STUDIES ON POLY(LACTIC ACID) AND POLYACRYLATE BASED ANISOTROPIC MICROPARTICLES MODIFIED WITH POLYMER BRUSHES

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DEPARTMENT OF MATERIALS SCIENCE AND ENGINEERING

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STUDIES ON POLY(LACTIC ACID) AND POLYACRYLATE BASED ANISOTROPIC MICROPARTICLES MODIFIED WITH POLYMER BRUSHES

by

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Department of Materials Science and Engineering

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Dedicated to my family

CERTIFICATE

This is to certify that the thesis entitled, **"Studies on poly(lactic acid) and polyacrylate based anisotropic microparticles modified with polymer brushes"** being submitted by **Mrs. Ifra** to Indian Institute of Technology Delhi for the award of degree of **Doctor of Philosophy** is a record of bonafide research work carried out by her. Mrs. Ifra has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my 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.

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ABSTRACT

Recently, biocompatible anisotropic particles have emerged as a powerful platform in the biomedical field, especially in the areas such as therapeutics, theranostics, biosensor, targeted drug delivery, triggered drug delivery, cellular uptake, targeted cellular internalization, etc., because of their unique characteristics and superior performances over their isotropic analogues. Macromolecular anisotropic particles can primarily be classified into three different categories, such as shape anisotropy, compositional anisotropy, and surface anisotropy, i.e., heterogeneous surface chemistry leading to anisotropic surface patches. We were particularly interested to fabricate biocompatible/biodegradable anisotropic particles based on biodegradable poly(lactic acid) and biocompatible polyacrylates.

In order to achieve the target, we have synthesized a random copolymer of methyl methacrylate (MMA) and 2-hydroxy ethyl methacrylate (HEMA) via Atom Transfer radical polymerization (ATRP) whose hydroxyl groups were later modified as bromo functionalized moieties named as poly(MMA-*co*-BEMA) (poly(methyl methacrylate-co-2-(2-bromopropionyloxy) ethyl methacrylate). In chapter 2, this bromo functionalized random copolymer, poly(MMA-co-BEMA) was blended with poly(lactic acid) by dissolving both in a mixture of chloroform and dimethyl formamide and the resultant polymer solutions were used to fabricate cup shaped microparticles of ~6 μm size via electrohydrodynamic jetting technique. The polymer solutions were jetted at different solution parameters (concentration, polymer composition, solvent system) and processing parameters (flow rate). And several properties of the jetted particles such as electrical conductivity, viscosity, surface tension etc. were studied to have a good understanding of the mechanism involved in cup shape formation. The mechanistic understandings also provide insight into the transition from cup, sphere to disc shape of the jetted particles.

In chapter 3, two hydrophilic brushes i.e., poly(HEMA) (poly(2-hydroxy ethyl methacrylate)) and poly(DMAEMA) (poly(2-(Dimethylamino) ethyl methacrylate)) were separately and individually grown from the surface of cup shaped microparticles. The shape-shifting of cup-shaped particles occurred when surface initiated ATRP of HEMA (2-hydroxy ethyl methacrylate) was carried out for 1 hour because of the immobilization of self-crosslinkable poly(HEMA) brushes onto the surface of the cup shaped particles. Post polymerization, these particles underwent controlled bending leading to the formation of spherical ball with one small opening (hole). However, no change of shape was observed while growing non-crosslinkable hydrophilic poly(DMAEMA) (poly(2-(Dimethylamino) ethyl

methacrylate)) brush from the surface of cup shaped particles. To understand the underlying phenomena of shape shifting, simulation studies were also performed. Dissipative particle dynamics (DPD) simulation of the ATRP process at the cup surface further confirmed that the use of HEMA monomer indeed led to the desired structure of the cup particle due to the crosslinking connectivity across the interface. We have also calculated the radial distribution function (RDF) and radius of gyration to study the structure of modified particles.

In chapter 4, responsive properties of poly(DMAEMA) (poly(2-dimethylamino ethyl methacrylate)) brush modified cup shaped particles were studied and a small molecule (Rhodamine B) was adsorbed at different pH. An enhanced dye adsorption at specific pH was observed. Dye released study showed the burst release of dye at acidic pH due to the swelling of poly(DMAEMA) brushes. In another study, a model enzyme (macromolecule) such as α-glucosidase was immobilized onto poly(DMAEMA) (poly(2-dimethyl amino ethyl methacrylate)) brush modified anisotropic (cup and disc shaped) biocompatible polymeric particles. We have also demonstrated the role of swollen polymer brush grafted on the surface of cup shaped particles via surface initiated atom transfer radical polymerization, in immobilizing unprecedentedly high loading of enzyme (440 mg/g (cup) – 589 mg/g (disc) of particles, 15-20 times higher than literature reported system) as compared to non-brush modified particles. Circular dichroism spectroscopy was used to predict the structural changes of the enzyme upon immobilization onto the carrier particles. An enormously high amount of enzyme with preserved activity (~85±13% for cups and ~78±15% for discs) was found to adhere onto brush modified particles at pH 7 via electrostatic adsorption and the enzyme loading capacity was observed to be progressively higher with increase of enzyme concentration and grafting density as well, till the saturation limit. In addition, accelerated particle separation was also achieved via magnetic force induced aggregation within 20 min (without centrifuge) by incorporating magnetic nanoparticles into disc shaped particles while electrojetting.

In last chapter, we have focused to make compositional anisotropic microparticles, i.e, Janus microparticles consisting of two different phases where poly(MMA-*co*-BEMA) was incorporated into one compartment only and hydrophilic brushes, poly(DMAEMA) was grown from the this particular compartment only, These selectively brush modified Janus particles which contained one part hydrophilic (poly(DMAEMA)) and another part hydrophobic (poly(lactic acid)). These types of amphiphilic particles were shown to be well suited for the Pickering emulsion stabilization to stabilize octanol(oil)/water emulsion. Metal nanoparticles such as gold nanoparticles and iron (0) nanoparticles were incorporated into two different

compartments of these brush modified Janus particles where gold and iron nanoparticles were simultaneously demonstrated to catalyze the reduction of *p*-nitrophenol to *p*-aminophenol (100% conversion within 1 min) and the dechlorination of trichloroethylene in same octanol (oil)/water emulsion, respectively.

सार

हाल ही में, बायोकम्पैटिबल अनिसोट्रोपिक कण बायोमेडिकल क्षेत्र में एक शक्तिशाली मंच के रूप में उभरे हैं, विशेष रूप से चिकित्सा विज्ञान, चिकित्सा विज्ञान, बायोसेंसर, लक्षित दवा वितरण, ट्रिगर दवा वितरण, सेलुलर तेज, लक्षित सेलुलर आंतरिककरण, आदि जैसे क्षेत्रों में, उनके अद्वितीय कारण उनके आइसोट्रोपिक एनालॉग्स पर विशेषताओं और बेहतर प्रदर्शन। मैक्रोमोलेक्यूलर अनिसोट्रोपिक कणों को मुख्य रूप से तीन अलग-अलग श्रेणियों में वर्गीकृत किया जा सकता है, जैसे कि आकार अनिसोट्रॉपी, कंपोजिटल अनिसोट्रॉपी, और सतह अनिसोट्रॉपी, यानी विषम सतह रसायन जो अनिसोट्रोपिक सतह पैच के लिए अग्रणी है। हम विशेष रूप से बायोकम्पैटिबल/बायोडिग्रेडेबल अनिसोट्रोपिक कणों को बायोडिग्रेडेबल पॉली (लैक्टिक एसिड) और बायोकंपैटिबल पॉलीएक्रिलेट्स पर आधारित बनाने में रुचि रखते थे।

लक्ष्य को प्राप्त करने के लिए, हमने एटम ट्रांसफर रेडिकल पोलीमराइजेशन (एटीआरपी) के माध्यम से मिथाइल मेथैक्रिलेट (एमएमए) और 2-हाइड्रॉक्सी एथिल मेथैक्रिलेट (एचईएमए) के एक यादृच्छिक कॉपोलीमर को संश्लेषित किया है, जिसके हाइड्रॉक्सिल समूहों को बाद में पॉली (पॉली) नामक ब्रोमो फंक्शनल मोएट के रूप में संशोधित किया गया था। (पॉली(मिथाइल मेथैक्रिलेट-को-2 (2 ब्रोमोप्रोपियोनीलोक्सी) एथिल मेथैक्रिलेट))। अध्याय 2 में, इस ब्रोमो ने रैंडम कॉपोलीमर, पॉली (MMA-co-BEMA) को पॉली (लैक्टिक एसिड) के साथ मिश्रित किया था। क्लोरोफॉर्म और डाइमिथाइल फॉर्मामाइड के मिश्रण में घुलने और परिणामी बहुलक समाधानों का उपयोग इलेक्ट्रोहाइड्रोडायनामिक जेटिंग तकनीक के माध्यम से ~ 6 माइक्रोन आकार के कप के आकार के माइक्रोपार्टिकल्स बनाने के लिए किया गया था। बहुलक समाधान विभिन्न समाधान मापदंडों (एकाग्रता, बहुलक संरचना, विलायक प्रणाली) पर जेट किए गए थे। और प्रसंस्करण पैरामीटर (प्रवाह दर) और जेटेड कणों के कई गुणों जैसे विद्युत चालकता, चिपचिपाहट, सतह तनाव इत्यादि का अध्ययन किया गया ताकि उन्हें अच्छी समझ हो f कप के आकार के निर्माण में शामिल तंत्र। यंत्रवत समझ कप, गोले से डिस्क आकार में जेट कणों के संक्रमण में भी अंतर्दृष्टि प्रदान करती है।

अध्याय 3 में, दो हाइड्रोफिलिक ब्रश यानी, पॉली (एचईएमए) (पॉली (2-हाइड्रॉक्सी एथिल मेथैक्रिलेट)) और पॉली (डीएमएईएमए) (पॉली (2- (डाइमिथाइलैमिनो) एथिल मेथैक्रिलेट)) अलग-अलग और व्यक्तिगत रूप से कप की सतह से उगाए गए थे। आकार के सूक्ष्म कण। कप के आकार के कणों का आकार-स्थानांतरण तब हुआ जब सतह पर शुरू हुआ HEMA (2-हाइड्रॉक्सी एथिल मेथैक्रिलेट) का

ATRP कप के आकार के कणों की सतह पर सेल्फ-क्रॉसलिंकेबल पॉली (HEMA) ब्रश के स्थिरीकरण के कारण 1 घंटे के लिए किया गया था। . पोलीमराइजेशन के बाद, इन कणों को नियंत्रित झुकाव से गुजरना पड़ा, जिससे एक छोटे से उद्घाटन (छेद) के साथ गोलाकार गेंद का निर्माण हुआ। हालांकि, कप के आकार के कणों की सतह से गैर-क्रॉसलिंकेबल हाइड्रोफिलिक पॉली (डीएमएईएमए) (पॉली (2-(डाइमिथाइलैमिनो) एथिल मेथैक्रिलेट)) ब्रश उगाते समय आकार में कोई बदलाव नहीं देखा गया। आकार बदलने की अंतर्निहित घटनाओं को समझने के लिए, सिमुलेशन अध्ययन भी किए गए थे। कप की सतह पर एटीआरपी प्रक्रिया के विघटनकारी कण गतिकी (डीपीडी) सिमुलेशन ने आगे पुष्टि की कि एचईएमए मोनोमर के उपयोग ने वास्तव में इंटरफ़ेस में क्रॉसलिंकिंग कनेक्टिविटी के कारण कप कण की वांछित संरचना का नेतृत्व किया। हमने संशोधित कणों की संरचना का अध्ययन करने के लिए रेडियल डिस्ट्रीब्यूशन फंक्शन (आरडीएफ) और रेडियस रेडियस की भी गणना की है।

अध्याय 4 में, पॉली (डीएमएईएमए) (पॉली (2 डाइमिथाइलैमिनो एथिल मेथैक्रिलेट)) ब्रश संशोधित कप के आकार के कणों के प्रतिक्रियाशील गुणों का अध्ययन किया गया था और एक छोटे अणु (रोडामाइन बी) को विभिन्न पीएच में सोख लिया गया था। विशिष्ट पीएच पर एक बढ़ाया डाई सोखना देखा गया। डाई जारी किए गए अध्ययन ने पॉली (डीएमईएमए) ब्रश की सूजन के कारण अम्लीय पीएच पर डाई के फटने को दिखाया। एक अन्य अध्ययन में, एक मॉडल एंजाइम (मैक्रोमोलेक्यूल) जैसे कि α-ग्लूकोसिडेज़ को पॉली (डीएमएईएमए) (पॉली (2-डाइमिथाइल एमिनो एथिल मेथैक्रिलेट)) ब्रश संशोधित अनिसोट्रोपिक (कप और डिस्क आकार) बायोकंपैटिबल पॉलीमेरिक कणों पर स्थिर किया गया था। हमने सतह पर शुरू किए गए परमाणु हस्तांतरण कट्टरपंथी पोलीमराइजेशन के माध्यम से कप के आकार के कणों की सतह पर ग्राफ्ट किए गए सूजे हुए बहुलक ब्रश की भूमिका का भी प्रदर्शन किया है, जो एंजाइम (440 मिलीग्राम / जी (कप) - 589 मिलीग्राम / जी (डिस्क) के अभूतपूर्व उच्च लोडिंग को स्थिर करता है कण, गैर-ब्रश संशोधित कणों की तुलना में साहित्य रिपोर्ट प्रणाली से 15-20 गुना अधिक)। वाहक कणों पर स्थिरीकरण पर एंजाइम के संरचनात्मक परिवर्तनों की भविष्यवाणी करने के लिए सर्कुलर डाइक्रोइज्म स्पेक्ट्रोस्कोपी का उपयोग किया गया था। इलेक्ट्रोस्टैटिक सोखना के माध्यम से पीएच 7 पर ब्रश संशोधित कणों का पालन करने के लिए संरक्षित गतिविधि (~ 85 ± 13% कप के लिए और ~ 78 ± 15% डिस्क के लिए) के साथ एंजाइम की एक बड़ी मात्रा में पाया गया था और एंजाइम लोडिंग क्षमता को उत्तरोत्तर देखा गया था। संतृप्ति सीमा तक एंजाइम सांद्रता और ग्राफ्टिंग घनत्व में वृद्धि के साथ उच्च। इसके अलावा, इलेक्ट्रोजेटिंग करते समय डिस्क के आकार के कणों में चुंबकीय नैनोकणों को शामिल करके 20 मिनट (अपकेंद्रित्र के बिना) के भीतर चुंबकीय बल प्रेरित एकत्रीकरण के माध्यम से त्वरित कण पृथक्करण भी प्राप्त किया गया था।

पिछले अध्याय में, हमने कंपोजिटल अनिसोट्रोपिक माइक्रोपार्टिकल्स बनाने पर ध्यान केंद्रित किया है, यानी, दो अलग-अलग चरणों से युक्त जानूस माइक्रोपार्टिकल्स जहां पॉली (एमएमए-को-बीईएमए) को केवल एक डिब्बे में शामिल किया गया था और हाइड्रोफिलिक ब्रश, पॉली (डीएमईएमए) को इसी से उगाया गया था। केवल विशेष डिब्बे, ये चुनिंदा ब्रश संशोधित जानूस कण जिसमें एक भाग हाइड्रोफिलिक (पॉली (डीएमएईएमए)) और दूसरा भाग हाइड्रोफोबिक (पॉली (लैक्टिक एसिड)) होता है। इस प्रकार के एम्फीफिलिक कणों को ऑक्टेनॉल (तेल)/पानी इमल्शन को स्थिर करने के लिए पिकरिंग इमल्शन स्थिरीकरण के लिए अच्छी तरह से अनुकूल दिखाया गया था। सोने के नैनोकणों और लोहे (0) नैनोकणों जैसे धातु के नैनोकणों को इन ब्रश संशोधित जानूस कणों के दो अलग-अलग डिब्बों में शामिल किया गया था, जहां सोने और लोहे के नैनोकणों को एक साथ पी-नाइट्रोफेनॉल की कमी को पी-एमिनोफेनोल में उत्प्रेरित करने के लिए प्रदर्शित किया गया था (1 के भीतर 100% रूपांतरण मिनट) और एक ही ऑक्टेनॉल (तेल)/पानी के पायस में क्रमशः ट्राइक्लोरोइथिलीन का डीक्लोरीनीकरण।

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LIST OF ABBREVIATIONS

RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
PLGA	Poly(Lactic-Co-Glycolic Acid
PDMS	Poly(dimethylsiloxane)
TPGDA	Tripropyleneglycol Diacrylate
DVB	Divinylbenzene
DMOS	Dimethacrylate Oxypropyldimethylsiloxane
PEG-DA	Poly(ethylene glycol) Diacrylate
PLA	Poly(lactic acid)
DMAEMA	2-dimethylamino Ethyl Methacrylate
PDMAEMA	Poly(2-dimethylamino ethyl methacrylate)
ATRP	Atom Transfer Radical Polymerization
SIATRP	Surface Initiated Atom Transfer Radical Polymerization
PMMA	Poly(methylmethacrylate)
SEM	Scanning Electron Microscopy
TMEDA	Tetramethylethylenediamine
SORP	Self-organization Rapid Precipitation
PFS	Poly(ferrocenylsilane)
P2VP	Poly(2-vinylpyridine)
CTAB	Cetyl Trimethylammonium Bromide
CTAB-OH	Hydroxy-cetyl Trimethylammonium Bromide
PISA	Polymerization Induced Self-assembly
PMAAz	Azobenzene Containing Poly(methacrylate)
PMAA	Poly(methacrylic acid)
LC	Liquid Crystal
Tg	Glass Transition Temperature
PLGE	Poly(lactide-*co*-glycolide-*b*-ethylene glycol-*b*-lactide-*co*-glycolide)
NR	Nile Red
PEMA	Poly(ethylene-alt-maleic acid)
PVA	Poly(vinyl alcohol)
DOPC	1,2-dioleoyl-sn-glycero-3-phosphocholine
PRINT	Particle Replication in Non-wetting Templates
PFPE	Perfluoropolyether
PCL	Poly(ε-caprolactone)
PVP	Poly(vinyl pyrrolidone)
PEO	Poly(ethylene oxide)
PEG	Poly(ethylene glycol)
EHDC	Electrohydrodynamic Co-jetting
PD	Parkinson's Disease
LD	Levodopa
CD	Carbidopa

PEO	Poly(ethylene oxide)
CLSM	Confocal Laser Scanning Microscope
PEI	Poly(ethyleneimine)
SERS	Surface-Enhanced Raman Scattering
PVCi	Poly(vinyl cinnamate)
PLLA	Poly(L-lactic acid)
O/W	Oil-in-Water
W/O	Water-in-Oil
PAAm	Poly(acrylamide)
PNIPAM	Poly(N-isopropylacrylamide)
DCC	N,N'-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
TRITC	Tetramethyl Rhodamine Isothiocyanate
BSA	Bovine Serum Albumin
RAFT	Reversible Addition-Fragmentation Chain Transfer
ROMP	Ring Opening Metathesis Polymerization
NMP	Nitroxide Mediated Polymerization
HEMA	2-Hydroxy Ethyl Methacrylate
pHEMA	Poly(2-hydroxy ethyl methacrylate)
LAMMPS	Large-scale Atomic/Molecular Massively Parallel Simulator
DPD	Dissipative Particle Dynamics
MPS	Mononuclear Phagocyte System
ID	Injected Dose
HUVEC	Human Umbilical Vein Endothelial Cells
BMDC	Bone Marrow Dendritic Cells
EDTA	Ethylene Diamine Tetraacetate
NMR	Nuclear Magnetic Resonance
GPC	Gel Permeation Chromatography
HPLC	High Performance Liquid Chromatography
DSC	Differential Scanning Calorimetry
DMF	Dimethylformamide
THF	Tetrahydrofuran
FTIR	Fourier Transform Infrared Spectroscopy
BEMA	2-(2-Bromopropionyloxy) Ethyl Methacrylate
DIC	Differential Interference Contrast
DLS	Dynamic Light Scattering
OM	Optical Microscopy
AFM	Atomic Force Microscopy
TGA	Thermal Gravimetric Analysis
p-NP	*p*-nitrophenol
p-PNPG	*p*-nitrophenyl-α-D-glucopyranoside
PMDETA	Pentamethyl Diethylene Tetraacetate
EDX	Energy Dispersive X-ray

CD	Circular Dichroism Spectroscopy
ATR-FTIR	Attenuated Total Reflectance-Fourier Transform Infrared
TEM	Transmission Electron Microscope
ZP	Zeta Potential
SR	Swelling Ratio
TMPTA	Trimethylopropane triacrylate
LPS	Linear Polystyrene
FESEM	Field Emission Scanning Electron Microscopic
GNPs	Gold Nanoparticles
TCE	Trichloroethylene