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Evaluation of single-dose inhalation of clarithromycin-loaded solid lipid nanoparticles in rat model

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ABSTRACT

This study aimed to explore the effective utilization of clarithromycin (CLA) through the development of clarithromycin-loaded solid lipid nanoparticles (CLA-loaded SLN), designed for nebulizer-based delivery for the first time. Wistar albino rats were divided into seven groups (n=8) based on time points (0.5, 1, 2, 4, 12, 24 hours, and a control group). At the respective time points, lung tissues and blood samples were collected and analyzed for CLA concentrations using HPLC-MS/MS. The maximum serum concentration (Cmax) was 6.74 µg/ mL, with average serum CLA concentrations of 5.06, 2.5, 2.18, 1.13, and 0.5 µg/mL across the groups. CLA was undetectable in the control group and in the serum of the last group. Using the linear trapezoidal method (LTM), the area under the curve (AUC 0-24) for serum CLA was calculated as 17.06 µg*h/mL. Significant differences ($p<0.001$) were observed between several groups in serum CLA levels. In lung tissue, the highest Cmax was 2.66 µg/g, with average concentrations of 1.99, 1.8, 1.76, 0.36, 0.14, and 0.04 µg/g. The AUC for lung CLA concentration was 7.43 µg*h/g. The findings show that inhalation of CLA-loaded SLN reaches sufficient plasma and lung concentrations. It shows that serum CLA levels are enough up to 12 hours after inhalation. However, serum CLA levels could not be detected after 12 hours. It proves that CLA concentrations in lung tissue are sufficient for up to 24 hours. As a result, it was concluded that CLA can be used in treatment with inhaled exposure. The necessity of focusing on inhaled exposure as a treatment method, the infrastructure established with this scientific research, has been revealed.

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Sıçan modelinde klaritromisin yüklü katı lipid nanopartiküllerinin tek doz inhalasyonunun değerlendirilmesi

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ÖZ

Bu çalışmanın amacı, ilk kez nebülizatör tabanlı uygulama için tasarlanmış klaritromisin yüklü katı lipit nanopartiküllerinin (CLA-SLN) geliştirilmesi yoluyla CLA'nın etkin kullanımını araştırmaktır. Wistar albino sıçanları zaman noktalarına (0.5, 1, 2, 4, 12, 24 saat ve kontrol grubu) göre yedi gruba (n = 8) ayrıldı. İlgili zaman noktalarında, akciğer dokuları ve kan örnekleri toplandı ve HPLC-MS/MS kullanılarak CLA konsantrasyonları açısından analiz edildi. Maksimum serum konsantrasyonu (Cmax) 6,74 µg/mL iken, gruplar arasında ortalama serum CLA konsantrasyonları sırasıyla 5,06, 2,5, 2,18, 1,13 ve 0,5 µg/mL idi. CLA, kontrol grubunda ve son grubun serumunda tespit edilemedi. Doğrusal trapezoidal yöntem kullanılarak, serum CLA için eğri altında kalan alan (AUC 0-24) 17,06 µg*h/mL olarak hesaplandı. Serum CLA seviyelerinde birkaç grup arasında anlamlı farklılıklar ($p<0.001$) gözlendi. Akciğer dokusunda en yüksek Cmax 2,66 µg/g iken, ortalama konsantrasyonlar 1,99, 1,8, 1,76, 0,36, 0,14 ve 0,04 µg/g idi. Akciğer CLA konsantrasyonu için AUC 7,43 µg*h/g idi. Bulgular, CLA yüklü SLN'nin inhalasyonunun yeterli plazma ve akiğer konsantrasyonlarına ulaştığını gösterir. İnhalasyon sonrası 12 saate kadar serumm CLA seviyesinin yeterli olduğunu göstermektedir. Ancak serum CLA düzeyleri 12 saat sonra tespit edilemedi. Akciğer dokusunda ise CLA konsantrasyonunun 24 saate kadar yeterli düzeyde oluştuğunu kanıtlamaktadır. Sonuçta CLA'nın inhaler maruziyet ile tedavide kullanımının mümkün olduğu kanaatine varılmıştır. Bu bilimsel araştırma ile altyapısı oluşturulan inhaler maruziyetin tedavi yöntemi olarak kullanımı üzerinde yoğunlaşmanın gerekliliği ortaya konulmuştur.

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INTRODUCTION

Clarithromycin (CLA) is a semisynthetic macrolide antibiotic derived from erythromycin, with a broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria. It disrupts protein synthesis by inhibiting peptidyl transferase activity, leading to bacteriostatic or bactericidal effects depending on the microorganism and drug concentration. CLA is both a substrate and inhibitor of CYP3A4, affecting its metabolism and interactions (1,2). Orally administered CLA is rapidly absorbed, reaching peak concentrations within two hours, with bioavailability of approximately 50%. In the liver, it is metabolized into 14-OH-CLA, a compound with superior antimicrobial activity. This enhances overall absorption, which exceeds 50% of the administered dose. CLA binds extensively to plasma proteins, though binding decreases when concentrations exceed 72%. It demonstrates excellent tissue penetration, particularly in the lungs, where concentrations are about five times higher than in serum. Approximately 22% of an oral dose is excreted as the parent compound: 18% in urine and 4% in feces. Clearance is inversely proportional to dose, likely due to saturable hepatic metabolism, and is unaffected by age (3,4).

CLA is highly effective in treating lung infections, including chronic obstructive pulmonary disease (COPD) exacerbations (3,5,6), due to its antimicrobial and anti-inflammatory properties (7,8). Inhaled medications are advantageous for lung diseases such as asthma, COPD, and cystic fibrosis, as well as systemic conditions like diabetes and migraines. This route avoids invasive methods, bypasses first-pass metabolism, and minimizes side effects by targeting the drug directly to the respiratory tract or systemic circulation (4,9). Inhalation is a standard method for toxicological exposures (8). In terms of pharmacological exposure, drug exposure is used as a method for COPD, asthma, and cystic fibrosis (6, 9, 10). Inhaled drug treatment protocols for lung treatment are also evaluated based on inhaler efficiency (5, 11,15).

Inhaled CLA-loaded SLNs provide targeted delivery with efficient lung accumulation, offering potential for treating pulmonary and systemic diseases. This pharmacokinetic study investigated tissue accumulation of CLA after pulmonary delivery to rats, providing insights into its effectiveness and potential applications in inhalation therapy.

MATERIALS AND METHODS

Clarithromycin (CLA), with a purity of 98.7%, was procured in powder form, soluble in acetone and methylene chloride (Ind-Swift Laboratories Ltd.), while Compritol® 888 and Tween 80® were obtained from Merck® Schuchardt (Darmstadt, Germany). Additional materials, including heparinized tubes, phosphate-buffered saline (PBS, pH 7.4), and nebulizers, were commercially available and utilized for the experiments.

Preparation of CLA-Loaded SLN

The hot homogenization method described by Müller (10) was employed to produce CLA-loaded solid lipid nanoparticles (CLA-loaded SLN). A lipid melt was created at 80°C using 5% CLA, 5% Compritol 888, and 3% Tween 80 as a surfactant. CLA was incorporated into the lipid melt, and Tween 80 was added gradually, followed by vigorous mixing with an Ultra-Turrax device (T25, Janke & Kunkel IKA®, Germany) for 10 minutes. The mixture was further homogenized at 20.500 rpm for 1 minute to obtain the CLA-loaded SLN complex. The product was cooled to room temperature, filtered, and stored in sterile, colored glass tubes. Control SLNs were prepared using identical procedures, excluding CLA (1).

Characterization and Surface Morphology

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The particle size and polydispersity index (PI) of the prepared SLNs were analyzed using photon correlation spectroscopy (Nano Zetasizer ZS, Malvern, UK). The surface morphology and structural attributes of the SLNs were examined using electron microscopy, operating at varying voltages (60-120 kV) and temperatures (+/- 80°C) for enhanced imaging performance.

Experimental Protocol

In this study, eight-week-old male Wistar albino rats (350 ± 20 g) were used. Before the experimental procedures began, the rats were acclimated to the laboratory environment for five days. A total of six experimental groups and one control group were formed, each consisting of 10 rats. Among the 10 rats in each experimental group, 8 were designated for experimental analyses, while 2 were kept as backups. The rats were housed in well-ventilated cages under controlled conditions (22°C ± 2, 55-60% humidity) with a 12-hour light/dark cycle. Food and water were provided ad libitum throughout the study (2-4).

A 10L/min air flow nebulizer was used for passive inhalation of CLA-loaded SLN. The nebulizer was operated at a concentration of 0.5mL/min. Particle Size 0.5–10 μm, MMAD 4 μm were taken as reference according to manufacturer data. The drug concentration was adjusted for dosing (6.25mg/mL) (5-8). It was calculated based on a dose of 20mg/kg adjusted for rats' mean tidal volume and respiratory minute volume (85 breaths/min) (9,10). Drug deposition in the lungs was calculated using a lung deposition factor (DF) and measured via HPLC-MS/MS analysis at Tekirdağ Namık Kemal University. Blood and lung tissue samples (11-13) were collected at multiple time intervals for pharmacokinetic evaluation (14,15). Analytical instrumental parameters, mobile phase flow gradient, and MRM data are given in Table 1.

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Table 1. MRM data with analytical instrument parameters (LOD:0,5 mcg/mL, LOQ: 1 mcg/mL Blood and Lung CLA 25, 50 µg/mL spike result was obtained (Figure 1A-B).

LC Method Properties							
Injection volume	2.00 ul						
Mobile phase A	UPW containing 0,2%FA						
Flow method	Mob A: 20% Mob B 80% Isocratic						
Flow rate	0.500 mL/min						
CFT	40 ºC						
Analytical instrument parameters							
Curtain gas	30						
Collision gas	Medium						
Ion spray voltage	5500						
Temperature	500						
Ion source gas-1 (GS-2)	50						
Ion source gas-2 (GS-2)	50						
Mobile phase gradient flow program							
Time (min)	Mobile phase A (%)	Mobile phase B (%)	Flow rate (mL/min)				
00:00	50	50	0.30				
01:00	50	50	0.30				
01:10	5	95	0.30				
06:00	5	95	0.30				
06:10	50	50	0.30				
08:00	50	50	0.30				
MRM DATA							
Molecules	Q1 Mass (Da)	Q3 Mass (Da)	DP (volt)	EP (volt)	CEP (volt)	CE (volt)	CXP (volt)
CLA 1	749,27	158,11	61	6	82	35	34
CLA 2	749,27	83,1	61	8	32	77	4
UPW	Ultrapure water						
CFT	Column furnace temperature						

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Blood and Lung CLA 25, 50 µg/mL spike result was obtained (Fig. 1A-B). Blood and lung CLA (Fig. 1C-D) as well as lung (Fig. 2) calibration linearity was determined by making sufficient injections for linearity.

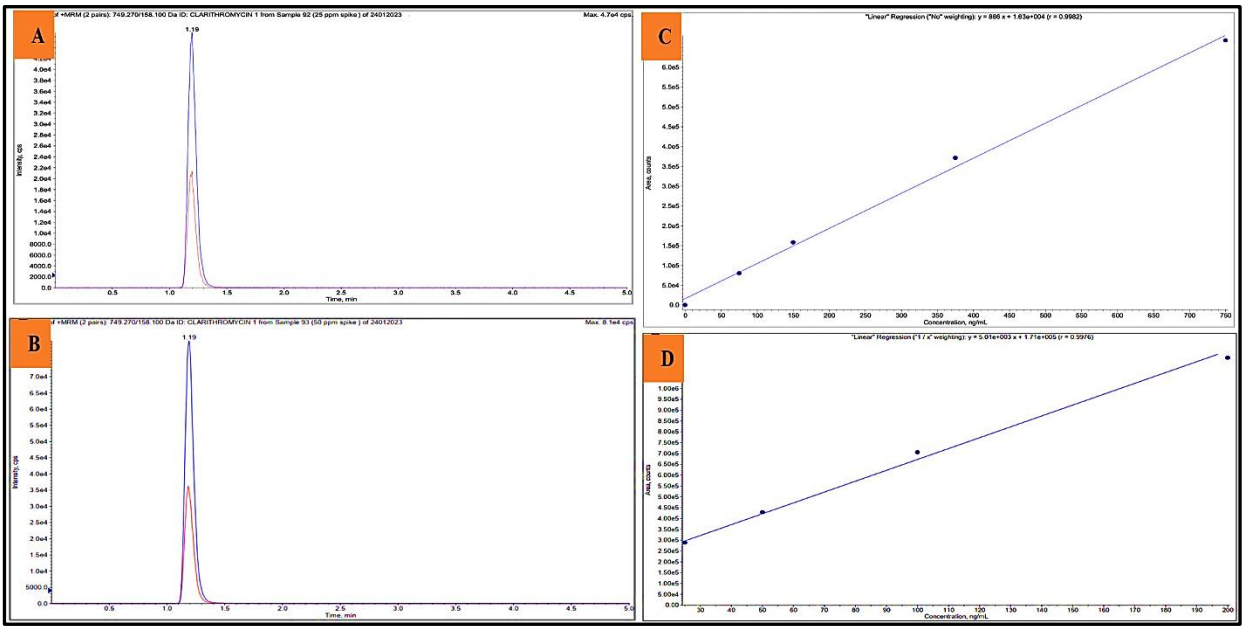

Figure 1A-D. Lung CLA 25 and 50 µg/mL spike example. Blood (C) and Lung CLA (D) calibration

Statistical Analysis

Continuous quantitative variables are expressed as mean and standard deviation; qualitative variables are expressed as n, median value, and (Q1) and (Q3) percentage values. Kolmogorov-Smirnov and Shapiro-Wilk tests were used in normality tests of variables. Kruskal-Wallis One Way Analysis of Variance on Ranks test was applied to independent variables that did not show normal distribution. Probability values of $p<0.05$ were accepted as significant. All data analyses were performed with IBM SPSS Statistics 22 package programs.

Ethical Aspects of the Research

This study adhered to ethical standards outlined in the EU Directive 2010/63/EU and was approved by the Zonguldak Bülent Ecevit University Ethics Committee (Approval No: 2021/05).

Conflict of Interest

No conflict of interest was declared by the authors. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CONCLUSIONS AND DISCUSSION

Solid lipid nanoparticles (SLNs) have emerged as a promising drug delivery system due to their ability to enhance the solubility, stability, and controlled release of poorly water-soluble drugs (1). The present study successfully formulated CLA-loaded SLNs with a particle size of approximately 300 nm, which is within the optimal size range for pulmonary drug delivery (11). Previous studies suggest that SLNs within this size range exhibit enhanced bioavailability and deeper penetration into the alveolar region, improving systemic absorption (12). Additionally, the use of Tween 80 as a surfactant played a crucial role in stabilizing the formulation, consistent with findings demonstrating that surfactants prevent particle aggregation and enhance dispersion stability (13).

Our study demonstrated that serum CLA concentrations remained at detectable levels for up to 12 hours post-inhalation, although stable detection at 24 hours was not possible. This pattern aligns with studies on other lipophilic drugs delivered via inhalation, where rapid pulmonary absorption leads to an initial high plasma concentration followed by a gradual decline (14). The area under the curve (AUC) analysis further supports that CLA remains bioavailable within a clinically relevant timeframe, comparable to other lipid-based drug formulations administered via inhalation (15).

Compared to oral CLA formulations (Table 2) inhaled CLA-loaded SLNs bypass hepatic metabolism, leading to more efficient systemic absorption. This is consistent with previous studies showing that pulmonary drug delivery can significantly enhance the bioavailability of lipophilic drugs, reducing the required dosage and minimizing systemic side effects (16).

Table 2. Polydispersity index values of CLA-SLN

Formulation	**Particle Size (nm)**	**Polidispers index (PI)**
	Mean ± S.D. (n=3)	**Mean ± S.D. (n=3)**
CLA-loaded SLN	3896±3,49	0,385±0,07

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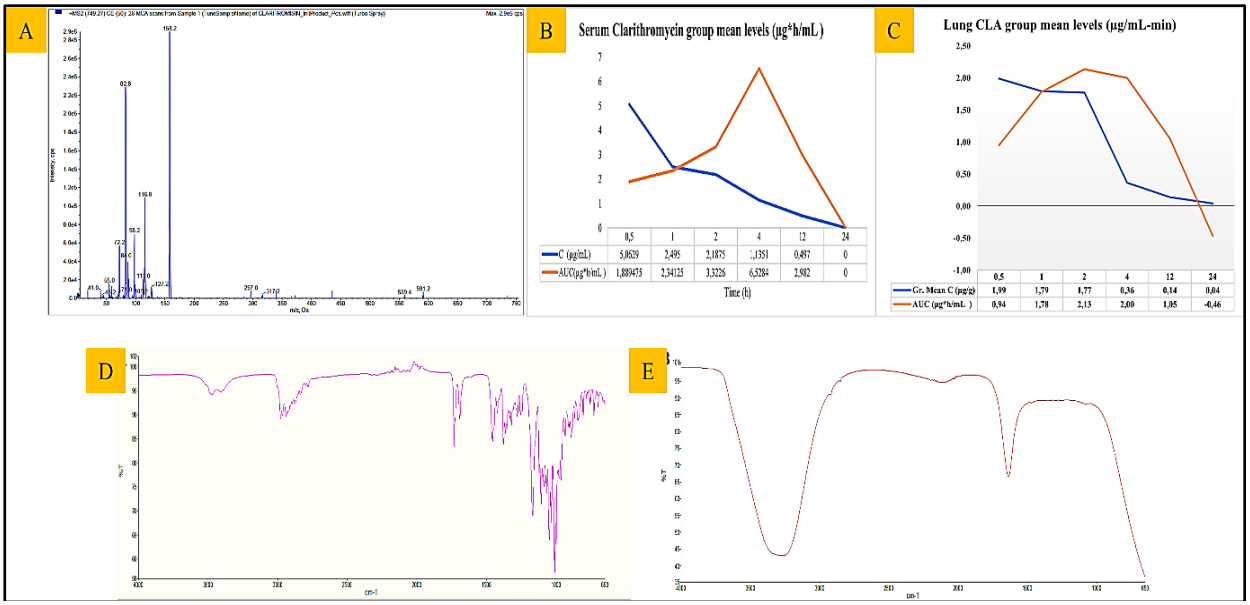

Figure 2. CLA product ion in lung sample (A), measurements of CLA-loaded SLN (D-E), Serum CLA group mean levels (B), and lung CLA group mean levels (C) (µg*h/mL)

Lung tissue accumulation data revealed a peak concentration at 0.5 hours, followed by a slow decline over 12 hours before becoming undetectable at 24 hours (Table 3). This trend aligns with studies on inhaled corticosteroids, where prolonged lung retention is influenced by lipid solubility and nanoparticle composition (7). The fact that lung CLA levels remained above the inhibitory concentration for up to 12 hours suggests that SLN formulations enhance pulmonary drug retention compared to conventional nebulized formulations, which often exhibit more rapid clearance (17).

Significant differences between experimental groups further highlight the role of formulation parameters in lung tissue accumulation. Previous studies indicate that particle size, lipid composition, and surfactant type can influence the rate of pulmonary drug clearance (18). The observed variations between groups in our study are consistent with this, suggesting that further optimization of lipid matrix composition could enhance lung retention and systemic bioavailability.

This study represents an important step toward the development of SLN-based pulmonary drug delivery systems for clinical use. The findings are particularly relevant for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), where inhalation therapy has been shown to improve drug efficacy while minimizing systemic toxicity. Similar to how inhaled corticosteroids have revolutionized asthma treatment by reducing systemic exposure, SLN formulations could offer a new strategy for delivering lipophilic drugs with challenging pharmacokinetic properties (19).
Future studies should focus on optimizing SLN formulations to improve lung retention and systemic absorption while evaluating long-term safety profiles. Additionally, comparative studies with existing nebulized formulations and dry powder inhalers would provide valuable insights into the relative advantages of SLN-based pulmonary delivery.

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Table 3. Statistical differences in serum and lung CLA concentrations of the groups

Variables	Groups	N	Mean±Std. Deviation	Median (Q1-Q3)	P	Multiple Comparisons
Lung-CLA	1	8	198,50±43,62	199,00 (175,50-224,50)	**<0,001 ***	1-4, 1-5, 1-6, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, 5-6
	2	8	179,09±48,15	173,50 (146,00-211,00)		
	3	8	176,88±34,08	192,00 (148,00-200,00)		
	4	8	36,26±16,70	35,95 (21,60-51,10)		
	5	8	13,63±4,60	12,40 (10,22-16,30)		
	6	8	3,86±1,37	3,80 (3,64-3,885)		
Serum-CLA	1	8	575,50±219,26	487,00 (439,50-652,50)	**<0,001 ****	1-2, 1-3, 1-4, 1-5, 2-4, 2-5, 3-4, 3-5, 4-5
	2	8	249,50±54,46	245,50 (217,50-289,00)		
	3	8	218,75±74,03	212,00 (167,00-262,50)		
	4	8	113,51±38,77	105,65 (88,85-133,50)		
	5	8	49,78±14,68	52,25 (40,80-60,20)		

**CLA lung accumulation between groups is statistically significant. Inhaled CLA accumulated in the lungs at a high rate after 4 hours.*

***CLA serum accumulation between groups is statistically significant. CLA has significant serum concentration before lung tissue accumulation.*

In conclusion, the findings of this study align with existing literature on pulmonary drug delivery and SLN-based formulations. The results suggest that inhalable SLNs offer a viable alternative for enhancing the bioavailability of poorly soluble drugs while maintaining lung tissue drug levels within therapeutic ranges. Given the increasing interest in inhaled nanoparticles for drug delivery, further research into SLN formulations may contribute to the development of novel therapeutic approaches for respiratory and systemic diseases.

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