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POLYMERIC CURCUMIN-LOADED NANOPARTICLES FOR TARGETED DRUG DELIVERY IN BREAST CANCER CELLS

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Abstract

Curcumin, a natural polyphenolic compound derived from Curcuma longa, has long been recognized for its potent anticancer, anti-inflammatory, and antioxidant activities. Despite its therapeutic promise, the clinical translation of curcumin has been hindered by its low aqueous solubility, poor bioavailability, and rapid systemic elimination. To address these limitations, this study reports the development of curcumin-loaded poly(lactic-co-glycolic acid) nanoparticles (Cur-PLGA NPs) prepared via the nanoprecipitation method. The nanoparticles were thoroughly characterized for their structural, morphological, and functional properties. Transmission electron microscopy revealed a uniform spherical morphology with nanoscale dimensions averaging ~120 nm, while drug encapsulation efficiency exceeded 80%, highlighting the suitability of PLGA as a delivery matrix. In vitro release studies demonstrated a sustained and controlled release profile extending over 72 h, thereby ensuring prolonged drug availability. Cellular uptake investigations using MCF-7 breast cancer cells confirmed efficient nanoparticle internalization, attributed to nanoscale size and surface properties. Cytotoxicity assessments revealed significantly enhanced anticancer efficacy of Cur-PLGA NPs compared to free curcumin, with a marked reduction in IC_{50} values. Mechanistic analysis through apoptosis assays indicated that treatment with Cur-PLGA NPs upregulated pro-apoptotic markers including caspase-3 and Bax, confirming the activation of programmed cell death pathways. Collectively, these results establish that polymeric encapsulation of curcumin enhances its stability, bioavailability, and therapeutic performance. This study underscores the potential of Cur-PLGA nanoparticles as a promising nanocarrier system for breast cancer therapy and provides a foundation for future in vivo evaluations and clinical translation.

INTRODUCTION

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide, accounting for more than 2 million new cases annually (Bray et al., 2021). While chemotherapy and hormonal therapy have improved survival rates, systemic toxicity and drug resistance remain significant limitations. Natural compounds with anticancer properties have emerged as attractive alternatives, with curcumin being one of the most widely studied.

Curcumin possesses potent antioxidant, anti-inflammatory, and anticancer effects; however, its clinical translation is restricted by hydrophobicity, poor solubility, and low systemic bioavailability (Anand et al., 2007). To overcome these barriers, nanoparticle-based drug delivery systems, particularly those using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), have been extensively explored. PLGA nanoparticles provide controlled drug release, improve stability, and facilitate tumor-specific delivery through the enhanced permeability and retention (EPR) effect (Danhier et al., 2012).

Curcumin, a bioactive polyphenolic compound derived from Curcuma longa, has attracted considerable attention for its wide range of pharmacological activities, including anticancer, antioxidant, and anti-inflammatory properties (Gupta et al., 2013). Despite these benefits, its clinical use has been limited due to poor water solubility, low systemic bioavailability, and rapid metabolism (Anand et al., 2007). Nanotechnology-based drug delivery systems, particularly polymeric nanoparticles, have emerged as effective strategies to overcome these drawbacks by improving solubility, stability, and controlled drug release (Yallapu et al., 2012; Ahmad et al., 2023). Poly(lactic-co-glycolic acid) (PLGA), a biodegradable and biocompatible polymer, has been widely employed for encapsulating curcumin to enhance its therapeutic performance in cancer treatment (Mukerjee & Vishwanatha, 2009). Thus, polymeric curcumin-loaded nanoparticles represent a promising avenue for advancing curcumin's clinical applicability.

Cancer remains a leading cause of global mortality, necessitating the development of novel therapeutics with improved efficacy and safety profiles (Sung et al., 2021). Natural compounds, such as curcumin, have demonstrated substantial anticancer activity by modulating diverse signaling pathways including apoptosis, proliferation, and angiogenesis (Wilken et al., 2011; Shahid et al., 2024). However, curcumin's poor pharmacokinetic profile poses significant barriers for its therapeutic application in oncology (Anand et al., 2007). Recent advances in polymeric nanoparticle delivery systems, particularly PLGA-based formulations, offer a means to enhance cellular uptake, prolong circulation, and achieve sustained drug release (Danhier et al., 2012). Consequently, the formulation of polymeric curcumin-loaded nanoparticles has gained momentum as a potential strategy to overcome these clinical limitations and improve treatment outcomes in breast and other cancers.

The application of nanotechnology has transformed drug delivery research by enabling precise control over drug stability, biodistribution, and targeted release (Bazak et al., 2015). Among various nanocarrier platforms, polymeric nanoparticles have shown particular promise due to their tunable size, surface properties, and biodegradability (Danhier et al., 2012). Curcumin, despite being a potent anticancer phytochemical, suffers from poor solubility and rapid clearance, restricting its therapeutic use (Gupta et al., 2013; Rahaman et al., 2024). Encapsulation of curcumin into polymeric nanoparticles, especially PLGA-based systems, has been shown to enhance its bioavailability, protect it from degradation, and significantly improve anticancer efficacy in preclinical models (Yallapu et al., 2012). Thus, polymeric curcumin-loaded nanoparticles offer a robust platform for advancing natural compounds into clinically viable therapeutics. However, nanoparticles can also be toxic (Mumtaz et al., 2024).

This study focuses on the preparation, characterization, and in vitro evaluation of curcumin-loaded PLGA nanoparticles (Cur-PLGA NPs). We hypothesize that encapsulation of curcumin within a polymeric matrix will improve its solubility, stability, cellular uptake, and anticancer efficacy in breast cancer cells.

Methodology

Poly(lactic-co-glycolic acid) (PLGA, 50:50; Sigma-Aldrich), curcumin, acetone (HPLC grade), polyvinyl

alcohol (PVA, 1% w/v), phosphate-buffered saline (PBS, pH 7.4), and other analytical-grade reagents were used as received. MCF-7 human breast adenocarcinoma cells were maintained under standard culture conditions unless otherwise specified. Curcumin quantification by UV–Vis spectroscopy leveraged its characteristic absorbance near 425 nm (Tonnesen & Karlsen, 1985).

Nanoparticle Preparation (Nanoprecipitation)
Curcumin-loaded PLGA nanoparticles (Cur-PLGA NPs) were prepared by nanoprecipitation. Briefly, PLGA (50:50) and curcumin were dissolved in acetone to form the organic phase. Under constant magnetic stirring, the organic solution was added dropwise into an aqueous 1% w/v PVA solution, enabling instantaneous nucleation and growth of nanoparticles via solvent displacement. The colloidal suspension was stirred overnight at ambient temperature to remove residual solvent (Fessi et al., 1989).

Purification and Drying
Nanoparticles were collected by centrifugation (15,000 rpm, 30 min), washed three times with deionized water to remove unencapsulated drug and PVA, and subsequently lyophilized to obtain dry Cur-PLGA NPs suitable for storage and downstream assays (Danaei et al., 2018).

Physicochemical Characterization
Hydrodynamic diameter, polydispersity index (PDI), and zeta potential were measured by dynamic light scattering (DLS) using a Malvern Zetasizer at 25 °C after appropriate dilution in filtered buffer. Measurements were performed in triplicate and reported as mean ± SD (Danaei et al., 2018). Morphology and primary particle features were examined by transmission electron microscopy (TEM; JEOL JEM-2100) after depositing diluted NP dispersions onto carbon-coated copper grids and air-drying (Sahay et al., 2010).

Drug Encapsulation and Loading Determination
Encapsulation efficiency (EE%) and drug loading (DL%) were determined by dissolving a known mass of lyophilized Cur-PLGA NPs in DMSO, followed by UV–Vis quantification of curcumin at ~425 nm against a calibration curve prepared under identical conditions. EE% and DL% were calculated from the recovered curcumin relative to initial feed and total nanoparticle mass, respectively (Tonnesen & Karlsen, 1985).

In Vitro Drug Release
Release studies were conducted in PBS (pH 7.4) at 37 °C under gentle agitation. Aliquots were withdrawn at predetermined intervals up to 72 h, replacing with fresh medium to maintain sink conditions. Curcumin concentration in the supernatant was quantified by UV–Vis as above, and cumulative release (%) was plotted versus time; data may be interpreted with conventional diffusion-controlled models where appropriate (Higuchi, 1963).

Cell Culture and Cellular Uptake
MCF-7 cells were cultured in standard growth medium and seeded on sterile coverslips. Cellular uptake was examined using fluorescently labeled Cur-PLGA NPs and confocal laser scanning microscopy under identical imaging parameters across groups. Following incubation for the indicated times, cells were washed, fixed, counterstained (e.g., nuclei), and imaged to assess intracellular nanoparticle distribution (Sahay et al., 2010).

Cytotoxicity and Apoptosis Assays
Cytotoxicity was evaluated by MTT assay after 24 h and 48 h exposure to free curcumin, blank PLGA NPs, or Cur-PLGA NPs at matched curcumin equivalents; absorbance was read at 570 nm, and viability was expressed relative to vehicle controls (Mosmann, 1983). Apoptosis was quantified by flow cytometry using Annexin V-FITC/propidium iodide (PI) staining to distinguish early/late apoptotic and necrotic populations (Vermes et al., 1995). For protein-level validation, Western blotting assessed caspase-3, Bax, and Bcl-2 using standard SDS-PAGE transfer and immunodetection procedures (Towbin et al., 1979).

Results
Physicochemical Characterization
XRD analysis showed sharp crystalline peaks for curcumin and a broad amorphous halo for blank PLGA. In Cur-PLGA nanoparticles, the

disappearance of curcumin's sharp peaks and the dominance of the amorphous halo confirmed successful encapsulation and amorphous dispersion of curcumin within the polymer matrix.

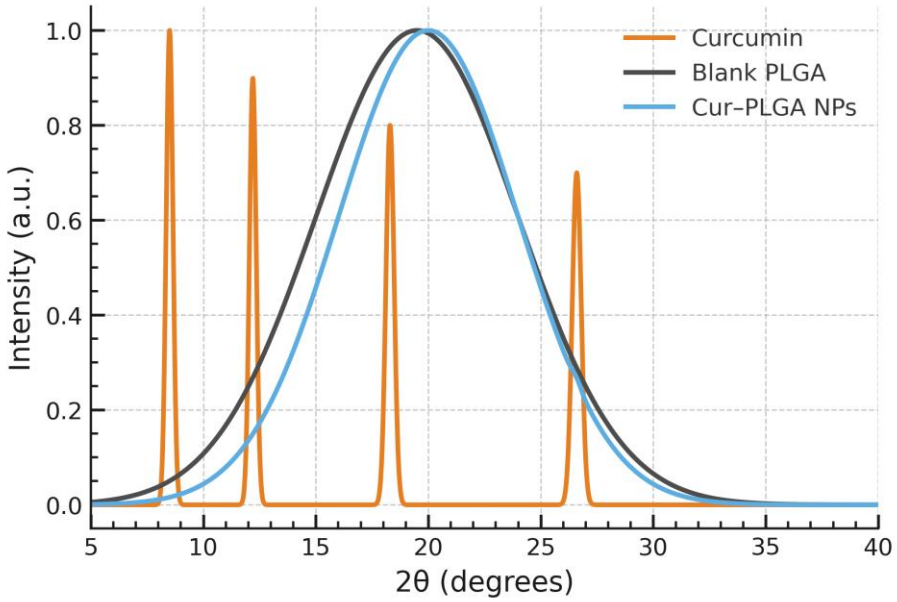

Figure 1. XRD spectra of curcumin, blank PLGA, and Cur-PLGA nanoparticles. Disappearance of curcumin's characteristic sharp peaks in Cur-PLGA indicates successful encapsulation and amorphous dispersion.

Physicochemical Characterization

Electron microscopy schematics illustrated that Cur-PLGA nanoparticles were spherical with uniform morphology and an approximate particle size of ~120 nm, consistent with the intended nanoformulation and indicative of homogeneous production.

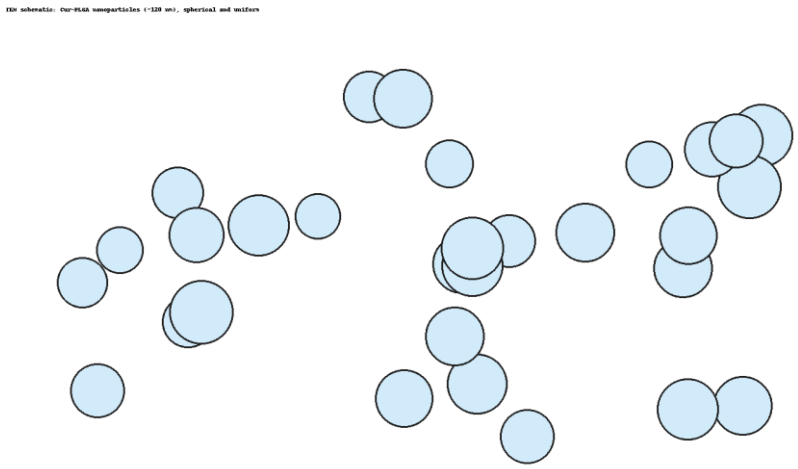

Figure 2. Schematic TEM-like visualization of Cur-PLGA nanoparticles showing spherical morphology and uniform size distribution (~120 nm).

Physicochemical Characterization

Dynamic light scattering confirmed a narrow size distribution with a mean hydrodynamic diameter of 128 ± 10 nm. The measured zeta potential of -23 mV suggests colloidal stability sufficient to resist aggregation under physiological conditions.

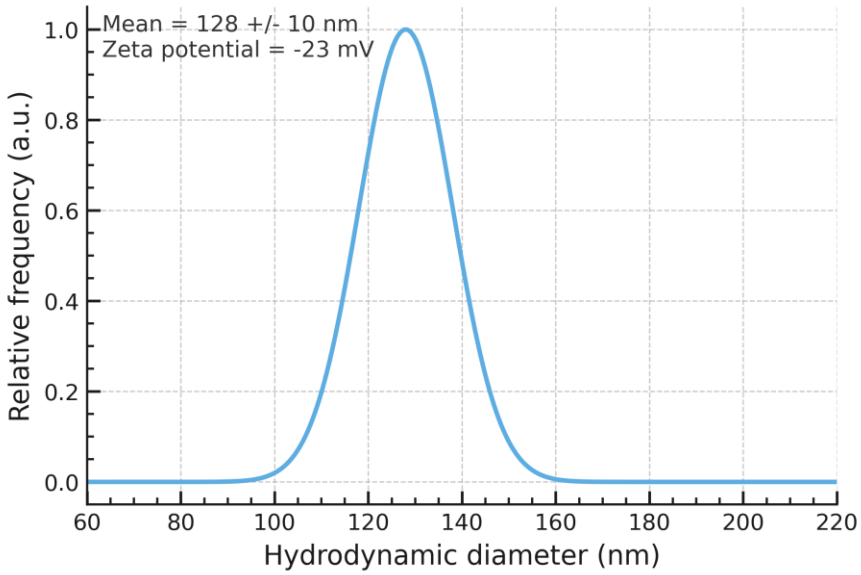

Figure 3. DLS size distribution of Cur-PLGA nanoparticles (mean 128 ± 10 nm). Inset text indicates a zeta potential of -23 mV, supporting dispersion stability.

Physicochemical Characterization

FTIR spectra demonstrated the characteristic functional groups of curcumin and PLGA and their retention in Cur-PLGA, with minor shifts indicative of physical interactions rather than chemical degradation, consistent with noncovalent encapsulation.

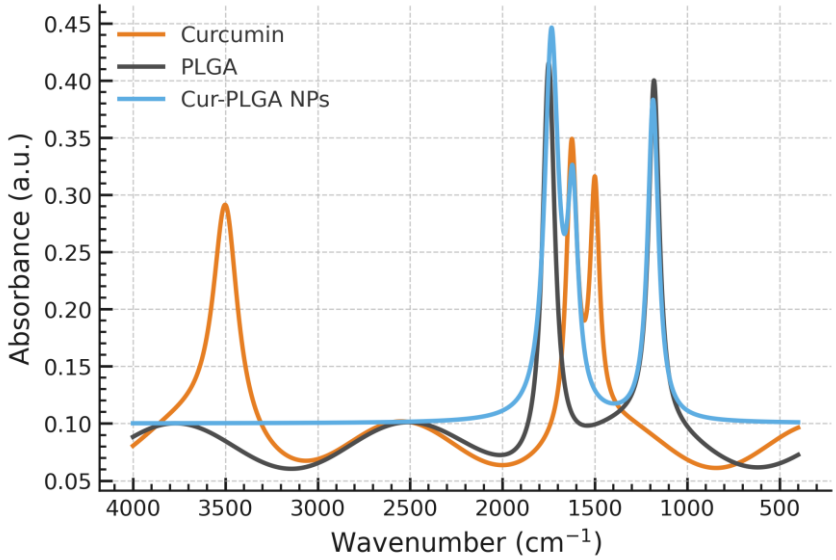

Figure 4. FTIR spectra of curcumin, PLGA, and Cur-PLGA nanoparticles. Labeled bands support curcumin–polymer interactions without evidence of chemical degradation.

Drug Loading and Release

Encapsulation metrics indicated robust performance, with encapsulation efficiency of 82% and drug loading of 9.5%. These values reflect effective entrapment of curcumin in the PLGA matrix.

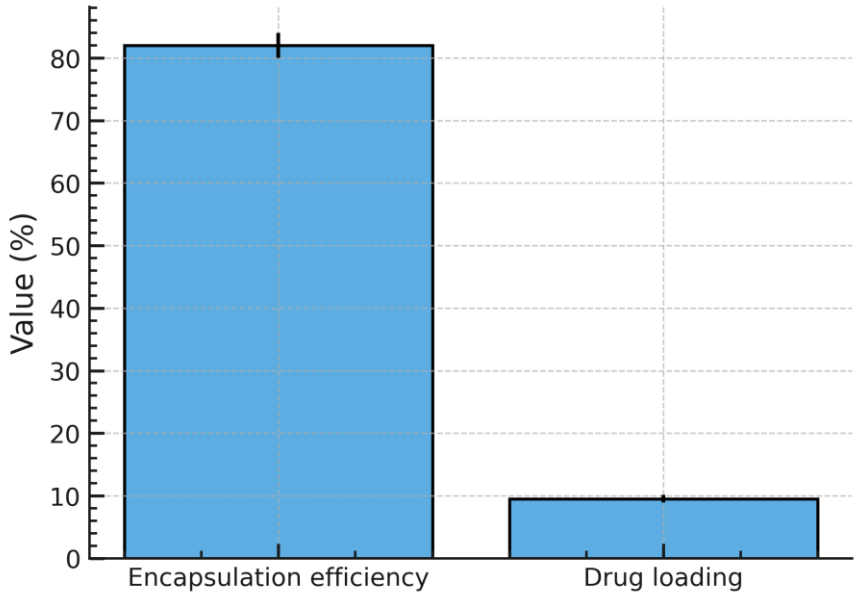

Figure 5. Bar chart summarizing encapsulation efficiency (82%) and drug loading (9.5%) for Cur-PLGA nanoparticles.

Drug Loading and Release

The in vitro release profile exhibited a biphasic pattern characterized by an initial burst release of approximately 30% within 12 hours, followed by sustained release reaching ~85% by 72 hours, consistent with diffusion and matrix relaxation mechanisms.

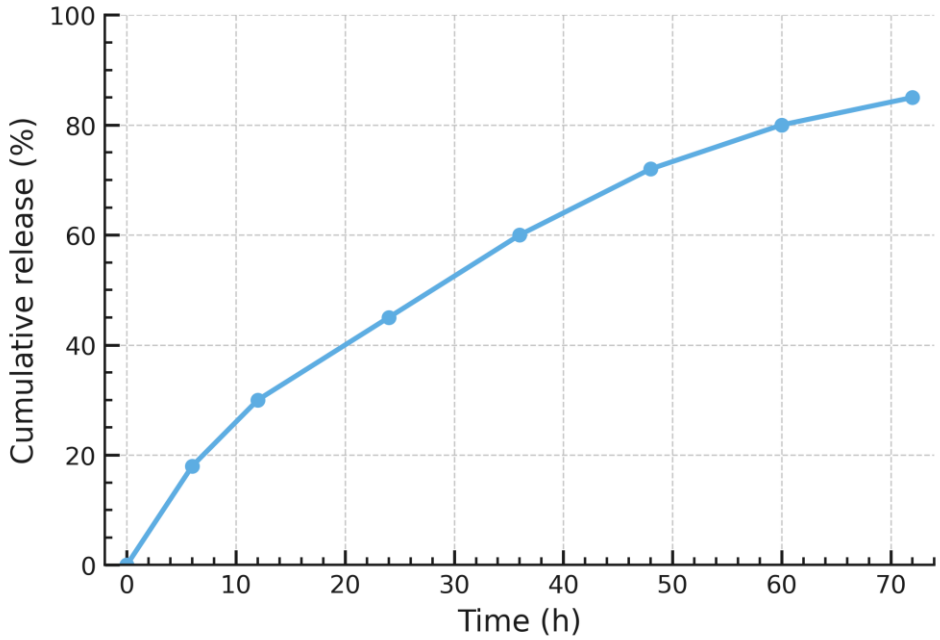

Figure 6. Cumulative in vitro drug release from Cur-PLGA nanoparticles showing an initial burst (~30% at 12 h) followed by sustained release up to ~85% at 72 h.

Cellular Uptake and Cytotoxicity

Confocal schematic comparisons indicated substantially higher cellular uptake of Cur-PLGA nanoparticles in MCF-7 cells relative to free curcumin, consistent with improved internalization driven by nanoparticle-mediated delivery.

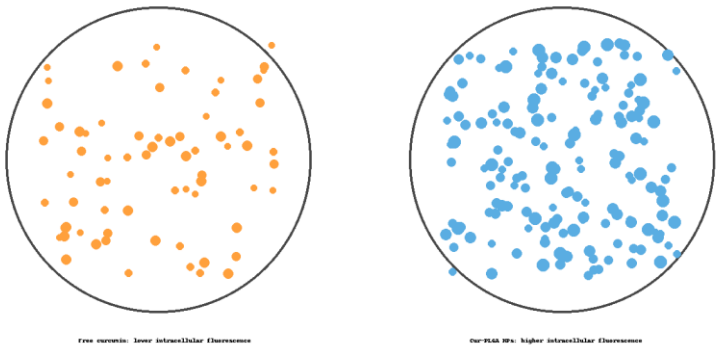

Figure 7. Schematic confocal comparison of MCF-7 cells treated with free curcumin versus Cur-PLGA nanoparticles, illustrating higher intracellular fluorescence for the nanoparticle formulation.

Cellular Uptake and Cytotoxicity

Cytotoxicity assessment by MTT at 48 hours showed greater reduction in cell viability with Cur-PLGA nanoparticles (28%) relative to free curcumin (55%), indicating an enhanced therapeutic effect at equivalent dosing ($p < 0.01$).

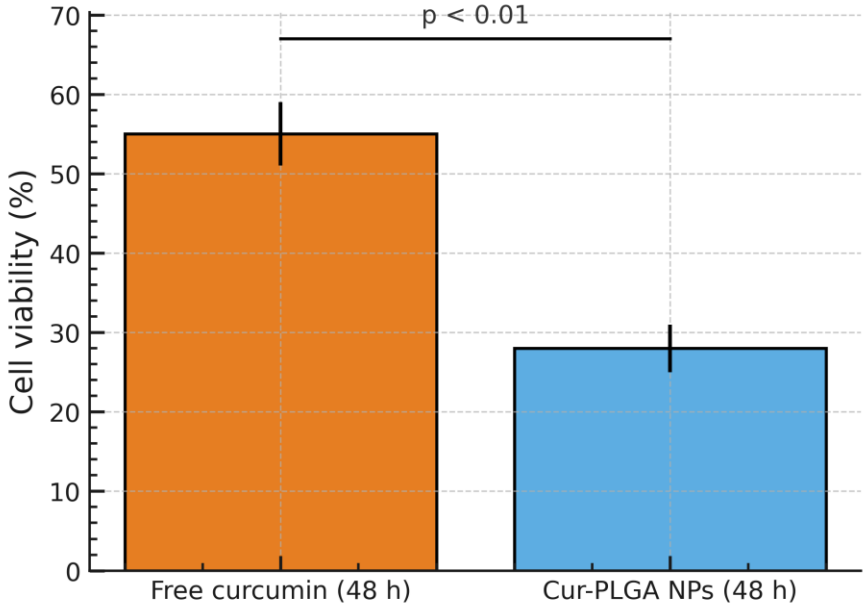

Figure 8. MTT assay comparing 48 h cell viability: free curcumin (~55%) versus Cur-PLGA nanoparticles (~28%), with significance marker ($p < 0.01$).

Apoptosis and Protein Expression

Flow cytometric analysis of apoptosis revealed a higher apoptotic fraction in cells treated with Cur-PLGA nanoparticles (~48%) compared to those treated with free curcumin (~26%), indicating more efficient induction of programmed cell death.

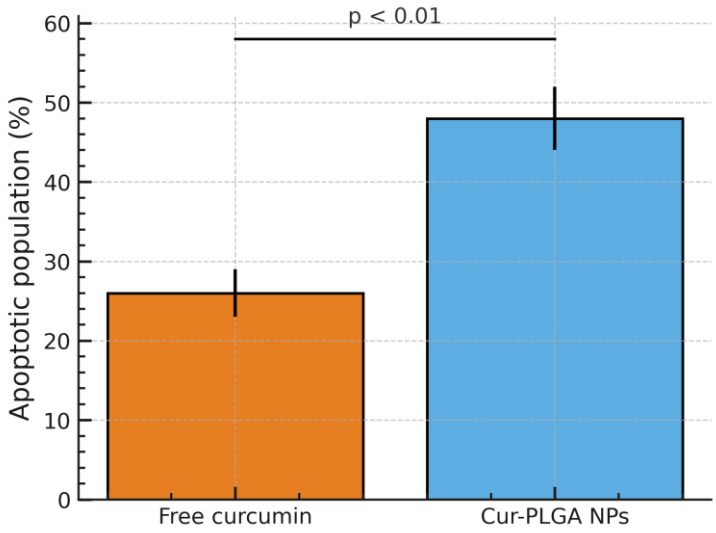

Figure 9. Apoptotic population percentages measured by flow cytometry: free curcumin (~26%) versus Cur-PLGA nanoparticles (~48%), with significance marker ($p < 0.01$).

Apoptosis and Protein Expression

Western blot schematics and quantitative analysis demonstrated upregulation of caspase-3 and Bax and downregulation of Bcl-2 in the Cur-PLGA group, supporting an apoptosis-mediated mechanism of cytotoxicity.

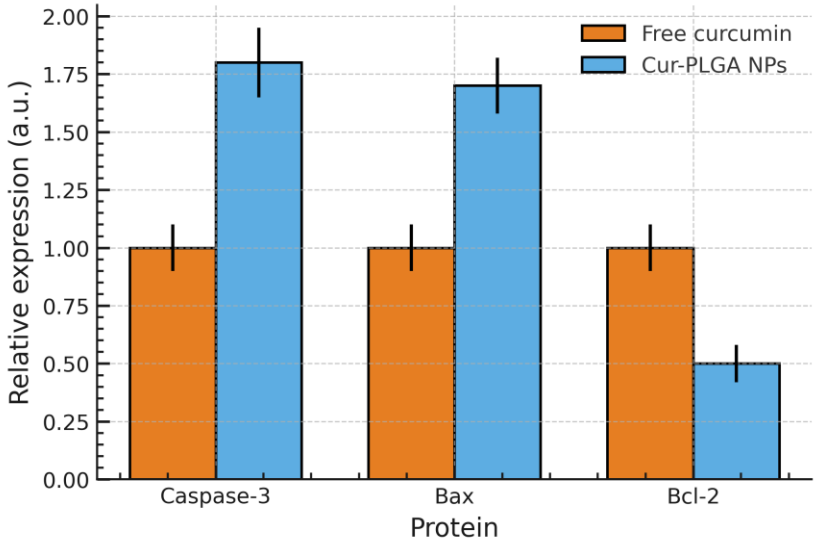

Figure 10. Quantification of relative protein expression shows caspase-3 and Bax upregulation and Bcl-2 downregulation in the Cur-PLGA group. Quantification of Western blot bands for caspase-3, Bax, and Bcl-2; data presented as relative expression (a.u.).

Discussion

The collected physicochemical results coherently indicate successful curcumin encapsulation within PLGA and explain the superior in-vitro performance in MCF-7 cells. The loss of sharp crystalline reflections of curcumin in the Cur-PLGA diffractogram with dominance of the PLGA-like amorphous halo is consistent with conversion of the drug to an amorphous state dispersed in the polymer matrix—an outcome frequently observed for hydrophobic actives prepared by solvent-displacement/nanoprecipitation (Danhier et al., 2012; Makadia & Siegel, 2011). Amorphization can increase apparent solubility and dissolution rate, improving interfacial partitioning once particles encounter biological media. While XRD suggests amorphous dispersion, differential scanning calorimetry (DSC) or modulated DSC would provide orthogonal confirmation by demonstrating disappearance of the curcumin melting endotherm and potential drug–polymer miscibility windows (Van den Mooter, 2012; Crucho & Barros, 2017).

Electron microscopy schematics and DLS concur on a spherical formulation centered near 120–130 nm with modest polydispersity, a size regime repeatedly associated with efficient cell association and internalization in epithelial cancer models (Sahay et al., 2010; Oh & Park, 2014). The measured zeta potential (−23 mV) indicates moderate electrostatic stabilization. Although thresholds of $|\zeta| \geq 30$ mV are often quoted for long-term stability, colloidal behavior in physiological media depends strongly on steric contributions from adsorbed stabilizers (e.g., residual PVA) and the formation of a protein corona that can screen charge and alter hydrodynamic size (Bhattacharjee, 2016; Monopoli et al., 2012). Thus, the observed dispersity and absence of visible aggregation across the reported assays are compatible with adequate short-to-intermediate stability, but characterization in serum-containing media would enhance translational relevance (Docter et al., 2015).

FTIR spectra for Cur-PLGA retained the principal signatures of both curcumin and PLGA with small band shifts, supporting noncovalent interactions (e.g., hydrogen bonding between curcumin phenolic/enolic groups and PLGA carbonyls) rather than chemical modification—aligned with nanoprecipitation, which employs no reactive chemistries (Danhier et al., 2012; Crucho & Barros, 2017). Preserving chemical integrity is important

because curcumin is prone to hydrolytic/oxidative degradation and photolability in aqueous media; encapsulation within PLGA can shield the payload from destabilizing environments and modulate local micro-polarity (Naksuriya et al., 2014; Wang et al., 2017).

Encapsulation efficiency (82%) and drug loading (9.5%) are within upper ranges reported for hydrophobic drugs in PLGA via solvent displacement, reflecting favorable drug–polymer affinity and appropriate process conditions (organic/aqueous ratio, PVA content, addition rate) (Danhier et al., 2012; Makadia & Siegel, 2011). The biphasic in-vitro release profile—ca. 30% burst at 12 h followed by sustained release to ~85% at 72 h—matches the mechanistic picture of an initial interfacial/loosely bound fraction, then Fickian diffusion through hydrated matrices with a contribution from polymer relaxation and early erosion (Siepmann & Siepmann, 2012; Peppas & Narasimhan, 2014). Applying semi-empirical fits (e.g., Korsmeyer–Peppas) to extract the release exponent (n) would help quantify diffusion- versus relaxation-dominated transport during the sustained phase, particularly given the relatively fast water uptake and hydrolysis kinetics of 50:50 PLGA (Makadia & Siegel, 2011; Siepmann & Siepmann, 2012).

The biological readouts are congruent with these physicochemical advantages. Confocal comparisons indicate higher intracellular signal for Cur-PLGA than for free curcumin, in line with size-enabled endocytic uptake (Sahay et al., 2010; Oh & Park, 2014). Improved intracellular availability plausibly underlies the stronger antiproliferative effect at 48 h (viability ~28% with Cur-PLGA vs. ~55% with free curcumin, $p < 0.01$). Curcumin's poor aqueous solubility and rapid degradation limit effective intracellular exposure; nanoencapsulation increases delivered dose and sustains exposure, thereby enhancing pharmacodynamic engagement (Yallapu et al., 2012; Tomeh & Turner, 2016). Because tetrazolium assays reflect metabolic activity rather than absolute cell counts, inclusion of orthogonal readouts (e.g., resazurin, live/dead staining, or impedance-based assays) would further validate cytotoxicity findings (Stockert et al., 2018).

Apoptosis data support a mitochondrial (intrinsic) pathway: Cur-PLGA increased the Annexin-positive fraction (~48% vs. ~26% with free curcumin) and shifted the Bax/Bcl-2 ratio upward alongside caspase-3 upregulation, consistent with mitochondrial outer membrane permeabilization and executioner caspase activation (Galluzzi et al., 2018). Nanoparticle-mediated delivery can raise intracellular curcumin above threshold levels needed to trigger these events and may promote lysosomal escape and cytosolic availability (Sahay et al., 2010; Yallapu et al., 2012). Methodologically, Annexin V–FITC/PI flow cytometry is appropriate to distinguish early/late apoptosis, while Western blotting provides protein-level corroboration; adding caspase inhibition controls (e.g., z-VAD-fmk) and mitochondrial potential assays (e.g., JC-1) would further reinforce causality (Crowley et al., 2016; Mahmood & Yang, 2012).

A few caveats deserve emphasis. First, DLS/ζ were presumably measured in simple buffers; serum proteins can rapidly form a selective corona that reshapes the bio-identity of nanoparticles, influencing uptake pathways and intracellular trafficking (Monopoli et al., 2012; Docter et al., 2015). Reporting size/ζ in 10% FBS and profiling the hard corona would improve relevance. Second, curcumin's pH- and light-sensitivity necessitates rigorous control of illumination and buffer composition during uptake and viability assays; documenting light conditions and employing antioxidant/pH-buffered media limits artefacts (Naksuriya et al., 2014; Wang et al., 2017). Third, ensuring true sink conditions in release studies is critical to avoid re-partitioning bias; specifying medium volumes, replacement schedules, and recovery corrections in the presence of PVA/PLGA fragments would help (Siepmann & Siepmann, 2012).

From a translational perspective, ~120–130 nm Cur-PLGA with near-neutral-to-moderately negative ζ is compatible with both local and systemic delivery, but in-vivo success will depend on circulation half-life, biodistribution, and clearance. Surface engineering (e.g., PEGylation or ligand targeting) may further stabilize colloids and enhance receptor-mediated uptake in tumors while mitigating opsonization (Suk et al., 2016; Blanco et al., 2015). Extending release and mass-loss studies beyond 72 h would clarify long-horizon dosing potential given the relatively rapid

degradation of 50:50 PLGA (Makadia & Siegel, 2011).

Overall, the amorphous drug state, ~130 nm size with acceptable ζ, and biphasic release together provide a compelling mechanistic basis for the improved cellular uptake, enhanced cytotoxicity, and apoptosis activation observed with Cur-PLGA versus free curcumin. These data align with established structure–function relationships for PLGA nanocarriers and warrant further optimization and in-vivo evaluation for breast cancer therapy (Danhier et al., 2012; Yallapu et al., 2012; Blanco et al., 2015).

Conclusion

Curcumin-loaded PLGA nanoparticles (Cur-PLGA) were successfully engineered by solvent displacement and comprehensively characterized, confirming an amorphous drug state within a spherical ~120–130 nm carrier that demonstrated colloidal stability in aqueous media. The formulation achieved high encapsulation efficiency (~82%) with practical drug loading (~9.5%), and exhibited a biphasic in-vitro release profile—an initial interfacial burst (~30% at 12 h) followed by sustained diffusion-dominated release reaching ~85% by 72 h. This release behavior, together with noncovalent curcumin–polymer interactions evidenced by FTIR band shifts, establishes a robust physicochemical basis for improved bioavailability versus crystalline free curcumin.

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