Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 22 May 2026
Revised 16 June 2026
Accepted 04 July 2026

Natural Resources for Human Health 2026, Vol. 6 (4s): 844-855

KEYWORDS:
Micafungin sodium, PLGA, pulmonary drug delivery, nanoformulation, nebulization, aerosol characterization.

Physicochemical Characterization and in Vitro Aerosol Performance of a Nebulizable PLGA Micafungin Nanoformulation for Sino-Pulmonary Fungal Infections

Aqsa B. Quazi[1*], Mohamed H. Dehghan[2]

[1]Author, YB Chavan College of Pharmacy: Aurangabad, Maharashtra, IN
E-mail: quaziaqsa@gmail.com, ORCID No: 0000-0003-2795-0164
[2]Co-author, YB Chavan College of Pharmacy: Aurangabad, Maharashtra, IN
E-mail: mhdehghan@hotmail.com, ORCID No: 0000-0002-8082-9454
Corresponding author: Ms. Aqsa B. Quazi

ABSTRACT: Pulmonary fungal infections remain a major therapeutic challenge, and localized drug delivery through inhalation offers the potential to improve treatment efficacy while reducing systemic adverse effects. The present study aimed to characterize an optimized nebulizable micafungin-loaded PLGA nanoformulation for pulmonary drug delivery. The optimized formulation, developed using a 2^3 full factorial design, was evaluated for its physicochemical properties, morphological characteristics, residual solvent content, nebulization performance, and aerodynamic behavior. Particle size, polydispersity index, zeta potential, and entrapment efficiency were determined, while transmission electron microscopy (TEM), polarized light microscopy (PLM), and gas chromatography–mass spectrometry (GC–MS) were employed for morphological and residual solvent analysis. Nebulization performance and aerosol characteristics were further assessed using a vibrating mesh nebulizer and cascade impactor, respectively. The optimized nanoformulation exhibited desirable physicochemical and aerosolization characteristics, efficient nebulization performance, and no detectable residual organic solvent, indicating its suitability for pulmonary administration. These findings demonstrate the potential of the developed micafungin-loaded PLGA nanoformulation as a promising inhalable antifungal drug delivery system for the management of pulmonary fungal infections.

INTRODUCTION

Pulmonary fungal infections represent a growing global health burden, particularly among immunocompromised patients, individuals receiving chemotherapy, transplant recipients, and critically ill patients requiring mechanical ventilation. Opportunistic pathogens such as *Candida* species are frequently implicated in pulmonary infections and colonization, contributing significantly to morbidity and mortality in susceptible populations[1]. Despite advances in antifungal therapy, effective management remains challenging due to inadequate drug concentrations at the site of infection and variability in clinical response.

Micafungin sodium, a member of the echinocandin class, exerts its antifungal activity by inhibiting β-(1,3)-D-glucan synthesis, a key structural component of the fungal cell wall. It demonstrates potent fungicidal activity against *Candida* species and is

widely used for invasive candidiasis. However, its clinical application is limited to intravenous administration due to poor oral bioavailability and physicochemical constraints[2]. Although systemic administration provides therapeutic plasma levels, it may not ensure optimal drug distribution within pulmonary tissues and is associated with systemic exposure and potential adverse effects.

Pulmonary drug delivery has emerged as a promising alternative approach for targeting respiratory infections, offering advantages such as localized drug deposition, rapid onset of action, and reduced systemic toxicity. Inhaled antifungal therapy is increasingly being explored; however, its clinical utility remains under investigation due to challenges associated with formulation stability, aerosolization efficiency, and variability in lung deposition[4]. Previous studies have demonstrated the feasibility of delivering micafungin via nebulization, achieving favorable aerodynamic properties such as high fine particle fraction and suitable mass median aerodynamic diameter for deep lung deposition[5].

The development of effective pulmonary formulations requires careful optimization of physicochemical properties, including particle size distribution, surface charge, morphology, viscosity, and drug encapsulation efficiency. Polymeric systems such as poly(lactic-co-glycolic acid) (PLGA) have been extensively investigated due to their biodegradability, biocompatibility, and ability to provide controlled drug release[6]. Additionally, surfactants like Poloxamer 188 play a crucial role in stabilizing emulsion systems and influencing aerosol performance[7]. Importantly, pulmonary conditions such as the presence of lung surfactant can significantly affect antifungal drug activity, highlighting the need for formulation-specific evaluation[8].

Therefore, the present study aims to develop a nebulizable oil-in-water emulsion of micafungin sodium using PLGA and to perform comprehensive physicochemical characterization of the formulation. Furthermore, the study seeks to generate critical input parameters that can support future PBPK[9] modeling and facilitate the translation of this formulation into an effective pulmonary drug delivery system for antifungal therapy.

2.MATERIALS AND METHODS

2.1 Materials

Micafungin sodium was obtained as a gift sample Bicon Ltd. Poly(lactic-co-glycolic acid) (PLGA) was purchased from Nomisma healthcare. Dichloromethane (DCM) of analytical grade was used as the organic solvent. Poloxamer 188 procured from a certified supplier. All other reagents and chemicals used were of analytical grade, and distilled water was used throughout the study.

2.2 Preliminary Screening of Variables

Preliminary trials were conducted and Placket-Burman design for screening was used to identify critical and non-critical formulation variables. Based on these studies, the following parameters were found to have insignificant effects on the dependent variables and were therefore kept constant:

- Amount of micafungin: 50 mg
- Volume of dichloromethane: 5 mL
- Temperature: 20°C
- Homogenization time: 5 minutes
- Stirring speed: 300 RPM

This step ensured that further optimization focused only on the most influential variables.

2.3 Experimental Design

The optimized micafungin-loaded PLGA nanoformulation used in the present study was selected from formulations developed using a 2^3 full factorial design. The experimental design evaluated the influence of three independent variables, namely PLGA concentration (100 and 200 mg), Poloxamer 188 concentration (100 and 200 mg), and sonication amplitude (40% and 70%), on the physicochemical characteristics of the nanoformulation. Eight experimental formulations (FD-1 to FD-8) representing all possible combinations of the selected variables were prepared and evaluated. Particle size,

polydispersity index (PDI), zeta potential, and entrapment efficiency were used as the critical quality attributes for formulation optimization. Based on the optimization results, batch FD-4 was selected for further physicochemical characterization, nebulization studies, aerosol performance evaluation, and morphological analysis.

2.4 Preparation of Micafungin O/W Emulsion

Micafungin-loaded emulsions were prepared using the solvent evaporation technique. Briefly, micafungin sodium and PLGA were dissolved in dichloromethane to form the organic phase. The aqueous phase was prepared by dissolving Poloxamer 188 in distilled water. The organic phase was then slowly added to the aqueous phase under continuous stirring to form a coarse emulsion.

The emulsion was subjected to homogenization at the specified amplitude (as per factorial design) to obtain a fine emulsion. Subsequently, the system was stirred continuously to allow evaporation of dichloromethane, resulting in the formation of a stable polymeric dispersion.

All batches were prepared according to the design matrix.

2.5 Physicochemical Characterization

2.5.1 Particle Size and Polydispersity Index (PDI)

The average particle size and polydispersity index (PDI) of the optimized micafungin-loaded nanoformulation were determined by dynamic light scattering (DLS) using a Nanoplus Particle Size Analyzer (Micromeritics Instrument Corporation, USA). Prior to analysis, the formulation was appropriately diluted with distilled water to minimize multiple scattering effects. All measurements were performed at room temperature.

2.5.2 Zeta Potential

The zeta potential of the optimized nanoformulation was determined using the same instrument to assess the surface charge and colloidal stability of the nanoparticles. The samples were diluted with distilled water before analysis, and measurements were performed under standard operating conditions.

2.5.3 Entrapment Efficiency

The entrapment efficiency (EE) of the optimized nanoformulation was determined by the indirect method. The formulation was centrifuged to separate the unentrapped drug from the nanoparticle dispersion. An aliquot (1 mL) of the clear supernatant was collected and diluted to 10 mL with distilled water. The absorbance of the diluted sample was measured at 271 nm using a UV–Visible spectrophotometer. The concentration of free micafungin was determined from the previously established calibration curve. The entrapment efficiency was calculated using the following equation:

$$EE\% = \frac{Total\ drug\ concentration - free\ drug\ concentration}{Total\ drug\ concentration}\ 100$$

2.5.4 Statistical Analysis and Optimization

The experimental data obtained from the factorial design were analyzed to evaluate the effect of independent variables on the responses. The optimized formulation was selected based on minimum particle size, low PDI, adequate zeta potential, and maximum entrapment efficiency.

2.5.5 Morphological Analysis

2.5.5.1 Polarised light microscopy

The morphology of formulation was examined using polarized light microscopy (PLM). A small drop of the formulation was placed on another glass slide, covered with a coverslip, and both were observed under a polarized light microscope. The presence or absence of birefringence was noted.

2.5.5.2 Transmission electron microscopy

The morphology and particle size of the optimized micafungin-loaded nanoformulation were examined using a Transmission Electron Microscope (TEM) (Thermo Fisher Scientific, Talos L120C G2, Czech Republic). The samples were examined at an accelerating voltage of 120 kV. TEM images were acquired at appropriate magnifications within the instrument's operating range (34×–650,000×)

2.5.6 Differential scanning calorimetry

Pure Micafungin sodium drug was analyzed using differential scanning calorimeter, DSC 60 plus Shimadzu (Shimadzu,Kyoto,Japan). Scanning temperature ranged from 0 to 200 ^{0}C at a heating range of 10^0/min under a constant nitrogen purge flow of 50 ml/ min.

2.5.7 pH Measurement

The pH of the formulation was measured using a calibrated digital pH meter at room temperature to ensure suitability for pulmonary administration.

2.5.8 Density and Viscosity Measurement

Density of the formulation was determined using a density bottle at 25 ± 1 °C. The bottle was weighed empty, filled with distilled water, and subsequently with the formulation. Density was calculated based on the weight difference relative to water

Viscosity of the formulation was determined using a Brookfield viscometer at controlled temperature 25±2^{0}C. S61 spindle and rotation speed of 100 RPM were selected based on the viscosity range of the sample.

2.6 Residual solvent analysis by GCMS

Residual dichloromethane in the nanoformulation was analyzed by headspace gas chromatography–mass spectrometry (HS-GC-MS) using a GCMS-QP 2020 system. The sample was sealed in a headspace vial, equilibrated at elevated temperature, and the vapor phase was injected into the GC-MS. Separation was achieved on a capillary column using helium as the carrier gas, and detection was performed by electron ionization mass spectrometry. Dichloromethane was identified by retention time and mass spectral comparison with an authentic standard.

2.7 Nebulization performance

2.7.1 Nebulization time

The nebulization time of the developed nanoformulation was evaluated using a mesh nebulizer (Mini Vaporizer). Briefly, 2 mL of the formulation was transferred into the medication reservoir of the nebulizer. The nebulizer was operated under ambient laboratory conditions. The time required for complete nebulization, from the onset of aerosol generation until no visible aerosol was produced, was recorded using a stopwatch. The experiment was performed in triplicate, and the nebulization time was expressed as mean ± standard deviation (SD).

2.7.2 Nebulization output

After nebulization, the residual volume remaining in the medication reservoir was measured, and the nebulization output was calculated using formula:

$$Output\ rate = \frac{Initial\ \ volume - residual\ volume}{Nebulisation\ time}.$$

All measurements were performed in triplicate and expressed as mean ± SD.

2.7.3 Determination of Aerodynamic Particle Size Distribution

The aerodynamic particle size distribution (APSD) of the developed Micafungin Nanoformulation was evaluated using an Andersen Cascade Impactor (ACI) operated at a flow rate of 28.3 L/min[13-15]. Following aerosolization, the drug deposited on each stage of the impactor was quantitatively recovered. The recovered drug mass at each stage was used to determine the aerodynamic particle size distribution, fine particle fraction and Mass median aerodynamic diameter.

2.8 In vitro release

In vitro release of micafungin sodium from the nanoformulation was assessed by dialysis bag diffusion. The formulation-loaded dialysis bag was placed in phosphate-buffered saline (pH 7.4) at 37 ± 0.5 °C with stirring at 200 rpm. At fixed intervals, aliquots were collected and replaced with fresh buffer to ensure sink conditions. Drug content in each sample was quantified spectrophotometrically at 271 nm, and cumulative release (%) was plotted against time to characterize release kinetics. Experiments were conducted in triplicate.

2.9 Stability Studies

Intermediate, long-term and accelerated stability studies were carried out in accordance with ICH guidelines. The optimized formulation was stored in amber-colored glass bottles to protect from light exposure.

Samples were maintained under the following conditions:

• 30 ± 2 °C / 65 ± 5% RH (intermediate conditions)

• 25 ± 2°C / 60% RH (long-term conditions)

• 40 ± 2°C / 75% RH (accelerated conditions)

All samples were stored in a dark environment, and temperature and humidity were monitored using calibrated digital instruments.

The formulations were evaluated at predetermined intervals for changes in particle size, polydispersity index, phase separation, and visual appearance.

3. RESULTS AND DISCUSSION

3.1 Physicochemical Characterization

3.1.1 Selection of the Optimized Nanoformulation

The physicochemical characteristics of the experimental formulations generated using the 2^3 factorial design were evaluated to identify the optimized nanoformulation for subsequent characterization studies. The formulations exhibited particle sizes ranging from 153 to 182 nm**,** with PDI values between 0.118 and 0.196, indicating a narrow particle size distribution. The zeta potential ranged from −8.66 to −14.70 mV, suggesting moderate electrostatic stability, while entrapment efficiency varied from 78.68% to 86.39%**,** demonstrating efficient encapsulation of micafungin within the PLGA matrix.

Among the investigated formulations, FD-4 was selected as the optimized batch because it exhibited a desirable combination of physicochemical characteristics, including a particle size of 155 nm**,** PDI of 0.159**,** zeta potential of −14.70 mV, and entrapment efficiency of 85.38%. These characteristics are considered suitable for pulmonary drug delivery, as nanosized particles with a narrow size distribution facilitate reproducible aerosolization and efficient lung deposition. Therefore, the optimized formulation (FD-4) was selected for subsequent PLM, TEM GC–MS, nebulization performance, and cascade impactor studies.

3.1.2 Morphological Analysis

3.1.2.1 Polarized light microscopy

The nanoemulsion formulation exhibited a uniform, featureless field with no observable crystalline morphology (**Figure 1)**, indicating successful molecular dispersion of the drug within the formulation matrix.

3.1.2.2 Transmission electron microscopy

TEM analysis demonstrated the formation of discrete nanoparticles exhibiting quasi-spherical morphology (**Figure 2)**. The particles were well dispersed with minimal aggregation. The observed particle size was approximately 200–250 nm. The presence of electron-dense regions within and around some nanoparticles may indicate successful incorporation of micafungin within the polymeric matrix. Overall, the TEM micrographs confirmed the successful formation of nanosized polymeric particles suitable for pulmonary drug delivery applications.

3.1.3 Differential scanning calorimetry

Differential scanning calorimetry of the pure drug did not show a sharp melting endotherm (**Figure 3**); instead, a gradual decline in heat flow was observed, suggesting thermal degradation prior to melting. This indicates that micafungin sodium is heat-labile, which is consistent with its structural complexity and peptide-like nature. The absence of defined crystalline features in the formulation, together with the thermal behavior of the pure drug, supports the effective transformation of micafungin into a dispersed or amorphous state, which is expected to enhance its dissolution and pulmonary bioavailability.

3.1.4 pH Measurement

The optimized nanoemulsion exhibited a pH of 6.90 ± SD (n = 3), which is close to the physiological pH of the respiratory tract and is therefore expected to minimize airway irritation upon pulmonary administration. The pH of the formulation being close to physiological lung pH suggests good compatibility and minimal risk of irritation upon pulmonary delivery[10].

3.1.5 Density and viscosity

The density was determined to be 0.995 g/mL. The density, being comparable to that of water, supports efficient aerosolization. Viscosity measurements using a Brookfield viscometer (spindle S61, 100 rpm, 25 ± 2°C) showed a value of 12 cP, indicating a low-viscosity system suitable for nebulization. Viscosity is a critical parameter influencing nebulization performance; the observed value (12 cP) lies within the acceptable range for nebulizable formulations (<15 cP), ensuring ease of atomization and formation of fine droplets[11].

Collectively, these physicochemical properties confirm the suitability of the optimized nanoemulsion for pulmonary drug delivery.

3.2 Residual solvent analysis

Residual solvent analysis by GC–MS was carried out to determine the presence of residual dichloromethane (DCM) in the optimized micafungin-loaded nanoformulation. No detectable DCM peak was observed in the chromatogram, indicating efficient removal of the solvent during the formulation process. The absence of residual dichloromethane suggests that the solvent evaporation technique was effective in eliminating the organic solvent from the final product. As dichloromethane is classified as a Class 2 residual solvent under the ICH Q3C (R8) guideline[12]**,** its complete removal is important to reduce the risk of solvent-related toxicity, particularly for pulmonary drug delivery. These results confirm that the optimized nanoformulation meets the recommended safety requirements for residual solvents and is suitable for further development as an inhalable formulation.

3.3 Nebulization performance

3.3.1 Nebulization time

The nebulization performance of the optimized micafungin-loaded nanoformulation was evaluated using a mesh nebulizer. The formulation exhibited complete nebulization with a mean nebulization time of 4 min 30 s**.** These findings suggest that the developed formulation is appropriate for inhalation therapy and can generate aerosol efficiently.

The mean nebulization time of 4 min 30 s obtained in the present study is in agreement with the findings of Slator *et al*, indicating that the optimized formulation is suitable for rapid and efficient pulmonary administration [13].

3.3.2 Nebulization output

The nebulization output rate of the optimized micafungin-loaded nanoformulation wa**s** 0.44 mL/min, calculated from an initial formulation volume of 2 mL and a mean nebulization time of 4 min 30 s. The obtained output rate is comparable with those reported for commercially available vibrating mesh nebulizers. Hatley et al. reported a mean output rate of approximately 0.55 mL/min for the InnoSpire Go mesh nebulizer, demonstrating consistent aerosol generation and treatment times[14]. Similarly, Beck-Broichsitter et al. observed that the output rate of vibrating mesh nebulizers varies with formulation properties such as viscosity and conductivity, with reported values ranging from 0.2 to 1.0 mL/min[15]. Therefore, the output rate of the developed nanoformulation falls well within the range reported for efficient mesh nebulizers.

3.3.3 Determination of Aerodynamic Particle Size Distribution

The aerodynamic performance of the developed formulation was evaluated using the Andersen Cascade Impactor[16&17]. The recovered drug mass was distributed across all impactor stages, indicating efficient aerosol dispersion **(Table 1)**

The formulation exhibited an estimated MMAD of approximately 4.3 μm, which falls within the recommended aerodynamic size range (1–5 μm) for pulmonary drug delivery. Aerosol particles within this size range are capable of bypassing deposition in the oropharyngeal region and efficiently reaching the lower respiratory tract[18].

The calculated Fine Particle Fraction (FPF) was 53.8%**,** indicating that more than half of the recovered dose consisted of respirable particles with an aerodynamic diameter below 4.7 μm. A high FPF is indicative of efficient aerosolization and enhanced pulmonary deposition[18].

Based on the MMAD value, the developed formulation is expected to deposit predominantly in the bronchi and bronchioles, while a proportion of the particles may also reach the alveolar region**,** thereby improving drug delivery to the lower respiratory tract. The obtained aerodynamic characteristics suggest that the formulation possesses suitable inhalation properties for pulmonary administration.

3.4 In Vitro Drug Release

The optimized formulation exhibited a sustained release profile over 24 hours, with approximately 95% cumulative drug release (**Figure 4)**.

The release pattern showed initial burst release due to surface-associated drug which was later followed by sustained release governed by diffusion through PLGA matrix. The kinetic modeling revealed the release best fits Higuchi model ($R^2 \approx 0.9896$) indicating diffusion is controlled release

This sustained release profile supports prolonged drug residence in the lungs, which is beneficial for antifungal therapy.

3.5 Stability Studies

Table 3 provides results obtained for Stability Studies of Micafungin sodium nanoformulation.

The optimized formulation remained physically stable under all ICH storage conditions. Throughout the study, the formulation exhibited no signs of phase separation, creaming, or cracking**,** indicating good physical integrity of the nanoemulsion system. The formulation consistently maintained a uniform white appearance**,** characteristic of oil-in-water nanoemulsions, with no visible aggregation or instability. Additionally**,** no changes in color or odor were observed during the storage period.

The absence of instability phenomena under all storage conditions may be attributed to effective steric stabilization provided by the surfactant system and the optimized droplet size distribution. Furthermore, the maintained physical characteristics indicate resistance to destabilization mechanisms such as coalescence and Ostwald ripening.

The quantitative stability assessment of the optimized micafungin formulation demonstrated only minimal variations in physicochemical parameters**.** A slight increase in particle size was observed, particularly under accelerated conditions; however, the values remained within the nanoscale range, indicating the absence of significant droplet aggregation or coalescence. Similarly, the polydispersity index showed a marginal increase but remained below 0.2, confirming the preservation of a relatively uniform size distribution.

The zeta potential exhibited a minor reduction in magnitude over time, which may be attributed to slight changes in interfacial characteristics; nevertheless, the values remained sufficiently negative to maintain electrostatic and steric stabilization of the system. Entrapment efficiency showed a gradual but limited decrease under elevated temperature and humidity conditions, possibly due to minimal drug diffusion from the dispersed phase; however, the retention of high drug content indicates effective encapsulation stability.

Importantly, these changes were more pronounced under accelerated conditions compared to long-term and intermediate storage, which is consistent with the expected impact of temperature and humidity on emulsion systems. Despite these minor

variations, no significant instability phenomena such as phase separation, creaming, or cracking were observed, and the formulation maintained its physical integrity.

Table 1. Drug deposition profile of the optimized micafungin sodium nanoemulsion determined using the Andersen Cascade Impactor (n = 3).

Stage	**Cut-off Diameter (µm)**	**Drug Deposition (mg, Mean ± SD)**	**Drug Deposition (%, Mean ± SD)**
Stage 0	9.0	**0.47 ± 0.06**	**7.23 ± 0.24**
Stage 1	5.8	**0.70 ± 0.10**	**10.77 ± 0.27**
Stage 2	4.7	**1.80 ± 0.10**	**27.69 ± 0.71**
Stage 3	3.3	**1.00 ± 0.10**	**15.39 ± 1.08**
Stage 4	2.1	**1.47 ± 0.15**	**22.57 ± 1.09**
Stage 5	1.1	**1.07 ± 0.12**	**16.35 ± 1.43**
Total recovered dose	—	**6.50 ± 0.20**	**100.00**

Table 2. Aerodynamic performance parameters of the optimized micafungin sodium nanoemulsion (n = 3).

Parameter	**Mean ± SD**
Total recovered dose (mg)	**6.50 ± 0.20**
Fine particle dose (Stages 3–5, mg)	**3.53 ± 0.15**
Fine Particle Fraction (FPF, %)	**54.31 ± 0.95**
Estimated MMAD (µm)	**4.3 ± 0.2**

Table 3: Stability studies of the optimized micafungin sodium nanoemulsion under ICH storage conditions.

Parameter	**Initial**	**Long-term (25 ± 2 °C / 60 ± 5% RH, 12 months)**	**Intermediate (30 ± 2 °C / 65 ± 5% RH, 6 months)**	**Accelerated (40 ± 2 °C / 75 ± 5% RH, 6 months)**
Appearance	White, homogeneous	White, homogeneous	White, homogeneous	White, homogeneous
Phase separation	Absent	Absent	Absent	Absent
Creaming / Cracking	Absent	Absent	Absent	Absent
Color	No change	No change	No change	No change
Odor	Characteristic	No change	No change	No change
Parameter	**Initial**	**12 months (LT)**	**6 months (INT)**	**6 months (ACC)**
Particle size (nm)	155 ± 0.961	158 ± 892	155 ± 0.962	156 ± 0.881

PDI	0.159	0.162	0.160	0.165
Zeta potential (mV)	−14.7	−14.2	−14.8	−14.1
EE (%)	85.3	84.5	83.8	82.6

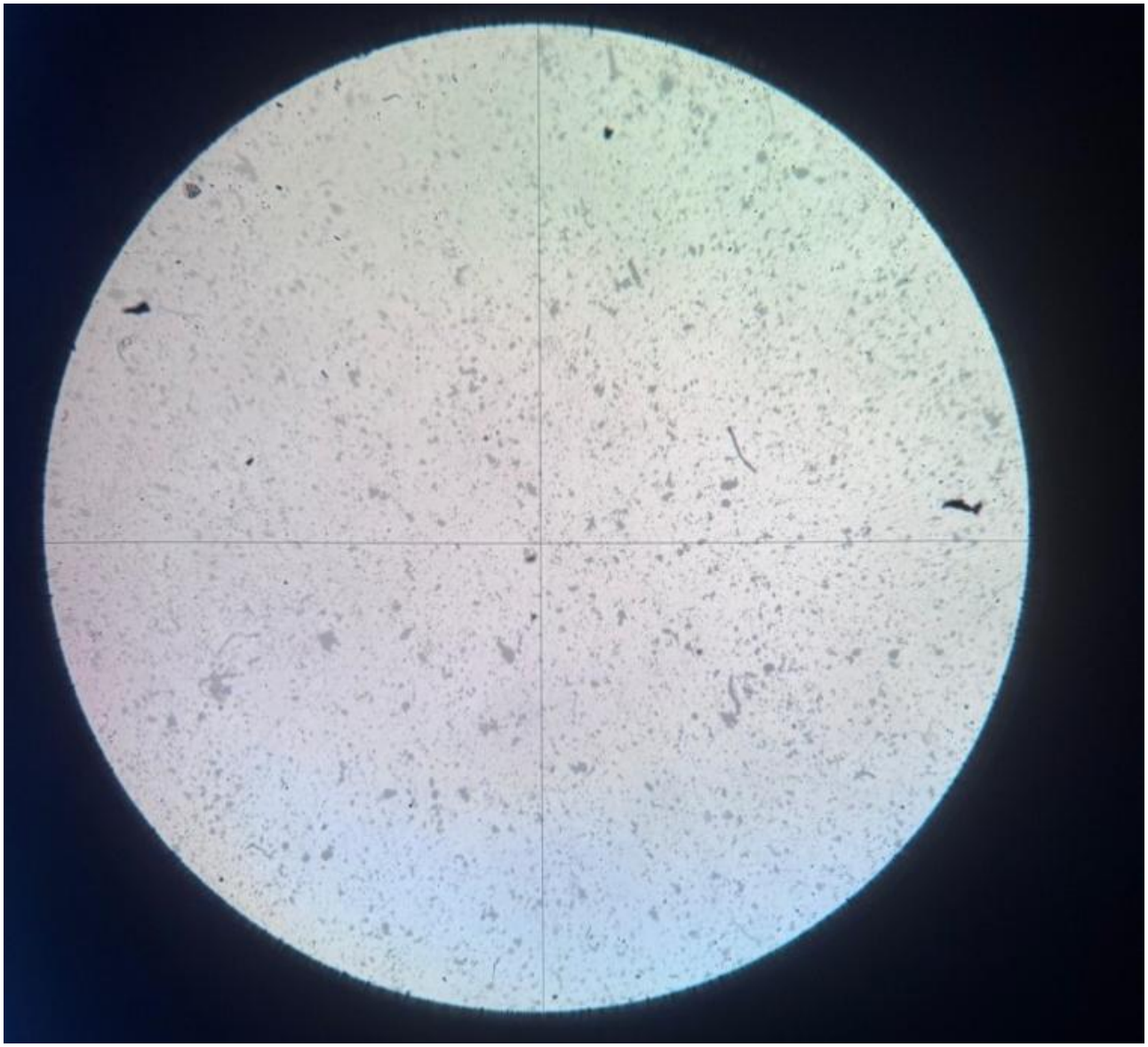

Figure 1. Polarized light microscopy (PLM) images of the optimized micafungin sodium nanoemulsion showing the absence of visible crystalline drug particles, indicating successful molecular dispersion of the drug within the formulation.

Natural Resources for Human Health
eISSN: 2583-1194

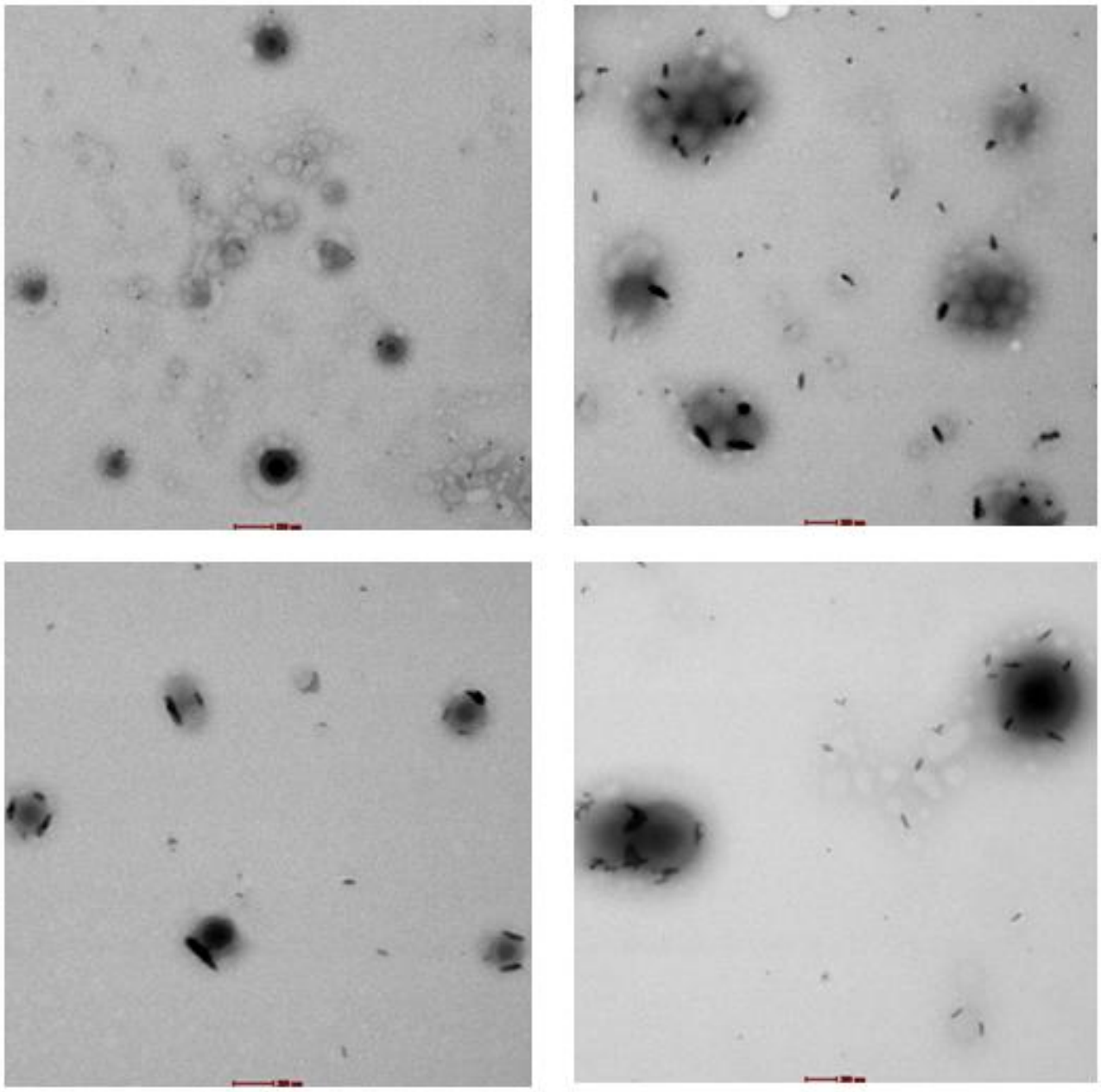

Figure 2: Representative transmission electron microscopy (TEM) micrographs of the optimized micafungin sodium nanoemulsion.

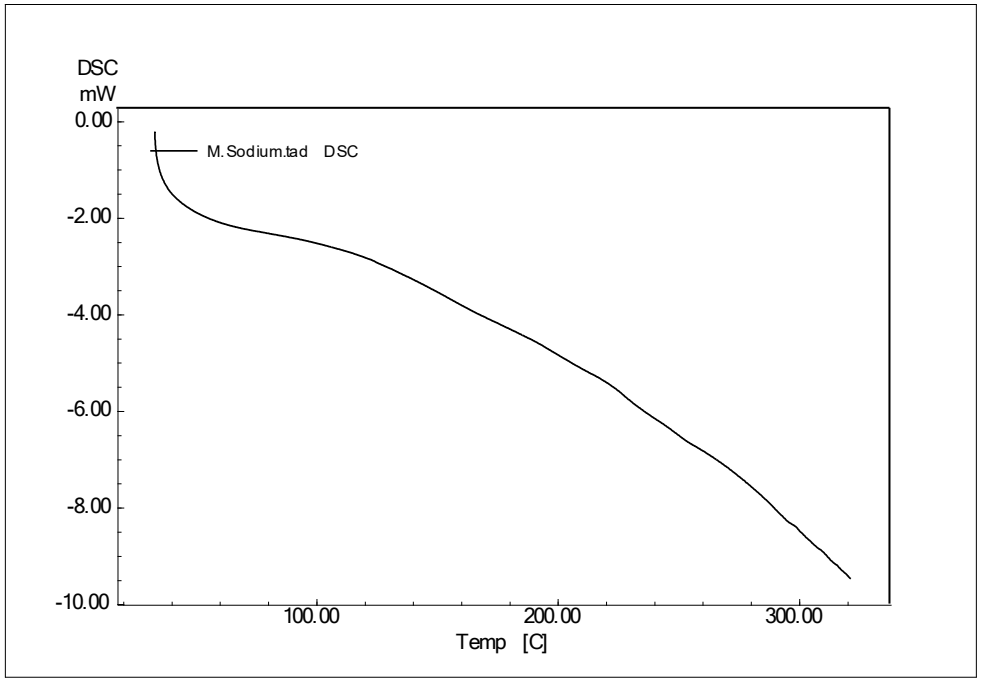

Figure 3: Differential scanning calorimetry (DSC) thermograms of pure micafungin sodium

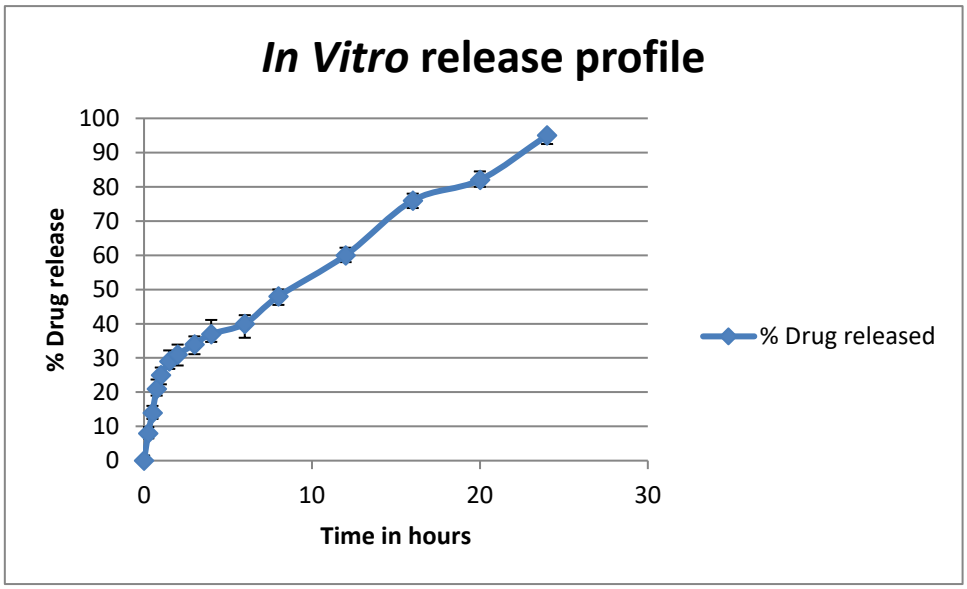

Figure 4: In vitro drug release profile of the optimized micafungin sodium nanoemulsion

REFERENCES

[1] Li L, Su S, Yang H, Xie HB. Clinical outcomes of antifungal therapy on Candida pulmonary colonisation in immunocompetent patients with invasive ventilation: a systematic review and meta-analysis. BMJ Open. 2024;14(10):e083918. doi:10.1136/bmjopen-2024-083918.

[2] Wiederhold NP, Cota JM, Frei CR. Micafungin in the treatment of invasive candidiasis and invasive aspergillosis. Infect Drug Resist. 2008;1:63–77. doi:10.2147/IDR.S3882.

[3] Wasmann RE, Muilwijk EW, Burger DM, Verweij PE, Knibbe CAJ, Brüggemann RJM. Clinical pharmacokinetics and pharmacodynamics of micafungin. Clin Pharmacokinet. 2018;57(3):267–286. doi:10.1007/s40262-017-0578-5.

[4] Vuong NN, Hammond D, Kontoyiannis DP. Clinical uses of inhaled antifungals for invasive pulmonary fungal disease: promises and challenges. J Fungi (Basel). 2023;9(4):464. doi:10.3390/jof9040464.

[5] Shi S, Ashley ES, Alexander BD, Hickey AJ. Initial characterization of micafungin pulmonary delivery via two different nebulizers and multivariate data analysis of aerosol mass distribution profiles. AAPS PharmSciTech. 2009;10(1):129–137. doi:10.1208/s12249-009-9185-6.

[6] Makadia HK, Siegel SJ. Poly(lactic-co-glycolic acid) (PLGA) as biodegradable controlled drug delivery carrier. Polymers (Basel). 2011;3(3):1377–1397. doi:10.3390/polym3031377.

[7] Yegorov A, Pushkin S, Arshintseva E, Molchanov M, Timchenko M. Influence of parameters used to prepare sterile solutions of Poloxamer 188 on their physicochemical properties. Polymers (Basel). 2025;17(1):62. doi:10.3390/polym17010062.

[8] Nussbaumer-Pröll A, Matzneller P, Eberl S, Zeitlinger M. Pulmonary surfactant impacts in vitro activity of selected antifungal drugs against Candida krusei and Candida albicans. Eur J Clin Microbiol Infect Dis. 2024;43(5):927–936. doi:10.1007/s10096-024-04799-7.

[9] Albanell-Fernández M. Echinocandins pharmacokinetics: a comprehensive review of micafungin, caspofungin, anidulafungin, and rezafungin population pharmacokinetic models and dose optimization in special populations. Clin Pharmacokinet. 2025;64(1):27–52. doi:10.1007/s40262-024-01461-5.

[10] Pezzulo AA, Tang XX, Hoegger MJ, Alaiwa MH, Ramachandran S, Moninger TO, et al. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. Nature. 2012;487(7405):109–113. doi:10.1038/nature11130.

[11] Le Brun PPH, de Boer AH, Heijerman HGM, Frijlink HW. A review of the technical aspects of drug nebulization. Pharm World Sci. 2000;22(3):75–81. doi:10.1023/A:1008786600530.

[12] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline Q3C(R8): Impurities: Guideline for Residual Solvents. Geneva: ICH; 2021.

[13] Slator L, Quadrelli F, von Hollen D, Hardaker L. Evaluation of delivered dose and treatment time of several mesh nebulizers under in vitro simulated use. Eur Respir J. 2017.

[14] Hatley RHM, Hardaker LEA, Metcalf AP, et al. Ensuring the consistency of performance of mesh nebulizers. In: Proceedings of Drug Delivery to the Lungs 27 (DDL27). Edinburgh, UK: The Aerosol Society; 2016.

[15] Beck-Broichsitter M, Oesterheld N, Knuedeler MC, Seeger W, Schmehl T. On the correlation of output rate and aerodynamic characteristics in vibrating-mesh-based aqueous aerosol delivery. Int J Pharm. 2014;461(1–2):34–37. doi:10.1016/j.ijpharm.2013.11.033.

[16] United States Pharmacopeial Convention. United States Pharmacopeia–National Formulary (USP–NF). General Chapter <601> Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers. Rockville (MD): United States Pharmacopeial Convention.

[17] European Directorate for the Quality of Medicines & HealthCare (EDQM). European Pharmacopoeia. Chapter 2.9.18. Preparations for Inhalation: Aerodynamic Assessment of Fine Particles.

[18] Mitchell JP, Nagel MW. Cascade impactors for the size characterization of aerosols from inhalers. J Aerosol Med. 2003;16(4):341–377. doi:10.1089/089426803322994482.