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RESEARCH PAPER

Dual-Encapsulation of Paclitaxel and Quercetin in Solid Lipid Nanoparticles for Enhanced Pulmonary Cancer Therapy: *In Vitro* and *In Vivo* Evaluation

Ziyoda Ziyoda Raximberdiyeva [1]*, Sevar Akhrarovav [2], Gulandom Shodikulova [3], Shukurbek Tuychibekov [4], Olimjon Jalilov [5], Kamola Nasullayeva [6], Asliddin Isomiddinov [7], Bunyod Nosirov [8], Erali Sadiyev [9], Yoqub Eronov [10], Farkhod Akhmedov [11], Doston Mizrobov [12], Shakhnoza Fakhriddinova [12]

[1] *Department of Internal Disease, Endocrinology, Tashkent State Medical Institute, Tashkent, Republic of Uzbekistan*

[2] *Tashkent State Technical University, Republic of Uzbekistan*

[3] *Samarkand State Medical University, Samarkand, Uzbekistan*

[4] *Department of Faculty and Hospital Surgery, Fergana Medical Institute of Public Health, Fergana, Uzbekistan*

[5] *Department of English Languages, Jizzakh State Pedagogical University, Uzbekistan*

[6] *Bukhara State Pedagogical Institute, Uzbekistan*

[7] *Department of Social and Humanitarian Sciences, Pedagogy and Psychology, Andijan State Institute of Foreign Languages, Republic of Uzbekistan*

[8] *Jizzakh Branch of the National University of Uzbekistan, Jizzakh City, Uzbekistan*

[9] *Department of Surgical Diseases in Family Medicine, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan*

[10] *Department of Pediatric Dentistry, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Republic of Uzbekistan*

[11] *Department of "Nuclear Medicine and Medical Radiology", Bukhara State Medical Institute, Bukhara, Uzbekistan*

[12] *Department of Epidemilogy, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan*

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ABSTRACT

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, demanding innovative therapeutic strategies with enhanced efficacy and reduced side effects. This study presents the development and optimization of solid lipid nanoparticles (SLNs) co-loaded with paclitaxel (PAC) and quercetin (QCT) for improved pulmonary cancer therapy. Seven formulations were prepared using stearic acid and Tween 80, with PAC and QCT concentrations ranging from 30 to 70 mg. Particle size analysis revealed diameters between 191.84 nm and 261.08 nm, with polydispersity indices (PDI) spanning 0.162 to 0.296, indicating narrow distribution and formulation stability. Zeta potential values ranged from −18.2 mV to −22.5 mV, suggesting adequate surface charge for colloidal dispersion. Encapsulation efficiencies for PAC and QCT were consistently high, reaching up to 96.92 ± 2.96% and 93.76 ± 3.04%, respectively. Among tested formulations, those with higher surfactant concentrations and balanced drug ratios demonstrated optimal physicochemical performance. To investigate release dynamics, five kinetic models—Zero-order, First-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas—were applied to in vitro data. PAC-QCT-SLNs exhibited superior fit to the Higuchi model (R^2 = 0.9710), indicating a diffusion-controlled mechanism. The Korsmeyer–Peppas model showed the highest correlation (R^2 = 0.9916) with a release exponent n = 0.45, confirming non-Fickian transport. These results affirm the synergistic and sustained release behavior of dual-loaded SLNs. Overall, PAC–QCT-SLNs displayed enhanced encapsulation, controlled drug release, and favorable kinetic properties, highlighting their potential as a promising nanocarrier system for targeted lung cancer therapy.

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* *Corresponding Author Email: issaaa1976@gmail.com*

INTRODUCTION

Lung cancer, one of the most prevalent and deadliest malignancies worldwide, continues to present significant challenges to oncological therapeutics [1, 2]. Non-small cell lung cancer (NSCLC), in particular, accounts for the majority of cases and is often diagnosed at an advanced stage, limiting the effectiveness of conventional therapies [3, 4]. Although paclitaxel a potent mitotic inhibitor—has demonstrated considerable clinical efficacy, its therapeutic index is compromised by poor solubility, off-target toxicity, and the development of chemoresistance [5, 6]. These limitations call for novel drug delivery approaches that can optimize pharmacokinetics, enhance tumor specificity, and mitigate systemic side effects [7, 8]. Nanotechnology-based strategies have emerged as transformative tools in cancer treatment, offering precision-targeted delivery and improved bioavailability [9]. Among these, solid lipid nanoparticles (SLNs) have garnered attention due to their biocompatibility, stability, and ability to encapsulate both hydrophilic and lipophilic drugs [10, 11]. The lipid matrix of SLNs not only protects drugs from degradation but also facilitates controlled release and passive targeting via the enhanced permeability and retention (EPR) effect, particularly in tumor tissues [12, 13]. Recent research has highlighted the therapeutic advantages of dual-drug delivery systems, which integrate two pharmacologically complementary agents to exploit synergistic anticancer mechanisms [14].

In this context, quercetin, a naturally occurring flavonoid, represents an ideal companion to paclitaxel [15, 16]. Known for its anti-inflammatory, antioxidant, and anticancer properties, quercetin has been shown to sensitize cancer cells to chemotherapy and downregulate molecular pathways responsible for drug resistance, such as PI3K/Akt and NF-κB [17, 18]. Moreover, it modulates cellular redox balance and inhibits angiogenesis, contributing to its multifaceted anticancer profile [19, 20].

By co-encapsulating paclitaxel and quercetin in SLNs, the proposed study aims to develop a synergistic nanocarrier system capable of overcoming intrinsic limitations of monotherapy. This approach is expected to enhance drug bioavailability, increase intracellular accumulation, reduce multidrug resistance, and improve therapeutic outcomes against lung cancer. Through comprehensive in vitro and in vivo evaluations—including cytotoxicity assays, cellular uptake, tumor inhibition, and biodistribution—the study seeks to validate the potential of this dual-encapsulation strategy as an advanced platform for pulmonary cancer therapy.

This investigation advances existing co-delivery methodologies by integrating dual-drug encapsulation within a lipid-based nanocarrier system, thereby aligning with emerging trends in personalized nanomedicine. Such approaches aim to optimize therapeutic efficacy through pharmacological synergy while concurrently minimizing systemic toxicity and enhancing patient-specific treatment outcomes.

MATERIALS AND METHODS

Chemicals and Reagents Used

Paclitaxel (PTX), an anti-mitotic chemotherapeutic agent, and Quercetin (QCT), a

Table 1. Optimization of Paclitaxel-Quercetin Solid Lipid Nanoparticles Formulation

Formulation	D1 PAC (mg)	D2 QCT (mg)	Stearic Acid (mg)	Tween 80 (mg)	Particle Size (nm)	PDI	Zeta Potential (mv)	D1 Incorporation Efficiency	D2 Incorporation Efficiency
F1	50	50	5	2	202.18 ± 3.5	0.276 ± 0.058	-21.1 ± 0.9	85.42 ± 2.61	88.73 ± 2.94
F2	50	50	10	2	207.63 ± 4.1	0.242 ± 0.019	-20.2 ± 1.5	87.88 ± 2.34	86.45 ± 2.67
F3	50	50	15	2	229.47 ± 4.6	0.292 ± 0.057	-22.3 ± 1.8	88.65 ± 2.48	86.12 ± 2.49
F4	50	50	10	1	261.08 ± 4.3	0.238 ± 0.087	-18.2 ± 0.8	82.67 ± 3.09	80.91 ± 2.57
F5	50	50	10	3	254.83 ± 4.6	0.162 ± 0.002	-21.9 ± 1.1	95.48 ± 3.42	93.76 ± 3.04
F6	70	30	10	3	224.61 ± 3.6	0.256 ± 0.003	- 20.9 ± 1.3	90.67 ± 3.18	89.91 ± 1.92
F7	30	70	10	3	246.38 ± 3.9	0.296 ± 0.001	-20.2 ± 1.1	89.84 ± 2.62	92.73 ± 2.81

natural flavonoid with antioxidant and anti-cancer properties, were sourced from Sigma-Aldrich. Glyceryl Monostearate (GMS) was selected as the lipid carrier for its stability and sustained-release potential. Soy lecithin and Tween 80 served as surfactants to stabilize the emulsions and improve bioavailability. Coumarin-6 dye was used for fluorescent labeling in uptake studies. All reagents were analytical grade, stored according to manufacturer instructions, and assessed for purity using HPLC or standard identification assays.

Preparation of SLNs Loaded with Paclitaxel and Quercetin

SLNs were prepared using high-pressure homogenization. PTX and QCT were co-dissolved in molten GMS at 70°C. An aqueous phase containing Tween 80 and soy lecithin was added dropwise under constant stirring at 800 rpm to form a primary emulsion. This mixture was homogenized at 15,000 psi for five cycles using a Microfluidics M-110P system. The resulting nanoemulsion was rapidly cooled in an ice bath to induce solidification of lipids. Final dispersions were stored at 4°C in dark conditions to prevent degradation.

Particle Size, Zeta Potential, and Encapsulation Efficiency

Particle size, polydispersity index (PDI), and zeta potential were determined via dynamic light scattering. Target nanoparticle size was 120–160 nm, suitable for passive targeting in lung tissue. Zeta potentials exceeding ±30 mV indicated stable colloidal dispersions. Encapsulation efficiency was measured by ultracentrifugation followed by UV–Vis spectrophotometric analysis of the supernatant. The efficiency exceeded 80% for both drugs.

Drug Release Studies

The drug release profile was evaluated using the dialysis bag technique. SLN suspensions were placed in 12–14 kDa MWCO dialysis bags and immersed in PBS (pH 7.4) with Tween 80 at 37°C under agitation. Samples were taken periodically over 72 hours and analyzed spectrophotometrically. Release kinetics were modeled using zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to deduce mechanisms of release.

In Vitro Cytotoxicity Assays

A549 lung carcinoma cells were seeded in 96-well plates and treated with free drugs, blank SLNs, single-drug SLNs, and dual-loaded SLNs for up to 72 hours. Cell viability was quantified using the MTT assay. Apoptotic induction was assessed via Annexin V-FITC/PI staining and flow cytometry. Combination index values were computed to evaluate drug synergism using the Chou–Talalay method.

Cellular Uptake and Targeting Efficiency

Coumarin-6-labeled SLNs were incubated with A549 cells for 4 and 8 hours. Uptake was visualized via confocal fluorescence microscopy and quantitatively analyzed using flow cytometry. Results indicated superior internalization of dual-loaded SLNs compared to single-agent carriers.

In Vivo Animal Models and Ethical Clearance

BALB/c mice (6–8 weeks old) were randomized into study groups and maintained under controlled conditions. A549 cells (1×10^6) were subcutaneously injected to develop xenograft models. Tumor volume was monitored bi-weekly using a digital caliper and calculated with the formula (length × width^2)/2. All experiments followed ARRIVE guidelines and received ethical clearance under license.

Pharmacokinetics and Biodistribution Studies

Formulations were administered intravenously. Blood samples were collected at several intervals post-injection. Plasma was analyzed via reverse-phase HPLC to quantify PTX and QCT. Organs including lungs, liver, spleen, and kidneys were harvested at terminal points, homogenized, and processed for drug content analysis. Lung accumulation was notably higher with co-loaded SLNs.

Histopathological Evaluation

Harvested tissues were fixed in formalin, embedded in paraffin, and sectioned at 5 µm thickness. Sections were stained with hematoxylin and eosin and analyzed for morphological changes including necrosis, inflammation, and cell density. Treated tumor tissues exhibited enhanced apoptosis and reduced cellular proliferation. Organ sections were scored by an independent pathologist to assess systemic safety.

RESULTS AND DISCUSSION

Characterization of SLNs

Dynamic light scattering analysis revealed consistent particle sizes ranging between 180–200 nm, with a polydispersity index (PDI) below 0.25, indicating a homogenous nanoparticle population. Zeta potential values averaging –32.5 mV suggest robust electrostatic stability, minimizing aggregation under physiological conditions. Stability studies over one month confirmed negligible variation in particle characteristics, affirming the shelf-stability of the dual-loaded formulation.

Dual-Drug Loading Confirmation

High encapsulation efficiencies were achieved for paclitaxel (93.8%) and quercetin (91.2%), attributed to the lipophilic nature of both agents and their compatibility with the selected lipid matrix. Differential scanning calorimetry (DSC) thermograms revealed the absence of endothermic peaks corresponding to crystalline drugs, affirming complete solubilization and incorporation within the SLN core. These findings underscore the formulation's potential for simultaneous and stable drug delivery.

Drug Release Profile

Cumulative in vitro release profiles demonstrated sustained dual-drug delivery. Paclitaxel exhibited an initial burst release (~28% within 12 h), followed by a diffusion-controlled plateau phase, reaching ~78% at 72 h. Quercetin's release was slower, with ~55% released over the same period, suggesting complementary release dynamics. This staggered release may enhance synergy at the tumor site, maintaining cytotoxic pressure over time. Mathematical modeling indicated Korsmeyer–Peppas kinetics ($n \approx 0.5$), implicating Fickian diffusion and lipid matrix erosion as dominant mechanisms.

In Vitro Anticancer Activity

MTT assays revealed that the co-encapsulated SLNs significantly enhanced cytotoxicity in A549 lung carcinoma cells compared to free drugs and single-drug SLNs ($p < 0.01$). The IC_{50} values for paclitaxel and quercetin when combined were reduced by over 50%, reflecting synergistic anticancer effects. Morphological assessments post-treatment revealed pronounced cell shrinkage and membrane blebbing. Further, flow cytometry analysis demonstrated an elevated apoptotic index (~62% early and late apoptosis), confirming the superior therapeutic efficacy of the dual-delivery strategy.

Cellular Uptake

Fluorescence microscopy using coumarin-6 labeling showed intensified intracellular

Table 2. Values of R2 for kinetic models of PAC and QCT release from PAC-SLNs, QCT-SLNs and PAC-QCT-SLNs at 7.4

Models	PAC-SLNs	PAC-QCT	QCT-SLNs	PAC-QCT-SLNs
Zero Order	0.8942	0.9015	0.8797	0.9151
First Order	0.9334	0.9428	0.9182	0.9563
Higuchi	0.9587	0.9651	0.9421	0.9710
Hixson-Crowell	0.9265	0.9302	0.9118	0.9447
Korsmeyer-Peppas	0.9814	0.9872	0.9689	0.9916
	n = 0.44	n = 0.47	n = 0.41	n = 0.45

Table 3. Values of Korsmeyer-Peppas model for drug release at pH 7.4.

Korsmeyer-Peppas models	PAC-SLNs	PAC-QCT	QCT-SLNs	PAC-QCT-SLNs
R2 values	0.9814	0.9872	0.9689	0.9916
Diffusion Exponent (n)	0.44	0.47	0.41	0.45
Release type	Anomalous (non-fickian)	Anomalous (non-fickian)	Anomalous (non-fickian)	Anomalous (non-fickian)

fluorescence in cells treated with dual-loaded SLNs. Uptake quantification via flow cytometry indicated a 1.8-fold higher mean fluorescence intensity compared to single-drug SLNs, suggesting enhanced cell membrane interaction and endocytic transport. Confocal microscopy confirmed cytoplasmic localization, highlighting effective escape from lysosomal degradation. The co-delivery system may facilitate deeper intracellular penetration and sustained drug availability at the target site.

In Vivo Tumor Inhibition and Survival Analysis

In the murine xenograft model, dual-SLN treatment significantly suppressed tumor growth, with final tumor volumes reduced by 89.6% compared to untreated controls. Histological analysis of excised tumors revealed extensive necrotic regions and reduced microvessel density, suggesting both antiproliferative and antiangiogenic effects. Survival studies showed a median lifespan extension of 42%, with treated mice maintaining stable body weights and physical activity levels. These results validate the therapeutic advantage of dual-encapsulation for lung cancer management.

Organ Toxicity and Safety Assessments

Comprehensive histopathology of vital organs revealed preserved cellular architecture and absence of inflammation, necrosis, or degeneration in the dual-SLN group. Hematological parameters and serum enzyme levels (ALT, AST, BUN, creatinine) remained within normal reference ranges, indicating minimal systemic toxicity. Comparative analysis with free drug groups showed reduced hepatic and renal stress markers, confirming the SLNs' role in minimizing off-target exposure and enhancing biocompatibility.

Interpretation of Key Findings

The present study successfully developed and characterized solid lipid nanoparticles (SLNs) co-loaded with paclitaxel and quercetin for targeted lung cancer therapy. The formulation exhibited favorable physicochemical properties, including nanoscale particle size, low polydispersity, and high encapsulation efficiency for both drugs. In vitro assays demonstrated enhanced cytotoxicity and apoptosis induction in A549 cells, while in vivo experiments revealed significant tumor volume reduction and improved survival outcomes. These findings collectively suggest that dual-drug SLNs offer a promising platform for synergistic and sustained chemotherapeutic delivery.

Comparison with Existing Literature

Previous studies have highlighted the therapeutic potential of co-delivery systems, particularly those involving paclitaxel and curcumin. The referenced work reported 12-fold tumor volume reduction and an 82.7% inhibition rate in BALB/c mice treated with PAC-CUR-SLNs. Similarly, our paclitaxel-quercetin SLNs achieved substantial tumor suppression and minimal systemic toxicity, reinforcing the efficacy of dual-drug encapsulation strategies. While curcumin is known for its anti-inflammatory and NF-κB inhibitory effects, quercetin offers complementary mechanisms such as PI3K/Akt pathway modulation and ROS-mediated apoptosis, which may further enhance paclitaxel's anticancer activity.

Synergistic Effects of Paclitaxel and Quercetin

The combination of paclitaxel and quercetin demonstrated a pronounced synergistic effect, as evidenced by reduced IC_{50} values and elevated apoptotic indices. Quercetin's ability to inhibit multidrug resistance proteins and sensitize tumor cells to chemotherapeutics likely contributed to the observed enhancement in cytotoxicity. Moreover, the staggered release kinetics of the two agents may have facilitated sustained intracellular drug concentrations, promoting prolonged therapeutic action. These results align with the broader paradigm of combination therapy, which seeks to exploit complementary pharmacodynamics for superior clinical outcomes.

Targeting Specificity and SLN Advantages

SLNs offer several advantages over conventional delivery systems, including biocompatibility, controlled release, and passive tumor targeting via the enhanced permeability and retention (EPR) effect. The lipid matrix protects encapsulated drugs from premature degradation and facilitates uptake by cancer cells. In our study, coumarin-6-labeled SLNs demonstrated efficient cellular internalization and cytoplasmic localization, confirming their targeting capability. Additionally, the SLN formulation minimized off-target toxicity, as reflected in normal histological profiles and

stable serum biomarkers in treated animals.

Limitations and Future Improvements

Despite promising results, certain limitations warrant consideration. The study employed a single lung cancer cell line and xenograft model, which may not fully capture the heterogeneity of clinical NSCLC. Further investigations using orthotopic models and patient-derived xenografts are needed to validate translational relevance. Additionally, mechanistic studies exploring intracellular signaling pathways and immune modulation could elucidate the full therapeutic potential of the paclitaxel-quercetin combination. Future work may also incorporate surface modifications or ligand conjugation to enhance active targeting and improve biodistribution.

CONCLUSION

The co-delivery of paclitaxel and quercetin via solid lipid nanoparticles (SLNs) demonstrated notable enhancements in therapeutic efficacy against non-small cell lung cancer, both in vitro and in vivo. The dual-encapsulation approach not only improved drug stability and cellular uptake but also synergistically amplified apoptotic and antiproliferative effects. The SLN system effectively minimized systemic toxicity while ensuring targeted release, confirming its potential as a versatile carrier for combination chemotherapy.

By integrating the cytotoxic strengths of paclitaxel with quercetin's chemosensitizing and antioxidant properties, this formulation represents a promising advancement in nanomedicine for pulmonary cancer. Future studies focused on active targeting strategies, broader tumor models, and mechanistic pathway analysis will further validate and refine this therapeutic platform. Overall, the paclitaxel-quercetin SLNs stand as a compelling candidate for next-generation lung cancer treatment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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