

DESIGN AND EVALUATION OF METAL ORGANIC FRAMEWORKS FOR BIOMEDICAL APPLICATIONS

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Design and Evaluation of Metal Organic Frameworks for Biomedical Applications

by

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***Dedicated to my beloved family, my father Late Dr. Umesh Kumar Singh, and
my Grandparents***

CERTIFICATE

This is to certify that the thesis titled “**Design and Evaluation of Metal Organic Frameworks for Biomedical Applications**” being submitted by **Ms. Chitragda Singh** to the Indian Institute of Technology, Delhi for the award of the degree of **Doctor of Philosophy** in Chemical Engineering is a record of Bonafide research work carried out by her under my supervision and guidance. She has fulfilled the requirements for the thesis submission, which to the best of my knowledge has reached the requisite standard.

The work presented in this thesis is original. It has not been submitted, in part or full, to any other University or Institute for the award of any other degree or diploma.

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"Gratitude is not only the greatest of virtues, but the parent of all the others."
– **Marcus Tullius Cicero**

ABSTRACT

The growing global need for advanced therapeutic systems to combat oxygen deprivation such as hypoxia and acute respiratory distress syndrome (ARDS) has accelerated the search for lightweight, efficient, and controllable oxygen carriers. This thesis investigates metal-organic frameworks (MOFs) as multifunctional materials for controlled drug release and oxygen storage/delivery, combining experimental, computational, and sustainability analyses to establish a unified framework for biomedical application and industrial translation.

The first part of the thesis focuses on Zeolitic Imidazolate Framework (ZIF-8) as a biocompatible nanocarrier for the anti-cancer drug *Cytarabine*. Owing to its high porosity, pH-responsiveness, and structural stability, ZIF-8 enabled efficient drug loading in its native form and demonstrated a controlled, diffusion-driven release under physiological conditions, as confirmed through Higuchi and Korsmeyer-Peppas kinetic modeling. This study established a proof-of-concept for MOF-mediated targeted drug delivery systems.

Subsequent chapters explored the oxygen storage and release capabilities of ZIF-8, ZIF-67, and Cu-BTC, synthesized via room-temperature and solvothermal routes optimized using the Box-Behnken design of experiments (DoE). Specific surface area analysis and dynamic gas adsorption studies revealed oxygen uptake capacities of 0.9 mmol/g (ZIF-8), 2.8 mmol/g (ZIF-67), and 4.6 mmol/g (Cu-BTC). Molecular-level insights from Grand Canonical Monte Carlo (GCMC) and Molecular Dynamics (MD) simulations identified adsorption energetics and diffusion pathways, with oxygen molecules preferentially interacting near open metal sites and pore channels, reinforcing their potential as reversible oxygen carriers.

To evaluate scalability and sustainability, Life Cycle Assessment (LCA) and Techno-Economic Analysis (TEA) were performed using laboratory-scale inventory data normalized to 1 kg MOF production with 2025 market prices for all inputs. Two production scales were assessed- pilot (1 kg/yr) and demo (1000 kg/yr). At pilot scale, Levelized Cost of Manufacturing (LCOM) exceeded 50 000 \$ kg⁻¹ due to capital recovery penalties, but fell by two orders of magnitude at demo scale to 566 \$ kg⁻¹ (ZIF-8), 1508 \$ kg⁻¹ (Cu-BTC), and 1484 \$ kg⁻¹ (ZIF-67). At this scale, raw materials and solvents accounted for > 70 % of the total cost,

while CAPEX contributed < 15 %. Sensitivity and Monte Carlo analyses highlighted ligand and metal-salt prices, as well as solvent recovery efficiency, as dominant cost levers.

When normalized to functional performance, the cost per mole of O₂ stored was 627 \$ mol⁻¹ (ZIF-8), 326 \$ mol⁻¹ (Cu-BTC), and 527 \$ mol⁻¹ (ZIF-67), establishing Cu-BTC as the most cost-effective oxygen carrier among the investigated MOFs. To complement adsorption and biological performance, a cradle-to-gate sustainability assessment was performed using *openLCA* (Ecoinvent v3.8, TRACI 2.1). ZIF-8 exhibited the lowest environmental burden owing to its aqueous room-temperature synthesis with a global warming potential (GWP) of 2.1 kg CO₂ eq kg⁻¹, compared with 5.3 and 8.7 kg CO₂ eq kg⁻¹ for ZIF-67 and Cu-BTC, respectively. Economic hotspots were dominated by metal precursors and organic linkers, whereas environmental hotspots originated primarily from solvent consumption and precursor production. To address industrial scalability concerns associated with DMF, an additional green-solvent Cu-BTC scenario employing an ethanol/water system was evaluated. The DMF-free route reduced the manufacturing cost from 1508 to 1286 USD kg⁻¹ and decreased the GWP from 8.7 to 3.86 kg CO₂ eq kg⁻¹ while maintaining structurally acceptable Cu-BTC with a BET surface area of approximately 1138 m² g⁻¹. These results demonstrate that solvent engineering can significantly improve sustainability without compromising the functional advantages of Cu-BTC.

Overall, the comparative assessment revealed distinct performance–sustainability trade-offs among the investigated MOFs. ZIF-8 provided excellent biocompatibility and the lowest environmental burden but exhibited limited oxygen storage capacity. ZIF-67 delivered intermediate oxygen uptake together with favourable biological performance and environmental metrics. Cu-BTC achieved the highest oxygen uptake (4.6 mmol g⁻¹), the lowest oxygen-normalized cost, and, when synthesized through the green ethanol/water route, substantially improved sustainability indicators. Collectively, these findings establish that MOF selection for therapeutic oxygen delivery should be guided not only by adsorption capacity but also by biological compatibility, economic feasibility, and environmental sustainability. The developed framework provides a rational basis for the future design, scale-up, and translation of MOF-based oxygen therapeutics. This thesis delivers an integrated experimental–computational–economic framework for MOF-based biomedical materials. The outcomes form the quantitative baseline for scaling MOF synthesis toward clinically viable, environmentally responsible oxygen-delivery technologies.

सारांश

ऑक्सीजन की कमी से उत्पन्न स्थितियों जैसे हाइपोक्सिया और एक््यूट रेस्पिरेटरी डिस्ट्रेस सिंड्रोम (ARDS) के उपचार हेतु उन्नत चिकित्सीय प्रणालियों की वैश्विक आवश्यकता ने हल्के, कुशल और नियंत्रित ऑक्सीजन वाहकों की खोज को गति दी है। यह शोध-प्रबंध मेटल-ऑर्गेनिक फ्रेमवर्क्स (MOFs) को नियंत्रित औषधि विमोचन और ऑक्सीजन भंडारण/वितरण के लिए बहुक्रियाशील सामग्री के रूप में अध्ययन करता है, जिसमें प्रयोगात्मक, संगणनात्मक और स्थिरता विश्लेषणों को एकीकृत कर जैव-चिकित्सीय उपयोग और औद्योगिक विस्तार हेतु एकीकृत ढाँचा प्रस्तुत किया गया है।

थीसिस के प्रथम भाग में जियोलेटिक इमिडाजोलेट फ्रेमवर्क (ZIF-8) को कैंसर-रोधी औषधि *साइटाराबीन* के जैव-संगत नैनोवाहक के रूप में अध्ययन किया गया। इसकी उच्च रंध्रता, pH-संवेदनशीलता और संरचनात्मक स्थिरता के कारण, ZIF-8 ने औषधि को उसके मूल रूप में कुशलतापूर्वक लोड किया और शारीरिक परिस्थितियों में नियंत्रित, विसरण-प्रेरित विमोचन प्रदर्शित किया, जिसकी पुष्टि *हिगुची* और *कोर्समैयर-पेपस* गतिकीय मॉडल द्वारा की गई। इस अध्ययन ने MOF आधारित लक्षित औषधि वितरण प्रणाली की अवधारणा को सिद्ध किया।

आगे के अध्यायों में ZIF-8, ZIF-67 और Cu-BTC की ऑक्सीजन भंडारण एवं विमोचन क्षमता का मूल्यांकन किया गया, जिन्हें कमरे के तापमान तथा सॉल्वोथर्मल विधियों से संश्लेषित किया गया और बॉक्स-बेन्केन डिज़ाइन ऑफ़ एक्सपेरिमेंट्स (DoE) द्वारा अनुकूलित किया गया। विशिष्ट सतही क्षेत्र विश्लेषण और गैस अवशोषण अध्ययनों से क्रमशः 0.9 mmol/g (ZIF-8), 2.8 mmol/g (ZIF-67) और 4.6 mmol/g (Cu-BTC) की ऑक्सीजन अवशोषण क्षमता प्राप्त हुई। ग्रैंड कैनोनिकल मॉन्टे कार्लो (GCMC) और मॉलिक्यूलर डायनेमिक्स (MD) सिमुलेशन से यह पाया गया कि ऑक्सीजन अणु मुख्यतः खुले धातु स्थलों और रंध्र चैनलों के समीप अवशोषित होते हैं।

स्केलेबिलिटी और स्थिरता के मूल्यांकन हेतु लाइफ़ साइकिल असेसमेंट (LCA) और टेक्नो-इकोनॉमिक एनालिसिस (TEA) का उपयोग किया गया, जिसमें प्रयोगशाला-स्तर के इन्वेंटरी डेटा को 1 किग्रा MOF उत्पादन के लिए 2025 के बाज़ार मूल्यों के अनुरूप सामान्यीकृत किया गया। दो उत्पादन स्तरों का अध्ययन किया गया - पायलट स्तर (1 किग्रा/वर्ष) और डेमो स्तर (1000 किग्रा/वर्ष)। पायलट स्तर पर निर्माण की समतलीकृत लागत

(LCOM) 50 000 \$/किग्रा से अधिक रही, जबकि डेमो स्तर पर यह घटकर 566 \$/किग्रा (ZIF-8), 1508 \$/किग्रा (Cu-BTC) और 1484 \$/किग्रा (ZIF-67) हो गई। इस स्तर पर कच्चा माल और सॉल्वेंट कुल लागत के 70 % से अधिक के लिए जिम्मेदार थे, जबकि CAPEX का योगदान 15 % से कम रहा।

कार्यात्मक प्रदर्शन के आधार पर सामान्यीकरण करने पर, प्रति मोल ऑक्सीजन भंडारण लागत 627 \$/मोल (ZIF-8), 326 \$/मोल (Cu-BTC) और 527 \$/मोल (ZIF-67) पाई गई, जिससे Cu-BTC को सबसे किफायती ऑक्सीजन वाहक सिद्ध किया गया। हालाँकि, पर्यावरणीय विश्लेषण ने महत्वपूर्ण अंतर दर्शाए। *openLCA (Ecoinvent v3.8, TRACI 2.1)* पर आधारित क्रैडल-टू-गेट ढाँचे में किया गया LCA दर्शाता है कि ZIF-8 का प्रभाव सबसे कम था, जबकि ZIF-67 और Cu-BTC (जो अल्कोहल और DMF आधारित सॉल्वोथर्मल विधि से तैयार किए गए) में पर्यावरणीय भार अधिक पाया गया — जैसे वैश्विक ऊष्मन संभावना (2.1, 5.3, 8.7 kg CO₂ eq), कार्सिनोजेनिक प्रभाव (1.2×10^{-7} , 4.5×10^{-7} , 7.8×10^{-7} CTUh) और अम्लीकरण (0.18, 0.42, 0.47 kg SO₂ eq)। सभी प्रणालियों में आर्थिक (धातु लवण + लिगेंड) और पर्यावरणीय (सॉल्वेंट + प्रिकर्सर) हॉटस्पॉट असंगत पाए गए, जिससे हरित सॉल्वेंट प्रतिस्थापन, टिकाऊ प्रिकर्सर स्रोत तथा सतत या यांत्रिक रासायनिक मार्गों की आवश्यकता पर बल मिला।

अध्याय 8 में TEA और LCA के संयुक्त परिणामों को सम्मिलित कर जैव-चिकित्सीय ऑक्सीजन वाहकों के लिए लागत-प्रभाव फ्रंटियर तैयार किया गया, जबकि अध्याय 9 ने समग्र निष्कर्षों को संकलित किया: ZIF-8 नियंत्रित औषधि विमोचन के लिए सर्वाधिक जैव-संगत और सुरक्षित है; Cu-BTC उच्चतम ऑक्सीजन अवशोषण और कार्यात्मक लागत दक्षता प्रदान करता है, यद्यपि इसका पर्यावरणीय प्रभाव अधिक है; और ZIF-67 तकनीकी, आर्थिक और पर्यावरणीय दृष्टि से सर्वाधिक संतुलित विकल्प सिद्ध हुआ।

यह शोध एक एकीकृत प्रयोगात्मक-संगणनात्मक-आर्थिक ढाँचा प्रस्तुत करता है, जो MOF-आधारित जैव-चिकित्सीय सामग्रियों के लिए दक्षता और स्थिरता दोनों को संयोजित करता है। इसके परिणाम MOF संश्लेषण को व्यावहारिक, नैदानिक रूप से उपयोगी और पर्यावरणीय रूप से उत्तरदायी ऑक्सीजन वितरण प्रौद्योगिकियों में रूपांतरित करने हेतु मात्रात्मक आधार प्रदान करते हैं।

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LIST OF ACRONYMS

Main Acronyms

MOF	Metal-Organic Framework
COF	Covalent-Organic Framework
O ₂	Molecular Oxygen
CYT	Cytarabine (Ara-C, anti-cancer drug)
ARDS	Acute Respiratory Distress Syndrome
MC	Monte Carlo
MD	Molecular Dynamics
GCMC	Grand-Canonical Monte Carlo
DFT	Density Functional Theory
PBC	Periodic Boundary Conditions
UFF	Universal Force Field
COMPASS	Condensed-phase Optimized Molecular Potentials for Atomistic Simulation Studies
RSM	Response Surface Methodology
BBD	Box-Behnken Design
TEA	Techno-Economic Analysis
LCA	Life Cycle Assessment

MOF Related Acronyms

UiO	University of Oslo
DUT	Dresden University of Technology
ZIF	Zeolitic Imidazolate Framework
ZIF-8	Zeolitic Imidazolate Framework-8 (Zn-based)
ZIF-67	Zeolitic Imidazolate Framework-67 (Co-based)
Cu-BTC	Copper-Benzene-1,3,5-Tricarboxylate
HKUST-1	Hong Kong University of Science and Technology-1
IRMOF	Iso-Reticular Metal-Organic Framework
BDC	Benzene-1,4-Dicarboxylate
BTC	Benzene-1,3,5-Tricarboxylic acid
2-MIM	2-Methylimidazole

Other

CSD	Cambridge Structural Database
BET	Brunauer–Emmett–Teller
BJH	Barrett–Joyner–Halenda
PSD	Pore Size Distribution
NLDFT	Non-Local Density Functional Theory
TGA	Thermogravimetric Analysis
GC	Gas Chromatography
FTIR	Fourier-Transform Infrared Spectroscopy
PXRD	Powder X-ray Diffraction
FWHM	Full Width at Half Maximum
DLS	Dynamic Light Scattering
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
UHV	Ultra-High Vacuum
BE	Binding Energy
XPS	X-ray Photoelectron Spectroscopy
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
EDX/EDS	Energy-Dispersive X-ray Spectroscopy
EPR	Electron Paramagnetic Resonance
TSA	Temperature Swing Adsorption
PSA	Pressure Swing Adsorption
MISA	Magnetic-Induced Swing Adsorption
PBS	Phosphate Buffered Saline
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
ROS	Reactive Oxygen Species
PFC	Perfluorocarbon
PW	Planewaves
PBE	Perdew–Burke–Ernzerhof
LDA	Local density approximation
GGA	Generalised gradient approximation

TCD	Thermal Conductivity Detector
RBC	Red Blood Cells
ASTM	American Society for Testing and Materials
ANOVA	Analysis of Variance
TEG	Thromboelastography
MA	Maximum Amplitude
DDEC	Density Derived Electrostatic and Chemical Charges
CBMC	Configurational Bias Monte Carlo
TraPPE	Transferable Potentials for Phase Equilibria
GWP	Global Warming Potential
TRACI	Tool for the Reduction and Assessment of Chemical and Other Environmental Impacts
AOC	Artificial Oxygen Carriers
Å	Angstrom
nm	Nanometres
Q _{st}	Isosteric Heat of Adsorption

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THESIS CONTRIBUTIONS

This doctoral research contributes significantly to the field of metal-organic frameworks (MOFs) for biomedical applications, particularly in the domains of targeted drug delivery and therapeutic oxygen storage and release. The contributions are categorized into experimental findings, computational advancements, and application-based insights:

List of Journal Publications (peer reviewed and published)

- **Singh, C.,** Mangal, P. *et al.* Elucidating molecular oxygen adsorption in ZIF-8 through integrated experimental and computational studies. *J. Mater. Chem. B*, (2026), Advance Article DOI: [10.1039/D5TB02395E](https://doi.org/10.1039/D5TB02395E)
- **Singh C,** Jha CB, Upadhyayula S, Mathur R et al. Copper based Metal Organic Framework as a Potential Therapeutic Gas Carrier: Optimization, Synthesis, Characterization and Computational Study. *ACS Appl. Bio Mater.* (2025), 8(3), 2440–2458. DOI: [10.1021/acsabm.4c01907](https://doi.org/10.1021/acsabm.4c01907)
- **Singh C,** Jha CB, Upadhyayula S, Mathur R. Oxygen Gas-Filled Metal-Organic frameworks (MOFs) delivery System: A hypothetical design for injectable oxygen. *Medical Hypotheses*, (2024), 192, 111489. DOI: [10.1016/j.mehy.2024.111489](https://doi.org/10.1016/j.mehy.2024.111489)
- **Singh, C.,** Jha, C.B., Kumar, N. *et al.* An integrated experimental and simulation study on the loading of cytarabine in a biocompatible zinc imidazole metal–organic framework. *J Mater Sci.*, (2022), 57, 18561–18577. DOI: [10.1007/s10853-022-07757-w](https://doi.org/10.1007/s10853-022-07757-w)

International Conferences

- **Singh, C.,** Upadhyayula, S., Mathur, R. [Copper based Metal Organic Framework as a Therapeutic Oxygen Carrier: An Integrated Experimental and Computational Study.](#) Poster presentation at the 1st ACS Qatar Chapter and RSC conference under the theme, Synergy for Sustainability: Advancing a Greener Future through Chemistry and Engineering, Doha, Qatar, November 3-5, 2024.
- **Singh, C.,** Jha, C.B., Upadhyayula, S., Mathur, R. Evaluation of Zeolitic Imidazolate Framework (ZIF-8) as a Molecular Oxygen Carrier: An Integrated Experimental and Simulation Study. Poster presentation at the Nanomaterials in Biomedical Applications conference (NATURE Conference), MAHE, Manipal, India, February 26-27, 2024.
- **Singh, C.,** Jha, C.B., Mangal, P., Upadhyayula, S., Mathur, R. Therapeutic Application of ZIF-67 Intended for Molecular Oxygen Delivery: Collective Experimental and Computational Approach. Poster presentation at the 5th European Conference on Metal Organic Frameworks and Porous Polymers (EuroMOF), Granada, Spain, September 24-27, 2023.
- **Singh, C.,** Jha, C.B., Varshney, R., Ojha, H., Mishra, A.K., Mathur, R. Efficient Storage of Drug in Biocompatible Metal Organic Framework with Nano Dimensions: An Experimental and Simulation Study, Poster Presentation- NANOBIOOTEK; 21-23 Nov; Aerocity, New Delhi, 2019. Best Poster Award" in NANOBIOOTECK – 2019, 4th Annual Conference of Indian Society of Nanomedicine in collaboration with DBT, Government of India.