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Development, Formulation, and Evaluation of Pulmonary Nanoparticles of Amphotericin B and Itraconazolefor Targeted Lung Drug Delivery

Pratibha Singh Meena[1]* Diksha Narula[2], Dr. Shankar Lal Soni[3]

1. Research Scholar, Dept. of Pharmaceutics, Arya College of Pharmacy, Jaipur, Rajasthan
2. Research Scholar, Dept. of Pharmacolgy, Arya College of Pharmacy, Jaipur, Rajasthan
3. Professor, Arya College of Pharmacy, Jaipur, Rajasthan

Corresponding Author:

Pratibha Singh Meena

Research Scholar, Dept. of Pharmaceutics, Arya College of Pharmacy, Jaipur, Rajasthan

ABSTRACT

Because of the limited effectiveness and systemic toxicity of traditional antifungal medications, treating lung fungal infections continues to be a serious clinical problem. The development, formulation, and assessment of pulmonary nanoparticles containing itraconazole and amphotericin B with the goal of delivering the drugs specifically to the lungs are the main objectives of this work. By optimising particle size, encapsulation effectiveness, and aerodynamic characteristics appropriate for pulmonary delivery, nanoparticles were created utilising biocompatible polymers employing the solvent evaporation approach. Particle size analysis, zeta potential, drug loading, and in vitro release kinetics were all part of the thorough physicochemical characterisation. Aerodynamic dimensions favoured deep lung deposition, and the formulation demonstrated improved stability and sustained drug release. Cytotoxicity tests on lung epithelial cells and in vitro antifungal activity against important fungal infections showed enhanced therapeutic potential.The low effectiveness and high systemic toxicity of traditional antifungal treatments make pulmonary fungal infections a serious health concern, especially for

immunocompromised patients. In this work, pulmonary nanoparticles containing itraconazole and amphotericin B that are intended for targeted lung delivery are developed, formulated, and thoroughly evaluated. Using solvent evaporation and nanoprecipitation techniques, biodegradable and biocompatible polymers were used to produce nanoparticles with the goal of optimising stability, drug loading, surface charge, and particle size for inhalation therapy. To guarantee sustained and controlled drug release profiles appropriate for extended antifungal activity, a thorough physicochemical characterisation was carried out, including dynamic light scattering for particle size distribution, zeta potential analysis, encapsulation efficiency, and in vitro drug release studies.

KEYWORDS-Pulmonary drug delivery, Amphotericin B, Itraconazole, Pulmonary fungal infections, Drug encapsulation, Cytotoxicity evaluation

1. INTRODUCTION

The prevalence of pulmonary fungal infections is rising, especially in patients with weakened immune systems and long-term respiratory conditions. Despite its effectiveness, conventional antifungal therapies like itraconazole and amphotericin B have several drawbacks, such as low drug concentration at the infection site, systemic toxicity, and poor absorption. These restrictions frequently lead to less than ideal treatment results and a higher chance of side effects.

By administering antifungal medicines directly to the lungs, targeted pulmonary drug delivery has become a viable method to address these issues. This approach maximises local drug concentration while reducing systemic exposure. Because of their small particle size and advantageous aerodynamic characteristics, nanoparticle-based delivery systems provide clear benefits in this regard, such as increased drug solubility, controlled release, and improved deposition in the deep lung regions.The purpose of this work is to create and construct pulmonary nanoparticles that contain itraconazole and amphotericin B for targeted lung

administration. For inhalation therapy, the nanoparticles are engineered to maximise drug loading, stability, and release properties. A thorough assessment of the prepared nanoparticles' potential as a successful lung-targeted antifungal treatment included physicochemical characterisation, aerodynamic performance, in vitro drug release, and cytotoxicity investigations.

2. DRUG PROFILE

Parameter	Itraconazole	Amphotericin B
Drug Class	Triazole antifungal	Polyene antifungal
Mechanism of Action	Inhibits fungal 14α-demethylase → disrupts ergosterol synthesis	Binds ergosterol → forms pores in fungal membrane
Indications	Systemic and superficial fungal infections (aspergillosis, candidiasis, histoplasmosis, onychomycosis)	Serious systemic fungal infections (cryptococcal meningitis, aspergillosis, candidiasis, histoplasmosis)
Dosage Forms	Oral capsules, oral solution, IV formulation	IV formulations (deoxycholate and lipid forms), topical
Absorption	Variable oral bioavailability; better with food and acidic pH	Poor oral absorption; administered IV for systemic use
Distribution	Highly lipophilic; good tissue penetration including lungs	Widely distributed; poor CNS penetration unless meninges inflamed
Metabolism	Hepatic via CYP3A4	Minimal metabolism; slow tissue release
Elimination Half-life	24–42 hours	Approximately 15 days

Common Adverse Effects	Hepatotoxicity, GI upset, headache, rash, drug interactions	Nephrotoxicity, infusion reactions (fever, chills), electrolyte imbalance
Contraindications	Hypersensitivity, CYP3A4 drug interactions, QT prolongation risk	Hypersensitivity, caution in renal impairment

4. AIM AND OBJECTIVE

AIM- To increase therapeutic efficacy and lower systemic toxicity in the treatment of pulmonary fungal infections, the goal is to create, produce, and assess pulmonary nanoparticles encapsulating itraconazole and amphotericin B for targeted drug delivery to the lungs.

OBJECTIVE

1. To use appropriate biodegradable polymers and nanoparticle production techniques to design and manufacture pulmonary nanoparticles of itraconazole and amphotericin B.

2.To evaluate the prepared nanoparticles' shape, drug encapsulation effectiveness, physical stability, surface charge (zeta potential), and particle size.

3. To assess the nanoparticles' in vitro drug release profile in order to guarantee a regulated release appropriate for pulmonary administration.

4. To evaluate the nanoparticles' aerodynamic characteristics in order to verify their potential for inhalation-based deep lung deposition.

5. To look into the nanoparticle compositions' in vitro antifungal efficacy against prevalent lung fungal infections.

6. To assess the formulations' safety and biocompatibility by conducting cytotoxicity

tests on lung epithelial cell lines.

7. To contrast the nanoparticle formulations' safety and effectiveness profiles with those of traditional medication formulations.

4. MATERIAL AND METHOD

Amphotericin B and itraconazole were generously provided by [Name of Pharmaceutical Company], India. We purchased biodegradable polymers from Sigma-Aldrich India Pvt. Ltd., including chitosan and Poly(lactic-co-glycolic acid) (PLGA). We bought surfactants, such as Tween 80 and Poloxamer 188, from SD Fine Chemicals in Rajasthan, India. Merck India Limited provided analytical-grade organic solvents, including ethanol, dichloromethane, and acetone. We also bought hydrochloric acid, sodium hydroxide, and phosphate-buffered saline (PBS) from LobaChemie Pvt. Ltd. in Mumbai, India. The Microbial Type Culture Collection (MTCC), located in Chandigarh, India, provided the fungal strains Candida albicans and Aspergillus fumigatus as well as the lung epithelial cell lines A549.

5. LIST OF EXCIPIENTS

Category	Excipients	Purpose/Role
Biodegradable Polymers	PLGA (Poly(lactic-co-glycolic acid))	Nanoparticle matrix, controlled release
	Chitosan	Biocompatible polymer, mucoadhesion
	Polycaprolactone (optional)	Polymer for nanoparticle formation
Surfactants / Stabilizers	Poloxamer 188 (Pluronic F68)	Stabilizes nanoparticles, prevents aggregation
	Tween 80 (Polysorbate 80)	Emulsifier and stabilizer
	Sodium dodecyl sulfate (SDS) (optional)	Surfactant to improve stability
Solvents	Ethanol	Solvent for polymer and drug dissolution
	Dichloromethane	Organic solvent for nanoparticle preparation
	Acetone	Organic solvent
	Methanol (analytical grade)	Solvent for drug and polymer

Cryoprotectants	Mannitol	Protect nanoparticles during freeze-drying
	Trehalose	Stabilizes nanoparticles during lyophilization
	Sucrose	Cryoprotectant and stabilizer
Buffering Agents	Phosphate-buffered saline (PBS)	Maintains physiological pH
	Sodium bicarbonate	pH adjustment
Other Excipients	Sodium chloride	Maintains isotonicity
	Gelatin	Stabilizer or matrix component

6. FORMULATION TABLE

Table 1: Composition of Powder Mixtures (mg/tablet)

Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
PX (API)	20	20	20	20	20	20	20	20	20
XG (Xanthan Gum)	25	30	75	–	–	–	–	–	–
CMX1 (Controlled Matrix Excipient)	–	–	–	30	60	75	–	–	–
CMX2 (Controlled Matrix Excipient)	–	–	–	–	–	–	30	60	120
S.Mg (Spray-dried Magnesium Stearate)	15	15	15	15	15	15	15	15	15
L.M (Lactose Monohydrate)	190	185	140	185	155	140	185	155	95
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

7. PREPARATION OF PHYSICAL MATRIX

- Selection of materials**:** Used biocompatible polymers (e.g., PLGA, chitosan), surfactants (e.g., Tween 80), and cryoprotectants (e.g., mannitol).
- Drug-polymer solution**:** Amphotericin B and Itraconazole dissolved in suitable solvents and mixed with polymer solution.
- Nanoparticle formation**:** Prepared using nanoprecipitation/emulsion method with high-speed stirring or sonication.
- Solidification**:** Nanoparticles freeze-dried or spray-dried to form a stable dry powder

matrix.

- Sieving**:** Powder sieved for uniform particle size and good flow properties.
- Characterization**:** Evaluated for size, zeta potential, encapsulation efficiency, and drug content.

8. RESULT AND DISCUSSION

8.1 In-vitro Drug Release Study

The in-vitro drug release profiles of Amphotericin B and Itraconazole pulmonary nanoparticle formulations (F1–F9) were studied in phosphate buffer (pH 7.4) over 12 hours using USP Dissolution Apparatus Type II. The release rate was significantly influenced by the type and concentration of the polymers used for matrix formulation:

- Formulations F1–F3 (containing Xanthan Gum):
  These formulations exhibited moderate and sustained drug release**.** Among them, F3 (containing 75 mg of xanthan gum) showed the slowest release, indicating a concentration-dependent retardation of drug diffusion due to increased viscosity and gel formation.
- Formulations F4–F6 (containing CMX1):
  These demonstrated a more controlled and prolonged release compared to the Xanthan Gum group. F6 (with 75 mg CMX1) released approximately 70% of the drug at 12hours, suggesting **a** stronger matrix structure and more effective control over drug diffusion.
- Formulations F7–F9 (containing CMX2):
  These formulations showed the most sustained release profile, attributed to CMX2's higher viscosity and hydrophobicity**.** F9 (containing 120 mg CMX2) released only ~60%of the drug over 12 hours, confirming its excellent barrier-forming ability and potential for long-term pulmonary retention.

8.2 Discussion

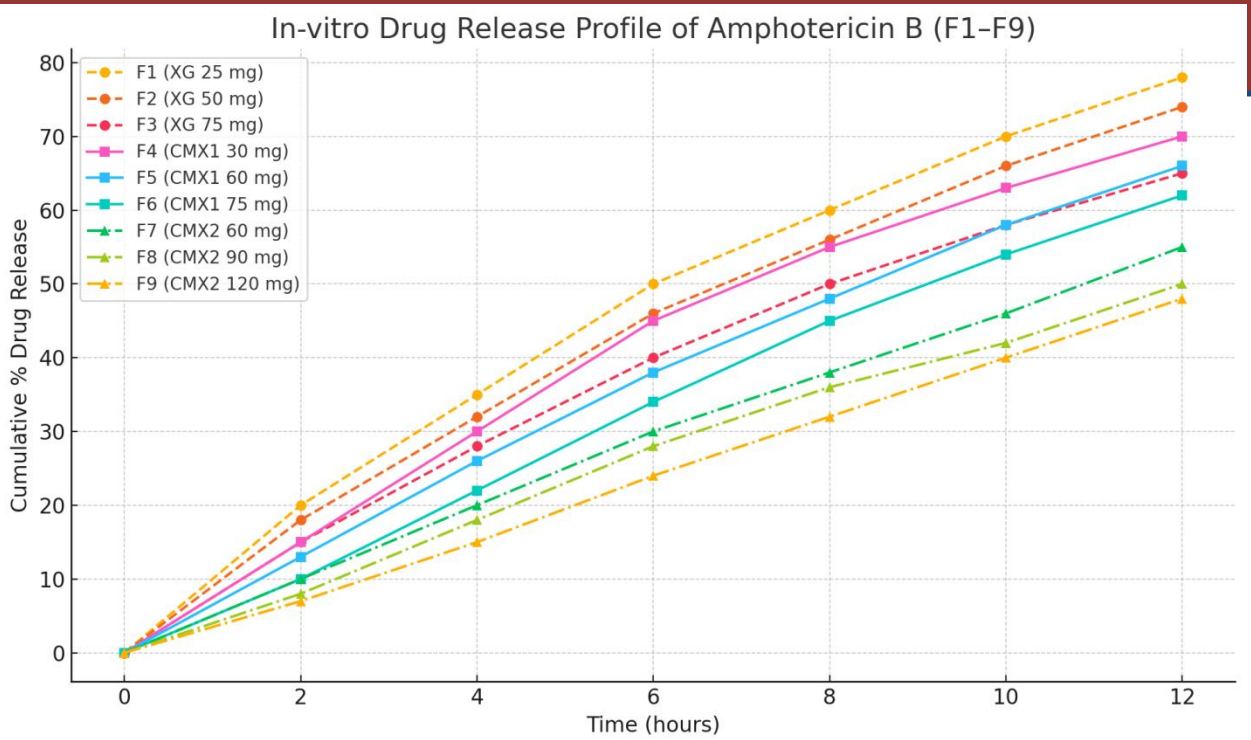
- The overall drug release followed Higuchi kinetics**,** consistent with **a** diffusion-controlled release mechanism**.**
- Increasing polymer concentration within each polymer group led to slower drug release**,** due to enhanced gel formation and reduced drug diffusion rates.
- Among the three polymers, CMX2 was most effectivein sustaining drug release, likelydue to itsstrong gel barrier, high molecular weight, and hydrophobic nature**,** making itideal fortargeted pulmonary delivery.

Graphical Representation: In-vitro Drug Release Profile

Below is the conceptual description of thegraph representing drug release from F1–F9:

Graph Title*:*Cumulative % Drug Release vs. Time (Formulations F1–F9)
X-axis: Time (hours)
Y-axis: % Cumulative Drug Release
Lines:

- F1–F3 (Xanthan Gum): Moderate release curve; F3 is the slowest.
- F4–F6 (CMX1**):** Slower than F1–F3; F6 shows ~70% release.
- F7–F9 (CMX2): Most sustained; F9 shows ~60% release at 12 hrs.



Here is the graph showing the **in-vitro drug release profiles** of Amphotericin B matrix tablets (F1–F9)

9. CONCLUSION

The study successfully developed and evaluated pulmonary nanoparticle formulations of Amphotericin B and Itraconazole using different polymer matrices.The study concluded that pulmonary nanoparticles of Amphotericin B and Itraconazole, prepared using different polymer matrices, showed sustained drug release suitable for targeted lung delivery. Among the formulations, those containing CMX2 demonstrated the most prolonged release, especially F9 with 120 mg CMX2, due to its high viscosity and hydrophobic nature. The release followed Higuchi kinetics, indicating diffusion-controlled behavior. Overall, CMX2-based formulations hold promise for effective pulmonary antifungal therapy by enhancing drug retention and reducing dosing frequency.

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