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RESEARCH PAPER

Co-Loaded Solid Lipid Nanocarriers of Resveratrol and Paclitaxel for Improved Bioavailability and Antitumor Efficacy in Lung Cancer Models: *In Vitro* and *In Vivo* Evaluation

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ABSTRACT

Lung cancer persists as a critical global health challenge, exhibiting high incidence and mortality rates. Conventional chemotherapeutics such as paclitaxel (PAC) suffer from limited aqueous solubility, dose-limiting toxicity, and resistance mechanisms that significantly compromise clinical efficacy. In this study, we engineered and evaluated solid lipid nanoparticles (SLNs) co-loaded with PAC and resveratrol (RES)—a polyphenolic antioxidant with known anticancer activity—as a novel combinatorial nanotherapeutic platform for lung cancer. The SLNs were fabricated via high-pressure homogenization using glyceryl monostearate (GMS) as the lipid core, and stabilized by Tween 80 and soy lecithin. The nanoparticles exhibited mean sizes ranging from 190.5 to 254.7 nm with narrow polydispersity indices (PDI < 0.3), and zeta potentials between −18.9 and −21.6 mV, indicative of satisfactory colloidal stability. The encapsulation efficiencies for PAC and RES exceeded 90%, ensuring robust payload retention. In vitro release kinetics followed a biphasic sustained-release profile and were best described by the Korsmeyer–Peppas model (R^2 = 0.9904; n = 0.46), indicating an anomalous diffusion-controlled mechanism. Cytotoxicity assays against A549 human lung carcinoma cells demonstrated enhanced antiproliferative effects for dual-loaded SLNs compared to free drugs or single-drug-loaded formulations. The IC_{50} value for PAC–RES SLNs was significantly reduced to 2.1 µg/mL. Flow cytometric analysis revealed a substantial elevation in total apoptotic cells (\~60%) for the dual-loaded formulation. Furthermore, in vivo antitumor efficacy was validated using a BALB/c nude mouse xenograft model, where PAC–RES SLNs elicited superior tumor suppression and improved survival outcomes without inducing systemic toxicity. These findings support the potential utility of PAC–RES SLNs as a rationally designed nanomedicine for enhanced lung cancer therapy.

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INTRODUCTION

Lung cancer remains the foremost cause of cancer-related deaths globally, accounting for over 1.8 million deaths annually. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases and is often diagnosed at advanced stages when therapeutic options are limited [1-3]. Standard chemotherapy regimens using agents like paclitaxel (PAC) have demonstrated clinical efficacy; however, treatment success is often constrained by drug resistance, poor pharmacokinetics, and debilitating side effects that compromise patient quality of life [4-7]. Paclitaxel is a potent antineoplastic agent that exerts its cytotoxic effects by stabilizing microtubules, thereby arresting cell division during mitosis. Despite its effectiveness, PAC suffers from low aqueous solubility, necessitating the use of solubilizing agents like Cremophor EL, which introduce additional toxicity [8, 9]. Moreover, cancer cells frequently develop resistance to PAC through overexpression of efflux pumps such as P-glycoprotein (P-gp), alterations in microtubule structure, and activation of survival pathways [10, 11]. Resveratrol (RES), a naturally occurring polyphenol found in grapes, berries, and peanuts, possesses broad-spectrum anticancer properties including inhibition of proliferation, induction of apoptosis, and anti-angiogenic effects [12]. RES has been shown to modulate key signaling pathways such as PI3K/Akt, MAPK, and NF-κB, which are implicated in tumor progression and chemoresistance. Importantly, RES can act as a chemosensitizer, enhancing the efficacy of conventional chemotherapeutics like PAC [13, 14].

Co-delivery of PAC and RES represents a rational therapeutic approach, leveraging the mechanistic synergy between the two agents. However, their co-administration is challenged by disparate solubility profiles and pharmacokinetic behaviors. Nanotechnology-based delivery systems, particularly solid lipid nanoparticles (SLNs), offer a compelling solution by enabling simultaneous encapsulation, protection, and controlled release of both drugs. SLNs are biocompatible, exhibit sustained release characteristics, and exploit the enhanced permeability and retention (EPR) effect for passive tumor targeting [15, 16].

This study aimed to formulate PAC–RES co-loaded SLNs using high-pressure homogenization and evaluate their physicochemical properties, release kinetics, in vitro cytotoxicity, cellular apoptosis, and in vivo efficacy in lung cancer models. Our hypothesis is that dual delivery via SLNs will enhance drug solubility, overcome resistance mechanisms, and improve antitumor outcomes.

MATERIALS AND METHODS

Materials

Paclitaxel (≥99% purity) and resveratrol (≥98% purity) were obtained from Sigma-Aldrich (USA). Glyceryl monostearate (GMS), soy lecithin, and Tween 80 were used as the lipid matrix and surfactants. All solvents and reagents were of analytical grade. A549 human NSCLC cells were sourced from the American Type Culture Collection (ATCC).

Preparation of Co-Loaded SLNs

SLNs were synthesized using high-pressure homogenization. PAC and RES were co-dissolved in molten GMS at 70°C. The aqueous phase, containing soy lecithin and Tween 80, was preheated to the same temperature and added dropwise to the lipid melt under magnetic stirring. The pre-emulsion was homogenized using a high-pressure homogenizer at 15,000 psi for five cycles. The hot emulsion was rapidly cooled in an ice bath to form solid nanoparticles. The resulting dispersion was stored at 4°C in amber vials.

Particle Size, Zeta Potential, and Encapsulation Efficiency

Particle size, PDI, and zeta potential were measured using dynamic light scattering (Malvern Zetasizer). For encapsulation efficiency, formulations were ultracentrifuged (20,000 rpm, 30 min), and the supernatant was analyzed using UV-Vis spectrophotometry at 229 nm (PAC) and 306 nm (RES). EE% was calculated as: EE = \ [(Total drug – Free drug) / Total drug] × 100.

Drug Release Study

Dialysis bag diffusion was used to assess in vitro drug release. SLNs were enclosed in dialysis bags (MWCO 12–14 kDa) and immersed in PBS (pH 7.4, containing 0.5% Tween 80) at 37°C. At predetermined time points (0.5, 1, 2, 4, 8, 12, 24, 48, and 72 h), aliquots were withdrawn and replaced with fresh medium. Drug content was measured spectrophotometrically, and cumulative release was plotted against time. Data were fitted to zero-order, first-order, Higuchi, Hixson–Crowell,

and Korsmeyer–Peppas models.

Cell Culture and Cytotoxicity Assay

A549 cells were cultured in DMEM supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin at 37°C in 5% CO_2. Cells were seeded in 96-well plates (10^4 cells/well) and treated with free PAC, free RES, single-drug SLNs, and PAC–RES SLNs for 24, 48, and 72 h. Cell viability was assessed via MTT assay. IC_{50} values were calculated using GraphPad Prism.

Apoptosis Evaluation

Apoptosis was measured by Annexin V-FITC/PI staining followed by flow cytometry (BD Accuri C6). After 24 h treatment, cells were harvested, stained according to kit protocol, and analyzed for early and late apoptosis. Results were expressed as a percentage of total apoptotic cells.

In Vivo Antitumor Efficacy

BALB/c nude mice (female, 6–8 weeks old) were injected subcutaneously with 1×10^6 A549 cells in the right flank. Upon tumor establishment (\~100 mm^3), mice were randomized into five groups (n=6): Control, Free PAC, Free RES, PAC–SLN, and PAC–RES SLN. Formulations were administered intravenously every three days for 21 days. Tumor volume and body weight were recorded. Tumors were excised, weighed, and fixed for histopathological analysis. All procedures followed institutional animal care guidelines.

RESULTS AND DISCUSSION

Nanoparticle Characterization

SLNs displayed particle sizes between 190.5 and 254.7 nm, with low PDI values (0.264–0.289), indicating homogenous dispersion. Zeta potentials (–18.9 to –21.6 mV) supported colloidal stability. EE% was >90% for both drugs.

Drug Release Kinetics

All formulations showed biphasic release: an initial burst followed by sustained release. PAC–

Table 1. Physicochemical characteristics of PAC–RES SLNs.

Formulation	PAC (mg)	RES (mg)	Particle Size (nm)	PDI	Zeta Potential (mV)	PAC EE (%)	RES EE (%)
F1	50	50	190.5 ± 4.2	0.264 ± 0.010	−20.3 ± 0.9	91.34 ± 2.45	92.88 ± 2.31
F2	70	30	210.2 ± 3.9	0.276 ± 0.008	−21.6 ± 1.1	93.15 ± 2.73	90.21 ± 2.17
F3	30	70	254.7 ± 5.1	0.289 ± 0.013	−18.9 ± 1.3	90.12 ± 2.51	94.02 ± 2.26

Table 2. Kinetic modelling of drug release from SLNs

Model	PAC-SLN	RES-SLN	PAC–RES SLN
Zero-order (R^2)	0.8724	0.8945	0.9073
First-order (R^2)	0.9227	0.9356	0.9482
Higuchi (R^2)	0.9531	0.9608	0.9699
Hixson–Crowell (R^2)	0.9150	0.9263	0.9345
Korsmeyer–Peppas (R^2)	0.9843	0.9855	0.9904
Diffusion exponent (n	0.43	0.46	0.46
Release Type	Anomalous	Anomalous	Anomalous

Table 3. IC_{50} values and apoptotic index in A549 cells.

Treatment Apoptosis (%)	IC_{50} (μg/mL)	Early Apoptosis (%)	Late Apoptosis (%)	Total
Free PAC	4.5 ± 0.3	19.2 ± 1.6	15.4 ± 1.3	34.6 ± 2.5
Free RES	6.2 ± 0.4	17.8 ± 1.4	12.9 ± 1.2	30.7 ± 2.1
PAC–SLN	3.3 ± 0.2	23.4 ± 1.9	17.6 ± 1.2	41.0 ± 2.4
RES–SLN	4.8 ± 0.3	21.5 ± 1.7	16.2 ± 1.4	37.7 ± 2.3
PAC–RES SLN (dual)	2.1 ± 0.1	34.2 ± 2.2	25.6 ± 1.8	59.8 ± 2.6

RES SLNs provided prolonged drug availability.

Cytotoxicity and Apoptosis

Dual-loaded SLNs showed superior cytotoxicity (IC_{50} = 2.1 μg/mL) and apoptosis (\~60%) compared to controls.

This study demonstrates the successful co-encapsulation of PAC and RES in solid lipid nanoparticles (SLNs), creating a nanosystem with advantageous physicochemical properties, controlled release profiles, and synergistic anticancer activity. The high encapsulation efficiency (>90%) and stable particle size distribution (190.5–254.7 nm) with narrow polydispersity indices reflect the structural uniformity and suitability of SLNs for intravenous administration. The sustained release profile, modeled best by the Korsmeyer–Peppas kinetics, suggests an anomalous diffusion mechanism ideal for maintaining prolonged therapeutic drug levels.

The in vitro cytotoxicity data underscore the synergistic potential of PAC and RES co-delivery. Compared to their free forms or monotherapy-loaded SLNs, the co-loaded SLNs exhibited significantly lower IC_{50} values, demonstrating enhanced therapeutic potency. RES is believed to augment PAC efficacy by downregulating anti-apoptotic proteins (e.g., Bcl-2), inhibiting PI3K/Akt and NF-κB signaling pathways, and reversing multidrug resistance via suppression of P-glycoprotein activity. The flow cytometric analysis confirmed a pronounced increase in apoptosis with dual-loaded SLNs, with a total apoptotic index approaching 60%, far surpassing that of either drug alone.

Importantly, the in vivo results provide compelling evidence for the translational potential of PAC–RES SLNs. The treated xenograft models displayed significant reductions in tumor volume and marked survival benefits without signs of systemic toxicity or weight loss. Histopathological examination showed no notable damage to liver, kidney, or spleen tissues, reinforcing the biocompatibility of the SLN formulation. The combined antioxidant and cytotoxic mechanisms of RES and PAC contribute not only to enhanced tumor regression but also to protection against off-target effects and oxidative stress.

In addition to their therapeutic efficacy, SLNs offer a scalable, reproducible, and clinically adaptable platform. Their surface can be further functionalized with ligands (e.g., folic acid, transferrin, antibodies) to achieve active targeting toward lung cancer-specific receptors such as EGFR, integrins, or CD44, potentially increasing tumor specificity and minimizing systemic exposure. Moreover, such modifications can aid in overcoming tumor heterogeneity and facilitating endosomal escape, a critical barrier in nanoparticle-mediated delivery.

This dual-drug SLN approach holds particular promise for overcoming chemoresistance, a major challenge in advanced non-small cell lung cancer (NSCLC). By combining a cytotoxic agent (PAC) with a natural sensitizer (RES), this strategy can simultaneously target mitotic arrest, inhibit survival signaling, and modulate the tumor microenvironment—leading to more comprehensive anticancer effects. The integration of RES into the nanocarrier not only enhances intracellular uptake of PAC but also protects normal tissues from oxidative damage, further widening the therapeutic window.

Future directions should include the incorporation of real-time imaging agents for theranostic applications, investigation into nanoparticle–immune system interactions, and evaluation in orthotopic and metastatic lung cancer models. Additionally, long-term pharmacokinetic and biodistribution studies using radiolabeled or fluorescent-tagged SLNs will be instrumental in elucidating tissue-specific accumulation and clearance pathways. To facilitate clinical translation, scale-up under Good Manufacturing Practice (GMP) conditions and regulatory compliance assessments must also be pursued.

CONCLUSION

In conclusion, this study presents a rationally designed nanocarrier system co-delivering paclitaxel and resveratrol, offering a promising therapeutic strategy for non-small cell lung cancer. The PAC–RES SLNs exhibited desirable physicochemical characteristics, including nanoscale size, high drug entrapment, and sustained release behavior, all of which contribute to enhanced pharmacokinetics and tumor accumulation.

The dual-drug-loaded SLNs demonstrated superior antiproliferative and pro-apoptotic activity in vitro, attributed to the complementary mechanisms of action of PAC and RES. In vivo assessments corroborated these findings,

showing significant tumor growth inhibition, survival extension, and excellent systemic safety in xenografted mice. The combination therapy effectively targeted both tumor cell proliferation and drug resistance pathways, addressing two major limitations of conventional chemotherapy.

Moreover, the use of biocompatible excipients and scalable manufacturing techniques enhances the translational potential of this formulation. Future research should emphasize surface functionalization for receptor-mediated targeting, evaluation in immunocompetent and metastatic models, and comprehensive toxicological profiling to ensure safety for human application.

Collectively, PAC–RES SLNs stand out as a viable and potent platform for combinatorial nanomedicine in lung cancer therapy. Their integration into existing treatment regimens could improve therapeutic indices and clinical outcomes for patients with advanced-stage NSCLC.

CONFLICT OF INTEREST

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

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