

**MULTICOMPARTMENTAL POLYMERIC CARRIERS
FOR PROGRAMMABLE DRUG DELIVERY**

Nidhi Gupta



DEPARTMENT OF MATERIALS SCIENCE AND ENGINEERING

INDIAN INSTITUTE OF TECHNOLOGY DELHI

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PROGRAMMABLE DRUG DELIVERY**

by

Nidhi Gupta

Department of Materials Science and Engineering

Submitted

in the fulfilment of the requirement for the degree of

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to the



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....dedicated to my ma-papa

CERTIFICATE

This is to certify that the thesis entitled, “Multicompartmental Polymeric Carriers For Programmable Drug Delivery” being submitted by Ms. Nidhi Gupta to the Indian Institute of Technology Delhi for the award of the degree of Doctor of Philosophy is a record of bonafide research work carried out by her. Ms. Nidhi Gupta has worked under our guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to our knowledge has reached the requisite standard. The results contained in this thesis are original and have not been submitted, in part or full, to any other University or Institute for the award of any other degree or diploma.

Dr. Sampa Saha
Associate Professor
Department of Materials Science &
Engineering
Indian Institute of Technology Delhi,
Hauz Khas, New Delhi-110016



Dr. Yang-Hsiang Chan
Professor
Department of Applied Chemistry
National Yang-Ming Chaio Tung
University, Hsinchu, Taiwan

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Abstract

Drug delivery vehicles are devices designed to deliver therapeutics to the target site in the body to enhance the treatment's safety and efficacy. These carriers improve the solubility, stability, and bioavailability of poorly soluble drugs and facilitate drug transport at a desired location in a programmable fashion, thus minimizing the side effects. Among several types of drug carriers, polymeric particles sit at the forefront due to their abundant possibilities for physical and chemical alteration, leading to the development of innovative characteristics such as biomimetic shape, size, and easy fabrication. Apparently, suitably designed particles have the ability to cross biological barriers and deliver the therapeutics precisely to the target site. This dissertation focuses on the latest advancements in the design and shape of multicompartmental polymeric particles for drug delivery applications. These innovations have greatly improved the ability to target drugs, regulate their release, and boost the treatment outcome, though many critical challenges still need to be carefully assessed prior to their widespread use in clinical studies.

The electrohydrodynamic co-jetting was used to precisely design and engineer multicompartmental carriers for combination therapy. For instance, in Chapter 2A the aim of this work was to engineer polymeric microcarriers to encapsulate three PD (Parkinson's disease) drugs. The developed Tricompartamental system incorporated all three drugs, Levodopa(LD), Carbidopa (CD), and Entacapone(ENT), with high encapsulation efficiency (~100%) in a single carrier at a fixed drug ratio of 4:1:8 (LD: CD: ENT). Upon oral administration, the drug ratio needs to be maintained on subsequent release from microparticles to enhance the bioavailability of primary drug LD. That was a notable challenge, as all three drugs vary in their aqueous solubility (LD>CD>ENT). The equilibrium between the release of therapeutics was achieved by combining FDA-approved polymers (PLA, PLGA, PCL, and PEG) and the disc shape of particles. The *in vitro* studies demonstrated the simultaneous release of all three therapeutics in a sustained and controlled fashion.

To validate the parameter obtained by an experimentally optimized tricompartamental system, in Chapter 2B, tricompartamental microcarriers with controlled release profiles were investigated employing the Taguchi orthogonal L9 design-of-experiment approach by systematically varying the processing parameters, i.e., solvent ratio, polymer concentration, and flow rate. The "smaller-the-better" norm for the S/N ratio demonstrated the solvent ratio (DMF content) and polymer concentration as the most influential parameter in ensuring the RBC shape

and controlling the release of drugs. Analysis of variance and Response surface methodology approach provided insights into the optimal influence of control factors on response variables. Confirmation experiments further validated the optimized microparticles ($P_{\text{optimized}}$), demonstrating an error of only $\sim 0.13\%$ in AR_{DEV} (Aspect ratio) and $\sim 19\%$ (within tolerance limit) in RF (Release Factor) from the predicted experiment. Moreover, $P_{\text{optimized}}$ exhibits $\sim 100\%$ encapsulation efficiency of all three PD drugs, with the cumulative release of $\sim 100\%$ LD, $\sim 97\%$ CD, and $\sim 65\%$ ENT within the 5h of the *in vitro* study.

The *in vivo* study of the developed tricompartmental system was investigated in Chapter 3 for the pharmacokinetics (healthy/diseased rat) and pharmacodynamics characteristics of rotenone and MPTP-induced Parkinson's animal model. A pharmacokinetic study elucidates the improvement in delivery metrics of LD from the tricompartmental system, a two-fold increase in maximum plasma concentration ($C_{\text{max}} \sim 520 \text{ ng/mL}$), a three-fold augmentation in area under the curve ($AUC_{0-\infty} \sim 5088 \text{ ng/mL}$), and a doubled mean residence time (MRT $\sim 13.5 \text{ h}$) compared to free LD. MPTP and rotenone-induced models further supported these advancements. Meanwhile, pharmacodynamic studies concentrated on evaluating the drug's efficacy in easing motor and non-motor symptoms and reducing neurodegeneration. This work utilizes complementary models to offer extensive insights into the therapeutic potential of the established system and its translational significance for human Parkinson's disease.

Chapter 4 presents the development of innovative bicompartamental particles for pH-responsive dual-drug delivery utilizing PLGA and crosslinked PEI polymer systems. Two formulations were developed: DGPI (Doxorubicin in the PLGA phase, Paclitaxel in the PLGA+PEI+BTDA phase) and DIPG (Doxorubicin in the PLGA+PEI+BTDA phase, Paclitaxel in the PLGA phase). The particles were analyzed using SEM, FTIR, DSC, and TGA techniques. Scanning electron microscopy (SEM) demonstrated a consistent spherical morphology with average diameters of $11.73 \mu\text{m}$ for DGPI and $6.15 \mu\text{m}$ for DIPG. FTIR and thermal study validated the effective inclusion of the drugs and the crosslinking of the polymer. Drug release investigations performed at pH levels of 5.0, 6.5, and 7.4 exhibited notable pH-dependent release profiles. DGPI exhibited fast DOX release ($\sim 100\%$ after 24 hours) at pH 5.0 while ensuring regulated PTX release. DIPG demonstrated prolonged release profiles for both drugs, with increased release under acidic circumstances. The pH-responsive characteristics and capacity to regulate specific drug release via strategic compartmentalization render these particles highly

advantageous for targeted cancer therapy, as the acidic tumor microenvironment may initiate localized drug release while ensuring minimal release under physiological conditions.

Further utilization of the same system for combinational therapy was often done to reduce drug resistance or improve the delivery system's efficiency. In Chapter 5, bicompartamental nanoparticles were fabricated using the electrohydrodynamic co-jetting (EHDC) technique. The nanoparticles consist of a PLGA compartment for controlled drug release and a PLGA-PEI compartment for enhanced biomolecular interactions. By optimizing fabrication parameters, including polymer concentration, flow rate, and dielectric properties, precise control over particle size was achieved, transitioning from micro to nano dimensions. The resulting nanoparticles exhibited high biocompatibility, maintaining cell viability above 80% in HEK293T cells across a broad concentration range. Cellular uptake studies revealed efficient internalization in both HEK293 and HeLa cells, with uptake levels reaching 79.7% and 83.4%, respectively. Incorporating PEI enabled effective DNA binding at optimized N/P ratios, while the encapsulation of rhodamine B allowed for tracking and visualization of intracellular distribution. Enzymatic delivery of β -galactosidase demonstrated preserved catalytic activity and efficient delivery, as validated through X-gal staining by fluorescence microscopy. Ethanol dissolution studies confirmed the integrity of the bicompartamental architecture, highlighting the system's capability to provide dual functionality. Initial integration of NIR-II dye demonstrated potential for bioimaging applications, with future efforts directed towards optimizing dye compatibility with the solvent system. These findings position the bicompartamental nanoparticles as a promising platform for combination therapies and multi-modal treatments, offering simultaneous capabilities for drug delivery, gene therapy, and diagnostic imaging.

सारांश

दवा वितरण वाहनों (ड्रग डिलीवरी व्हीकल्स) का उद्देश्य शरीर में लक्षित स्थान पर चिकित्सकीय पदार्थों को सुरक्षित और प्रभावी रूप से पहुँचाना होता है। ये वाहक, कम घुलनशील दवाओं की घुलनशीलता, स्थिरता और जैवउपलब्धता को बढ़ाते हैं और दवाओं को एक वांछित स्थान पर नियोजित तरीके से पहुँचाने में सहायक होते हैं, जिससे दुष्प्रभावों में कमी आती है। विभिन्न प्रकार के दवा वाहकों में, बहुलकीय कण (पॉलीमरिक पार्टिकल्स) भौतिक और रासायनिक परिवर्तनों की प्रचुर संभावनाओं के कारण सबसे महत्वपूर्ण हैं, जिनसे जैवमिमेटिक आकार, माप और आसान निर्माण जैसी नवीन विशेषताओं का विकास होता है। उपयुक्त रूप से डिज़ाइन किए गए कणों में जैविक बाधाओं को पार करने और लक्षित स्थान पर चिकित्सकीय पदार्थों को सटीक रूप से पहुँचाने की क्षमता होती है। यह शोध प्रबंध दवा वितरण अनुप्रयोगों के लिए बहु-विभाजित बहुलकीय कणों के डिज़ाइन और आकार में नवीनतम प्रगति पर केंद्रित है। इन नवाचारों ने दवाओं को लक्षित करने, उनकी रिलीज़ को नियंत्रित करने और उपचार के परिणामों को बेहतर बनाने की क्षमता में सुधार किया है, हालाँकि इनके व्यापक उपयोग से पहले कई महत्वपूर्ण चुनौतियों का सावधानीपूर्वक आकलन करने की आवश्यकता है।

इलेक्ट्रोहाइड्रोडायनामिक को-जेटिंग का उपयोग बहु-विभाजित वाहकों (मल्टीकॉम्पार्टमेंटल कैरियर्स) को संयोजन चिकित्सा के लिए सटीक रूप से डिज़ाइन और इंजीनियर करने के लिए किया गया। उदाहरण के लिए, अध्याय 2A में इस कार्य का उद्देश्य तीन पार्किंसन (PD) दवाओं को संलग्न करने के लिए बहुलकीय माइक्रोकैरियर्स को इंजीनियर करना था। विकसित त्रि-विभाजित प्रणाली (ट्रिकॉम्पार्टमेंटल सिस्टम) में लिवोडोपा (LD), कार्बिडोपा (CD), और एन्टाकैपोन (ENT) नामक तीनों दवाओं को एक ही वाहक में 4:1:8 (LD: CD: ENT) के निश्चित अनुपात में उच्च कैप्सुलेशन दक्षता (~100%) के साथ शामिल किया गया। मौखिक प्रशासन के बाद, प्राथमिक दवा LD की जैवउपलब्धता को बढ़ाने के लिए माइक्रोकणों से दवाओं की रिलीज़ के दौरान इस अनुपात को बनाए रखना आवश्यक था। यह एक महत्वपूर्ण चुनौती थी, क्योंकि तीनों दवाओं की जलीय घुलनशीलता में भिन्नता थी (LD>CD>ENT)। चिकित्सकीय पदार्थों की रिलीज़ के बीच संतुलन प्राप्त करने के लिए, FDA-अनुमोदित बहुलकों (PLA, PLGA, PCL, और PEG) और कणों के डिस्क आकार का संयोजन किया गया। इन विट्रो अध्ययन में तीनों चिकित्सकीय पदार्थों की एक साथ, सतत और नियंत्रित रूप से रिलीज़ प्रदर्शित हुई।

प्रयोगात्मक रूप से अनुकूलित त्रि-विभाजित प्रणाली द्वारा प्राप्त मापदंडों को मान्य करने के लिए, अध्याय 2B में, नियंत्रित रिलीज़ प्रोफाइल वाले त्रि-विभाजित माइक्रोकैरियर्स की जांच की गई, जिसमें प्रसंस्करण

मापदंडों, जैसे सॉल्वेंट अनुपात, बहुलक सांद्रता और प्रवाह दर को व्यवस्थित रूप से भिन्न करते हुए Taguchi ऑर्थोगोनल L9 डिज़ाइन-ऑफ-एक्सपेरिमेंट दृष्टिकोण का उपयोग किया गया। S/N अनुपात के लिए "छोटा-से-छोटा" मानदंड ने सॉल्वेंट अनुपात (DMF सामग्री) और बहुलक सांद्रता को RBC आकार सुनिश्चित करने और दवाओं की रिलीज़ को नियंत्रित करने में सबसे प्रभावशाली मापदंड के रूप में प्रदर्शित किया। वैरिअंस और रिस्पॉन्स सरफेस पद्धति का विश्लेषण ने प्रतिक्रिया चर पर नियंत्रण कारकों के इष्टतम प्रभाव के बारे में अंतर्दृष्टि प्रदान की। पुष्टि प्रयोगों ने आगे अनुकूलित माइक्रोकणों (Poptimized) को मान्य किया, जिससे ARDEV (आस्पेक्ट अनुपात) में केवल ~0.13% त्रुटि और RF (रिलीज़ फैक्टर) में भविष्यवाणी किए गए प्रयोग से ~19% (सहिष्णुता सीमा के भीतर) त्रुटि प्रदर्शित हुई। इसके अलावा, Poptimized ने सभी तीन पार्किंसन रोग (Parkinson's disease) की दवाओं की ~100% कैप्सुलेशन दक्षता प्रदर्शित की, जिसमें 5 घंटे के इन विट्रो अध्ययन के भीतर ~100% LD, ~97% CD, और ~65% ENT का संचयी रिलीज़ हुआ।

विकसित त्रि-विभाजित प्रणाली के इन विवो अध्ययन को अध्याय 3 में रोटेनोन और MPTP-प्रेरित पार्किंसन पशु मॉडल के फार्माकोकाइनेटिक्स (स्वस्थ/रोगग्रस्त चूहों) और फार्माकोडायनामिक्स विशेषताओं के लिए जांचा गया। फार्माकोकाइनेटिक अध्ययन से यह स्पष्ट हुआ कि त्रि-विभाजित प्रणाली से LD की वितरण मेट्रिक्स में सुधार हुआ, जिसमें स्वतंत्र LD की तुलना में अधिकतम प्लाज्मा सांद्रता (C_{max} ~520 ng/mL) में दो गुना वृद्धि, क्षेत्र के तहत तीन गुना वृद्धि (AUC_{0-∞} ~5088 ng/mL), और औसत निवास समय (MRT ~13.5 h) में दोगुनी वृद्धि देखी गई। MPTP और रोटेनोन-प्रेरित मॉडल ने इन प्रगतियों को और समर्थन प्रदान किया। इसी बीच, फार्माकोडायनामिक्स अध्ययन ने मोटर और गैर-मोटर लक्षणों को कम करने और न्यूरोडीजेनेरेशन को कम करने में दवा की प्रभावशीलता का मूल्यांकन किया। यह कार्य पूरक मॉडलों का उपयोग करके स्थापित प्रणाली की चिकित्सीय क्षमता और मानव पार्किंसन रोग के लिए इसके अनुवादिक महत्व के व्यापक अंतर्दृष्टि प्रदान करता है।

अध्याय 4 में pH-संवेदनशील दोहरे-दवा वितरण के लिए नवीन द्वि-विभाजित कणों का विकास प्रस्तुत किया गया है, जिसमें PLGA और क्रॉसलिंकड PEI बहुलक प्रणालियों का उपयोग किया गया है। दो सूत्रीकरण विकसित किए गए: DGPI (PLGA चरण में डॉक्सोर्बिसिन, PLGA+PEI+BTDA चरण में पॉक्सिटाक्सेल) और DIPG (PLGA+PEI+BTDA चरण में डॉक्सोर्बिसिन, PLGA चरण में पॉक्सिटाक्सेल)। कणों का विश्लेषण SEM, FTIR, DSC, और TGA तकनीकों का उपयोग करके किया गया। स्कैनिंग इलेक्ट्रॉन माइक्रोस्कोपी (SEM) ने DGPI के लिए 11.73 μm और DIPG के लिए 6.15 μm के औसत व्यास के साथ एक सुसंगत गोलाकार संरचना प्रदर्शित की। FTIR और थर्मल अध्ययन ने दवाओं

के प्रभावी समावेश और बहुलक के क्रॉसलिंकिंग को मान्य किया। pH स्तर 5.0, 6.5, और 7.4 पर किए गए दवा रिलीज़ जांच ने उल्लेखनीय pH-निर्भर रिलीज़ प्रोफाइल प्रदर्शित किए। DGPI ने pH 5.0 पर तेजी से DOX रिलीज़ (~100% 24 घंटे बाद) प्रदर्शित किया, जबकि PTX की नियंत्रित रिलीज़ सुनिश्चित की। DIPG ने दोनों दवाओं के लिए लंबे समय तक रिलीज़ प्रोफाइल प्रदर्शित किए, जिसमें अम्लीय परिस्थितियों में रिलीज़ में वृद्धि देखी गई। pH-संवेदनशील विशेषताएं और विशिष्ट दवा रिलीज़ को रणनीतिक विभाजन के माध्यम से नियंत्रित करने की क्षमता इन कणों को लक्षित कैंसर चिकित्सा के लिए अत्यधिक लाभकारी बनाती है, क्योंकि अम्लीय ट्यूमर माइक्रोएनवायरनमेंट स्थानीय दवा रिलीज़ को प्रारंभ कर सकता है जबकि शारीरिक परिस्थितियों में न्यूनतम रिलीज़ सुनिश्चित करता है।

एकीकृत चिकित्सा के लिए इसी प्रणाली का आगे का उपयोग अक्सर दवा प्रतिरोध को कम करने या वितरण प्रणाली की दक्षता में सुधार के लिए किया गया। अध्याय 5 में, द्वि-विभाजित नैनोकणों को इलेक्ट्रोहाइड्रोडायनामिक को-जेटिंग (EHDC) तकनीक का उपयोग करके निर्मित किया गया। नैनोकणों में नियंत्रित दवा रिलीज़ के लिए एक PLGA विभाजन और बढ़ी हुई बायोमॉलिक्यूलर इंटरैक्शन के लिए एक PLGA-PEI विभाजन शामिल है। निर्माण मापदंडों, जैसे बहुलक सांद्रता, प्रवाह दर, और डाइलेक्ट्रिक गुणों का अनुकूलन करके, कण आकार पर सटीक नियंत्रण प्राप्त किया गया, जिससे माइक्रो से नैनो आयामों में संक्रमण हुआ। परिणामी नैनोकणों ने उच्च जैव-संगतता (बायोकोम्पैटिबिलिटी) प्रदर्शित की, HEK293T कोशिकाओं में 80% से अधिक कोशिका जीवन शक्ति बनाए रखी। सेलुलर अपटेक अध्ययनों ने HEK293 और HeLa कोशिकाओं में कुशल आंतरिककरण (इंटरनलाइज़ेशन) का खुलासा किया, जिसमें क्रमशः 79.7% और 83.4% का अपटेक स्तर प्राप्त हुआ। PEI का सम्मिलन अनुकूलित N/P अनुपात पर प्रभावी डीएनए बाइंडिंग को सक्षम बनाता है, जबकि रोडामाइन B का कैप्सुलेशन कोशिकाओं के अंदर वितरण को ट्रैक करने और देखने की अनुमति देता है। β -गैलेक्टोसिडेज़ का एंजाइमेटिक वितरण, फ्लोरोसेंस माइक्रोस्कोपी द्वारा X-गैल स्टेनिंग के माध्यम से, संरक्षित उत्प्रेरक गतिविधि और कुशल वितरण को प्रदर्शित करता है। इथेनॉल घुलनशीलता अध्ययनों ने द्वि-विभाजित संरचना की अखंडता की पुष्टि की, जिससे प्रणाली की दोहरी कार्यक्षमता प्रदान करने की क्षमता उजागर होती है। प्रारंभिक NIR-II डाई का एकीकरण बायोइमेजिंग अनुप्रयोगों की संभावना को प्रदर्शित करता है, जिसमें भविष्य के प्रयास डाई की संगतता को सॉल्वेंट प्रणाली के साथ अनुकूलित करने की दिशा में निर्देशित होंगे। ये निष्कर्ष द्वि-विभाजित नैनोकणों को संयोजन चिकित्सा और बहु-मॉडल उपचार के लिए एक आशाजनक मंच के रूप में स्थापित करते हैं, जो एक साथ दवा वितरण, जीन थेरेपी, और नैदानिक इमेजिंग के लिए क्षमताएं प्रदान करते हैं।

Contents

CERTIFICATE.....	i
ACKNOWLEDGMENTS	iii
Abstract.....	iv
सारांश	vii
LIST OF FIGURES	xvi
LIST OF TABLES	xviii
LIST OF SCHEMES	xxx
LIST OF ABBREVIATIONS	xxxii
.....	1
CHAPTER 1: INTRODUCTION AND LITERATURE SURVEY -----	2
1.1 Motivation and Background	2
1.2. Fundamental requirements of polymeric carriers for delivering drug.....	5
1.3. Fabrication Methods.....	11
1.4. Significance of carrier design	22
1.5. Designer Particles	24
Rod-shaped carrier.....	24
RBC Shaped Carrier	27
Worms shaped	27
Fiber-based particulate carrier	28
Multi-compartmental Polymeric Carrier	30
Micelles	31
Stimuli-Responsive Carriers.....	43
1.6. Bioimaging:	48
Deep-Tissue Fluorescence Imaging.....	50
Combinational therapy	52
1.7. Research Gap.....	52

1.8. Objective.....	53
1.9. Plan of Work.....	54
1.10. Thesis Format	55
.....	58
CHAPTER 2A: TRICOMPARTMENTAL MICROCARRIERS WITH CONTROLLED RELEASE FOR EFFICIENT MANAGEMENT OF PARKINSON'S DISEASE -----	59
2A.1. Motivation and Background	59
2A.2. Materials And Methods	62
2A.2.1. Materials	62
2A.2.2 Fabrication of microparticles.....	63
2A.2.3 Characterization.....	64
2A.2.4 Encapsulation of therapeutics	66
2A.2.5 <i>In vitro</i> Release Study.....	68
2A.3 Results And Discussion	69
2A.3.1. Fabrication of Tri-compartmental Particles.....	69
2A.3.3. <i>In-vitro</i> drug release study.....	79
2A.4. Summary.....	83
CHAPTER 2B: OPTIMAL DESIGNING THE SHAPE AND CONTROLLED RELEASE OF THERAPEUTICS FROM TRI-COMPARTMENTAL MICROCARRIERS FOR MANAGING PARKINSON’S DISEASE-----	85
2B.1. Motivation and Background	85
2B.2. Experimental section.....	87
2B.2.1. Materials	87
2B.2.2. Microparticles’ fabrication.....	87
2B.2.3. Experimental design	89
2B.2.1. Nonlinear regression analysis:	91
2B.3. Characterization of the particles as an output of the DoE	92
2B.3.1. Morphological Analysis.....	92

2B.3.2. Determination encapsulation efficiency of of therapeutics	92
2B.4. Drug release study <i>in vitro</i>	93
2B.5 Results and Discussions	93
2B.5.1. Morphological analysis of electrojetted particles	93
2B.5.2. Analysis of Taguchi DoE outcomes from L9 Orthogonal array (OA)	99
2B.5.2.1. Taguchi optimization of particle shape and release factor.....	99
2B.5.3. Relative contribution of control factors	100
2B.5.4 . Validation of Taguchi’s model	101
2B.5.5. Characterization of optimized microparticles	102
2B.5.6. Nonlinear regression analysis	104
2B.5.7. Validation of regression model.....	104
2B.5.8. Analysis of variance (ANOVA)	105
2B.5.9. Geometry confined dimensional influence of microcarriers on EE and RF .	106
2B.6. Summary	109
.....	110
CHAPTER 3 : <i>INVIVO</i> STUDIES OF DEVELOPED TRICOMPARTMENTAL CARRIER TO ANALYSE THE EFFICACY OF DEVELOPED SYSTEM -----	111
3.1. Motivation and Background	111
3.2. Materials	112
3.3. <i>In vivo</i> study.....	113
3.3.1. Animal	113
3.4. Pharmacokinetic Study	113
3.4.1. LC-MS/MS Methodology:.....	113
3.4.2. Sample preparation:.....	114
3.5. Pharmacodynamic Study:	114
3.5.1. Experimental Design: Rotenone Treatment.....	114
3.6. Pharmacodynamics study	115

3.3. Pharmacokinetics in diseased rats	116
3.3.1. LC-MS/MS Methodology.....	117
3.4. Experimental Design: MPTP treatment.....	117
3.4.1. Neurobehavioral Evaluation:.....	118
3.4.2. Immunohistochemistry:	119
3.5. Statistical Analysis.....	119
3.6. Results and Discussions.....	119
3.6.1. Rotenone induced rats.....	123
3.6.2. MPTP Induced Mice.....	128
3.7. Summary.....	131
.....	133
CHAPTER 4 : TUNEABLE BICOMPARTMENTAL CARRIER SYSTEM FOR CO- DELIVERY OF DOXORUBICIN AND PACLITAXEL WITH INDIVIDUAL RELEASE RATES -----	134
4.1. Motivation and Background	134
4.2. Materials & Methodology	135
4.2.1. Materials.....	135
4.2.2. Methodology.....	136
4.2.3. Characterization	137
4.2.4. Cross-linking Kinetics	138
4.2.5. Co-loading of incompatible drugs	138
4.2.6. Drug distribution.....	138
4.2.7. Encapsulation of therapeutics	138
4.2.8. Invitro Study	139
4.2.9. Degradation of Microparticles	140
4.2.10. Cell-Viability study	140
4.3. Results & Discussion:.....	141
4.3.1. Fabrication and Characterization of Bicompartmental particles	141

4.3.2. Swelling Kinetics.....	146
4.3.3. Co-delivery of Incompatible Drugs	148
4.3.4. Co-delivery of multiple drugs at tuneable release	150
4.3.5. Drug loaded microparticles.....	151
4.3.6. <i>In vitro</i> study	156
4.3.7. Cell Viability.....	161
4.4. Summary.....	162
.....	164
CHAPTER 5 : DESIGN OF BICOMPARTMENTAL NANOPARTICLES FOR COMBINATIONAL THERAPY-----	165
5.1. Motivation and Background	165
5.2. Materials	166
5.3. Methodology.....	167
5.3.1. Fabrication of nanoparticles	167
5.3.2. Characterization	167
5.3.3. Bicompartmental morphology of nanoparticles.....	168
5.3.4. Encapsulation of therapeutics	168
5.3.5. Stability Study	169
5.3.6. Brightness Optimization of NIR-II Nanoparticles for Bioimaging	169
5.3.7. Kinetics of β -Gal and X-Gal.....	169
5.3.8. Estimation of β -Gal loading in Polymeric nanoparticles	169
5.4. Cell culture	170
5.4.1. Cell viability studies	170
5.4.2. Localization study by confocal laser scanning microscopy.....	171
5.4.3. Cell-penetrating efficiency analysis via Flow cytometry	171
5.4.4. Cargo-carrying potency of nanoparticles.....	171
5.4.5. Gel retardation assay for DNA binding affinity	171

5.5. Result & Discussion	172
5.5.1. Fabrication of bicompartmental nanoparticles	172
5.5.2. Brightness Optimization of NIR-II Nanoparticles for Bioimaging	177
5.5.4. Fabrication of bicompartmental particles for combination therapy.....	179
5.5.5. Cell viability assay.....	180
5.5.6. Translocation of nanoparticles into HeLa cells	181
5.5.7. Quantitative assessment using Flow cytometry.....	184
5.5.8. Nanoparticles-mediated cargo delivery	186
5.5.9. DNA binding ability of nanoparticles.....	187
5.6. Summary.....	189
.....	190
CHAPTER 6 : SUMMARY AND FUTURE SCOPE -----	191
6.1. Summary.....	191
6.2. Future Outlook.....	193
References	195
APPENDIX	240
Supplementary Information: Chapter-2A.....	241
Supplementary Information: Chapter-2B.....	249
Supplementary Information: Chapter-3.....	253
Supplementary Information: Chapter-4.....	256
Supporting Information: Chapter-5	268
List of Publications.....	271
Biodata.....	274

LIST OF FIGURES

- Figure 1.1** a) Mechanisms of degradation of polymeric drug delivery carrier, b) SEM pictures of small and large, lidocaine-loaded, PLGA-based microparticles after 7 d exposure to phosphate buffer pH 7.4 (surfaces and cross-sections, as indicated in the figure) [52].c) PEGylated nanoparticles are able to avoid clearance from the blood stream by repelling protein adsorption, thus prolonging nanoparticle circulation time within the body[64], d) Schematic illustrations of basic mechanical property terms and their definitions. Elasticity and stiffness[72] e) Distribution of soft and stiff hydrogel micelles in fluorescently labelled tumour spheroids: blue, DAPI (nuclei); green, micelles; purple, DiD (cell membrane) [73]. Adapted by permission from Ref. [52](b), Ref.[64] (c), Ref[72] (d), and Ref[73](e) Copyright b, d 2005, 2019 © American Chemical Society, c and e Elsevier and Copyright Clearance Centre. **9**
- Figure 1.2** a) Schematic representation of the formation of multilayered microparticles and attainment of different configurations depending on the viscosity of Polymer A [81], b) (i) LbL adsorption of polymers on colloid templates.(ii) After the dissolution of the multilayer-coated core-shells, the hollow multilayer capsules are obtained. iii) After polymer multilayer on a sacrificial core is crosslinked and iv) the second component is released from the network, e) the core-shells coated with multilayer hydrogel network are obtained, and v) the core dissolution results in a multilayer hydrogel capsule. Adapted with permission from Ref. [81] (a) and Ref. [83] (b) copyright by John Wiley and Sons and Copyright Clearance Center. **13**
- Figure 1.3** a) Schematic representation of Microfluidic technique [89]. b) a) Preparation of PRINT mold and fabrication of PRINT particles. A liquid PFPE precursor can completely wet the silicon wafer with micro- and nanosized patterns because of its positive spreading coefficient on almost all surfaces and can be photocured to generate an elastomeric PRINT mold with negative micro/nanofeatures derived from the patterns on the silicon wafer. A liquid pre-particle material (red) is filled into the cavities without wetting the land area surrounding the cavities using a roll-to-roll process which involves a film-split technique against a high-surface-energy polyethylene terephthalate (PET) counter sheet when passed through a nip of a roller which applies pressure to the mold. The liquid in the mold cavities is then converted into a solid through a number of different processes **15**

including photocuring, or perhaps through vitrification by filling at an elevated temperature and cooling down, or by solvent evaporation. Once the liquid in the mold cavities is solidified, the array of particles (red) can be removed from the mold by bringing the mold in contact with an adhesive layer (yellow) which can pull the particles from the low-surface-energy mold. The particles can now be easily freed from the surface by dissolving the adhesive layer[94]. c) Schematic representation of electrohydrodynamic co-letting exhibiting fabrication of cup-shape, disc shape and donut shape particles by manipulating process parameters (electrical conductivity, viscosity, flow rate)[95]. Adapted with permission from Ref. [89](a), Ref. [94](b), Ref.[95](c) copyright by John Wiley and Sons and Copyright Clearance Centre, © 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, © 2019 Elsevier.

Figure 1.4

a) Schematic diagram of preparing PLGA microspheres and microrods, as well as DOX@PLGA microrods and DOX@PLGA microspheres, and the calculated entrapment efficiency and drug-loading capacity, n = 3, [108] b) *In vitro* A549 cell relative viabilities normalized to the untreated control after co-cultured with DOX@PLGA microrods or DOX@PLGA microspheres at the concentrations of 0.0625–4 mg mL⁻¹ for 48 h, n = 3, [108] c) Effect of particle shape on the phagocytic efficiency of neutrophils and intracellular release profile. Showing size distribution calculated from SEM images of PLGA nanoparticles with different aspect ratio and corresponding CLSM images. d) Schematic representation of tissue permeability of CCO-1, CCO-2, and CCO-3 micelles. CLSM images of tumor penetration of CCO-1, CCO-2, and CCO-3 in MCF-7. The scale bar was 200 μm[113]. e) Hemolysis rate resulting from red blood cells (RBCs) incubated for 2 h with increasing concentrations of MSs. RBCs exposed to ultrapure water (+) and phosphate buffered saline (–) were employed as controls and Bright field light microscopy images of RBCs post incubation with various MSs concentrations during the hemolysis rate assay[112]. Adapted with permission from Ref. [108] (a,b), Ref. [113] (c,d), Ref. [112] (e) copyright Elsevier and Copyright Clearance Center, CC-BY and Royal Society of Chemistry.

26

Figure 1.5

a) Confocal images displaying penetration of SMs and NWs co-incubated with 3D HeLa: 3T3 multicellular spheroids (MCSs, Scanning depth: 30 μm. Blue: Hoechst; Green: BODIPY dye-labeled NWs; Red: SMs, scale bar = 100 μm, inset: zoom in of the imaging)[117], b) The TEM images of micelles, c) Representative *in vivo* bioluminescence imaging of the orthotopic colorectal tumor at the indicated time. The HCT-116 cells were labeled with luciferase (n = 3). Scale bar: 2 cm d) Representative photos of the tumors harvested at the end of the experiment (Day 14). Scale bar: 1 cm [121] e) Schematic

29

representation of fabrication of carboxylated nanofibrillated cellulose using citric acid hydrolysis followed by TEMPO mediated oxidation., f) TEM images of cNFC [123] g) Visual examination of bacterial keratitis after 24 h, 48 h and 72 h of disease induction. Bacterial keratitis was induced in male Wistar rats by 5 μ l intrastromal injection of *Staphylococcus aureus*. In treatment group, rats (n = 5) were treated after 24 h of disease induction with carboxylated Nanofibrillated cellulose particle (cNFC), moxifloxacin (Mox) and moxifloxacin loaded particle (Mox-cNFC) either t.i.d, b.i.d or o.i.d for 48 h. Slit-lamp images were captured at 24 h, 48 h, and 72 h of infection; Infection size was measured at 72 h of infection (h). Eyes treated with Mox and Mox-cNFC showed a reduction in infection from 48 h to 72 h, however significant difference was not observed[124]. Adapted with permission form Ref. [117] (a), Ref. [121] (b,c,d), Ref. [123], (e), Ref.[124] (f,g,h) copyright CC-NC WILEY-VCH, Elsevier and Copyright Clearance Center.

Figure 1.6 a) Synthetic scheme for the formation of HA-poly(PEGMA)-b- 32

poly(MMA-co-Cy5MA) block copolymer, self-assembly, encapsulation, and oral delivery for site-specific release, b) Percentage of micelle positive tumor nodules 24 h post-administration of micelle-loaded alginate microcapsules, c) tissue distribution of targeted micelles in tumor [125]. Adapted with permission from Ref., Copyright by John Wiley and Sons and Copyright Clearance Centre.

Figure 1.7 a) Synthetic Route of PEG(PAA-b-PS)20 (top row) and Schematic 34

Models/TEM Images (bottom row) of the Self-Assembled Multicompartment (i, iv) Micelle, (iii, v) Vesicle, and (iv, vi) String. Orange, Blue, and Green Represent PS, PAA, and PEG Chains, Respectively) b) Evolution of the structure of single core-shell bottlebrush polymer chains deposited on mica from a dilute solution at $C_p = 10 \mu\text{g/mL}$. The scale of the inset images is $500 \times 500 \text{ nm}^2$ for parts i and iv; $400 \times 400 \text{ nm}^2$ for part iv; and $700 \times 700 \text{ nm}^2$ for parts ii, iii, and vi [129]. Adapted with permission from Ref. [127] and Ref. [129], copyright © 2020 and 2023 American Chemical Society.

Figure 1.8 a) Schematic illustration of the drug release process for the core-shell 36

particles. (b) Optical microscopy images and CLSM images of the DOX- and VEGF-loaded core-shell microparticles[130]. The images of microparticle with single core, double cores, and triple cores. The red and green fluorescence indicates DOX and FITC-BSA, respectively[130]. (c) A) PDMS mold. (B) Deposition of polymeric solution on PDMS mold. (C) Dried layer. (D) MNs filled with MPs. (E) Compacted and HL applied. (F) MNs extracted from mold. MPs, which are pressed and plasticized by using a non-invasive soft plasticization method previously reported (d) Stereomicroscope micrographs of microneedle patches with rhodamine-loaded tips. (e)

Scheme 1. Schematic Illustration of the Preparation Process and Thrombolysis Mechanism of Pc/Ca@r-JRs. Adapted with permission from Ref. [130](a,b), [131](c,d), [132](e), copyright © 2021 American Chemical Society, CC-NC and 2021 Elsevier Ltd. All rights reserved.

- Figure 1.9** a) Microscopic and fluorescent images of droplets and particles with different concentrations of span 80[133]; b) Schematic of the fabrication and performance of bubble-containing multicompartmental particles (BCMPs) c) An image of two-compartment alginate BCMPs loaded with black tracker beads. Side and top views show a bubble located within the top of the particle [136]. Adapted with permission from Ref. [133](a), and Ref. [136] (b,c) copyright CC-BY and © 2023 Wiley-VCH GmbH. **38**
- Figure 1.10** a) Microscopic and fluorescent images of droplets and particles with different concentrations of span 80[133]; b) Schematic of the fabrication and performance of bubble-containing multicompartmental particles (BCMPs) c) An image of two-compartment alginate BCMPs loaded with black tracker beads. Side and top views show a bubble located within the top of the particle [136]. Adapted with permission from Ref. [133](a), and Ref. [136] (b,c) copyright CC-BY and © 2023 Wiley-VCH GmbH. **40**
- Figure 1.11** a) Schematic setup of electrohydrodynamic co-jetting (EHDC) b) CLSM images of PLA/PLGA biphasic particles having PLGA compartment containing red dye c) *In vitro* release study of LD and CD from i) system A (LD in PLA and CD in PLGA) and ii) system B (LD in PLGA and CD in PLA) in SGF for 5 h followed by release into SIF for 24 h at 37 °C e) (i,ii) Light and (iii,iv) SEM images of JPMP1 and JPMP2. JPMP1 with ×1 PPYNP and ×2 MNPs (external phase containing PVA/SDBS cosurfactants) JPMP2 with ×1 PPYNP and ×2 MNPs (external phase containing SDS/SDBS cosurfactants) [135]. Adapted with permission from Ref. [116] (a,b,c,d) Ref. [135] copyright © 2024, American Chemical Society and CC-BY-4.0 **42**
- Figure 1.12** a) The morphology changes of MTSs within 7 days after incubation with free-DOX, HSA-PEPA-DOX nanospheres or nanoworms (Scale bar = 100 μm). b) Changes in MTSs diameter after different incubation times with free-DOX and HSA-PEPA-DOX (n = 3). **p < 0.01 [120] c) NQO1-responsive PEG-PTU-PEG triblock copolymer micelles for redox-triggered intracellular drug delivery[146].d) DLS measurement and TEM images of NPs-2 before and after irradiation with the 630 nm light for 20 min. The experiment was repeated three times[148]. Adapted with permission from Ref. [120] (a,b), Ref.[146](c), Ref. [148] (d) copyright by John Wiley and Sons and Copyright Clearance Center, © 2023 and, © 2024, American Chemical Society. **46**

Figure 1.13	a) Schematic diagram of the interactions between the photons and tissue when executing fluorescence imaging. B) absorption spectrum of water in the range of 400–1800 nm measured through a 1-mm-long path. C) reduced scattering of different biological tissues and intralipid solution in the 400–1700 nm range. D) autofluorescence spectra of ex vivo mouse liver (black), spleen (red), and heart tissue (blue) under 808 nm excitation. E) timeline of significant milestones in the development of NIR-II fluorophore. 50	50
Figure 1.14	a) Calibration curve of Indole from β -gal and X gal reaction product at different conc. b) Kinetics of β -gal and X gal reacting at 1:1 ratio (conc 100 μ M).	55
Figure 2A.1	Digital photograph of EHDC instrument used for the fabrication of tricompartmental particles.	64
Figure 2A.2	(a) Schematic of Electrohydrodynamic co-jetting (EHDC) set-up to fabricate tri-compartmental particles. (b) Digital image of the formation of (i) droplet and (ii) Taylor cone while running electrojetting process; TiO ₂ (white stain) and ZVI (black stain) containing polymeric solution was observed to come out from the three different needles tied together (i) at 0 KV (ii) at 10 KV.	68
Figure 2A.3	(a) Schematic diagram of optimized tricompartmental microcarrier system. (b) Optical Micrograph. (c) SEM Micrograph (zoom-in-image inset) (d) Particle size distribution (average particle diameter $4 \pm 0.99\mu\text{m}$; standard deviation 0.99) (e) Atomic Force Micrograph of microparticles, the phase contrast shows the presence of three distinct compartments. and (f-h) CLSM micrographs of tricompartmental particles (system, T-4). (f) Blue channel represents PLA+PCL phase loaded with LD and (g) red channel represents LPLGA phase of particle loaded with CD on one side and PEG+ENT on the other. (h) Overlays of both blue and red channels. Scale bars represent b, c and f-g 10 μm and e 5 μm for AFM micrograph.	72
Figure 2A.4	Represented Raman spectra of tricompartmental microparticles irradiated at (a) ‘position 1’ loaded with LD in the middle PLA/PCL phase-1, (b) ‘position 2’ loaded with CD in LPLGA phase-2, (c) and ‘position 3’ loaded with ENT in LPLGA/PEG phase-3. Corresponding spectra of the neat PLA, PCL, LPLGA, PEG, and drugs LD, CD, and ENT were given to compare drugs' presence in the localized compartment.	75
Figure 2A.5	(a) DSC thermogram of pure PLA, LPLGA, PCL, PEG, tri-compartmental microparticles (neat and drug-loaded), and simple blend (PLA/PLGA/PCL/PEG/drugs). (b) XRD spectra for pure drugs, i.e., LD, CD and ENT and drug loaded monophasic microparticles. Note: A single drug was loaded in the monophasic particles and the composition of the matrix for carrying that drug remained the same as that of their original composition for that particular compartment.	78

Figure 2A.6	(a) <i>in vitro</i> release study of therapeutics from a) system t-7, (b) commercially available tablet.	82
Figure 2B.1	Schematic representation of electro-jetting to show the formation of tri-compartmental microcarriers	89
Figure 2B.2	SEM images for experimental trials according to Taguchi L9 (P1 to P9), the corresponding zoom-in images shown as inset with a scale bar: 1 μ m.	96
Figure 2B.3	a) Main effect of S/N ratios on AR _{DEV} b) Release factor	100
Figure 2B.4	Control variables' relative contribution on the a) AR _{DEV} and b) RF	101
Figure 2B.5	a) SEM micrograph of optimized microcarrier b) particle size distribution c) CLSM micrograph of tricompartmental microcarrier loaded with polymeric dye in PLGA phase, 1- exhibited the blue fluorescence irradiated by 405 nm UV laser, 2- demonstrated the DIC micrograph, 3-overlay of DIC and blue fluorescence d) In-vitro cumulative release of LD, CD, and ENT from the optimized electrojetted microparticle (P _{optimized})	103
Figure 3.1	Plasma concentration-time profile of a) Levodopa (LD), b) Carbidopa (CD) and c) Entacapone (ENT), from rats fed with free drug (red lines) and DLM formulation (blue lines). Data were analysed by using two-way ANOVA followed by Sidak's post hoc multiple comparison test, Values are mean \pm SEM (n=3-5) and *p < 0.05, **p < 0.01 ***p < 0.001.	122
Figure 3.2	a) Body Weight evaluation, b) Rotarod c) Catalepsy d) Swim Test e) Passive avoidance. Values are mean \pm SEM values (n =5 in each group). ^{aaa} (P <0.001) compared to saline-treated normal group; *(P < 0.05), **(P <0.01), *** (P <0.001) compared to treatment group	125
Figure 3.3	Plasma concentration-time profile of Levodopa (LD) from the microparticles (red line) and the administered free drug (green line). Results are expressed as the mean \pm SD (n=4).	127
Figure 3.4	Effects of DLM and standard formulation on motor function and behaviour of mice assessed at 1 st week and 3 rd week after PD induction. a) Total distance travelled in open-field test, b) Catalepsy duration c) Fall latency in rotarod test d) Beam-walk score e) Forelimb withholding force in grip strength test f) total number of TH-positive neurons and g) representative microscopic images for TH-immunoreactivity in the substantia nigra shown for control (healthy mice), MPTP (diseased mice), Standard formulation (Diseased mice treated with standard formulation) and DLM (Diseased mice treated with DLM). Data were analysed by using two-way ANOVA followed by Tukey's (for fig a-e) and Dunnett's (for fig f) post hoc multiple comparison test. Values are mean \pm SEM (n=6) ^{##} p < 0.05 and ^{###} p < 0.001 when compared with healthy control group, *p < 0.05, **p < 0.01 ***p < 0.001 when compared with diseased control.	130

Figure 4.1	a) Experimental set-up of bicompartamental particles, b) Design of bicompartamental polymeric carrier.	142
Figure 4.2	SEM micrograph of biphasic microparticles at a) 0%, b) 10%, c) 25%, and d) 50% PEI concentration in one phase	143
Figure 4.3	SEM micrograph of bicompartamental microparticles with a) 10w/w %, b) 25w/w%, and c) 50w/w% PEI along with 5 w/w% BTDA of PEI in one phase	144
Figure 4.4	FTIR spectra of PLGA, PEI, PEI+crosslinker(BTDA), and PLGA+PEI+Crosslinker (BTDA).	145
Figure 4.5	Swelling ratio of microparticles by varying pH (5 and 7.4) , crosslinker percentage and PEI concentration a) 10% PEI, b) 25% PEI. Control group refers to 0w/w% of PEI concentration in bicompartamental system (PLGA microparticles).	147
Figure 4.6	Swelling Kinetics of biphasic particles with PLGA+RED dye in one phase and PLGA+PEI (10% w/w) +10%w/w BTDA)+ Blue dye in other at a) pH-5 and b) pH-7	147
Figure 4.7	Swelling Kinetics of biphasic particles with PLGA+RED dye in one phase and PLGA+PEI (25% w/w) +10%w/w BTDA)+ Blue dye in other at a) pH-5 and b) pH-7	148
Figure 4.8	CLSM Micrograph of bicompartamental microparticles with A) PLGA / PLGA, B)PLGA+CdSe / PLGA+BLUE dye, C) PLGA+CdSe / PLGA + PEI + BTAD+Blue dye, D) PLGA+Blue dye / PLGA+PEI+BTAD+CdSe+Red in different phase.	150
Figure 4.9	a) SEM micrograph of DGPI bicompartamental particles (zoom-in micrograph given at left corner, scale: 1µm) and its b) corresponding particle size distribution, c) SEM micrograph of DIPG bicompartamental particles (zoom-in micrograph given at right corner, scale: 1µm) and its d) corresponding particle size distribution, e) CLSM micrograph (overlay) of DGPI particles loaded with ADS129BE dye in PLGA/PEI phase along with PTX to give blue fluorescence and DOX in PLGA phase to give red fluorescence (zoom-in micrograph given at left corner, scale:5µm), f) CLSM micrograph (overlay) of DIPG particles loaded with ADS129BE dye in PLGA phase along with PTX to give blue fluorescence and DOX in PLGA/PEI phase to give red fluorescence (zoom-in micrograph given at left corner, scale:5µm), (note: No red dye was loaded in the given CLSM micrograph, red fluorescence was from DOX)	153
Figure 4.10	a) Figure 10 : FTIR spectra of PEI, PEI+BTDA (crosslinker), PLGA + PEI + BTDA, PLGA, NP (neat particles), DGPI (DOX loaded in PLGA phase and PTX in PLGA/PEI), DIPG (DOX loaded in PLGA/PEI and PTX in PLGA phase, neat drugs DOX and PTX. b)DSC thermograph of bicompartamental particles, c)TGA analysis	155

Figure 4.11	<i>In vitro</i> release at from a) pH-5, b) pH- 6.5 c) pH-7.4 from DGPI formulation and d)pH-5 e) pH-6.5 and f) pH-7.4 from DIPG formulation.	157
Figure 4.12	MTT-assay of microparticles with PLGA in one phase and various concentrations of PLGA+PEI in the other phase. a) PEI10: PLGA+10w/w% PEI, PEI10X: PLGA+10w/w% PEI+BTDA, PEI25: PLGA+25w/w%, b) PEI, PEI25X: PLGA+25w/w% PEI+BTDA, PEI50: PLGA+50w/w% PEI, PEI50X: PLGA+50w/w% PEI+BTDA, Control: PLGA (no PEI)	162
Figure 5.1	SEM micrograph of particles dispersed in a) acetone, b) water (lyophilized), c) TEM micrograph d) Particle size-distribution of nanoparticles fabricated from polymer concentration of 1 w/v % at a solvent concentration (DMF :CHCl ₃) of 6:4 at a flow rate of 20μl/h, by passing through syringe filter of 0.22μm. Biphasic particles with crosslinked PEI e) SEM micrograph f) TEM micrograph g) Particle size distribution measured from TEM micrograph through ImageJ.	173
Figure 5.2	SEM micrograph of particles fabricated at 1 w/v % polymer concentration with a) 0.5w/w%, b) 1w/w%, c) 1.5w/w% of CTAB, d) SEM micrograph of optimized biphasic nanoparticles with 10% NIR-II dye and e) the particle size distribution measured from SEM through ImageJ.	175
Figure 5.3	SEM micrograph of biphasic nanoparticles with a) 25w/w% of PEI in one phase after dispersing in ethanol, b) zoom-in image of (a), c) SEM micrograph of biphasic nanoparticles with 40% NIR-II dye, d) particle size distribution of individual particles measured through DLS, e) Scheme showing conjugation of DSPE-PEG-CM to nanoparticles by EDC/NHS coupling f) Particle size distribution of modified nanoparticles, g) Zeta-potential of developed nanoparticles system	176
Figure 5.4	Brightness intensity of nanoparticles loaded with a) 10% NIR-II dye in the PLGA phase, irradiated using a 793 nm laser and observed through an 1100 nm long pass filter at an exposure time of 100 ms, at concentrations of i) 30 mg/mL, ii) 15 mg/mL, iii) 10 mg/mL, and iv) 7.5 mg/mL. b) 40% NIR-II dye in the PLGA phase, with both DSPE-PEG-modified and unmodified samples, irradiated using a 793 nm laser and observed through an 1100 nm long pass filter at an exposure time of 100 ms, at concentrations of i) 30 mg/mL, ii) 20 mg/mL, iii) 12.5 mg/mL, iv) 10 mg/mL, v) 5 mg/mL, and vi) 2 mg/mL.	178
Figure 5.5	Rhodamine loaded bicompartamental nanoparticles a) SEM micrograph, zoom-in image inset at the right corner, b) TEM micrograph, zoom-in image inset at the top-left corner, c) Particle size distribution measured from TEM micrograph, d) Overlay CLSM micrograph overlay of bicompartamental nanoparticles loaded with rhodamine b(red fluorescence) and PEI phase conjugated with FITC-BSA.	180

Figure 5.6	MTT-Assay of bicompartmental nanoparticles loaded with rhodamine B dye in HEK293T cells.	181
Figure 5.7	Confocal laser scanning microscopy (CLSM) images demonstrating cellular uptake of rhodamine-B loaded bicompartmental PLGA/PLGA-PEI nanoparticles in HeLa cells after 5h incubation. (a) Control cells showing nucleus stained with DAPI (blue), red channel, and overlay with brightfield image. (b) Cells treated with nanoparticles (100 μ M) showing distinct punctate structures (yellow circles) indicating successful cellular internalization. Scale bar: 10 μ m.	182
Figure 5.8	Dose-dependent cellular uptake and intracellular distribution of rhodamine B-loaded bicompartmental PLGA/PLGA-PEI nanoparticles in HeLa cells after 24h. (a) Control cells showing nucleus (DAPI, blue) and cytoskeleton (Alexa Fluor, green) staining. (b-d) Cells treated with increasing concentrations of nanoparticles: (b) 20 μ M, (c) 40 μ M, and (d) 100 μ M. Scale bar: 10 μ m.	183
Figure 5.9	Quantitative analysis of cellular uptake of rhodamine B-loaded bicompartmental PLGA/PLGA-PEI nanoparticles using flow cytometry. (a) Flow cytometry scatter plots showing concentration-dependent cellular uptake in HEK293 cells at varying nanoparticle concentrations (control, 20, 60, and 100 μ M). (b) Similar analysis in HeLa cells demonstrating comparable uptake patterns. (c,d) Bar graphs representing the percentage of cell population showing successful nanoparticle uptake in HEK293 and HeLa cells respectively, illustrating consistent concentration-dependent internalization patterns across different cell types. Data presented as mean \pm SD.	185
Figure 5.10	Evaluation of cargo delivery efficiency using β -galactosidase as a model enzyme. epifluorescence microscopy images showing X-gal staining in (a) control cells, (b) cells treated with β -galactosidase alone, (c) PLGA nanoparticles without PEI, (d,e) bicompartmental nanoparticles at 1:60 and 1:100 ratios respectively. Scale bar: 150 μ m(f) Quantitative analysis of β -galactosidase activity through fluorescence intensity measurements of blue staining measured from the micrograph through ImageJ	187
Figure 5.11	Gel retardation assay demonstrating plasmid DNA binding efficiency of bicompartmental PLGA/PLGA-PEI nanoparticles. Analysis performed with varying PEI concentrations (10% and 25%) and N/P ratios (1:10, 1:50, and 1:100) shows optimal DNA binding at 10% PEI concentration, while higher PEI content (25%) resulted in reduced complexation efficiency.	188
Figure 2A.S.1	(a) FESEM micrograph of TiO ₂ nanoparticles, inset shows the particles size distribution and their corresponding (b) EDX spectrum.	241
Figure 2A.S.2	(a) FESEM micrograph of microparticles loaded with ZVI in the centre and TiO ₂ on either side. (b) FESEM of single particle selected for EDX spectrum and (c) their corresponding EDX spectrum. Note: the	241

microparticles were rupturing due to ZVI and TiO₂ loading under high intensity beam during EDX scan, also the resolution of image was compromised for the same reason.

Figure 2A.S.3	Representative (a) TEM micrograph of microparticles loaded with ZVI in the centre and TiO ₂ on either side. (b) (i) HR-TEM micrograph of microparticles from which centre (scale bar: 500nm) (ii) area was selected to capture the EDX scan (scale bar:200nm), and their corresponding EDX spectrum, exhibiting the presence of TiO ₂ and ZVI in the matrix. (c) Table showing the weight% of the corresponding elements present in the particles. Note. Due to high intensity of beam used during EDX, particles were rupturing.	242
Figure 2A.S.4	Comparison between the Proton NMR spectra of (a) LD, CD and (b) ENT after extracting from electrojetted particles with their corresponding neat spectrum. The spectra were run in D ₂ O and MeOD, respectively.	245
Figure 2A.S.5	Digital micrograph of microparticles suspended in simulated gastric fluid (SGF) for <i>in vitro</i> study. Image was captured right after adding the particles in SGF.	245
Figure 2A.S.6	<i>In vitro</i> release study of therapeutics (LD, CD and ENT) from different formulations a) T-1, b) T-2, c) T-3, d) T4, e) T5, f) T-6.	246
Figure 2A.S.7	SEM micrograph of drug loaded particles taken after 24h of <i>in vitro</i> release study	247
Figure 2A.S.8	Linear forms of drug release kinetic model (a) Zero Order, (b) First Order, (c) Higuchi, (d) Hixon-Crowell, (e) Ritger-Peppas were applied for the <i>in vitro</i> release of LD, CD and ENT from the optimized T-7 system given in Figure-5A(for the first 5h).	248
Figure 2B.S.1	RBC AR 1.25 ± 0.1 (calculated using <i>ImageJ</i>) Copyright (1996) National Academy of Sciences, U.S.A ¹ .	249
Figure 2B.S.2	<i>In vitro</i> release study of 3 drugs from a)P1, b)P2, c)P3, d)P4, e)P5, f)P6, g)P7, h)P8, i)P9 in SGF for 5 h followed by release into SIF for 24 h at 37 °C for L9 Taguchi experiments	250
Figure 2B.S.3	Confocal laser scanning microscopy (CLSM) image of low ARDEV & low RF and high ARDEV & high RF	250
Figure 2B.S.4	Linear forms of drug release kinetic model (a) Zero Order, (b) First Order, (c) Higuchi, (d) Hixon-Crowell, (e) Ritger-Peppas were applied for the <i>in vitro</i> release of LD, CD and ENT from the optimized system given in Figure-5d (for the first 5h)	252
Figure 3.S.1	Representative Mass spectra of CD, MD, LD, and ENT	254
Figure 3S.2	Flowchart showing the division of animals (rats) and steps involved in <i>in vivo</i> study	254
Figure 3S.3	Representative microscopic images for TH-immunoreactivity in the substantia nigra of mice a) Control, b) MPTP, c) Standard formulation, and d) DLM. Left panel shows respective hemisphere with acquired image at 4X and their respective zoom in image in the right at 20X	255

Figure 4S.1	SEM Micrograph of bicompartmental particles after incubating in pH-5 for 24h	256
Figure 4S.2	DIC micrograph of particles with 0%PEI (bicompartment PLGA microparticles) a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	257
Figure 4S.3	DIC micrograph of particles with 10 w/w %PEI in one phase with 0 w/w % crosslinker (BTDA) in a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	258
Figure 4S.4	DIC micrograph of particles with 10 w/w %PEI in one phase with 5w/w % crosslinker (BTDA) in a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	259
Figure 4S.5	DIC micrograph of particles with 10 w/w%PEI in one phase with 10w/w % crosslinker (BTDA) in a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	260
Figure 4S.6	DIC micrograph of particles with 10 w/w %PEI in one phase with 15 w/w% crosslinker (BTDA) in a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	261
Figure 4S.7	DIC micrograph of particles with 25 w/w %PEI in one phase in a) pH-7 and b) pH-5. c) Showing the change in particle size over time in pH-5 and pH-7	262
Figure 4S.8	DIC micrograph of particles with 25 w/w %PEI in one phase with 5w/w % crosslinker(BTDA) in a) pH-7 and b) pH-5. c) Showing the change in particle size over time in pH-5 and pH-7.	263
Figure 4S.9	DIC micrograph of particles with 25w/w %PEI in one phase with 10w/w% crosslinker(BTDA) in a) pH-7 and b) pH-5, c) Showing the change in particle size over time in pH-5 and pH-7	264
Figure 4S.10	DIC micrograph of particles with 25w/w%PEI in one phase with 15w/w% crosslinker (BTDA) in a) pH-7 and b) pH-5. c) Showing the change in particle size over time in pH-5 and pH-7	265
Figure 4S.11	Fluorescence spectra of pure CdSe NPLs (BA-36), CdSe NPLs(BA-36) added in PEI (BA-36+PEI)	265
Figure 4.S.12	Cumulative release profile of model drug Rhodamine B(RB) and Ibuprofen (IB) from PLGA+RB in one phase and Ibuprofen in with a) PLGA b)PLGA+5w/w%PEI, c) PLGA+5w/w%PEI+BTDA, d)PLGA+10w/w%PEI+BTDA, e)PLGA+25w/w%PEI+BTDA, and f) PLGA+50w/w%PEI+BTDA in another phase.	266
Figure 4.S.13	SEM micrograph of bicompartmental drug loaded particles after 7days of release study a) DGPI, B)DIPG	267
Figure 5.S.1	Biphasic nanoparticles through the EHDC technique. a) polymer concentration of 3, 2, 1 w/v% at a flow rate of 50 μ l/h and 100 μ l/h b) polymer concentration of 1, 0.8, 0.5 w/v% in at a flow rate of 30 μ l/h . Solvent ratio was maintained at CHCl ₃ : DMF (1:1)	268
Figure 5.S.2	Biphasic nanoparticles through EHDC technique. a) The polymer concentration of 1 w/v% in CHCl ₃ : DMF (6:4) at flow rates of 50 μ l/h,	269

- 30 μ l/h and 20 μ l/h, b)The SEM micrograph of nanoparticles at a polymer concentration of 1 w/v % in solvent concentration (DMF : CHCl₃) of 7:3, 8:2 and 95:5 at a flow rate of 20 μ l/h.
- Figure 5.S.3** MTT-Assay of nanoparticles loaded with 40% NIR-II polymer in PLGA phase with A) PEG conjugation and B) unmodified surface, respectively. **270**
- Figure 5.S.4** a) Calibration curve of Indole from β -gal and X gal reaction product at different conc.b) Kinetics of β -gal and X gal reacting at 1:1 ratio (conc 100 μ M). **270**

LIST OF TABLE

Table 1.1	Summarising the various fabrication methods for creating polymeric particles designed for drug delivery application.	17
Table 2A.1	Polymer used and their concentration taken to fabricate tricompartamental particles.	64
Table 2A.2	Composition of polymer solution taken to fabricate drug-loaded particles.	66
Table 2A.3	Composition of compartments, particle size and drug encapsulation efficiency in various systems	81
Table 2A.4	Kinetics parameters obtained by fitting to the <i>in vitro</i> release data of LD, CD and ENT from T-7 tricompartamental system.	83
Table 2B.1	Control factors (A, B, C) with three different levels (L, M, H)	88
Table 2B.2	Taguchi L9 OA experimental design	90
Table 2B.3	Encapsulation efficiency and cumulative release (5 h) for various particles	99
Table 2B.4	Design of Experiment (DoE Taguchi's L9 OA) of aspect ratio deviation (AR_{Dev}), RF(release factor), and S/N ratio	100
Table 2B.5	Control variables' relative contribution on the a) AR_{DEV} and b) RF	102
Table 2B.6	Regression validation analysis	103
Table 2B.7	ANOVA analysis for the Taguchi designed	104
Table 2B.8	Kinetics Model fitted to the <i>in vitro</i> release data of LD (levodopa), CD (Carbidopa) and ENT (Entacapone) from $P_{optimized}$ experiment	106
Table 3.1	Different animal groups studied <i>in vivo</i>	115
Table 3.2	Scores given to the rats during the swim test according to the type of swimming	116
Table 3.3	Single-dose pharmacokinetics parameters of drug-loaded microcarriers (DLM) given to healthy rats and their comparison with free drugs (LD, CD and ENT)	121
Table 3.4	Pharmacokinetics parameter of LD obtained from the treatment group, i.e, Group-I (fed with microparticles) after 24 hrs of oral administration and the same obtained from the animals fed with free drug.	127
Table 4.1	Electrical conductivity and particle size of electrojetted solution at different PEI concentrations.	144
Table 4.2	Kinetics Model fitted to the <i>in vitro</i> release data (pH-5) of PTX (Paclitaxel) and Dox (Doxorubicin hydrochloride) from DIPG and DGPI system.	159
Table 4.3	Molecular weight of polymer obtained from GPC	161
Table 2A.S 1	Wavenumber Assignment from Raman Spectrum of Compartment-1 (having LD)	243
Table 2A.S 2	Wavenumber Assingment from Raman Spectrum of Compartment-2 (having CD)	243

Table 2A.S 3	Wavenumber Assingment from Raman Spectrum of Compartment-3 (having ENT)	244
Table 2A.S 4	Transition temperatures and crystallinity obtained from DSC thermograms (Figure-2A.4a) (post second heating transition)	244
Table 2B.S 1	ARDEV and RF on the encapsulation efficiency of LD, CD, and ENT	251
Table 2B.S 2	Table exhibiting the characteristics of particles optimized by following DoE (P) and experimentally (DLM)	251
Table 3.S 1	Optimized MS/MS parameters of LD, CD, MD, and ENT	253
Table 3.S 2	Table exhibiting the characteristics of particles optimized by following DoE (P) and experimentally (DLM)	254

LIST OF SCHEMES

Scheme 1.1:	Schematic representing size-dependent delivery of carrier with respect to the delivery sites.	4
Scheme 1.2:	Schematic representation of advances in the design of polymeric particles for drug delivery application.	5
Scheme 2B.1	Pictorial representation of plausible mechanism of forming particle morphology on increasing the DMF (low volatile solvent) percentage in polymer solution.	97

LIST OF ABBREVIATIONS

Ace-DEX	Acetalated Dextran
ACN	Acetonitrile
ANOVA	Analysis Of Variance
AR _{dev}	Aspect Ratio
AFM	Atomic Force Microscope
BBB	Blood-Brain Barrier
BTDA	1,2,3,4 Butanetertacarboxylic Dianhydride
BSA	Bovine Serum Albumin
CD	Carbidopa
CNC	Cellulose Nanocrystals
CT	Computed Tomography
CPN	Cylindrical Polymer Brushes
COMT	Catechol-O-Methyltransferase
CV	Coefficient Of Variance
CLSM	Confocal Laser Scanning Microscope
DXM	Dexamethasone
DOE	Design Of Experiment
DCM	Dichloromethane
DMSO	Dimethyl Sulfoxide
DDC	Dopa Decarboxylase
EHDC	Electrohydrodynamic Co-Jetting
EE	Encapsulation Efficiency
ENT	Entacapone
FI	Fluorescence Imaging
GSH	Glutathione
H&E	Hematoxylin And Eosin
HCL	Hydrochloric Acid
IB	Ibuprofen
IUPAC	International Union Of Pure And Applied Chemistry
LD	Levodopa
MM	Malignant Mesothelioma
MOF	Metal-Organic Frame
MCNs	Multicompartment Nanoparticles
NMP	N, Methyl-2-Pyrrolidinone
DMF	N, N-Dimethylformamide
ONC	Onconase
OA	Orthogonal Array
PD	Parkinson's Disease
PRINT	Particle Replication In Nonwetting Template
PAI	Photoacoustic Imaging
PEGDA	Poly(Ethyleneglycol) Diacrylate
PVA	Poly (Vinyl Alcohol)

PEG	Poly(Ethylene Glycol)
PVP	Poly(Vinylpyrrolidone)
PCL	Polycaprolactone
PEI	Polyethyleneimine
PLA	Poly(lactic acid)
PLGA	Poly(lactic-Co-Glycolic Acid)
PET	Positron Emission Tomography
PS	Polystyrene
QD	Quantum Dots
QY	Quantum Yield
RB	Rhodamine B
RENP	Rare-Earth-Doped Nanoprobes
RBC	Red Blood Cell
RBCM	Red Blood Cell-Mimetic Micromotor
RF	Release Factor
ROS	Reactive Oxygen Species
SEM	Scanning Electron Microscopy
S/N	Signal-To-Noise Ratio
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
SPECT	Single-Photon Emission Computed Tomography
SWCNT	Single-Walled Nanotubes
SDS	Sodium Dodecyl Sulfate
SN	Substantia Nigra
TEMPO	2,2,6,6-Tetramethylpiperidine-1-Oxyl)
TH	Tyrosine Hydroxylase
UCNP	Upconverting Nanoparticles
VEGF	Vascular Endothelial Growth Factor