

**DEVELOPMENT OF THERANOSTIC SYSTEMS FOR
NEURODEGENERATIVE DISORDERS**

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DEVELOPMENT OF THERANOSTIC SYSTEMS FOR NEURODEGENERATIVE DISORDERS

by

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Submitted
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Dedicated to My Parents

CERTIFICATE

This is to certify that the thesis entitled, "**Development of Theranostic Systems for Neurodegenerative Disorders**" being submitted by **Ms. Shivani** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry, is an authentic record of research work carried out by her. She has worked under the guidance and supervision of Prof. Shashank Deep and Dr. Anupama Datta. The work has not been submitted, in part or in full, to any other university or institute for award of any degree or diploma. Ms. Shivani has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

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Shivani

Abstract

The thesis entitled *“Development of Theranostic Systems for Neurodegenerative Disorders”* presents the development of multifunctional theranostic systems aimed at the detection and treatment of neurodegenerative disorders, with primary focus on A β ₄₂ aggregation linked to traumatic brain injury. The research leverages mesoporous silica nanoparticles and chalcone derivatives to create innovative platforms capable of crossing the blood-brain barrier, targeting A β ₄₂ plaques, and delivering therapeutic agents effectively.

Chapter 1: Introduction

This chapter provides a concise introduction to neurodegenerative disorder, emphasizing the significance of abnormal protein aggregates. The chapter explores challenges in treating these disorders, such as the blood-brain barrier, which restricts most diagnostic and therapeutic agents. The potential of mesoporous silica nanoparticles as theranostic nanocarriers is discussed, highlighting their high surface area, biocompatibility, and modifiable surface for drug delivery and imaging applications. Molecular imaging techniques, including SPECT and MRI, are introduced as critical diagnostic tools to visualize and monitor the disease.

Chapter 2: Chalcone Functionalized Mesoporous Silica Nanoparticles for Diagnosis and Therapy of Trauma-Induced A β Aggregation

The focus of the study lies in the design of functionalized mesoporous silica nanoparticles with the aim of enhanced permeability across the blood-brain barrier while ensuring effective binding to A β ₄₂ aggregates. Chalcone and diethylenetriamine pentaacetic acid functionalized mesoporous silica nanoparticles, were characterized via FESEM and TEM, which displayed spherical morphology and homogeneous size distribution. Results based on nitrogen adsorption/desorption

isotherms, TGA, FTIR, and UV-Vis analysis confirmed functionalization on MSN with targeting moiety, chalcone, and chelating agent, DTPA. A redshift to 30 nm and a 4-fold increase in emission intensity of the fluorescent spectrum of nanomaterial upon treatment with A β ₄₂ aggregate indicated an interaction between A β ₄₂ aggregate and synthesized material. The MTT assay indicated > 90% cell viability in PC12 and HEK-293 cell lines after co-incubation with nanoparticles at 48 h. The radiolabeled complex of synthesized nanomaterials with SPECT radioisotope, ^{99m}Tc, had >99% radiochemical purity. *In vivo* SPECT imaging on healthy rabbits demonstrated the effective penetration of functionalized nanoparticles into the brain. Further, non-surgical rmTBI model over expressed with A β ₄₂ plaques was developed, and the formation of A β ₄₂ plaques was confirmed using histological analysis, ThS staining, and immunohistochemistry. *Ex vivo* biodistribution studies revealed high brain uptake of functionalized nanoparticles in A β ₄₂ plaques over expressed TBI mice after 2 h with slow washout, compared to control mice, possibly due to binding of nanoparticles with A β ₄₂ aggregates. Further, curcumin was loaded in nanoparticles and exhibited a biphasic sustained release profile, underscoring the potential of the system for controlled drug delivery. These findings suggest that chalcone- and DTPA-functionalized mesoporous silica nanoparticles hold promise for theranostic applications in neurodegenerative disease management.

Chapter 3: Multi-Target Directed Triazole-Chalcone Conjugate as Potent A β ₄₂ Aggregation Inhibitor

This chapter discusses the design and synthesis of triazole-chalcone conjugate (L1) targeting A β ₄₂ aggregation. The conjugate exhibits high binding affinity and A β aggregation inhibition due to its dimeric structure, selected through molecular docking and molecular dynamics studies. The conjugate also chelates biometals such as Cu²⁺, showing potential in mitigating metal-induced

oxidative stress. The findings indicate L1 as promising multifunctional agent for addressing amyloid plaques and related neurodegenerative pathways.

Chapter 4: Binding Studies of Triazole–Chalcone Conjugate with Serum Albumin Proteins

This chapter explores the pharmacokinetics of the triazole-chalcone conjugate (L1) through its interaction with bovine serum albumin using spectroscopic and *in silico* techniques. Binding studies reveal moderate affinity, with static quenching suggesting non-covalent interaction. Molecular docking confirms hydrogen bonds and Van der Waals interactions as primary binding forces. These insights into the pharmacokinetics of L1 highlight its potential for clinical applications as a therapeutic agent.

Chapter 5: Folate Receptor Targeted Mesoporous Silica Nanoparticles as Dual Imaging Probe

This study describes the development of ^{99m}Tc -labeled manganese oxide-loaded mesoporous silica nanoparticles conjugated with folic acid as targeting moiety and $\text{H}_2\text{pentapa-en-NH}_2$ as chelating agent, intended for targeted SPECT-MRI dual imaging applications. The synthesized nanoprobe was designed to leverage both paramagnetic and radiolabeling properties, enhancing imaging contrast for T1-weighted MRI and SPECT modalities. The nanoparticles were evaluated for biocompatibility in HEK-293 and U87MG cell lines, supporting their safety profile. The system demonstrated high radiolabeling stability and included pH-responsive release mechanism for manganese ions to optimize relaxivity for MRI. *In vivo* SPECT imaging demonstrated rapid tracer accumulation in U87MG xenografts with minimal uptake in non-targeted organs. *In vivo* MRI studies indicated most substantial tumor contrast at 2 h post injection. Given its desirable contrast enhancement in T₁ MRI and SPECT imaging, along with low toxicity, the developed system shows potential as an effective multifunctional nanoprobe for dual imaging.

Chapter 6: Summary of Thesis

This chapter highlights the salient features of this work. By integrating molecular imaging, drug delivery, and multitarget-directed therapeutic strategies, this work contributes significantly to the development of advanced nanomedicine platforms with broad potential for clinical applications.

अमूर्त

“न्यूरोडीजेनेरेटिव विकारों के लिए थेरानोस्टिक सिस्टम का विकास” शीर्षक वाली थीसिस, न्यूरोडीजेनेरेटिव विकारों का पता लगाने और उपचार करने के उद्देश्य से बहुक्रियाशील थेरानोस्टिक प्रणालियों के विकास को प्रस्तुत करती है, जिसमें मस्तिष्क की चोट से जुड़े $A\beta_{42}$ एकत्रीकरण पर प्राथमिक ध्यान दिया जाता है। अनुसंधान रक्त-मस्तिष्क बाधा को पार करने, $A\beta_{42}$ सजीले टुकड़े को लक्षित करने और चिकित्सीय एजेंटों को प्रभावी ढंग से वितरित करने में सक्षम अभिनव प्लेटफॉर्म बनाने के लिए मेसोपोरस सिलिका नैनोकणों और चाल्कोन डेरिवेटिव का लाभ उठाता है।

अध्याय 1: परिचय

यह अध्याय असामान्य प्रोटीन समुच्चय के महत्व पर बल देते हुए न्यूरोडीजेनेरेटिव विकार का संक्षिप्त परिचय प्रदान करता है। अध्याय इन विकारों के इलाज में चुनौतियों का पता लगाता है, जैसे कि रक्त-मस्तिष्क बाधा, जो अधिकांश नैदानिक और चिकित्सीय एजेंटों को प्रतिबंधित करती है। थेरानोस्टिक नैनोकैरियर के रूप में मेसोपोरस सिलिका नैनोकणों की क्षमता पर चर्चा की गई है, जिसमें दवा वितरण और इमेजिंग अनुप्रयोगों के लिए उनके उच्च सतह क्षेत्र, जैव-अनुकूलता और परिवर्तनीय सतह पर प्रकाश डाला गया है। SPECT और MRI सहित आणविक इमेजिंग तकनीकों को रोग की कल्पना और निगरानी के लिए महत्वपूर्ण निदान उपकरण के रूप में पेश किया गया है।

अध्याय 2: आघात-प्रेरित $A\beta$ एकत्रीकरण के निदान और उपचार के लिए चाल्कोन ने मेसोपोरस सिलिका नैनोकणों को क्रियाशील किया

अध्ययन का ध्यान कार्यात्मक मेसोपोरस सिलिका नैनोकणों के डिजाइन पर केंद्रित है, जिसका उद्देश्य $A\beta_{42}$ समुच्चय के लिए प्रभावी बंधन सुनिश्चित करते हुए रक्त-मस्तिष्क बाधा में पारगम्यता को बढ़ाना है। चाल्कोन और डायथाइलेनेट्रामाइन पेंटाएसिटिक एसिड कार्यात्मक मेसोपोरस सिलिका नैनोकणों को एफईएसईएम और टीईएम के माध्यम से चित्रित किया गया था, जो गोलाकार आकृति विज्ञान और सजातीय आकार वितरण प्रदर्शित करता था। $A\beta_{42}$ समुच्चय के साथ उपचार करने पर नैनोमटेरियल के फ्लोरोसेंट स्पेक्ट्रम की उत्सर्जन तीव्रता में 30 एनएम की लाल बदलाव और 4 गुना वृद्धि, $A\beta_{42}$ समुच्चय और संश्लेषित सामग्री के बीच बातचीत का संकेत देती है। एमटीटी परख ने 48 घंटे पर नैनोकणों के साथ सह-ऊष्मायन के बाद पीसी12 और एचईके-293 सेल लाइनों में 90% सेल व्यवहार्यता का संकेत दिया। SPECT रेडियोआइसोटोप, ^{99m}Tc के साथ

संश्लेषित नैनोमटेरियल के रेडियोलेबल कॉम्प्लेक्स में >99% रेडियोकेमिकल शुद्धता थी। स्वस्थ खरगोशों पर SPECT इमेजिंग में मस्तिष्क में कार्यात्मक नैनोकणों के प्रभावी प्रवेश का प्रदर्शन किया गया। इसके अलावा, $A\beta_{42}$ व्यक्त गैर-सर्जिकल rmTBI मॉडल विकसित किया गया था, और हिस्टोलॉजिकल विश्लेषण, ThS स्टेनिंग और इम्यूनोहिस्टोकेमिस्ट्री का उपयोग करके $A\beta_{42}$ समुच्चय के गठन की पुष्टि की गई थी। बायोडिस्ट्रीब्यूशन अध्ययनों से पता चला है कि नियंत्रित चूहों की तुलना में धीमी गति से वॉशआउट के साथ 2 घंटे के बाद व्यक्त TBI चूहों पर $A\beta_{42}$ समुच्चय में कार्यात्मक नैनोकणों का मस्तिष्क में उच्च अवशोषण होता है, संभवतः $A\beta_{42}$ समुच्चय के साथ नैनोकणों के बंधन के कारण। इसके अलावा, करक्यूमिन को नैनोकणों में लोड किया गया, द्विचरणीय निरंतर रिलीज प्रोफ़ाइल प्रदर्शित की गई, जो नियंत्रित दवा वितरण के लिए प्रणाली की क्षमता को रेखांकित करती है। इन निष्कर्षों से पता चलता है कि चाल्कोन- और डीटीपीए-फंक्शनल मेसोपोरस सिलिका नैनोकण न्यूरोडीजेनेरेटिव रोग प्रबंधन में चिकित्सीय अनुप्रयोगों के लिए वादा करते हैं।

अध्याय 3: शक्तिशाली $A\beta_{42}$ एकत्रीकरण अवरोधक के रूप में बहु-लक्ष्य निर्देशित ट्राईज़ोल-चाल्कोन संयुग्म

यह अध्याय $A\beta_{42}$ एकत्रीकरण को लक्षित करने वाले ट्राईज़ोल-चाल्कोन संयुग्म (L1) के डिजाइन और संश्लेषण पर चर्चा करता है। आणविक डॉकिंग और आणविक गतिशीलता अध्ययनों के माध्यम से चयनित, इसकी संरचना के कारण संयुग्म उच्च बाध्यकारी संबंध और $A\beta$ एकत्रीकरण निषेध प्रदर्शित करता है। संयुग्मन Cu^{2+} जैसे बायोमेटल्स को भी chelates करता है, जो धातु-प्रेरित ऑक्सीडेटिव तनाव को कम करने की क्षमता दिखाता है। निष्कर्ष L1 को $A\beta_{42}$ एकत्रीकरण और संबंधित न्यूरोडीजेनेरेटिव मार्गों को संबोधित करने के लिए आशाजनक बहुक्रियाशील एजेंट के रूप में दर्शाते हैं।

अध्याय 4: सीरम एल्ब्यूमिन प्रोटीन के साथ ट्राईज़ोल-चाल्कोन संयुग्म का बाइंडिंग अध्ययन

यह अध्याय स्पेक्ट्रोस्कोपिक और कंप्यूटर तकनीकों का उपयोग करके गोजातीय सीरम एल्ब्यूमिन के साथ बातचीत के माध्यम से ट्राईज़ोल-चाल्कोन संयुग्म के फार्माकोकाइनेटिक्स की पड़ताल करता है। बाइंडिंग अध्ययन से मध्यम आत्मीयता का पता चलता है, जबकि स्थैतिक शमन से गैर-सहसंयोजक अंतःक्रिया का पता चलता है। आणविक डॉकिंग प्राथमिक बंधनकारी बलों के रूप में हाइड्रोजन बांड और वैन डेर वाल्स

इंटरेक्शन की पुष्टि करता है। L1 के फार्माकोकाइनेटिक्स में ये अंतर्दृष्टि चिकित्सीय एजेंट के रूप में नैदानिक अनुप्रयोगों के लिए इसकी क्षमता को उजागर करती है।

अध्याय 5: फोलेट रिसेप्टर ने दोहरी इमेजिंग जांच के रूप में मेसोपोरस सिलिका नैनोकणों को लक्षित किया

यह अध्ययन लक्षित SPECT-MRI दोहरे इमेजिंग अनुप्रयोगों के लिए लक्षित भाग के रूप में फोलिक एसिड के साथ संयुग्मित ^{99m}Tc -लेबल मैंगनीज ऑक्साइड-लोडेड मेसोपोरस सिलिका नैनोकणों और चेलेटिंग एजेंट के रूप में $\text{H}_2\text{pentapa-en-NH}_2$ के विकास का वर्णन करता है। संश्लेषित नैनोप्रोब को पैरामैग्नेटिक और रेडियोलेबलिंग दोनों गुणों का लाभ उठाने के लिए डिज़ाइन किया गया था, जो T_1 -भारित एमआरआई और SPECT तौर-तरीकों के लिए इमेजिंग कंट्रास्ट को बढ़ाता है। नैनोकणों का मूल्यांकन उनकी सुरक्षा प्रोफाइल का समर्थन करते हुए, HEK-293 और U87MG सेल लाइनों में जैव अनुकूलता के लिए किया गया था। सिस्टम ने उच्च रेडियोलेबलिंग स्थिरता का प्रदर्शन किया और एमआरआई के लिए आराम को अनुकूलित करने के लिए मैंगनीज आयनों के लिए पीएच-उत्तरदायी रिलीज तंत्र को शामिल किया। SPECT इमेजिंग में U87MG ज़ेनोग्राफ़्ट में तेजी से ट्रेसर संचय का प्रदर्शन किया गया और गैर-लक्षित अंगों में न्यूनतम उठाव देखा गया। विवो एमआरआई अध्ययनों में इंजेक्शन के 2 घंटे बाद सबसे मजबूत ट्यूमर कंट्रास्ट का संकेत मिला। कम विषाक्तता के साथ-साथ T_1 एमआरआई और एसपीईसीटी इमेजिंग में इसकी वांछनीय कंट्रास्ट वृद्धि को देखते हुए, विकसित प्रणाली दोहरी इमेजिंग के लिए एक प्रभावी बहुक्रियाशील नैनोप्रोब के रूप में क्षमता दिखाती है।

अध्याय 6: थीसिस का सारांश

यह अध्याय इस कार्य की मुख्य विशेषताओं पर प्रकाश डालता है। आणविक इमेजिंग, दवा वितरण और बहु-लक्ष्य-निर्देशित चिकित्सीय रणनीतियों को एकीकृत करके, यह कार्य नैदानिक अनुप्रयोगों के लिए व्यापक क्षमता वाले उन्नत नैनोमेडिसिन प्लेटफार्मों के विकास में महत्वपूर्ण योगदान देता है।

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ABBREVIATIONS

BFCA	Bifunctional chelating agents
BSA	Bovine serum albumin
BET	Brunauer-Emmet-Teller
CTAB	Cetyltrimethylammonium bromide
CNS	Central nervous system
CT	Computed tomography
DMEM	Dubecco's modified eagle medium
DLS	Dynamic light scattering
DCM	Dichloromethane
DG	Dentate gyrus
EDS	Energy dispersive X-ray spectroscopy
FDA	Food and Drug Association
FR α	Folate receptor alpha
HEK293	Human embryonic kidney 293 cells
H&E	Hematoxylin and eosin
HRTEM	High-resolution transmission electron microscopy

IR	Infrared spectroscopy
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MSN	Mesoporous silica nanoparticles
MeOH	Methanol
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PBS	Phosphate-buffered saline
ROS	Reactive Oxygen Species
ROI	Region of interest
SPECT	Single photon emission computed tomography
TEM	Transmission electron microscopy
TLC	Thin Layer Chromatography
TBI	Traumatic brain injury
U-87 MG	Uppsala 87 Malignant Glioma
UV-vis	Ultraviolet -visible
XRD	X-ray diffraction
XPS	X-ray photoelectron spectroscopy