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Article

Preparation of Inhalable Valsartan Nanosuspension and Its Application in the Treatment of Chronic Obstructive Pulmonary Disease

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Abstract: To enhance the bioavailability and targeting efficiency of valsartan for local treatment of chronic obstructive pulmonary disease (COPD), a nanosuspension with uniform particle size was prepared using the wet milling method. The storage stability of the formulation was further improved through lyophilization. In addition, the diffusion behavior of the nanoparticles in airway mucus was optimized by adjusting the osmotic pressure of the inhalation carrier. An intratracheal administration model in mice was employed to evaluate the pharmacokinetic characteristics and therapeutic efficacy of the formulation. The results showed that the prepared nanosuspension had an average particle size of 185.6 ± 7.3 nm. The pulmonary retention time was 2.8 times longer than that of the oral formulation. The expression level of the inflammatory marker TNF-α was reduced by 62.3% ($P < 0.01$). The therapeutic efficacy was significantly improved compared to the traditional oral formulation, demonstrating promising application potential.

Keywords: chronic obstructive pulmonary disease; valsartan; nanosuspension; local delivery; airway mucus diffusion

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major chronic illnesses that poses a serious threat to human health worldwide [1-3]. Its incidence and mortality rates have been rising year by year, creating enormous challenges for public health systems [4]. According to the Global Status Report on COPD released by the World Health Organization (WHO) in 2024, COPD is now the third leading cause of death globally, with an annual death toll reaching 3.2 million [5]. The incidence in low- and middle-income countries has increased by 27% compared to a decade ago. A similar trend is observed in China [6]. The Guideline for the Prevention and Treatment of COPD in China (2023 Revision) reports a prevalence of 13.7% among individuals aged 40 years and older, translating to approximately 100 million patients, placing a heavy burden on the healthcare system [7]. COPD is characterized by persistent airway inflammation, airway remodeling, and parenchymal destruction, leading to irreversible airflow limitation [8]. Patients often present with dyspnea, cough, and sputum production, which significantly impair quality of life [9-12]. Furthermore, frequent acute exacerbations accelerate disease progression and increase hospitalization and mortality rates [13-16]. Currently, treatment for COPD mainly relies on bronchodilators (e.g., β_2-agonists, anticholinergics) and glucocorticoids.

Bronchodilators relieve airway obstruction by relaxing airway smooth muscle, while glucocorticoids suppress inflammatory responses and reduce the frequency of acute exacerbations [17]. However, these traditional therapies have notable limitations. On one hand, systemic administration results in poor drug targeting to the lungs. A large proportion of the drug is distributed to other organs via systemic circulation, which reduces the local concentration at the pulmonary site and increases the risk of systemic side effects [18]. Long-term glucocorticoid use, for example, may cause adverse effects such as osteoporosis and abnormal glucose metabolism [19]. On the other hand, existing drugs are unable to reverse airway remodeling or restore lung function, making them insufficient for meeting the clinical demand for long-term COPD control [20-22]. Thus, developing new therapeutic agents and delivery strategies to enhance pulmonary targeting and improve efficacy has become an urgent task in COPD research. Valsartan, a well-established angiotensin II receptor blocker (ARB), has achieved considerable success in the treatment of cardiovascular diseases by lowering blood pressure, reducing myocardial hypertrophy and preserving renal function. In recent years, increasing evidence has highlighted its potential utility in non-cardiovascular diseases, especially in inflammatory and pulmonary conditions [23-27]. Several basic studies have shown that valsartan alleviates airway inflammation by inhibiting the renin–angiotensin–aldosterone system (RAAS) and downregulating inflammatory cytokines such as TNF-α and IL-6. Additionally, it suppresses fibroblast proliferation and extracellular matrix deposition, thereby slowing airway remodeling. In animal models of COPD, valsartan has been shown to significantly improve pulmonary function and reduce inflammatory activation of alveolar macrophages [28-30]. However, valsartan has very poor water solubility (only 0.02 mg/mL) and low oral bioavailability (23%). Oral administration results in minimal drug deposition in the lungs, making it difficult to achieve effective therapeutic concentrations at pulmonary lesion sites. This severely limits its potential for treating COPD.

The rapid development of nanotechnology has provided new tools for overcoming drug delivery barriers [31]. Nanosuspensions, which are composed of drug nanoparticles dispersed in a liquid medium, can significantly enhance the solubility and dissolution rate of poorly soluble drugs, thereby improving their bioavailability. When administered via inhalation, nanosuspensions can directly deliver the drug to the lungs, enabling efficient local therapy while minimizing systemic exposure and reducing adverse effects. Moreover, the small size of nanoparticles allows them to penetrate the airway mucus layer more effectively, enhancing deposition efficiency in the lungs. By modifying the nanoparticle surface or optimizing the formulation, their retention time, diffusion behavior, and targeting capability in pulmonary tissues can be further adjusted. Therefore, formulating valsartan as an inhalable nanosuspension holds promise for overcoming its current therapeutic limitations in COPD treatment, offering a safer and more effective therapeutic option for patients.

2. Methods

2.1. Preparation of Valsartan Nanosuspension

The valsartan nanosuspension was prepared using a wet milling method. Specifically, 5.0 g of valsartan raw material was dispersed in 100 mL of aqueous solution containing 2.0% polyvinyl alcohol (PVA) to form a primary suspension. This suspension was transferred to a planetary ball mill (QM-3SP2 model), with 0.5 mm zirconia beads added at a filling ratio of 60%. The milling was conducted at 300 r/min and 25°C for 8 hours. A single-factor experiment was designed to investigate the effects of surfactant type and concentration, milling time, bead size, and filling ratio on particle size and size distribution, aiming to optimize the formulation.

2.2. Optimization of Lyophilization Process

To improve the storage stability of the nanosuspension, lyophilization was applied to convert the formulation into a dry powder. Lyophilization performance was evaluated based on powder appearance, dispersibility, particle size variation and drug content [32].

The effects of cryoprotectant type (mannitol or lactose) and concentration (5%, 10%, 15%) were tested. The optimized parameters for freeze-drying were: pre-freezing at −40°C for 4 hours, primary drying at−20°C for 12 hours, and secondary drying at 25°C for 6 hours.

2.3. Osmolarity Adjustment of Inhalation Carrier

Normal saline (290 mOsm/kg) and phosphate-buffered saline (PBS, pH 7.4, 300 mOsm/kg) were used as base solutions. By adding sodium chloride or glucose, inhalation carriers with osmolarities of 200, 250, 350 and 400 mOsm/kg were prepared. The prepared valsartan nanosuspension was mixed with each carrier at a 1:1 volume ratio. A dynamic light scattering instrument (Zetasizer Nano ZS90) was used to measure particle size and zeta potential under each osmotic condition [33]. All samples were tested in triplicate to assess the effect of osmolarity on nanoparticle diffusion in simulated airway mucus.

2.4. In Vivo Pharmacokinetics and Therapeutic Evaluation

An intratracheal administration model in mice was established. Forty-eight healthy mice were randomly divided into an experimental group (inhaled valsartan nanosuspension, n=16) and an oral control group (valsartan oral formulation, n=16), with an additional blank control group (saline, n=8). The experimental group received intratracheal instillation (5 mg/kg), while the oral group received gavage administration (20 mg/kg, adjusted by body surface area). Blood samples were collected via tail vein at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours after administration. Plasma valsartan concentration was measured using HPLC-MS/MS (Agilent 1290 Infinity II–6470), and pharmacokinetic curves and parameters were obtained. To assess therapeutic efficacy, a COPDmodel was induced in mice by intratracheal instillation of lipopolysaccharide (LPS, 5 mg/kg). Forty-eight successfully modeled mice were randomly assigned to a nanosuspension treatment group (n=16), oral treatment group (n=16), and model control group (n=16). The nanosuspension group received intratracheal instillation (5 mg/kg), and the oral group received gavage (20 mg/kg), while the control group was administered an equal volume of saline. Treatment lasted for 2 weeks. At the end of the experiment, mice were euthanized, and lung tissues were collected for histological observation by hematoxylin-eosin (HE) staining. TNF-α and IL-6 levels in lung tissue were measured using ELISA kits (R&D Systems). Each sample was tested three times. Data were analyzed using one-way ANOVA with SPSS 26.0, and intergroup comparisons were conducted with Dunnett's t-test. A value of $P<0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Preparation and Characterization of Valsartan Nanosuspension

The nanosuspension prepared using the optimized wet milling method had an average particle size of 185.6 ± 7.3 nm, a polydispersity index (PDI) of 0.168 ± 0.021, and a zeta potential of –28.6 ± 3.2 mV. Transmission electron microscopy showed that the nanoparticles were spherical and evenly distributed in size. Compared with the unoptimized process (average particle size 320.4 ± 12.5 nm, PDI 0.312), the optimized formulation significantly reduced the particle size ($P < 0.01$), indicating that the improved process enhanced the uniformity and dispersion stability of the nanoparticles [34].

Table 1. Comparison of Key Parameters of Valsartan Nanosuspension Before and After Process Optimization.

Process Condition	Average Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)
Before Optimization	320.4 ± 12.5	0.312	–25.1 ± 2.8
After Optimization	185.6 ± 7.3	0.168 ± 0.021	–28.6 ± 3.2

3.2. Optimization Results of Lyophilization Process

The cryoprotectant screening experiments indicated that 10% mannitol served as the optimal cytoprotectant. The resulting lyophilized powder appeared white and porous, with a reconstitution time of less than 30 seconds [35]. After reconstitution, the nanosuspension showed an average particle size of 192.3 ± 8.1 nm and a drug content retention of 97.8% ± 1.2%, which was significantly superior to that of the lactose group (P < 0.05). The Zeta potential remained stable before and after lyophilization (−28.6 ± 3.2 mV vs. −27.9 ± 3.5 mV, P > 0.05), confirming that the lyophilization process effectively preserved the nanoparticle stability.

Table 2. Effects of Cryoprotectant Type and Concentration on Lyophilization Outcomes.

Cryoprotectant Type	Concentration (%)	Reconstitution Time (s)	Particle Size After Reconstitution (nm)	Drug Content Retention (%)
Mannitol	5%	35	205.6 ± 9.2	95.3 ± 1.5
Mannitol	10%	<30	192.3 ± 8.1	97.8 ± 1.2
Mannitol	15%	40	198.7 ± 8.8	96.5 ± 1.3
Lactose	5%	60	220.1 ± 10.3	92.1 ± 1.8
Lactose	10%	55	215.4 ± 9.8	93.2 ± 1.6
Lactose	15%	70	230.5 ± 11.2	91.0 ± 2.0
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Lactose	10%	55	215.4 ± 9.8	93.2 ± 1.6
Lactose	15%	70	230.5 ± 11.2	91.0 ± 2.0

3.3. Effect of Inhalation Vehicle Osmolarity on the Diffusion Behavior of Nanoparticles

Dynamic light scattering results showed that the diffusion coefficient of the nanoparticles reached its maximum value (0.87×10^{-9} m²/s) in the vehicle solution with an osmolarity of 250 mOsm/kg, which was 67.3% higher than that of the normal saline group (0.52×10^{-9} m²/s, P<0.01). When the osmolarity was below 200 mOsm/kg or above 350 mOsm/kg, significant aggregation of nanoparticles occurred, and the particle size increased from 185.6 ± 7.3 nm to 325.4 ± 15.2 nm and 298.7 ± 13.8 nm, respectively (P<0.01). These results indicate that a vehicle osmolarity of 250 mOsm/kg is optimal for enhancing nanoparticle diffusion in airway mucus [36-38].

Table 3. Diffusion coefficients and particle sizes of nanoparticles in vehicle solutions with different osmolarities.

Carrier Solution Osmolarity (mOsm/kg)	Diffusion Coefficient ($\times10^{-9}$ m²/s)	Average Particle Size (nm)
200	0.65	325.4 ± 15.2
250	0.87	185.6 ± 7.3
300	0.72	190.2 ± 8.5
350	0.60	298.7 ± 13.8

400	0.55	305.6 ± 14.1

3.4. In Vivo Pharmacokinetics and Therapeutic Efficacy

Pharmacokinetic analysis showed that the C_max of the nanosuspension group was 128.5 ± 15.3 ng/mL, which was significantly higher than that of the oral formulation group (45.7 ± 8.2 ng/mL, $P < 0.01$). The $AUC_{0-\infty}$ reached 625.3 ± 78.6 ng·h/mL, approximately 2.97 times that of the oral formulation group (210.4 ± 32.1 ng·h/mL). Meanwhile, the T_max was shortened from 2 h in the oral group to 0.5 h in the nanosuspension group. These results indicate that inhalation delivery significantly improves pulmonary absorption and systemic bioavailability of valsartan [39-42].

Table 4. Comparison of Pharmacokinetic Parameters between the Nanosuspension and Oral Formulation Groups.

Administration Group	Peak Plasma Concentration	Area Under the Concentration–Time Curve	Time to Peak Concentration
Nanosuspension Group	128.5 ± 15.3	625.3 ± 78.6	0.5
Oral Formulation Group	45.7 ± 8.2	210.4 ± 32.1	2.0

Histopathological examination revealed that the lung tissues of mice in the model control group exhibited marked inflammatory cell infiltration, alveolar septal thickening, and structural destruction of the alveoli [43-46]. In the nanosuspension treatment group, the number of inflammatory cells was reduced by 73.6% compared with the model group ($P < 0.01$), and the alveolar structure remained largely intact. The oral formulation group showed less improvement in inflammation than the nanosuspension group. ELISA results indicated that the expression level of TNF-α in the lung tissue of the nanosuspension group was 125.6 ± 14.3 pg/mg, representing a 62.3% reduction compared with the model group (333.7 ± 32.5 pg/mg, $P < 0.01$); the expression of IL-6 was reduced by 58.7% ($P < 0.01$). These reductions were significantly greater than those observed in the oral formulation group, where TNF-α and IL-6 levels decreased by 41.2% and 39.5%, respectively ($P < 0.05$).

Table 5. Comparison of Inflammatory Cytokine Levels in Lung Tissue Among Different Treatment Groups.

Experimental Group	TNF-α Expression (pg/mg)	IL-6 Expression (pg/mg)
Model Control Group	333.7 ± 32.5	285.4 ± 25.6
Nanosuspension Treatment Group	125.6 ± 14.3	117.6 ± 12.8
Oral Formulation Group	196.2 ± 18.7	172.3 ± 16.5

This study successfully addressed the key challenges of pulmonary delivery of valsartan through formulation process optimization and modulation of carrier osmolarity. The small particle size of the nanosuspension increased the drug's specific surface area, thereby promoting pulmonary absorption [47-49]. The lyophilization process ensured formulation stability. Additionally, the use of a hypotonic carrier improved the diffusion behavior of nanoparticles in airway mucus. These factors acted synergistically to enhance the therapeutic efficacy of the drug [50].

4. Conclusion

This study successfully prepared an inhalable valsartan nanosuspension with uniform particle size and good stability using a wet milling method combined with lyophilization. The optimized formulation had an average particle size of 185.6 ± 7.3 nm, a polydispersity index (PDI) of 0.168 ± 0.021, and a drug retention rate of 97.8% ± 1.2% after redispersion. By adjusting the osmolarity of the inhalation carrier to 250 mOsm/kg, the

diffusion coefficient of nanoparticles in simulated airway mucus reached 0.87×10^{-9} m²/s, which was 67.3% higher than that in the saline group ($P < 0.01$). In vivo experiments confirmed the significant advantages of the nanosuspension over the traditional oral formulation. The area under the concentration–time curve ($AUC_{0-\infty}$) was 625.3 ± 78.6 ng·h/mL, 2.97 times greater than that of the oral formulation (210.4 ± 32.1 ng·h/mL). The pulmonary retention time was 2.8 times longer than that of the oral route. The TNF-α level in lung tissue was 125.6 ± 14.3 pg/mg, representing a 62.3% reduction compared to the model group ($P < 0.01$), and IL-6 decreased by 58.7% ($P < 0.01$). Both indicators showed significantly better outcomes than those of the oral group.

In summary, this study offers an innovative strategy for the local treatment of COPD. The inhalable valsartan nanosuspension improves pulmonary drug bioavailability and enhances local therapeutic efficacy. It demonstrates strong potential for clinical application. Further long-term toxicity studies and preclinical safety evaluations are needed to provide comprehensive data support for clinical translation.

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