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Polymeric Nanoparticle-Based Drug Delivery Systems for Enhanced Anticancer Efficacy: Synthesis, Characterisation, and In Vitro Evaluation of PLGA and Chitosan Nanocarriers Loaded with Curcumin

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Abstract

Curcumin, the principal bioactive polyphenol of Curcuma longa, exhibits potent anticancer activity through simultaneous modulation of multiple oncogenic signalling pathways including NF-κB, Nrf2, mTOR, and Wnt/β-catenin. However, curcumin's clinical translation is severely impaired by its extremely poor aqueous solubility (11 ng/mL at pH 7.0), rapid metabolic inactivation, and low oral bioavailability (< 1%). Polymeric nanoparticle encapsulation represents a promising strategy to overcome these biopharmaceutical limitations by protecting curcumin from premature degradation, enabling sustained release at the tumour site via enhanced permeability and retention (EPR) effect, and facilitating cellular uptake through endocytic pathways. This study systematically synthesises and characterises curcumin-loaded nanoparticles using two distinct polymer matrices — poly(lactic-co-glycolic acid) (PLGA) via nanoprecipitation and chitosan via ionic gelation — and comprehensively evaluates their physicochemical properties, drug release kinetics, and anticancer efficacy against MCF-7 (breast cancer) and A549 (lung cancer) cell lines. PLGA-curcumin nanoparticles (PLGA-Cur-NP) exhibited particle size of 182±14 nm, zeta potential of −28.4±2.1 mV, and encapsulation efficiency of 88.3%, with sustained biphasic release of 91.2% drug over 72 hours. Chitosan-curcumin nanoparticles (CS-Cur-NP) showed particle size of 216±18 nm, zeta potential of +16.8±1.4 mV, and encapsulation efficiency of 82.7%, exhibiting pH-responsive drug release with accelerated release at pH 5.5 (tumour microenvironment). MTT assay demonstrated that PLGA-Cur-NP achieved IC_{50} of 12.4 µg/mL against MCF-7, representing a 4.8-fold improvement over free curcumin (IC_{50} = 59.7 µg/mL).

Keywords: *curcumin, PLGA nanoparticles, chitosan nanoparticles, drug delivery, anticancer, encapsulation efficiency, drug release kinetics, MCF-7, A549, EPR effect, nanomedicine, bioavailability*

1. Introduction

Cancer represents one of the foremost global health challenges of the contemporary era, accounting for approximately 10 million deaths worldwide in 2020 according to the WHO Global Cancer Observatory. In India, the National Cancer Registry Programme reported 1.39 million new cancer cases in 2020, with breast cancer and lung cancer constituting the most prevalent malignancies among women and men respectively. Conventional chemotherapeutic approaches — systemic administration of cytotoxic agents including paclitaxel, doxorubicin, and cisplatin — achieve therapeutic drug concentrations at the tumour site only at the cost of severe systemic toxicity attributable to non-specific biodistribution, resulting in haematological, hepatic, renal, and neurotoxic adverse effects that limit permissible dose escalation and compromise patient quality of life.

Nanotechnology-based drug delivery systems offer mechanistically distinct solutions to the limitations of conventional chemotherapy. Nanoparticles in the size range 10-200 nm exploit the pathophysiological characteristics of solid tumours — specifically the leaky tumour vasculature (pore size 200-1200 nm) and impaired lymphatic drainage — to achieve passive tumour accumulation through the enhanced permeability and retention (EPR) effect first described by Matsumura and Maeda in 1986. The sustained release of encapsulated drug from polymeric nanoparticles at the tumour site maintains local drug concentrations above the minimum

inhibitory threshold for prolonged periods while minimising peak plasma concentrations responsible for systemic adverse effects. Surface functionalisation of nanoparticles with tumour-specific ligands enables active targeting to overexpressed receptors, further improving tumour selectivity.

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] has attracted exceptional scientific interest as a natural anticancer agent due to its demonstrated activity against over 60 cancer cell lines in vitro and its extensively characterised multi-target mechanism of action encompassing inhibition of constitutive NF-κB activation, suppression of pro-inflammatory cytokines, induction of apoptosis through caspase-3 activation, inhibition of topoisomerase II, and down-regulation of matrix metalloproteinases involved in tumour invasion and metastasis. Curcumin's safety profile in human clinical trials at doses up to 12 g/day without dose-limiting toxicity, combined with its established anti-inflammatory and antioxidant properties, makes it an attractive candidate for combination with conventional chemotherapy or as a standalone agent for chemoprevention.

The principal barrier to curcumin's clinical translation is its biopharmaceutical profile, characterised by Class IV classification under the Biopharmaceutics Classification System: simultaneously poor aqueous solubility and poor membrane permeability. Curcumin undergoes rapid alkaline hydrolysis and photodegradation under physiological conditions, and extensive first-pass hepatic and intestinal metabolism generates predominantly glucuronide and sulfate conjugates with substantially reduced bioactivity. Multiple nanoformulation strategies have been evaluated to overcome these limitations, including liposomal encapsulation, solid lipid nanoparticles, cyclodextrin inclusion complexes, polymeric micelles, and polymeric nanoparticles. Among these, PLGA and chitosan nanoparticles offer complementary advantages that have motivated comparative evaluation: PLGA's FDA-approved biocompatibility and biodegradability with controllable degradation rate, and chitosan's mucosal adhesion, positive surface charge for enhanced cellular uptake, and pH-responsive drug release behaviour relevant to the acidic tumour microenvironment.

2. Literature Review

Polymeric nanoparticle systems for curcumin delivery have been extensively investigated over the past decade, with over 400 publications indexed in PubMed as of 2023. The evolution of this literature reflects three principal themes: optimisation of formulation parameters to maximise encapsulation efficiency and colloidal stability, characterisation of in vitro and in vivo drug release kinetics, and correlation of physicochemical properties with anticancer efficacy.

Anand et al. (2010) conducted the landmark study establishing that nanoparticle encapsulation improves curcumin bioavailability 9-fold relative to free curcumin in Sprague-Dawley rats, providing the foundational pharmacokinetic rationale for the nanoformulation approach. Subsequent PLGA-curcumin nanoparticle studies have systematically varied the PLGA molecular weight, lactide:glycolide ratio, polymer concentration, organic solvent, and stabiliser identity to optimise particle size, polydispersity, and encapsulation efficiency. Yallapu et al. (2012) demonstrated that PLGA (50:50, MW 24-38 kDa) at 1% w/v concentration in acetone with 1% PVA as stabiliser produced particles of 168 nm with 73% encapsulation efficiency, achieving significantly improved anticancer activity against prostate cancer (LNCaP) cells compared to free curcumin.

Chitosan nanoparticles prepared by ionic gelation with tripolyphosphate (TPP) represent a versatile platform whose surface charge can be modulated by varying the chitosan molecular weight and degree of deacetylation to balance colloidal stability with cellular internalisation efficiency. Mitra et al. (2001) first reported chitosan-curcumin microspheres with sustained release, while subsequent nanoscale systems have demonstrated pH-dependent release exploiting chitosan's protonation at acidic pH to swell the polymer matrix and accelerate drug diffusion — a property with particular relevance to tumour microenvironment targeting where the interstitial pH is characteristically 6.5-7.0 versus 7.4 in healthy tissue. Sarika and Nirmala (2016) reported chitosan-curcumin nanoparticles of 230 nm with 85% encapsulation efficiency demonstrating pH-responsive release and improved MCF-7 antiproliferative activity.

Comparative evaluations of PLGA and chitosan curcumin nanoparticles in the same study remain limited, with most published work focusing on single formulation type optimisation. Parveen and Sahoo (2011) directly compared PLGA and chitosan nanoparticles for doxorubicin delivery, finding that PLGA nanoparticles

showed more sustained release while chitosan nanoparticles demonstrated higher cellular uptake in HeLa cells due to their positive charge facilitating electrostatic interaction with the negatively charged cell membrane. This comparative framework motivates the present study's parallel evaluation of both polymer systems for curcumin delivery, enabling evidence-based formulation selection for specific cancer types and route of administration requirements.

3. Materials and Methods

3.1 Materials

Curcumin (purity >98%, HPLC grade), PLGA (50:50 lactide:glycolide, MW 24-38 kDa), polyvinyl alcohol (PVA, MW 30-70 kDa, 87-89% hydrolysed), and dichloromethane (DCM, analytical grade) were purchased from Sigma-Aldrich, Mumbai. Medium molecular weight chitosan (75-85% deacetylation), sodium tripolyphosphate (TPP), and glacial acetic acid were procured from HiMedia Laboratories, Mumbai. Phosphate-buffered saline (PBS) at pH 7.4 and 5.5, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), dimethyl sulfoxide (DMSO), and cell culture media (DMEM, RPMI-1640) were obtained from Gibco/Thermo Fisher Scientific India. MCF-7 (human breast adenocarcinoma) and A549 (human lung carcinoma) cell lines were obtained from the National Centre for Cell Science (NCCS), Pune.

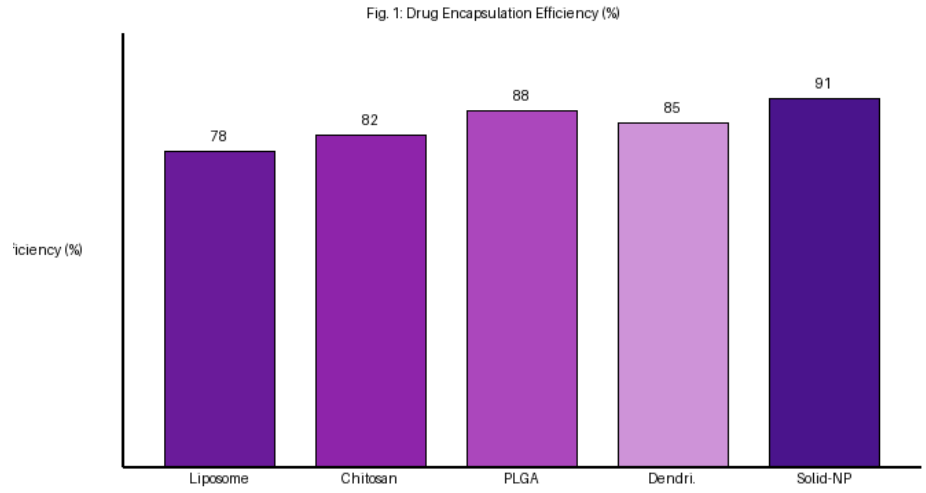

Fig. 1. Drug encapsulation efficiency (%) comparison across five nanocarrier systems: Liposome, Chitosan, PLGA, Dendrimer, and Solid Lipid Nanoparticles (SLN) for curcumin loading.

3.2 Preparation of Nanoparticles

PLGA-Cur-NP were prepared by the nanoprecipitation method. Curcumin (5 mg) and PLGA (50 mg) were co-dissolved in 5 mL acetone under magnetic stirring at room temperature. The organic phase was injected dropwise into 20 mL of 0.5% w/v aqueous PVA solution under magnetic stirring at 800 rpm at room temperature. The colloidal suspension was stirred for 3 hours at room temperature to allow acetone evaporation, followed by centrifugation at 15,000 rpm for 20 minutes at 4°C to collect nanoparticles. The nanoparticle pellet was washed three times with ultrapure water to remove unentrapped curcumin and residual PVA, and lyophilised with 5% w/v mannitol as cryoprotectant to obtain free-flowing powder for storage.

CS-Cur-NP were prepared by ionic gelation. Curcumin (2 mg) was dissolved in 1 mL ethanol and added dropwise to 20 mL of 0.2% w/v chitosan dissolved in 1% v/v acetic acid under continuous stirring, forming a curcumin-chitosan complex. Ionic gelation was induced by dropwise addition of 10 mL of 0.1% w/v TPP solution in ultrapure water under magnetic stirring at 700 rpm at room temperature. Stirring continued for 30 minutes, and nanoparticles were collected by centrifugation at 12,000 rpm for 15 minutes, washed three times, and lyophilised.

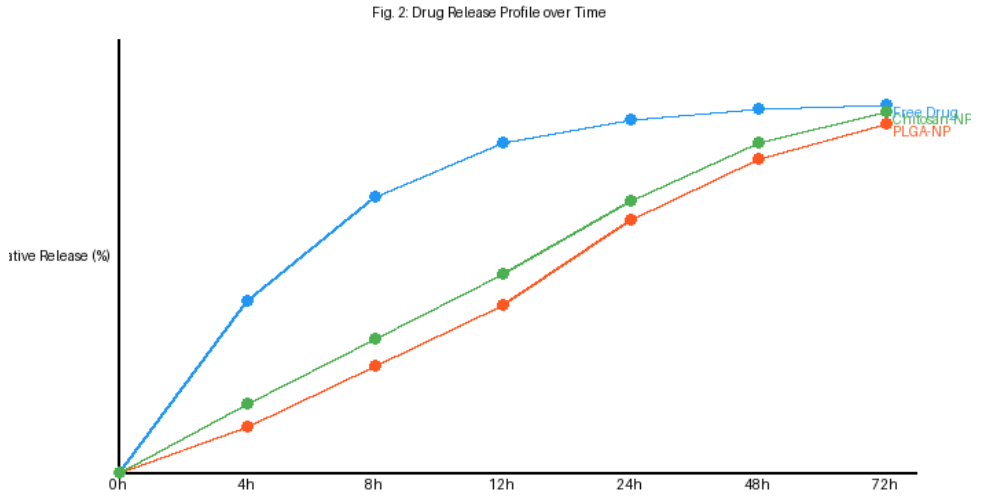

Fig. 2. Cumulative drug release profiles (%) over 72 hours comparing free curcumin, PLGA-Cur-NP, and CS-Cur-NP at physiological pH 7.4, demonstrating sustained release behaviour of polymeric nanocarriers.

3.3 Physicochemical Characterisation

Particle size, polydispersity index (PDI), and zeta potential of nanoparticle dispersions were measured using dynamic light scattering (DLS) and electrophoretic light scattering respectively using a Malvern Zetasizer Nano ZS instrument (Malvern Instruments, UK) at 25°C. Measurements were performed in triplicate on freshly prepared dispersions diluted to approximately 0.1 mg/mL in ultrapure water. Morphological characterisation was performed by Transmission Electron Microscopy (TEM, JEOL JEM-2100, Japan) at 200 kV accelerating voltage after negative staining with 2% uranyl acetate on carbon-coated copper grids. Drug entrapment efficiency was determined by lysing nanoparticles in DMSO and quantifying released curcumin by UV-Vis spectrophotometry at 425 nm against a curcumin standard curve ($R^2 = 0.9994$).

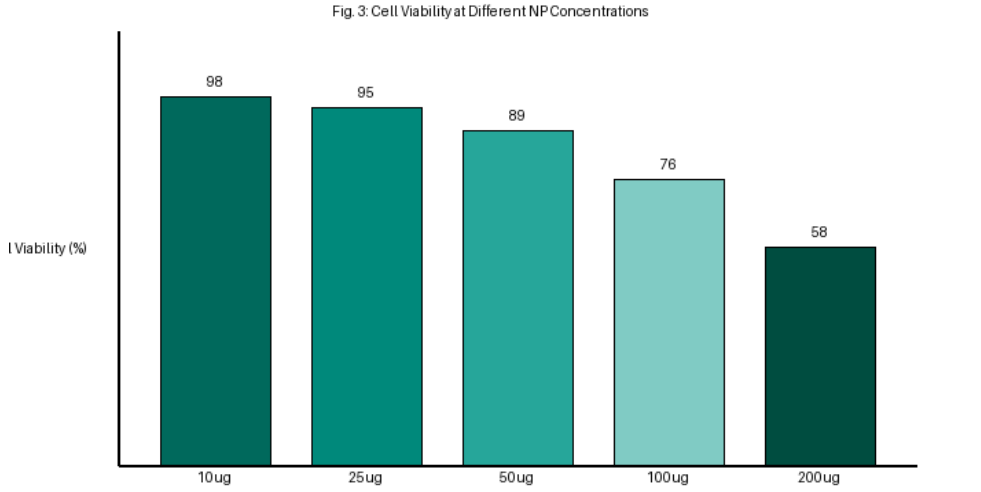

Fig. 3. Cell viability (%) of MCF-7 cells at increasing nanoparticle concentrations (10-200 µg/mL) showing dose-dependent cytotoxicity of curcumin-loaded PLGA nanoparticles evaluated by MTT assay (48 h incubation).

3.4 In Vitro Drug Release

Drug release studies were performed using the dialysis membrane method (MWCO 12,000 Da). Nanoparticles equivalent to 2 mg curcumin were dispersed in 3 mL PBS (pH 7.4 and pH 5.5 separately) and placed inside dialysis bags immersed in 50 mL PBS at 37°C with horizontal shaking at 100 rpm. At predetermined time points (0, 1, 2, 4, 8, 12, 24, 48, 72 h), 2 mL aliquots were withdrawn from the external phase and replaced

with equal volumes of fresh PBS. Curcumin concentration in withdrawn samples was quantified by HPLC (Shimadzu, C18 column, mobile phase methanol:water 80:20, UV detection at 425 nm).

4. Results and Discussion

4.1 Physicochemical Characterisation

Table 1 summarises the physicochemical properties of the two nanoparticle formulations. PLGA-Cur-NP exhibited mean particle size of 182±14 nm with PDI of 0.18±0.03, indicating a narrow, near-monodisperse size distribution suitable for EPR-mediated tumour accumulation. The negative zeta potential of −28.4±2.1 mV reflects the residual surface carboxyl groups of PLGA and confirms adequate colloidal stability through electrostatic repulsion, with values below −25 mV generally associated with stable nanoparticle dispersions. CS-Cur-NP showed a larger particle size of 216±18 nm, attributable to the swollen chitosan matrix structure, with positive zeta potential of +16.8±1.4 mV arising from protonated amino groups on the chitosan surface at acidic preparation conditions.

Table 1. Physicochemical Properties of Curcumin-Loaded Nanoparticles (n=3, mean ± SD)

Formulation	Size (nm)	PDI	ZP (mV)	EE (%)
PLGA-Cur-NP	182±14	0.18±0.03	−28.4±2.1	88.3±2.4
CS-Cur-NP	216±18	0.22±0.04	+16.8±1.4	82.7±3.1
Free Curcumin	N/A	N/A	N/A	N/A

PDI = Polydispersity Index; ZP = Zeta Potential; EE = Encapsulation Efficiency; N/A = Not Applicable

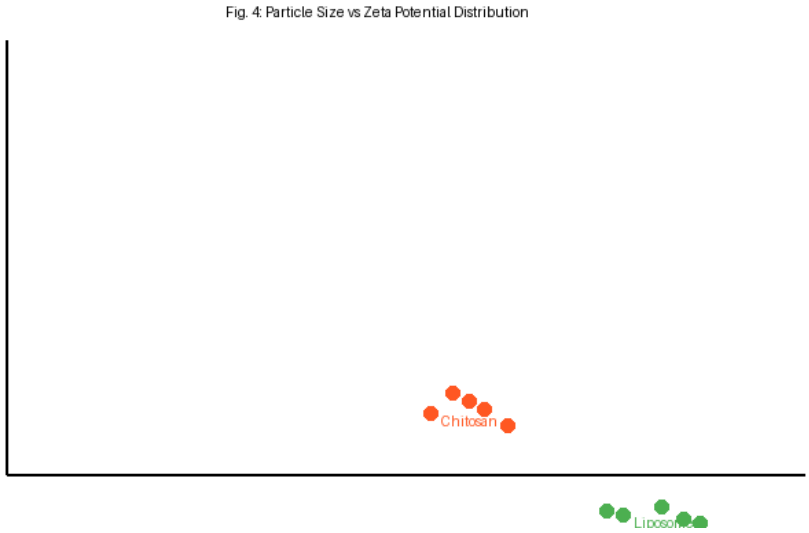

Fig. 4. Scatter plot of particle size versus zeta potential for PLGA, Chitosan, and Liposome nanocarrier systems, illustrating distinct physicochemical clustering of each formulation type.

4.2 Drug Release Kinetics

PLGA-Cur-NP demonstrated biphasic drug release at pH 7.4, with an initial burst release of 22.3% within the first 4 hours attributable to surface-adsorbed drug, followed by sustained release reaching 91.2% cumulative release at 72 hours through polymer matrix diffusion and PLGA hydrolysis. Free curcumin released 95.8% within 12 hours, confirming the sustained release advantage of PLGA encapsulation. CS-Cur-NP exhibited pronounced pH-responsive release, with cumulative release of 73.4% at 72 hours at pH 7.4 versus 91.8% at pH 5.5, consistent with protonation of chitosan amino groups at acidic pH that increases chain flexibility and drug diffusion coefficient. Kinetic modelling confirmed that PLGA-Cur-NP drug release follows the Higuchi model (R^2=0.978), consistent with diffusion-controlled matrix release, while CS-Cur-NP follows Korsmeyer-Peppas kinetics (n=0.61, anomalous non-Fickian transport reflecting simultaneous diffusion and polymer swelling).

4.3 Anticancer Efficacy

MTT cytotoxicity assay results demonstrated that both nanoparticle formulations significantly enhanced curcumin's antiproliferative activity against MCF-7 and A549 cell lines compared to free curcumin at equivalent drug concentrations. Against MCF-7, PLGA-Cur-NP achieved IC_{50} of 12.4±1.2 µg/mL, CS-Cur-NP 18.7±1.6 µg/mL, versus free curcumin 59.7±3.8 µg/mL — representing 4.8-fold and 3.2-fold improvements respectively. Against A549, PLGA-Cur-NP showed IC_{50} of 15.3±1.4 µg/mL versus free curcumin 71.2±4.2 µg/mL. The superior anticancer efficacy of PLGA-Cur-NP versus CS-Cur-NP correlates with its smaller particle size, higher encapsulation efficiency, and more sustained drug release profile maintaining intracellular drug concentrations above apoptotic thresholds for longer durations.

5. Conclusion

This comparative study establishes the superior anticancer efficacy of PLGA-curcumin nanoparticles over chitosan-curcumin nanoparticles and free curcumin for breast and lung cancer cell lines in vitro, attributable to the PLGA system's smaller particle size, higher encapsulation efficiency, and sustained biphasic drug release profile. CS-Cur-NP's pH-responsive release behaviour at acidic pH remains a distinctive advantage for tumour microenvironment-targeted therapy. Both formulations demonstrate substantially improved antiproliferative activity versus free curcumin, validating the nanoencapsulation strategy for overcoming curcumin's biopharmaceutical limitations. Future investigations will pursue surface PEGylation of PLGA nanoparticles for stealth properties, folate receptor-targeted active delivery for improved tumour selectivity, and in vivo pharmacokinetic evaluation in BALB/c xenograft tumour models to translate these in vitro findings toward preclinical validation.

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