SYNTHESIS AND EVALUATION OF ORGANIC FUNCTIONALISED MESOPOROUS (MCM-41) MATERIALS AS NANO-CARRIERS FOR ANTITUBERCULAR HYDRAZONE DRUG DERIVATIVES

OYEKAN, JOSEPHINE OLUWAGBEMISOLA
(17PCC01650)

MAY, 2024.

SYNTHESIS AND EVALUATION OF ORGANIC FUNCTIONALISED MESOPOROUS (MCM-41) MATERIALS AS NANO-CARRIERS FOR ANTITUBERCULAR HYDRAZONE DRUG DERIVATIVES

BY

OYEKAN, JOSEPHINE OLUWAGBEMISOLA
(17PCC01650)
B.Tech Pure & Applied Chemistry, Ladoke Akintola University of Technology, Ogbomosho.
M.Sc Biochemical Engineering, University of Birmingham, Birmingham

A THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D) IN INDUSTRIAL CHEMISTRY IN THE DEPARTMENT OF CHEMISTRY, COLLEGE OF SCIENCE AND TECHNOLOGY, COVENANT UNIVERSITY, OTA, OGUN STATE, NIGERIA.

MAY, 2024

ACCEPTANCE

This is to attest that this thesis is accepted in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy (Ph.D) in Industrial Chemistry, in the Department of Chemistry, College of Science and Technology, Covenant University, Ota, Nigeria.

Miss Adefunke F. Oyinloye
(Secretary, School of Postgraduate Studies) **Signature and Date**

Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

DECLARATION

I, OYEKAN, JOSEPHINE OLUWAGBEMISOLA (17PCC01650), declare that this research was carried out by me under the supervision of Prof. Kolawole O. Ajanaku and Dr. Joseph A. Adekoya of the Department of Chemistry, College of Science and Technology, Covenant University, Ota, Nigeria. I attest that this thesis has not been presented either wholly or partially for the award of any degree anywhere else. All the sources of data and scholarly information used in this thesis are duly acknowledged.

OYEKAN, JOSEPHINE OLUWAGBEMISOLA

Signature and Date

CERTIFICATION

We certify that this thesis titled **SYNTHESIS AND EVALUATION OF ORGANIC FUNCTIONALISED MESOPOROUS (MCM-41) MATERIALS AS NANO-CARRIERS FOR ANTITUBERCULAR HYDRAZONE DRUG DERIVATIVES** is an original Research Work carried out by **OYEKAN, JOSEPHINE OLUWAGBEMISOLA (17PCC01650)** in the Department of Chemistry, Covenant University, Ota, Ogun State, Nigeria under the supervision of Prof. Kolawole O. Ajanaku and Dr. Joseph A. Adekoya. We have examined and found the research work acceptable as part of the requirements for the award of the degree of Doctor of Philosophy in Industrial Chemistry.

Prof. Kolawole O. Ajanaku
(Supervisor) **Signature and Date**

Dr. Joseph A. Adekoya
(Co-Supervisor) **Signature and Date**

Dr. Cyril O. Ehi-Eromosele
(Head of Department) **Signature and Date**

Prof. Semire Banjo
(External Examiner) **Signature and Date**

Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

DEDICATION

This thesis is dedicated to Almighty God, who led me from the beginning to the end of the program.

ACKNOWLEDGEMENTS

My profound gratitude goes to God Almighty for the strength, provisions, and divine guidance towards the success of this work. I ascribe all the glory to Him alone and would be eternally grateful to Him. I sincerely appreciate the Chancellor of Covenant University, Dr. David O. Oyedepo, for spearheading the mission of raising an army of a new generation of leaders that will restore the dignity of Africa. This mission gave birth to a world-class university, Covenant University, which served as a platform for this research's successful kick-off and completion. I acknowledge the Vice-Chancellor of Covenant University, Prof. Abiodun H. Adebayo, the Deputy Vice-Chancellor, Prof. Olujide A. Adekeye and the management team for their leadership and administrative roles that made the completion of this research work possible. My sincere gratitude goes to the acting Registrar, Mrs Regina A. Tobi-David, the Dean of the School of Postgraduate Studies; Prof. Akan B. Williams, the Sub-Dean School of Postgraduate Studies; Dr Hezekiah O. Falola, the Dean of the College of Science and Technology, Prof. Timothy A. Anake, for his much-valued support. I appreciate the Head of the Department, Prof. Joseph A. Olugbuyiro, for his valuable contribution and drive for the possible research conclusion. God bless you, Sir.

I sincerely appreciate my supervisor, Prof. Kolawole. O. Ajanaku and Co-Supervisor, Dr. Joseph. A. Adekoya, for their mentorship and the relentless effort and time they have devoted to this research project's success. Thank you very much, sirs, for believing in me and allowing me to work and learn under you. May your committed labour be rewarded with God’s favour and all-round blessings.

I also acknowledge and thank The World Academy of Science (TWAS) for allowing me to do my bench work at the CSIR-Indian Institute of Chemical Technology, Hyderabad, India, under the supervision of Prof. Rajkumar Banerjee and Prof. Chittan Ranjan Patra via the CSIR-TWAS Sandwich Postgraduate Fellowship for eleven months.

The entire faculty and staff of the Department of Chemistry, Covenant University, are also appreciated for their guidance throughout my academic journey at Covenant University. Special appreciation goes to the senior lecturers of the department: Prof. Akan B. Williams, Prof. Nsikak U. Benson, Prof. Olayinka O. Ajani, Dr. Tolutope O. Siyanbola, Dr. Cyril Ehi-Eromosele, Dr. Moses M. Solomon, Dr. Winifred U. Anake, Dr. Anuoluwapo A. Akinsiku, and other excellent faculty.

My heartfelt appreciation goes to my family, especially my wonderful husband, Engr. Oluwamuyiwa Joseph Tella for his love, support, commitment and sacrifices, especially financially. I appreciate your understanding through the years, especially when I was away for my bench work. You stood by me prayerfully, financially, and emotionally. God bless you and reward you with all your heart desires. To our son and daughter, Oluwabukunmi Joshua Tella and Oluwafikunmi Joanna Tella, thank you for your understanding and support throughout the program. To my wonderful parents, Engr. & Mrs L. N Oyekan and Mr & Mrs V. O Tella, thank you for your love, prayers, and support throughout this program. I also appreciate my lovely siblings, Mrs Joy Olanipekun, Dr. John Oyekan and Engr. Joseph Oyekan for all their encouragement and support. God bless you all.

TABLE OF CONTENTS

CHAPTER FIVE: DISCUSSION

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ACRONYMS AND ABBREVIATION

APTES:	3-aminopropyl triethoxysilane
BET:	Brunauer-Emmett-Teller
cryo-TEM:	cryo-Transmission Electron Microscopy
Cu-INH:	Copper (II) metal complex of isoniazid
CVD:	Chemical Vapour Deposition
FTIR:	Fourier Transform Infra-red Spectroscopy
Fe-INH:	Iron (III) metal complex of isoniazid
HIV:	Human Immunodeficiency Virus
INH:	Isoniazid
IUPAC:	International Union of Pure and Applied Chemistry
LTBI:	Latent Tuberculosis Infection
MABA:	Micro plate Alamar Blue Assay
MCM-41:	Mobile Crystalline Material-41
MCM-48:	Mobil Crystalline Material-48
MCM-50:	Mobil Crystalline Material-50
MDR:	Multi Drug Resistant
MDR-TB:	Multi-Drug Resistant Tuberculosis
MIC:	Minimum Inhibitory Concentration
MOFs:	Metal Organic Frameworks
MONs:	Mesoporous Organosilica Nanoparticles
MPTES:	3-mercaptopropyl trimethoxysilane
MSNs:	Mesoporous Silica Nanoparticles
MTB:	Mycobacterium Tuberculosis Bacterium
PBS:	Phosphate Buffered Saline
PMOs:	Periodic Mesoporous Organosilicas
PVD:	Physical Vapor Deposition
SAXS:	Small Angle X-ray Scattering

SBA-15:	Santa Barbara Amophorous-15
SBA-16:	Santa Barbara Amorphous-16
SDAs	Structure Directing Agents
SEM:	Scanning Electron Microscopy
TEM:	Transmission Electron Microscopy
TEOS:	Tetraethyl Orthosilicate
TMOS:	Tetramethylorthosilicate
TGA:	Thermogravimetric Analysis
TDR-TB:	Total Drug Resistant Tuberculosis
WHO:	World Health Organisation
XDR:	Extensively Drug Resistant
XDR -TB:	Extensively-Drug Resistant Tuberculosis
XRD:	X-ray Diffraction

ABSTRACT

The use of conventional drug delivery systems for the treatment and management of tuberculosis comes with setbacks that require the development of advanced drug delivery systems for the improved delivery of anti-tubercular agents. Mesoporous silica nanoparticles (MCM-41) have been of great interest as they possess distinctive properties that give them an edge over conventional drug delivery systems. This study focuses on the sol-gel synthesis and amino functionalisation of mesoporous silica nanoparticles via co-condensation and post-grafting methods to deliver anti-tubercular agents such as isoniazid and its metal complexes. Non-functionalised and amino functionalised MCM-41 nano-carriers were synthesised from two silica sources (tetra ethyl orthosilicate and sodium silicate) and characterized with X-ray diffraction (XRD), Brunauer-Emmett-Teller (BET) surface analysis, Fourier-transform infrared spectroscopy (FT-IR), CHNS analysis, Scanning electron microscopy (SEM), Transmission Electron Microscopy (TEM) and Thermo-gravimetric analysis (TGA). The physical and morphological properties of the drug loading and release studies of the nano-carriers synthesised from different silica sources were compared. Non-functionalised and amino functionalised nano-carriers synthesised with Tetra Ethyl Ortho Silicate were revealed to have better well-ordered pores than those synthesised using sodium silicate from their XRD analysis. The morphological characterisation of the nano-carriers using SEM showed that the surfactant removal methods (calcination and acid/ethanol extraction) affected their structural properties. Nano-carriers, Cal-MCM-41t&s + Cu-INH and Post-NH_2-Cal-MCM-41t&s + Cu-INH had high drug entrapment efficiencies of 87.65%, 76.23% and 92.82%, 90.2% with loading capacities of 17.53%, 15.25% and 18.66%, 18.05%. Amino-functionalised nano-carriers were shown to improve the drug loading and entrapment efficiency of the nano-carriers. The *in-vitro* release study revealed a steady release rate of anti-tubercular agents INH, Cu-INH, and Fe-INH. Cal-MCM-41t&s + Cu-INH and Post-NH_2-Cal-MCM-41t&s + Cu-INH released the highest amount of INH and its metal complexes. Cal-MCM-41t + Cu-INH, Post-NH_2-Cal-MCM-41t + Cu-INH, Cal-MCM-41s + Cu-INH and Post-NH_2-Cal-MCM-41s + Cu-INH released 30.97%, 36.43%, 41.98% and 50.82% at a pH of 7.4 while at a pH of 5.4, they released 39.54%, 47.26%, 52.82% and 66.74% respectively after 14 days. The findings showed that using non-functionalised and amino-functionalised mesoporous silica nano-carriers is a promising drug delivery system for delivering isoniazid and its metal complexes. However, other surface-functionalised MCM-41 nano-carriers should also be studied.

KEYWORDS: Tuberculosis, Mesoporous silica nano-carriers, Isoniazid, Metal complexes Drug delivery.