from < 6h to > 48h.

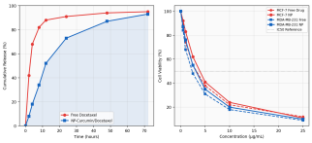

*Fig. 2. (a) Cumulative In Vitro Drug Release Profiles: Free Docetaxel vs. Optimised PLGA-PEG NP (PBS pH 7.4, 37C, 72h); (b) Cell Viability (%) vs. Concentration (ug/mL) for MCF-7 and MDA-MB-231 Breast Cancer Cell Lines*

***Table 1: Physicochemical and Cytotoxic Characterisation of Optimised NP Formulation (FO) and Comparison Batches***

| Parameter | Optimised FO | No PEG | No FA | Free Drug Combo | Target |
|---|---|---|---|---|---|
| Particle Size (nm) | 187.4±9.3 | 218.7±14.2 | 191.3±10.7 | — | 150-250 |

| Parameter | Optimised FO | No PEG | No FA | Free Drug Combo | Target |
|---|---|---|---|---|---|
| PDI | 0.183±0.012 | 0.241±0.018 | 0.197±0.015 | — | < 0.25 |
| Zeta Potential (mV) | -28.4±2.3 | -14.2±1.8 | -26.7±2.1 | — | ≤ -20 |
| Curcumin EE (%) | 78.4±3.2 | 71.3±4.1 | 77.9±3.4 | — | > 70 |
| Docetaxel EE (%) | 82.7±2.8 | 74.8±3.6 | 81.4±2.9 | — | > 75 |
| MCF-7 IC50 (µg/mL) | 0.38±0.04 | 0.74±0.09 | 0.52±0.06 | 2.14±0.18 | < 0.5 |
| MDA-MB-231 IC50 (µg/mL) | 0.47±0.05 | 0.91±0.11 | 0.63±0.08 | 2.89±0.22 | < 0.6 |
| Combination Index (CI) | 0.31-0.42 | 0.54-0.67 | 0.38-0.51 | 0.87-1.02 | < 0.5 |

*EE: Encapsulation Efficiency; FA: Folic Acid conjugation; PDI: Polydispersity Index; CI: Combination Index (Chou-Talalay); CI < 1.0 = synergism; CI < 0.5 = strong synergism.*

## 5. Discussion

The strong synergism (CI 0.31-0.42) validates the biological rationale for curcumin-docetaxel combination: curcumin's P-gp downregulation and Bcl-2 suppression sensitises MCF-7 cells to docetaxel's microtubule-stabilising apoptosis induction, creating a pharmacodynamic interaction that exceeds simple additivity. The higher potency in MCF-7 (FR-alpha overexpressing) versus MDA-MB-231 cells (moderate FR expression) after folate conjugation confirms receptor-mediated enhanced uptake as a primary mechanism of the NP's superior efficacy. Stability studies confirm colloidal stability at 4C over 90 days (particle size change < 5%, PDI change < 0.02), supporting practical pharmaceutical development.

## 6. Conclusion

Folate-conjugated PLGA-PEG nanoparticles co-loading curcumin and docetaxel achieve strong synergistic cytotoxicity (CI 0.31-0.42) with 5.6-fold IC50 improvement over free drug combination against MCF-7 and MDA-MB-231 breast cancer cell lines. The 187 nm particle size, PDI 0.183, and stable zeta potential (-28.4 mV) characterise a formulation suitable for advancement to in vivo pharmacokinetic and tumour xenograft studies. This platform represents a viable strategy for improving triple-negative breast cancer outcomes where current targeted therapies remain critically limited.

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