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Formulation and Evaluation Monoporous Hollow Microspheres of Itraconazole- for Pulmonary Drug Delivery

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***Abstract:** Background: Itraconazole is a broad-spectrum triazole antifungal drug, but its poor aqueous solubility, variable oral bioavailability and first-pass metabolism limit predictable therapeutic exposure. Pulmonary delivery can provide high local antifungal concentration in lung tissues while reducing systemic exposure. Objective: The present study aimed to formulate, optimize and evaluate itraconazole-loaded monoporous hollow microspheres as a sustained pulmonary drug delivery system. Methods: Microspheres were prepared by an emulsion solvent evaporation technique using PLGA and Eudragit RS100 as release-retarding polymers and ammonium bicarbonate as a gas-forming pore-forming agent. Formulations F1-F9 were prepared according to a factorial design and evaluated for preformulation attributes, drug-excipient compatibility, particle size, percentage yield, entrapment efficiency, morphology, mass median aerodynamic diameter (MMAD), flow properties, in-vitro drug release and accelerated stability. Results: Itraconazole was practically insoluble in water and showed lambda max at 262 nm in methanol. FTIR and DSC studies indicated no major drug-excipient incompatibility. Particle size ranged from 1.8 to 3.6 µm and entrapment efficiency from 70 to 99%. Batch F3, containing 100 mg itraconazole, 250 mg PLGA, 500 mg Eudragit RS100 and 50 mg ammonium bicarbonate, was optimized because it showed mean particle size of 2.4 µm, yield of 88%, entrapment efficiency of 99%, spherical hollow porous morphology, MMAD of 2.9 µm, Carr index of 16.7%, Hausner ratio of 1.20 and 95% drug release at 8 h. After 3 months, F3 retained particle size of 2.5 µm, entrapment efficiency of 97.9%, MMAD of 2.8 µm and 87.8% cumulative release at the stability endpoint. Conclusion: The optimized itraconazole monoporous hollow microspheres demonstrated suitable micromeritic, aerodynamic, entrapment and sustained-release characteristics, supporting their further investigation as a pulmonary antifungal delivery platform.*

***Keywords:** Itraconazole; Monoporous hollow microspheres; Pulmonary drug delivery; PLGA; Eudragit RS100; Ammonium bicarbonate; Sustained release; Emulsion solvent evaporation.*

I. INTRODUCTION

Microspheres are spherical polymeric carriers generally ranging from 1 to 1000 µm and are widely investigated for controlled and targeted drug delivery. Their structure may be monolithic or reservoir type, and drug release can occur by diffusion, swelling or polymer erosion. For inhalable delivery, low-density porous and hollow microspheres are particularly important because the aerodynamic diameter may remain suitable for deep lung deposition even when the geometric particle size is comparatively larger. This feature can enhance dispersibility, reduce premature clearance and provide sustained local drug exposure in the respiratory tract [1-4]. Itraconazole is a synthetic triazole antifungal agent used for superficial and systemic fungal infections, including diseases involving Aspergillus, Candida and dermatophyte species. Its antifungal activity is mainly associated with inhibition of fungal cytochrome P450-dependent enzymes involved in ergosterol synthesis, leading to disruption of fungal membrane integrity. However, itraconazole is classified as a BCS class II drug with very low aqueous solubility and pH-dependent dissolution. Conventional oral administration may show variable absorption, dependence on gastric acidity, food effects and hepatic first-pass metabolism, producing inconsistent therapeutic exposure and increasing the need for improved delivery strategies [5-8].

Pulmonary delivery represents an attractive alternative for lung-associated fungal infections because it can deliver itraconazole directly to the site of infection, achieve high local concentration and reduce systemic toxicity. Monoporous hollow microspheres are especially suitable for this purpose because ammonium bicarbonate or similar gas-forming agents can create an internal hollow structure and surface porosity during solvent evaporation. The present work therefore focused on development of itraconazole-loaded monoporous hollow microspheres using PLGA and Eudragit RS100 as polymeric carriers and ammonium bicarbonate as a pore-forming agent.

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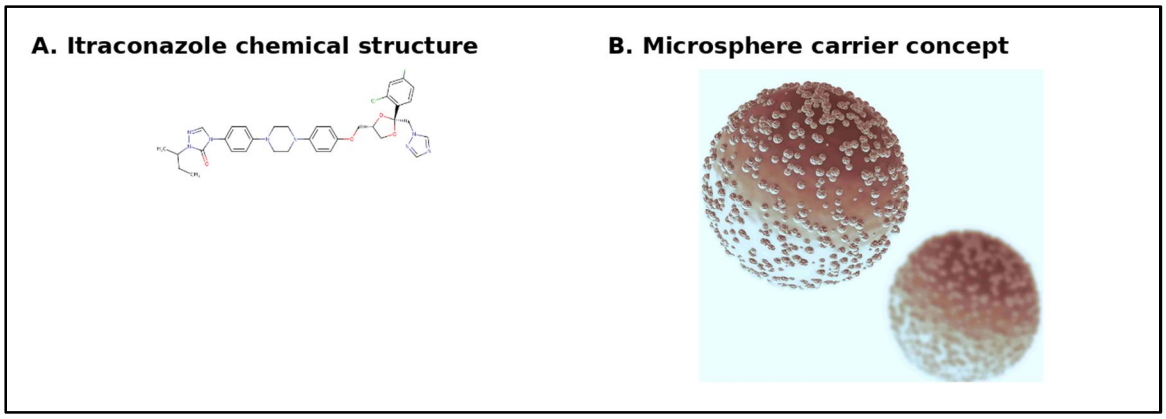

Figure 1. Itraconazole structure and microsphere carrier concept.

II. MATERIALS AND METHODS

A. Materials

Itraconazole was obtained from Shree Chemical. PLGA was procured from Sigma-Aldrich, USA, and Eudragit RS100 was obtained from Evonik Industries, Germany. Ammonium bicarbonate, dichloromethane, polyvinyl alcohol, methanol, phosphate buffer reagents, hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate were used as analytical and formulation excipients. Distilled water was prepared in the laboratory. The formulation materials were selected to provide a biodegradable polymer matrix, release retardation, emulsion stabilization and pore formation.

B. Preformulation and analytical studies

Itraconazole was evaluated for organoleptic properties, melting point and solubility in water, methanol, ethanol, chloroform and 0.1 N HCl. UV spectrophotometric analysis was performed by scanning the drug solution in methanol over 200-400 nm to determine the wavelength of maximum absorption. Calibration standards from 2 to 10 µg/mL were prepared in methanol and absorbance was measured at 262 nm. The calibration curve was used for drug content, entrapment and release analysis.

Table 1. Preformulation and analytical observations of itraconazole.

Parameter	Observation
Physical state	Solid powder
Colour	White to off-white
Odour	Odourless or faint characteristic
Taste	Slightly bitter
Melting point	166-170 °C
Solubility	Practically insoluble in water; freely soluble in methanol and chloroform; soluble in ethanol; slightly soluble in 0.1 N HCl
UV lambda max	262 nm in methanol

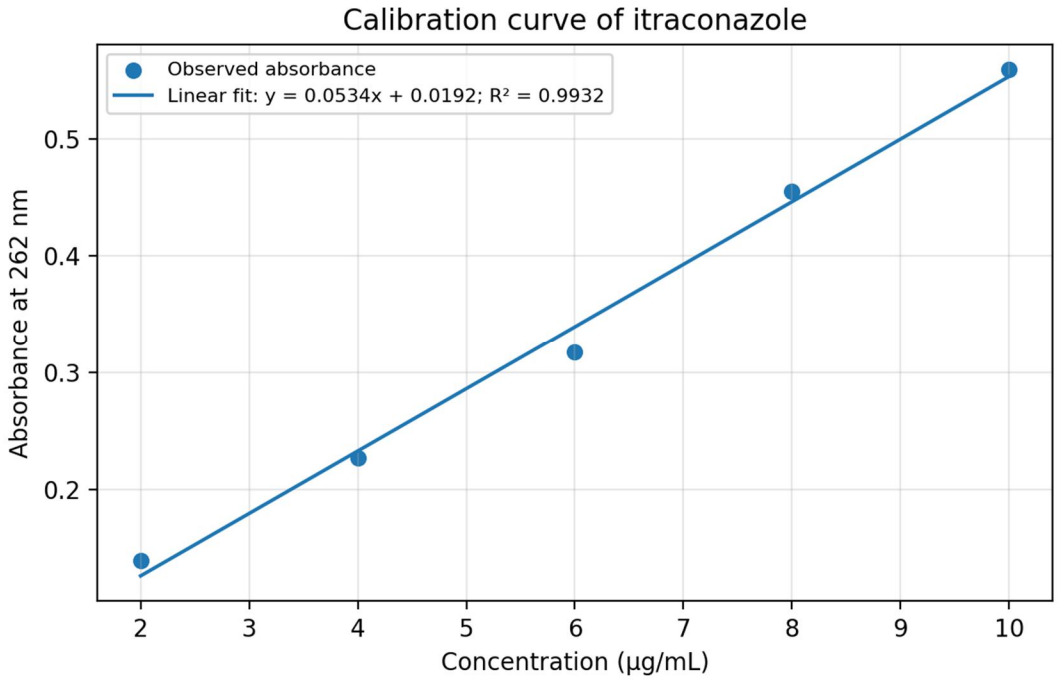

Figure 2. Calibration curve of itraconazole in methanol at 262 nm.

C. Drug-excipient Compatibility

FTIR spectroscopy was performed for pure itraconazole and the physical mixture with excipients using the KBr pellet method over 4000-400 cm-1. Characteristic peaks were compared for major shifting, disappearance or appearance of new peaks. DSC analysis was conducted for the pure drug and drug-excipient physical mixture using sealed aluminum pans under controlled heating. Thermal transitions were compared to determine possible incompatibility.

Table 2. FTIR interpretation of itraconazole.

Functional group	Observed peak (cm-1)	Interpretation
Aromatic C-H stretching	3089	Presence of aromatic ring
Aliphatic C-H stretching	2850	Alkyl groups
C=O stretching	1587	Carbonyl group
C-N stretching	1250	Amine linkage
C-O stretching	1098	Ether linkage
C-Cl stretching	754	Chlorinated group

Table 3. DSC observations of itraconazole and physical mixture.

Sample	Peak temperature	Nature of peak	Enthalpy
Pure itraconazole	164 °C	Sharp endothermic peak	High
Itraconazole + physical mixture	161 °C	Broad but identifiable peak	Reduced

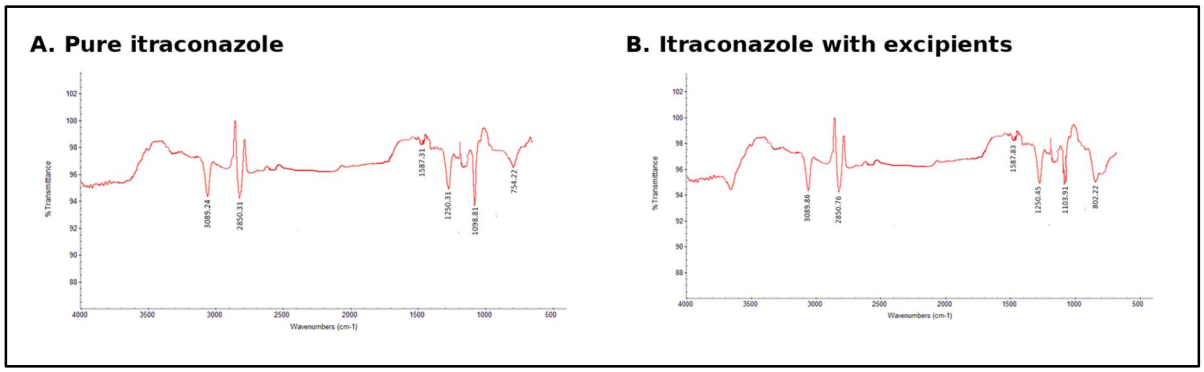

Figure 3. FTIR spectra of pure itraconazole and itraconazole-excipient mixture.

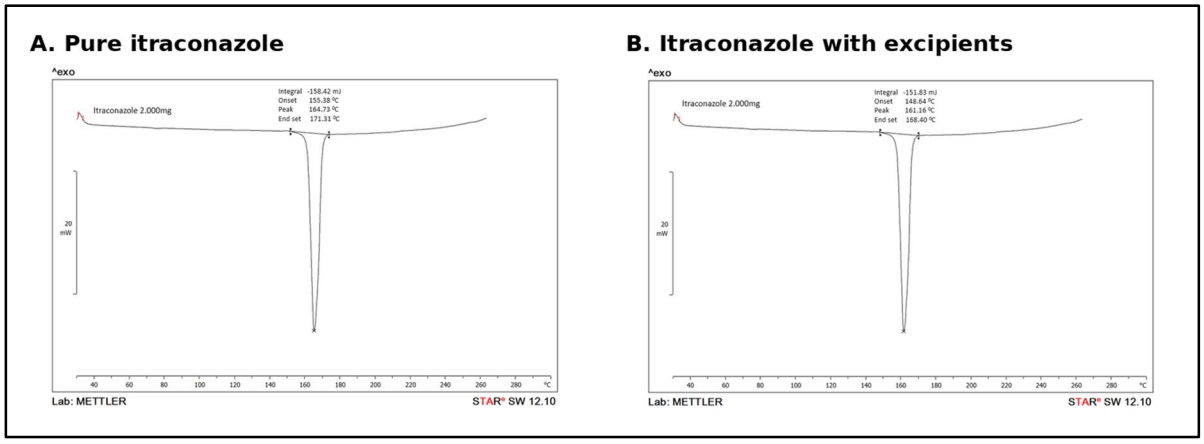

Figure 4. DSC thermograms of pure itraconazole and itraconazole-excipient mixture.

D. Experimental Design and Formulation Development

A 3-level factorial design was used to investigate the influence of formulation variables on microsphere characteristics. PLGA concentration, Eudragit RS100 concentration and ammonium bicarbonate concentration were selected as independent factors, while mean particle size and entrapment efficiency were selected as response variables. Nine formulations (F1-F9) were prepared. Design-Expert version 13.0.5.0 was used for statistical evaluation and response surface interpretation.

Table 4. Composition of itraconazole monoporous hollow microsphere batches.

Batch	Itraconazole (mg)	PLGA (mg)	Eudragit RS100 (mg)	Ammonium bicarbonate (mg)	DCM (mL)	PVA (% w/v)	Water (mL)
F1	100	250	250	50	10	1.0	100
F2	100	250	375	50	10	1.0	100
F3	100	250	500	50	10	1.0	100
F4	100	375	250	85	10	1.0	100
F5	100	375	375	85	10	1.0	100
F6	100	375	500	85	10	1.0	100
F7	100	500	250	120	10	1.5	100
F8	100	500	375	120	10	1.5	100
F9	100	500	500	120	10	1.5	100

E. Preparation of monoporous hollow microspheres

Itraconazole and the selected polymers were dissolved in dichloromethane to form the organic phase. Ammonium bicarbonate was dispersed into the drug-polymer solution as a gas-forming pore-forming agent. The organic phase was slowly introduced into an aqueous phase containing polyvinyl alcohol under homogenization to form an oil-in-water emulsion. The emulsion was stirred at room temperature to allow solvent evaporation. During this process, ammonium bicarbonate decomposed to produce carbon dioxide, ammonia and water, generating hollow cores and porous structures within the microspheres. The formed microspheres were collected by filtration, washed with distilled water to remove residual stabilizer and unentrapped drug, dried under vacuum and stored in a desiccator until evaluation.

F. Evaluation of Microspheres

The prepared microspheres were evaluated for particle size, percentage yield, drug entrapment efficiency, surface morphology, MMAD and micromeritic properties. Particle size was determined by microscopic measurement after dispersion and gentle sonication. Percentage yield was calculated from the ratio of practical yield to total theoretical weight. Entrapment efficiency was calculated by comparing actual drug content in microspheres with theoretical drug loading. Surface morphology was evaluated by scanning electron microscopy. MMAD was used to assess aerodynamic suitability for pulmonary deposition. Flow and compressibility were evaluated using angle of repose, bulk density, tapped density, Carr index and Hausner ratio.

In-vitro drug release was studied in phosphate buffer medium using dissolution apparatus conditions appropriate for microsphere evaluation. Aliquots were withdrawn at predetermined intervals up to 8 h, filtered, suitably diluted and analyzed by UV-visible spectrophotometry at 262 nm. The optimized formulation was subjected to accelerated stability testing for 3 months. Samples were evaluated for particle size, percentage yield, entrapment efficiency, morphology, MMAD, Hausner ratio and drug release at specified intervals.

III. RESULTS AND DISCUSSION

A. Preformulation and analytical method suitability

Itraconazole was observed as a white to off-white solid powder with no objectionable odor and slightly bitter taste. The melting range of 166-170 °C was consistent with the expected crystalline nature and indicated acceptable purity of the sample. The drug was practically insoluble in water but freely soluble in methanol and chloroform, confirming the poor aqueous solubility that necessitates a specialized delivery system. The UV spectrum showed lambda max at 262 nm, and the calibration curve over 2-10 µg/mL showed a direct concentration-dependent increase in absorbance from 0.139 to 0.559. These observations confirmed the suitability of the UV method for quantitative analysis of itraconazole during formulation evaluation.

B. Compatibility Studies

The FTIR spectrum of pure itraconazole showed characteristic bands for aromatic C-H stretching, aliphatic C-H stretching, carbonyl stretching, C-N stretching, C-O stretching and C-Cl stretching. The same major peaks were retained in the physical mixture with excipients, indicating that the principal functional groups of itraconazole were preserved and that no major chemical interaction occurred. DSC thermograms showed a sharp endothermic peak for pure itraconazole at 164 °C. The physical mixture showed a broad but identifiable endothermic peak at 161 °C with reduced enthalpy. This minor shift may be attributed to dilution and polymer mixing rather than incompatibility. Overall, FTIR and DSC results supported compatibility of itraconazole with PLGA, Eudragit RS100 and the selected excipients.

C. Optimization by Design of experiments

The experimental design showed that the selected formulation factors influenced particle size and entrapment efficiency. Particle size ranged from 1.8 to 3.6 µm, indicating formation of microspheres within a size range suitable for pulmonary delivery. Entrapment efficiency ranged from 70 to 99%, demonstrating the ability of the polymeric system to encapsulate itraconazole. Batch F3 showed the best overall response, with a particle size of 2.4 µm and entrapment efficiency of 99%. The higher entrapment in F3 may be related to a strong Eudragit-rich polymeric matrix and a lower level of ammonium bicarbonate, which minimized excessive pore formation and drug leakage.

Table 5. Experimental design batches and response data.

Batch	PLGA (mg)	Eudragit (mg)	Ammonium bicarbonate (mg)	Particle size (µm)	Entrapment efficiency (%)
F1	250	250	50	1.8	82
F2	250	375	50	2.1	96
F3	250	500	50	2.4	99
F4	375	250	85	2.2	91
F5	375	375	85	2.3	89
F6	375	500	85	2.2	87
F7	500	250	120	2.4	80
F8	500	375	120	3.6	96
F9	500	500	120	1.9	70

ANOVA for particle size showed a significant linear model with F-value 27.39 and $p < 0.0001$. PLGA was the significant model term, suggesting that polymer concentration had the strongest influence on particle size. The predicted R2 (0.7255) was in reasonable agreement with the adjusted R2 (0.8065), and adequate precision was reported as 18.420, indicating an adequate signal for navigating the design space. ANOVA for entrapment efficiency also showed a significant model with F-value 13.92 and $p = 0.0001$. For this response, PLGA again showed a significant contribution, while lack of fit was not significant, supporting acceptable model adequacy for optimization.

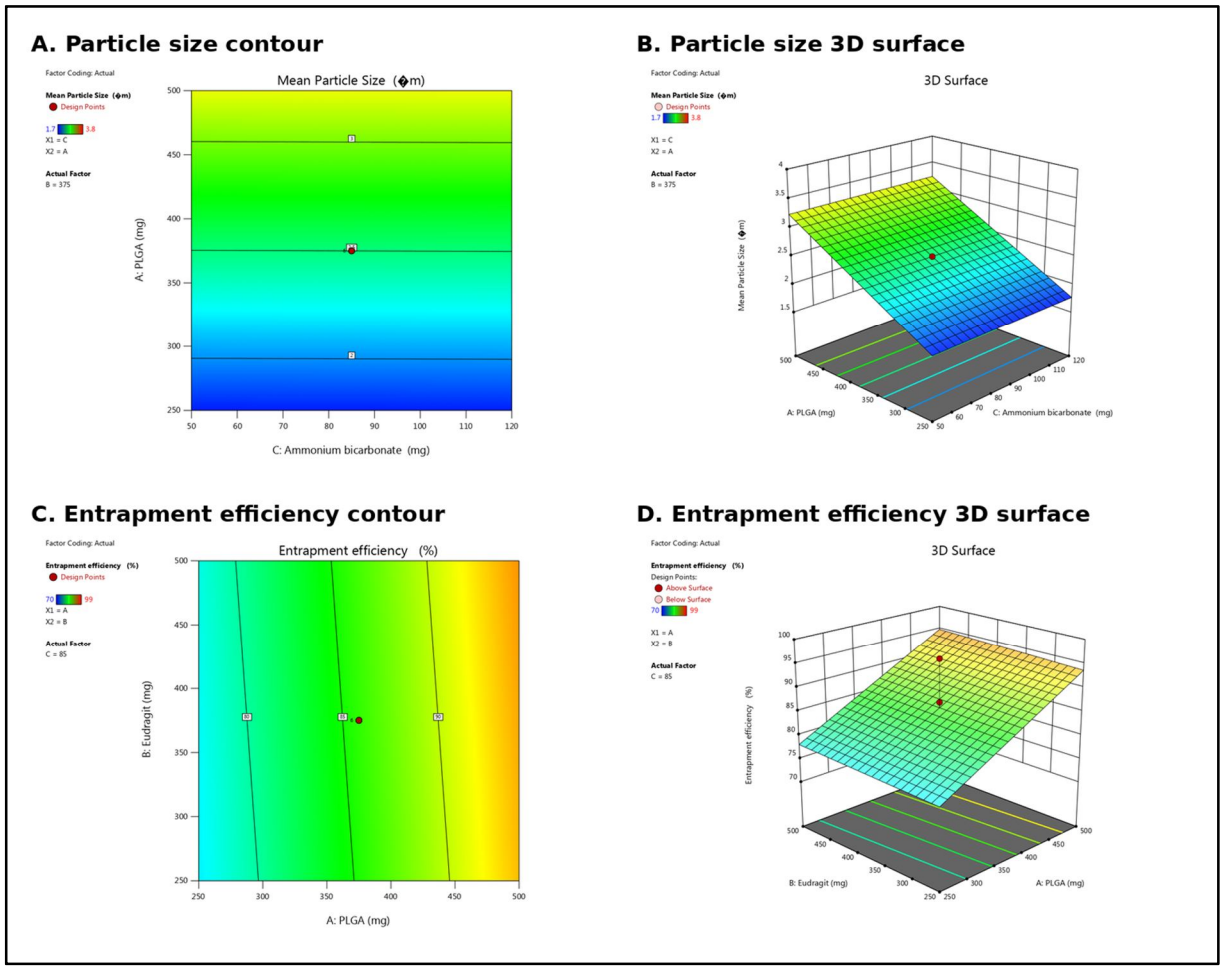

Figure 5. Representative contour and 3D response surface plots for particle size and entrapment efficiency.

D. Physicochemical, aerodynamic and micromeritic evaluation

The percentage yield of the microsphere batches ranged from 78 to 88%, with the highest yield observed for F3. The improved recovery of F3 suggests efficient polymer precipitation and minimal product loss during solvent evaporation and washing. Entrapment efficiency was highest in F3 (99%), followed by F2 and F8 (96%). In contrast, F9 showed the lowest entrapment efficiency (70%), which may be associated with excessive pore formation caused by higher ammonium bicarbonate content and polymer imbalance. SEM observations showed that all batches were spherical, hollow and porous, confirming successful formation of monoporous hollow microspheres. The MMAD values ranged from 2.0 to 2.9 µm. The optimized F3 showed an MMAD of 2.9 µm, which is within the desirable aerodynamic range for deep lung deposition. Flow properties were acceptable for all batches, with angle of repose values from 21° to 30°, Carr index values from 15.8 to 17.6% and Hausner ratio from 1.19 to 1.21. F3 showed angle of repose of 30°, bulk density of 0.30 g/mL, tapped density of 0.36 g/mL, Carr index of 16.7% and Hausner ratio of 1.20, indicating acceptable flowability and compressibility for dry powder handling.

Table 6. Summary evaluation of itraconazole monoporous hollow microspheres.

Batch	Size (µm)	Yield (%)	EE (%)	MMAD (µm)	Carr index (%)	Hausner ratio	Release 8 h (%)
F1	1.8	78	82	2.2	16.7	1.2	70
F2	2.1	79	96	2.4	16.1	1.19	71
F3 optimized	2.4	88	99	2.9	16.7	1.2	95
F4	2.2	81	91	2.6	17.6	1.21	73
F5	2.3	82	89	2.6	17.1	1.21	74
F6	2.2	83	87	2.0	16.7	1.2	74
F7	2.4	83	80	2.1	16.7	1.2	75
F8	3.6	84	96	2.2	16.2	1.19	75
F9	1.9	85	70	2.3	15.8	1.19	76

E. In-vitro drug release

All formulations showed controlled release of itraconazole over the 8 h study period. The cumulative release increased gradually with time, confirming diffusion-controlled release from the polymeric microsphere matrix. Among all formulations, optimized batch F3 showed the highest cumulative release of 95% at 8 h. This superior release may be attributed to an appropriate balance between polymeric matrix strength and pore formation. Formulations with excessive pore formation or less favorable polymer ratios showed comparatively lower release, ranging from 70 to 76% at 8 h. The release profile of F3 indicates that the monoporous hollow structure allowed improved medium penetration and drug diffusion while still maintaining sustained release characteristics.

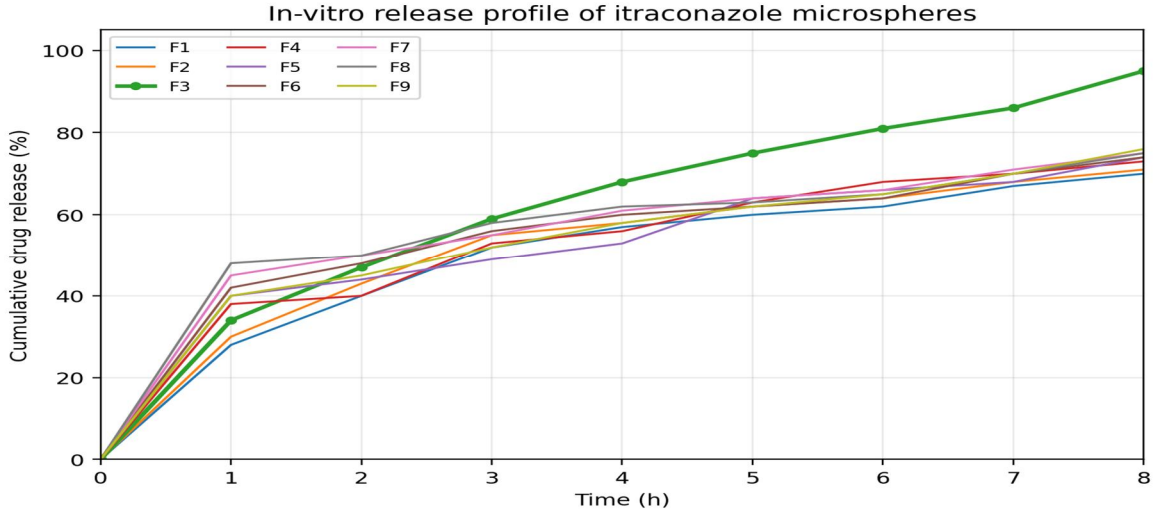

Figure 6. In-vitro cumulative drug release profile of itraconazole microsphere batches F1-F9.

F. Stability of Optimized Formulation

The optimized formulation F3 remained stable during the 3-month accelerated stability study. Particle size changed only slightly from 2.4 to 2.5 µm, suggesting absence of marked aggregation. Entrapment efficiency decreased marginally from 99 to 97.9%, indicating good drug retention within the polymer matrix. The surface morphology remained unchanged, and the microspheres retained their spherical, hollow and porous structure. MMAD remained within the pulmonary delivery range, decreasing only from 2.9 to 2.8 µm. Hausner ratio remained stable from 1.20 to 1.19, confirming preservation of flow behavior. Drug release at the stability endpoint decreased slightly from 89 to 87.8%, indicating that the formulation retained its sustained-release performance.

Table 7. Accelerated stability data of optimized batch F3.

Parameter	Initial	1 month	2 months	3 months
Particle size (µm)	2.4	2.4	2.5	2.5
Percentage yield (%)	88	87.8	87.5	87.2
Drug entrapment efficiency (%)	99	98.7	98.3	97.9
Surface morphology	Spherical, hollow, porous	No change	No change	No change
MMAD (µm)	2.9	2.9	2.8	2.8
Hausner ratio	1.20	1.20	1.19	1.19
Cumulative drug release at 12 h (%)	89	88.5	88.1	87.8

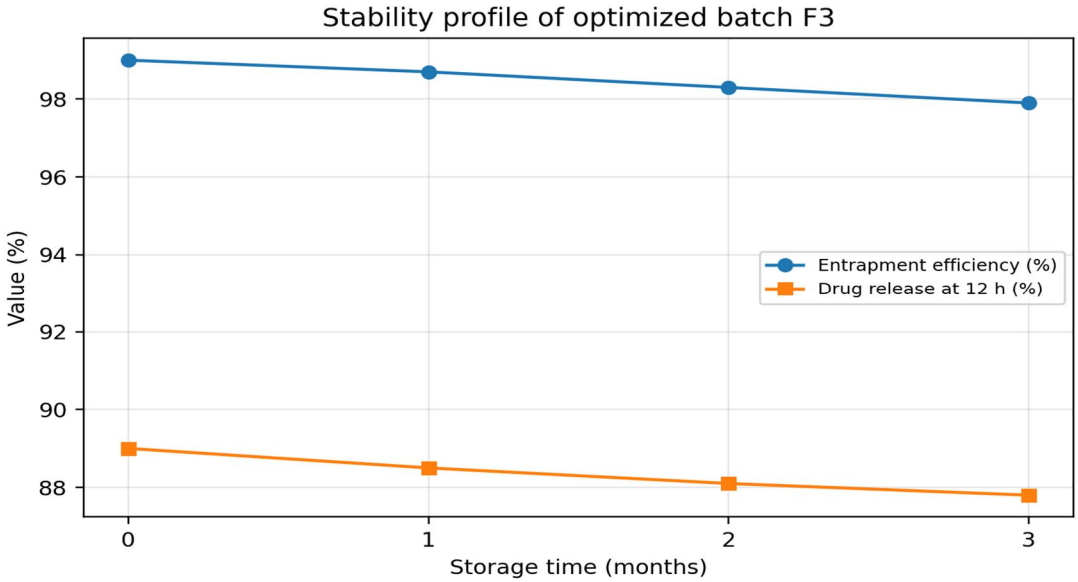

Figure 7. Stability trend of optimized batch F3 over 3 months.

IV. CONCLUSION

Itraconazole-loaded monoporous hollow microspheres were successfully formulated using the emulsion solvent evaporation technique with PLGA and Eudragit RS100 as polymeric carriers and ammonium bicarbonate as a pore-forming gas-forming agent. Preformulation studies confirmed the poor aqueous solubility of itraconazole and supported the need for a specialized pulmonary delivery system. FTIR and DSC studies indicated compatibility of itraconazole with selected excipients. Statistical optimization showed that polymer concentration, particularly PLGA, significantly affected particle size and entrapment efficiency. Among all formulations, batch F3 was selected as the optimized batch because it showed particle size of 2.4 µm, yield of 88%, entrapment efficiency of 99%, spherical hollow porous morphology, MMAD of 2.9 µm, acceptable flow properties and 95% release at 8 h. Stability testing for 3 months confirmed maintenance of physicochemical, aerodynamic and release characteristics.

The developed monoporous hollow microspheres may therefore serve as a promising carrier system for sustained pulmonary delivery of itraconazole. Further work should include aerodynamic cascade impactor studies, dry powder inhaler device compatibility, in-vivo lung deposition, pulmonary safety and pharmacokinetic evaluation.

V. DECLARATIONS

Ethics approval: Not applicable for the reported in-vitro formulation study. Any future in-vivo or animal study should be performed after approval from the appropriate institutional ethics committee.

Funding: No specific external funding was reported in the thesis data.

Conflicts of interest: The author declares no conflict of interest.

Data availability: The data used for manuscript preparation were taken from the submitted thesis and are included in the tables and figures of this manuscript.

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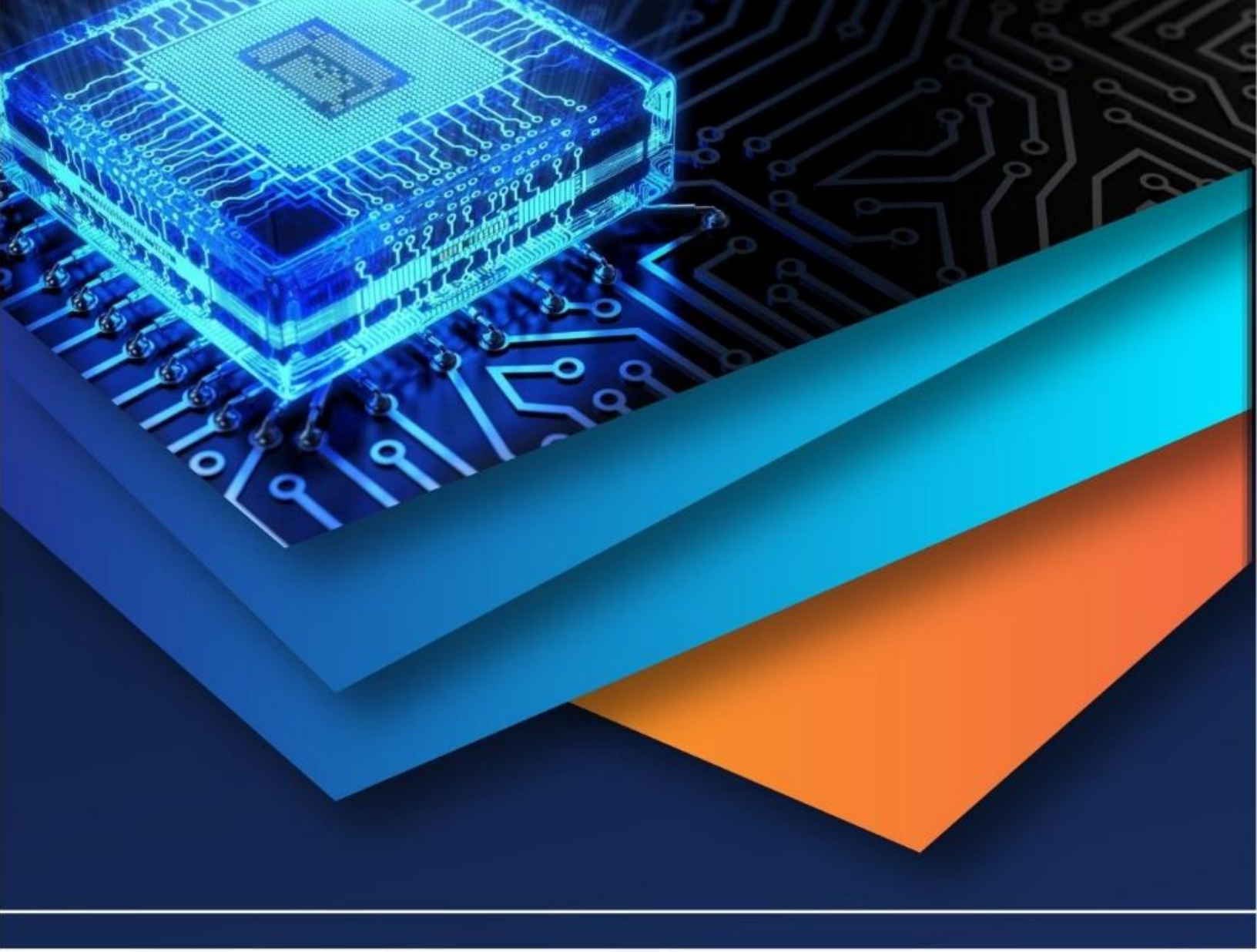

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