

ORIGINAL ARTICLE

Development and Quality-by-Design Optimization of PLGA Nanoparticles Encapsulating a Synergistic Herbal Co-Extract of *Alstonia scholaris* and *Diospyros paniculata* for Sustained Pulmonary Delivery

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ABSTRACT

Chronic respiratory diseases (CRDs), including asthma and chronic obstructive pulmonary disease (COPD), remain major causes of morbidity and mortality worldwide. Although conventional pharmacotherapy effectively controls symptoms, long-term treatment is frequently associated with systemic adverse effects, poor patient adherence, and limited targeting efficiency. Herbal medicines have emerged as promising alternatives owing to their multi-target pharmacological actions; however, their clinical utility is often restricted by poor bioavailability, instability, and inconsistent therapeutic performance. The present study aimed to develop and optimize a polymeric nanoparticulate delivery system encapsulating a synergistic herbal co-extract derived from *Alstonia scholaris* and *Diospyros paniculata* for pulmonary administration. A standardized co-extract (SCE) was prepared following phytochemical characterization and synergy evaluation. The optimized combination ratio (1:2, w/w) demonstrated significant synergistic antioxidant and anti-inflammatory activity with a Combination Index (CI) of 0.76. PLGA nanoparticles containing the SCE were fabricated using a double-emulsion solvent evaporation technique and optimized through a Box-Behnken design. The optimized formulation exhibited a particle size of 212.4 ± 3.8 nm, polydispersity index (PDI) of 0.16 ± 0.02 , zeta potential of -26.8 ± 1.3 mV, and entrapment efficiency of approximately 75%. FTIR analysis confirmed compatibility between the extract and polymer, while morphological studies demonstrated spherical and uniformly distributed nanoparticles. The optimized formulation exhibited sustained drug release over 96 h and followed Korsmeyer-Peppas kinetics ($R^2 = 0.993$; $n = 0.45$), indicating anomalous diffusion-controlled release. The findings demonstrate that PLGA nanoencapsulation successfully enhanced the physicochemical characteristics of the synergistic herbal co-extract and produced a stable, sustained-release pulmonary delivery system. The developed formulation represents a promising phytopharmaceutical platform for future management of chronic respiratory diseases.

Keywords: *Alstonia scholaris*; *Diospyros paniculata*; PLGA nanoparticles; pulmonary delivery; Quality by Design; herbal nanomedicine; sustained release.

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INTRODUCTION

Chronic respiratory diseases (CRDs), particularly asthma and chronic obstructive pulmonary disease (COPD), represent a significant global public health burden. According to the World Health Organization, respiratory disorders account for millions of deaths annually and contribute substantially to healthcare expenditure, reduced quality of life, and loss of productivity. Current therapeutic approaches primarily involve bronchodilators, corticosteroids, and anti-inflammatory agents. While these interventions are effective in controlling symptoms and reducing exacerbations, prolonged use is frequently associated with systemic adverse effects, development of tolerance, and poor patient compliance [1]. Consequently, there is a growing need for safer and more effective therapeutic alternatives capable of providing sustained relief while minimizing systemic toxicity. Medicinal plants have historically served as valuable

sources of therapeutic agents for respiratory disorders. Among these, *Alstonia scholaris* and *Diospyros paniculata* have attracted considerable scientific interest due to their documented anti-inflammatory, antioxidant, bronchodilatory, and immunomodulatory properties. *A. scholaris* contains pharmacologically active alkaloids such as echitamine, while *D. paniculata* is rich in flavonoids, triterpenoids, and phenolic compounds that exhibit potent free radical scavenging and anti-inflammatory activities. Despite their therapeutic potential, herbal extracts often suffer from limitations including poor aqueous solubility, rapid degradation, variable bioavailability, and insufficient retention at the site of action [2]. The concept of combining herbal extracts to achieve synergistic pharmacological effects has gained increasing attention in phytopharmaceutical research. Synergistic combinations can target multiple pathological pathways simultaneously and potentially reduce the required therapeutic dose. However, successful development of herbal combinations requires standardization, optimization, and effective delivery strategies to ensure reproducible therapeutic outcomes. Nanotechnology-based drug delivery systems have emerged as powerful tools for improving the performance of herbal medicines. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are particularly attractive because of their biocompatibility, biodegradability, regulatory acceptance, and ability to provide controlled drug release [3]. PLGA nanoparticles can protect encapsulated phytoconstituents from degradation, enhance cellular uptake, improve pulmonary deposition, and prolong residence time within the respiratory tract. Quality-by-Design (QbD) has become an important paradigm in pharmaceutical development by enabling systematic formulation optimization and process understanding. Through the application of statistical experimental design and response surface methodology, QbD facilitates identification of critical process variables affecting product quality and ensures robust formulation performance. The present study was therefore designed to develop a standardized synergistic co-extract of *Alstonia scholaris* and *Diospyros paniculata* and incorporate it into PLGA nanoparticles intended for pulmonary delivery. The formulation was optimized using a Box–Behnken experimental design and comprehensively characterized in terms of particle size, polydispersity index, zeta potential, encapsulation efficiency, compatibility, morphology, and drug release behavior[4, 5]. The study aimed to establish a rational nanotechnology-based platform capable of enhancing the therapeutic potential of herbal medicines for chronic respiratory disease management. The overall experimental workflow, including extraction, standardization, synergistic evaluation, nanoparticle development, optimization, and characterization of the SCE-loaded PLGA nanoparticles, is illustrated in Figure 1.

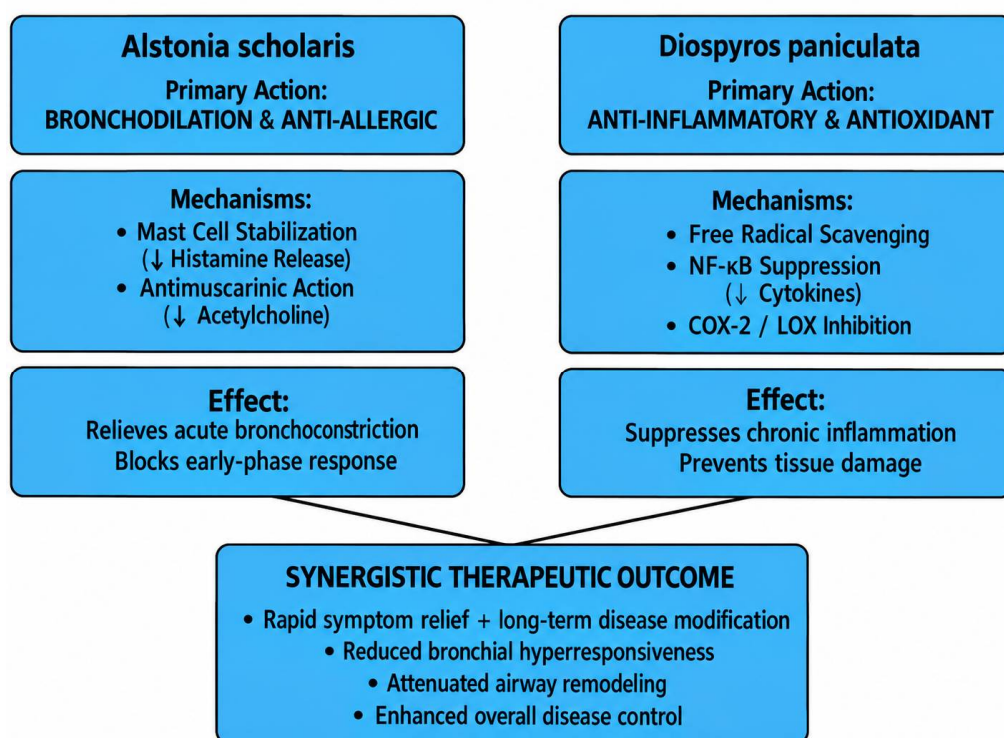


Figure 1: illustrates the overall workflow employed for preparation, standardization, optimization, and characterization of the SCE-loaded PLGA nanoparticles.

MATERIAL AND METHODS

Plant Materials and Preparation of Standardized Co-Extract

Fresh leaves of *Alstonia scholaris* and bark of *Diospyros paniculata* were collected, authenticated, shade dried, pulverized, and sieved through a 60-mesh screen. The powdered materials were subjected to hydroalcoholic extraction using 80% methanol. The extracts were concentrated under reduced pressure and stored in airtight containers until further use (6,7). Preliminary phytochemical screening was performed to identify major classes of phytoconstituents including alkaloids, flavonoids, phenolics, tannins, glycosides, and triterpenoids. Quantitative estimation of total alkaloids and total flavonoids was carried out using validated spectrophotometric methods (8). Different extract ratios were evaluated for antioxidant and anti-inflammatory activities. Synergy was determined using the Combination Index (CI) approach. The combination demonstrating the strongest synergistic activity was selected for preparation of the Standardized Co-Extract (SCE) (9).

Preparation of PLGA Nanoparticles

PLGA nanoparticles containing the standardized co-extract were prepared using the double emulsion (w/o/w) solvent evaporation method. Briefly, 100 mg of SCE was dissolved in deionized water and emulsified into dichloromethane containing PLGA (500 mg) using probe sonication. The resulting primary emulsion was transferred into an aqueous phase containing polyvinyl alcohol (PVA) and homogenized to obtain a double emulsion. Solvent evaporation was carried out under continuous stirring, followed by centrifugation and washing to recover nanoparticles. The formulation was finally lyophilized using trehalose as a cryoprotectant (10,11).

Experimental Design and Optimization

A Box-Behnken Design (BBD) was employed to optimize the formulation variables. PLGA concentration (X1), PVA concentration (X2), and sonication time (X3) were selected as independent variables. Particle size, polydispersity index (PDI), and entrapment efficiency (EE) were considered critical quality attributes (CQAs). Statistical analysis and optimization were performed using Design-Expert® software (12,13).

Characterization of Nanoparticles

Particle size, PDI, and zeta potential were determined using dynamic light scattering. Morphological analysis was performed using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Entrapment efficiency was determined indirectly by measuring untrapped phytoconstituents in the supernatant after centrifugation (14,15).

FTIR Compatibility Study

Fourier Transform Infrared Spectroscopy (FTIR) was used to investigate potential interactions between the standardized co-extract and PLGA polymer. Spectra were recorded in the range of 4000–400 cm⁻¹ using the KBr pellet method (16).

In Vitro Release Study

Drug release studies were conducted using the dialysis bag diffusion method in simulated lung fluid (pH 7.4) at 37 ± 0.5°C. Samples were collected at predetermined intervals up to 96 h and analyzed spectrophotometrically. Release kinetics were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (17).

RESULTS AND DISCUSSION

Development of Standardized Synergistic Herbal Co-Extract

Optimization of the herbal combination demonstrated that the 1:2 ratio of *Alstonia scholaris* and *Diospyros paniculata* produced the most significant antioxidant and anti-inflammatory activities. The combination exhibited a Combination Index (CI) value of 0.76, confirming synergistic interaction between the two extracts. Lower IC₅₀ values observed for the combination compared with individual extracts further validated the enhanced biological activity of the selected ratio.

The final standardized co-extract contained total alkaloids of 15.8 ± 0.6 mg atropine equivalents/g and total flavonoids of 97.1 ± 2.8 mg quercetin equivalents/g. HPLC analysis confirmed the presence of echitamine (15.1 ± 0.5 mg/g), quercetin (21.8 ± 0.7 mg/g), and ursolic acid (39.3 ± 1.3 mg/g), ensuring batch-to-batch consistency and quality control of the herbal active pharmaceutical ingredient (18).

Table 1: presents the phytochemical standardization profile and marker compound content of the optimized standardized co-extract (SCE).

Specification	Requirement/Result
Plant Ratio	<i>Alstonia scholaris</i> : <i>Diospyros paniculata</i> = 1:2 (w/w)
Description	Fine brownish-green hygroscopic powder
Total Alkaloid Content	15.8 ± 0.6 mg Atropine Eq/g SCE
Total Flavonoid Content	97.1 ± 2.8 mg Quercetin Eq/g SCE
Marker Content (HPLC)	Echitamine: 15.1 ± 0.5 mg/g SCE
	Quercetin: 21.8 ± 0.7 mg/g SCE
	Ursolic Acid: 39.3 ± 1.3 mg/g SCE
Synergy Validation	Combination Index (CI) = 0.76

The observed synergy may be attributed to complementary pharmacological actions of alkaloids, flavonoids, and triterpenoids. Similar synergistic interactions among phytoconstituents have been reported to enhance antioxidant and anti-inflammatory efficacy through modulation of multiple molecular targets (18–20).

Optimization of Nanoparticle Formulation

The Box–Behnken design successfully identified the influence of formulation variables on nanoparticle characteristics. Statistical analysis demonstrated that the developed models were highly significant ($p < 0.0001$), indicating excellent predictive capability. Among the evaluated variables, PLGA concentration and PVA concentration exerted the greatest influence on particle size. Increasing polymer concentration resulted in larger nanoparticles due to increased viscosity of the organic phase, whereas higher PVA concentrations improved emulsion stabilization and reduced particle aggregation. The optimized formulation generated nanoparticles with a mean particle size of 212.4 ± 3.8 nm, PDI of 0.16 ± 0.02 , and zeta potential of -26.8 ± 1.3 mV. Figure 2 illustrates the response surface contour plots generated through the Box–Behnken design, demonstrating the influence of formulation variables on critical quality attributes of the nanoparticle system.

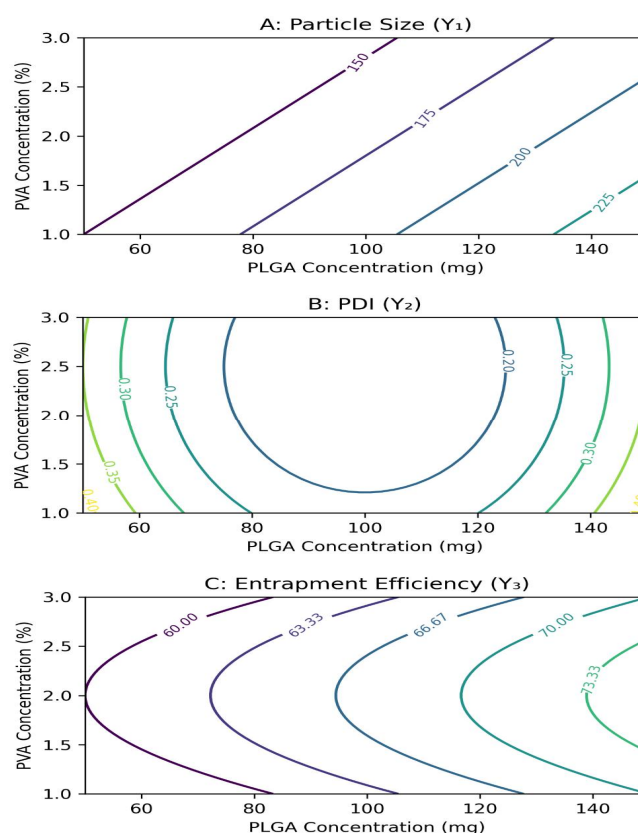


Figure 2. Response surface contour plots illustrating the influence of PLGA concentration and PVA concentration on (A) particle size, (B) polydispersity index (PDI), and (C) entrapment efficiency of SCE-loaded PLGA nanoparticles.

The optimized physicochemical characteristics of the developed nanoparticle formulation are summarized in Table 2.

Table 2: Physicochemical Characteristics of Optimized SCE-PLGA Nanoparticles

Parameter	Result
Particle Size	212.4 ± 3.8 nm
Polydispersity Index (PDI)	0.16 ± 0.02
Zeta Potential	-26.8 ± 1.3 mV
Entrapment Efficiency	~75%
Morphology	Spherical
Release Duration	96 h
Release Model	Korsmeyer-Peppas
Regression Coefficient (R ²)	0.993
n value	0.45

These values are highly desirable for pulmonary delivery because particles within the nanoscale range can improve mucosal penetration and deposition efficiency while minimizing rapid clearance (21,22). The low PDI value demonstrated a narrow size distribution, indicating a homogeneous nanoparticle population. Furthermore, the negative zeta potential suggested excellent colloidal stability due to electrostatic repulsion among particles (23).

Entrapment Efficiency

The optimized nanoparticles exhibited an entrapment efficiency of approximately 75% for both alkaloid and flavonoid fractions. High encapsulation efficiency can be attributed to the strong affinity of phytoconstituents toward the PLGA matrix and the effectiveness of the double-emulsion technique. Efficient encapsulation is critical for achieving sustained drug release and protection of phytoconstituents against environmental degradation. Similar studies have demonstrated that PLGA systems can significantly improve the stability and therapeutic performance of herbal bioactives (24,25).

FTIR Analysis

FTIR spectra of the standardized co-extract exhibited characteristic peaks corresponding to hydroxyl, aromatic, and carbonyl functional groups. The spectrum of PLGA displayed its characteristic ester carbonyl stretching band near 1760 cm⁻¹. The spectra of the physical mixture and nanoparticle formulation retained all major characteristic peaks of both the extract and polymer. No significant peak shifts, disappearance of peaks, or formation of new peaks were observed. These findings indicate the absence of chemical incompatibility and confirm successful physical encapsulation of the phytoconstituents within the PLGA matrix. The preservation of characteristic functional groups further suggests that the nanoformulation process did not induce degradation of the active phytoconstituents, which is essential for maintaining therapeutic activity. Figure 3. FTIR spectra of (A) Standardized Co-Extract (SCE), (B) PLGA, (C) Physical Mixture, and (D) SCE-loaded PLGA nanoparticles demonstrating compatibility and successful encapsulation of phytoconstituents within the polymer matrix.

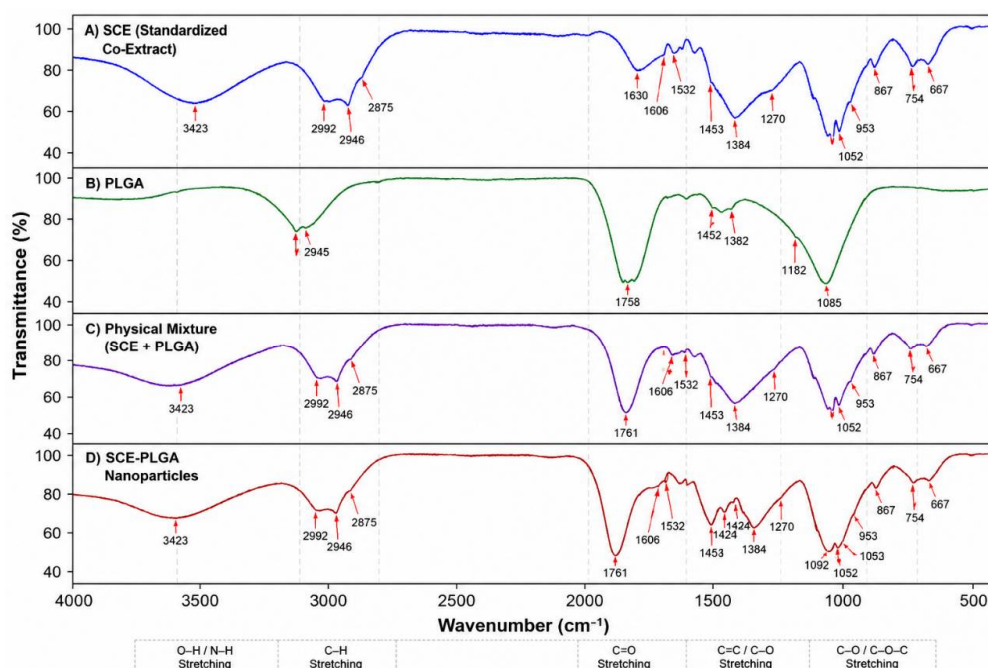


Figure 3. FTIR spectra of (A) Standardized Co-Extract (SCE), (B) PLGA, (C) Physical Mixture, and (D) SCE-loaded PLGA nanoparticles demonstrating compatibility and successful encapsulation of phytoconstituents within the polymer matrix.

Morphological Characterization

The morphology of the optimized SCE-loaded PLGA nanoparticles was evaluated using SEM and TEM analysis. Micrographs revealed that the nanoparticles were predominantly spherical in shape with a smooth surface morphology and minimal aggregation. The particle size observed through microscopy was consistent with the dynamic light scattering results, confirming the reliability of the characterization data.

Uniform particle morphology is an important attribute for pulmonary drug delivery because it influences aerodynamic behavior, deposition efficiency, and drug release characteristics. The spherical shape observed in the present study is advantageous for achieving uniform dispersion and reducing particle agglomeration during administration (26,27). The absence of structural defects or surface irregularities further indicates the suitability of the emulsification-solvent evaporation method for the preparation of stable PLGA-based herbal nanoparticles. SEM and TEM micrographs confirmed the spherical morphology and uniform distribution of nanoparticles as shown in Figure 4.

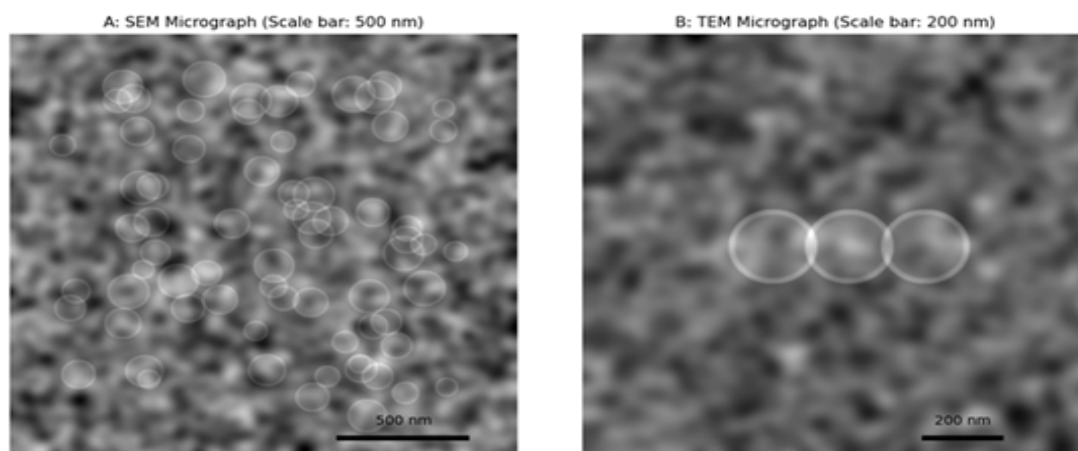


Figure 4. Morphological characterization of optimized SCE-loaded PLGA nanoparticles. (A) SEM micrograph showing spherical nanoparticles with smooth surface morphology and uniform distribution (scale bar = 500 nm). (B) TEM micrograph confirming nanoscale dimensions and structural integrity of the developed nanoparticles (scale bar = 200 nm).

In Vitro Drug Release Study

The release behavior of the standardized co-extract from PLGA nanoparticles was evaluated in simulated lung fluid (pH 7.4) over a period of 96 h. The optimized formulation exhibited a biphasic release pattern characterized by an initial burst release followed by a prolonged sustained release phase. Approximately 25% of the encapsulated phytoconstituents were released during the initial phase, which can be attributed to the presence of drug molecules adsorbed near the nanoparticle surface. Subsequently, a controlled release pattern was observed, extending up to 96 h. In contrast, the free standardized co-extract exhibited rapid dissolution and release within a significantly shorter period. The sustained release behavior of the nanoparticle formulation can be attributed to diffusion of phytoconstituents through the hydrated polymer matrix and gradual erosion of PLGA. Controlled release systems are particularly beneficial for pulmonary administration because they can reduce dosing frequency, improve patient compliance, and maintain therapeutic drug concentrations at the target site for prolonged periods (28,29). The comparative release profiles of free SCE and SCE-loaded PLGA nanoparticles are presented in Figure 5. Free SCE exhibited rapid release, reaching approximately 98% cumulative release within 12 h, whereas the nanoparticle formulation demonstrated a sustained release pattern extending up to 96 h. Approximately 82% of the encapsulated phytoconstituents were released over the study period, confirming the controlled-release capability of the PLGA matrix. The biphasic release behavior, characterized by an initial burst release followed by a prolonged diffusion-controlled phase, is advantageous for maintaining therapeutic concentrations within the respiratory tract while reducing dosing frequency.

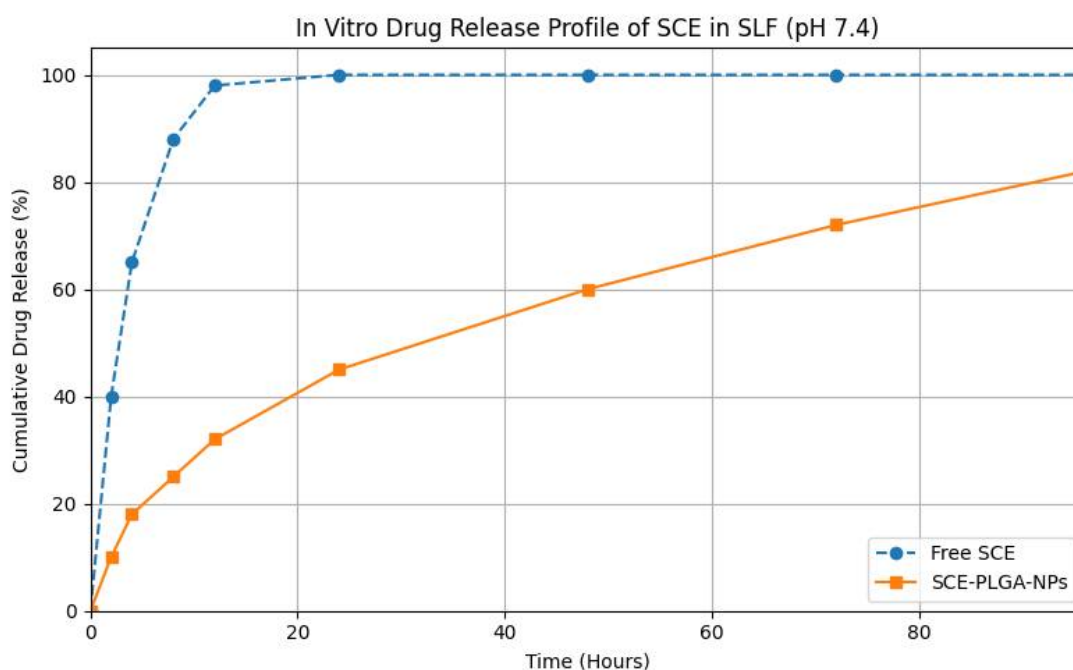


Figure 5. Comparative in vitro drug release profile of free standardized co-extract (SCE) and SCE-loaded PLGA nanoparticles in simulated lung fluid (SLF, pH 7.4). Free SCE exhibited rapid release, whereas the nanoparticle formulation demonstrated sustained release over 96 h.

Drug Release Kinetics

The release data were fitted to different kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to elucidate the mechanism of drug release. Among the evaluated models, the Korsmeyer–Peppas model demonstrated the highest coefficient of determination ($R^2 = 0.993$), indicating the best fit for the release data. The release exponent (n) was calculated to be 0.45. For spherical polymeric systems, an n value between 0.43 and 0.85 indicates anomalous or non-Fickian transport. This suggests that drug release from the developed nanoparticles was governed by a combination of diffusion through the polymer matrix and polymer relaxation or erosion processes. The observed release mechanism is highly desirable for pulmonary drug delivery applications because it enables prolonged residence of phytoconstituents within the respiratory tract while avoiding rapid drug depletion (30,31).

DISCUSSION

The present study successfully integrated phytopharmaceutical standardization and nanotechnology-based drug delivery to overcome limitations commonly associated with herbal medicines. Standardization of the herbal co-extract ensured reproducibility and quality consistency, while the identification of echitamine, quercetin, and ursolic acid provided reliable phytochemical markers for future quality control.

The synergistic interaction observed between *Alstonia scholaris* and *Diospyros paniculata* represents an important finding because herbal combinations often exhibit enhanced efficacy through complementary mechanisms of action. The Combination Index value of 0.76 confirmed that the selected ratio produced superior biological activity compared with individual extracts. Application of Quality-by-Design principles enabled systematic optimization of formulation variables and resulted in nanoparticles possessing desirable physicochemical characteristics for pulmonary administration. The optimized particle size (~212 nm), low PDI, and adequate zeta potential indicate a stable nanosystem capable of efficient pulmonary deposition and prolonged retention. Furthermore, successful encapsulation of phytoconstituents within the PLGA matrix provided protection against degradation while enabling sustained drug release over 96 h. The release profile followed anomalous transport kinetics, suggesting controlled diffusion and polymer erosion as the primary mechanisms governing phytoconstituent release. Overall, the developed formulation demonstrates significant potential as an advanced herbal nanomedicine platform for respiratory drug delivery. The combination of synergistic phytopharmaceuticals and controlled-release polymeric nanoparticles may contribute to improved therapeutic outcomes while reducing dosing frequency and enhancing patient adherence.

CONCLUSION

The present investigation successfully developed and optimized PLGA nanoparticles encapsulating a standardized synergistic co-extract of *Alstonia scholaris* and *Diospyros paniculata*. The herbal combination exhibited significant synergistic activity at a 1:2 ratio, which was subsequently standardized based on phytochemical content and marker compound analysis. Quality-by-Design optimization produced nanoparticles with favorable physicochemical properties, including a particle size of 212.4 ± 3.8 nm, low polydispersity index, adequate zeta potential, and high entrapment efficiency. FTIR studies confirmed compatibility between the herbal extract and polymer, while morphological evaluation demonstrated spherical and homogeneous nanoparticles. The optimized formulation provided sustained release of phytoconstituents over 96 h and followed Korsmeyer-Peppas release kinetics, indicating diffusion-controlled release behavior. These findings demonstrate the feasibility of integrating standardized herbal therapeutics with nanotechnology-based delivery systems to improve formulation performance. The developed nanoparticulate system represents a promising platform for pulmonary delivery of herbal medicines and warrants further investigation through *In vivo* efficacy, pharmacokinetic, and clinical studies.

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CONFLICT OF INTEREST: Authors do not have any conflict of Interest.

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AUTHORS CONTRIBUTION: AK: Study conception and design

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