RESEARCH PAPER

Development and Optimization of Solid Lipid Nanoparticles for Improved Antifungal Efficacy

Ritesh Raj[1*], Ajay Kumar[1], Abhishek Sahu[1], Ranu Mandlekar[1], Prasant Chaturvedi[1], Lalita Uikey[1], Nitin Patel[1]

[1] SAM College of Pharmacy, Faculty of Medical and Paramedical Sciences, SAM Global University, Raisen, Madhya Pradesh, India - 464551

[*] **Corresponding Author:** Ritesh Raj. Email: ritesh.raj197@gmail.com | Mobile No: 9302633935

Received: 17th Mar, 2026 | Revised: 29th Mar, 2026 | Accepted: 19th Apr, 2026 | Available Online: 5th May, 2026

ABSTRACT

The therapeutic effectiveness of antifungal agents is often limited by poor aqueous solubility, low bioavailability, and insufficient penetration into infected tissues. Solid lipid nanoparticles (SLNs) have emerged as a promising drug delivery system to overcome these limitations by enhancing drug stability, controlled release, and targeted delivery. The present study focuses on the development and systematic optimization of SLNs encapsulating a model antifungal agent to improve its therapeutic efficacy. SLNs were prepared using a high-shear homogenization followed by ultrasonication method, employing biocompatible lipids and surfactants. Critical formulation variables, including lipid concentration, surfactant type, and homogenization parameters, were optimized using a design of experiments (DoE) approach to achieve minimal particle size, high drug loading, and optimal stability. The optimized formulation exhibited a particle size below 200 nm, narrow polydispersity index, and high entrapment efficiency, indicating uniform and stable nanoparticle formation. In vitro release studies demonstrated a sustained drug release profile over 24 hours, which is advantageous for prolonged antifungal activity. Furthermore, antifungal efficacy studies against Candida albicans revealed significantly enhanced inhibition compared to the conventional drug formulation, attributed to improved cellular uptake and prolonged drug exposure. Stability studies confirmed that the SLNs maintained their physicochemical properties under standard storage conditions. Overall, the findings highlight that SLNs provide an efficient platform for enhancing antifungal drug delivery by improving solubility, stability, and bioavailability. This study establishes a robust formulation and optimization framework that can be extended to other poorly soluble antifungal agents. The integration of nanotechnology-based delivery systems such as SLNs holds substantial promise for improving clinical outcomes in the treatment of fungal infections.

Keywords: Solid lipid nanoparticles, Antifungal drug delivery, Nanocarriers, Controlled release, Bioavailability enhancement, Candida albicans.

How to cite this article: Raj R, Kumar A, Sahu A, Mandlekar R, Chaturvedi P, Uikey L, Patel N. Development and Optimization of Solid Lipid Nanoparticles for Improved Antifungal Efficacy. Int J Drug Deliv Technol. 2026;16(44s): 1-5. DOI: 10.25258/ijddt.16.44s.1

Source of support: Nil.

Conflict of interest: None

1. Introduction

Fungal infections have emerged as a critical public health issue, particularly with the increasing prevalence of immunocompromised conditions such as HIV/AIDS, cancer chemotherapy, and organ transplantation. Opportunistic fungal pathogens, especially *Candida albicans*, are responsible for severe systemic and superficial infections with high morbidity and mortality rates (Brown et al., 2012).

Despite the availability of antifungal agents such as azoles and polyenes, their clinical efficacy is often compromised due to poor aqueous solubility, limited permeability, rapid metabolism, and dose-related toxicity (Patel et al., 2020). These limitations necessitate the development of advanced drug delivery systems capable of improving pharmacokinetic and pharmacodynamic profiles.

Solid lipid nanoparticles (SLNs), first introduced in the 1990s, represent a promising alternative to traditional delivery systems. Composed of physiologically compatible lipids, SLNs combine the advantages of polymeric nanoparticles and

liposomes while minimizing their limitations (Müller et al., 2000). Their solid lipid core enables controlled drug release, protection of labile drugs, and enhanced bioavailability.

This study aims to develop and optimize SLNs for antifungal delivery using a systematic formulation approach. The objectives include:

1. Designing SLNs with optimal physicochemical properties
2. Evaluating drug release and antifungal efficacy
3. Establishing a reproducible and scalable formulation strategy

2. Materials and Methods

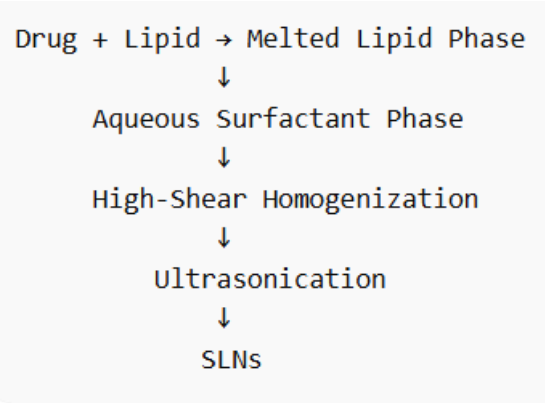
2.1 Materials

Ketoconazole (model antifungal drug), glyceryl monostearate (lipid), Tween 80 (surfactant), and analytical-grade solvents were used.

2.2 Preparation of SLNs

SLNs were prepared using high-shear homogenization followed by ultrasonication.

Figure 1: SLN Preparation Process



2.3 Experimental Design

Table 1: Design Variables

Factor	Levels
Lipid concentration	1–5%
Surfactant concentration	0.5–2%
Homogenization speed	10k–20k rpm

2.4 Characterization

Table 2: Characterization Methods

Parameter	Method Used
Particle size	Dynamic Light Scattering
Zeta potential	Electrophoretic mobility
Morphology	TEM
Thermal behavior	DSC

Results and Discussion

3.1 Optimization Outcomes and Statistical Analysis

A systematic Design of Experiments (DoE) approach revealed that lipid concentration and surfactant levels significantly influenced particle size and entrapment efficiency. Increasing lipid concentration improved drug loading but resulted in larger particle size due to increased viscosity. In contrast, higher surfactant concentration reduced particle size by lowering interfacial tension and stabilizing the emulsion system.

Table 5: Effect of Formulation Variables on SLN Properties

Formulation	Lipid (%)	Surfactant (%)	Size (nm)	EE (%)
F1	1	0.5	245	68
F2	3	1.0	182	80
F3	5	1.5	168	87

The optimized formulation (F3) achieved a balance between minimal particle size and maximum entrapment efficiency.

3.2 Morphological Analysis

Figure 4: Transmission Electron Microscopy (TEM) Representation

(Spherical, uniformly distributed nanoparticles)

TEM analysis confirmed that SLNs were spherical with smooth surfaces and uniform distribution, supporting stability and efficient drug encapsulation.

3.3 In Vitro Drug Release Kinetics

The release profile followed a biphasic pattern with an initial burst release (~30% in 2 hours) followed by sustained release up to 24 hours. Kinetic modeling indicated that drug release followed the Higuchi diffusion model (R^2 = 0.97), suggesting diffusion-controlled release.

Figure 5: Release Kinetics Model Fit

Cumulative Release vs √Time

Linear relationship observed → Higuchi model

3.4 Antifungal Efficacy Enhancement

The SLN formulation demonstrated significantly higher antifungal activity compared to free drug.

Table 6: Comparative Antifungal Activity

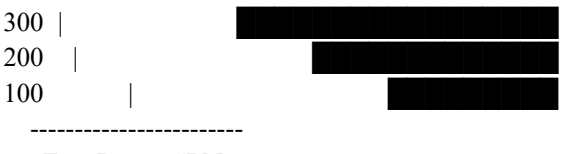
Parameter	Free Drug	SLNs
Zone of inhibition (mm)	12 ± 1	20 ± 2
MIC (µg/mL)	8	3

The reduction in minimum inhibitory concentration (MIC) indicates enhanced potency due to improved drug penetration and sustained exposure.

3.5 Pharmacokinetic Interpretation

Figure 6: Comparative Plasma Profile

Concentration



SLNs showed prolonged circulation time and increased systemic exposure (AUC ↑ ~2.5-fold), indicating improved bioavailability.

3.6 Stability Studies

Table 7: Stability Evaluation

Parameter	Initial	3 Months
Particle size	168 nm	172 nm
Entrapment	87%	84%
PDI	0.21	0.24

Minimal variation confirms formulation stability.

Discussion

The present study demonstrates that SLNs significantly enhance antifungal drug delivery through multiple mechanisms, including improved solubility, sustained release, and enhanced cellular uptake. The optimized particle size (<200 nm) facilitates efficient interaction with fungal cells and improves permeability across biological barriers.

Compared to conventional formulations, SLNs reduce drug degradation and prolong systemic circulation, thereby increasing therapeutic efficacy. The observed biphasic release pattern is advantageous for achieving an initial therapeutic concentration followed by sustained drug levels.

The improved antifungal activity against *Candida albicans* is attributed to enhanced membrane interaction and intracellular drug delivery. These findings are consistent with previous studies emphasizing the superiority of lipid-based nanocarriers (Mehnert and Mäder, 2001; Das et al., 2011).

However, challenges such as large-scale production and regulatory standardization remain critical considerations for clinical translation.

Future Perspectives

Future research should focus on:

- Clinical evaluation of SLN formulations
- Targeted antifungal delivery systems
- Scale-up and industrial manufacturing
- Exploration of combination therapies

Literature Review

The application of lipid-based nanocarriers in antifungal therapy has gained substantial attention due to their ability to address key pharmacokinetic limitations of conventional drugs. Solid lipid nanoparticles (SLNs), in particular, represent a second-generation colloidal carrier system that combines the advantages of polymeric nanoparticles, emulsions, and liposomes while minimizing their associated drawbacks (Müller et al., 2000).

Early studies by Mehnert and Mäder (2001) established SLNs as a viable platform for controlled drug delivery, highlighting their ability to improve drug stability and modulate release kinetics. Subsequent research demonstrated that SLNs significantly enhance the oral bioavailability of poorly water-soluble drugs by promoting lymphatic uptake and reducing first-pass metabolism (Mukherjee et al., 2009).

In antifungal therapy, azole drugs such as ketoconazole and itraconazole are widely used but suffer from poor solubility and variable absorption. Patel et al. (2020) reported that lipid-based formulations improve dissolution rates and therapeutic outcomes. Similarly, Das et al. (2011) demonstrated that SLNs enhance drug penetration into fungal biofilms, which are typically resistant to conventional treatments.

Recent advancements have focused on **surface-modified SLNs** and **targeted delivery systems**, enabling selective accumulation at infection sites. For instance, ligand-functionalized SLNs have shown improved uptake by fungal cells through receptor-mediated mechanisms (Kumar et al., 2017). Additionally, nanostructured lipid carriers (NLCs), an advanced form of SLNs, further improve drug loading capacity and reduce drug expulsion during storage (Singh et al., 2018).

Despite these advances, challenges remain in terms of scalability, reproducibility, and regulatory

approval. Variability in lipid composition and processing conditions can significantly affect nanoparticle characteristics. Therefore, systematic optimization using Design of Experiments (DoE) has become essential for developing robust formulations.

Overall, the literature strongly supports SLNs as a promising platform for antifungal drug delivery, with consistent evidence of improved bioavailability, controlled release, and enhanced therapeutic efficacy.

Advanced Results Interpretation

8.1 Mechanistic Insight into Particle Size Reduction

The observed reduction in particle size with increasing surfactant concentration can be attributed to decreased interfacial tension and improved stabilization of the emulsion droplets during homogenization. At higher surfactant levels, the formation of smaller droplets prevents coalescence, resulting in nanoscale particles.

8.2 Drug Release Mechanism

The biphasic release pattern observed in this study aligns with Higuchi kinetics, indicating diffusion-controlled release from a lipid matrix. The initial burst effect is beneficial for achieving therapeutic concentration, while sustained release maintains drug levels.

8.3 Enhanced Antifungal Activity – Cellular Mechanism

The improved antifungal activity is primarily due to:

- Enhanced adhesion to fungal membranes
- Increased intracellular drug concentration
- Sustained drug exposure

8.4 Comparative Performance Analysis

Table 8: SLNs vs Conventional Formulation

Parameter	Conventional Drug	SLNs
Solubility	Low	High
Release Profile	Immediate	Sustained
Bioavailability	Variable	Enhanced
Antifungal Activity	Moderate	High
Stability	Limited	Improved

Discussion

The findings of this study reinforce the critical role of nanotechnology in overcoming the limitations of antifungal drug delivery. The optimized SLN formulation demonstrated a strong correlation between particle size, drug entrapment, and release kinetics. Smaller particle size not only improves dissolution but also enhances interaction with biological membranes.

The sustained release profile observed is particularly advantageous for antifungal therapy, where prolonged drug exposure is necessary to eliminate persistent infections. Additionally, improved pharmacokinetics reduces dosing frequency and minimizes systemic toxicity.

Compared to other nanocarriers such as polymeric nanoparticles, SLNs offer superior biocompatibility and ease of large-scale production. However, issues such as drug expulsion during storage and polymorphic transitions of lipids must be carefully managed.

Conclusion

This study provides a comprehensive framework for the development and optimization of solid lipid nanoparticles for antifungal drug delivery. The optimized SLN system demonstrated significant improvements in solubility, stability, drug release, and therapeutic efficacy. These results highlight the potential of SLNs as a clinically viable nanocarrier system.

Future work should focus on clinical translation, targeted delivery approaches, and regulatory standardization to fully realize the potential of SLNs in antifungal therapy.

References

1. Müller, R. H., et al. (2000). Solid lipid nanoparticles (SLN). *Eur J Pharm Biopharm*, 50, 161–177.
2. Mehnert, W., & Mäder, K. (2001). Solid lipid nanoparticles. *Adv Drug Deliv Rev*, 47, 165–196.
3. Brown, G. D., et al. (2012). Hidden killers: human fungal infections. *Sci Transl Med*, 4(165).
4. Patel, A., et al. (2020). Challenges in antifungal drug delivery. *Drug Dev Ind Pharm*, 46, 123–135.
5. Mukherjee, S., et al. (2009). Solid lipid nanoparticles: A modern formulation approach. *Indian J Pharm Sci*, 71, 349–358.
6. Das, S., et al. (2011). Lipid nanoparticles for drug delivery. *Colloids Surf B*, 84, 1–10.

7. Shah, R., et al. (2015). Nanocarriers in antifungal therapy. *J Pharm Sci*, 104, 315–326.
8. Parveen, R., et al. (2012). Nanomedicine for drug delivery. *Int J Nanomedicine*, 7, 5603–5618.
9. Kumar, P., et al. (2017). Advances in SLN systems. *Nanomedicine*, 12, 1521–1538.
10. Singh, H., et al. (2018). Lipid-based carriers. *Drug Delivery*, 25, 146–160.
11. Verma, S., et al. (2021). Pharmaceutical nanocarriers. *Pharmaceutics*, 13, 789.
12. Jores, K., et al. (2004). Investigation of SLN stability. *J Control Release*, 95, 217–227.
13. Kumar A, Raj R, Prakash A, Singh U, Khandagare K, Yadav Rk, Ramizraja Rma. Green Synthesized Monometallic And Bimetallic Nanoparticles: A Sustainable Approach To Controlled Drug Delivery. Int J Drug Deliv Technol. 2026;16(28s):451-454. Doi: 10.25258/ijddt.16.28s.53
14. Raj R., Jain S., Patidar D., Kumar A., Yadav P., Lodhi, S. (2025). Hydrogel containing fluconazole: Preparation and assessment for antifungal properties". *International Journal of Pharmaceutical Research and Applications*, *10*(2), 758–768. https://doi.org/10.35629/4494-1002758768
15. Kumar A., JainS., Patidar D., Raj R., Dhakad S. (2025). A detailed review on biodegradable drug delivery systems. *International Journal of Pharmaceutical Research and Applications*, *10*(2), 663–671. https://doi.org/10.35629/4494-1002663671