POROUS SCAFFOLDS OF CROSSLINKED POLY(ε-CAPROLACTONE) *via* SINGLE-STEP HIGH INTERNAL PHASE EMULSION-RING OPENING POLYMERIZATION

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by

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Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the

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Dedicated to

My Parents and Family Members

CERTIFICATE

This is to certify that the thesis titled "**Porous Scaffolds of Crosslinked Poly(ε-Caprolactone) *via* Single-Step High Internal Phase Emulsion-Ring Opening Polymerization"**, being submitted by **Anilkumar Lalchand Yadav** 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 him. He has worked under our guidance and supervision and fulfilled the requirements for submission of the thesis which has attained the standard required for a Ph.D. degree of this Institute.

The results contained in this thesis have not been submitted, in part or in full, to any other university or institute for the award of any degree or diploma.

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ABSTRACT

Porous polymeric scaffolds available in form of monoliths, rods, beads, and films etc. have gained significant interest over past two decades due to their fascinating properties and applications in various fields. Amongst various techniques to prepare porous polymeric scaffolds, emulsion templating in the form of high internal phase emulsion (HIPE, volume fraction of dispersed phase, $\phi_d \geq 0.74$) polymerization is highly admired for being a single step process to synthesize porous scaffolds (known as polyHIPE) of interconnected pore-morphology, tailor-made properties, and customized functionalities. Aqueous and non-aqueous HIPE templates i.e. water-in-oil (w/o), oil-in-water (o/w), and oil-in-oil (o/o) stabilized using emulsifiers and/or Pickering stabilizers have been used to synthesize scaffolds suitable for various applications such as selective-sorption, adsorption, water-purification, and tissue engineering etc. Amongst different available polymerization chemistry, free radical polymerization is the most employed route in HIPE templating to synthesize porous scaffolds from unsaturated vinylic monomers. Very few reports are available on HIPE templated scaffold synthesis using other polymerization chemistry such as ATRP, RAFT, ROMP and step growth. Other polymerization routes such as ring opening polymerization (ROP) to synthesize porous scaffolds for tissue engineering based on a biodegradable aliphatic polyester specifically poly(ε-caprolactone) (PCL) by HIPE templating are scantly covered. All the PCL based scaffolds derived from HIPE templating are either based on pre-synthesized high molecular weight PCL or low molecular weight PCL macromers. Both of those approaches are multistep processes and require use of organic solvents to obtain low viscosity PCL solution for emulsification of dispersed phase during HIPE preparation. The scaffolds also showed poor mechanical strength and are of limited use specially in tissue engineering. Thus, there is an immense need and research prospects to generate mechanically strong PCL scaffolds in a single step using monomer (ε-caprolactone) (CL) as the continuous phase of HIPE.

In this study, we developed a single step synthesis of HIPE templated crosslinked PCL scaffolds *via* high internal phase emulsion-ring opening polymerization (HIPE-ROP). The challenges associated with preparation of stable HIPEs of CL and its polymerization to obtain crosslinked PCL scaffolds were overcome by judicious selection of dispersed phase, n-hexadecane, emulsifier, pluronic F127 and magnetic stirring (1500 rpm). CL-HIPEs were prepared by dispersing n-hexadecane in continuous phase of HIPE

and HIPEs were polymerized *via* HIPE-ROP at 120 °C for 8 h in non-inert condition. Bis-(ε-caprolactone-4-yl) (BCY) was used as crosslinker which was melt-dissolved in CL and it effectively crosslinked the PCL chains during stannous octoate ($Sn(Oct)_2$) catalyzed HIPE-ROP. Different generations of crosslinked PCL scaffolds were synthesized by varying the crosslink density (X_c) and ϕ_d. Polymer yield (>95%) and gel content values (>98%) signified high efficacy of adopted parameters for HIPE-ROP performed with moisture sensitive monomers and catalyst. The crosslinked PCL scaffolds were of interconnected pore-morphology, high porosity, high mechanical strength and possessed significant liquid uptake. The effect of dual confinement on crosslinked PCL chains locked in typical polyHIPE morphology caused by ϕ_d and X_c was clearly reflected on the melting and crystallization temperatures of crosslinked PCL scaffolds. Further, to resolve the concerns related to high emulsifier content, synthesis of crosslinked PCL nanocomposite scaffolds at relatively low emulsifier concentration was demonstrated by incorporating nano-graphene oxide dots, as Pickering stabilizer, in the continuous phase of HIPE. The *in-vitro* cell-growth and biomineralization experiments and controlled hydrolytic degradation study of crosslinked PCL scaffolds proved the suitability of synthesized crosslinked PCL scaffolds in tissue engineering. Overall, the single step HIPE-ROP process developed in this work paved a new route to prepare emulsion templated crosslinked scaffolds of other lactones and lactides. The HIPE-ROP process executed using as received monomers and reagents has high potential for commercial viability by conversion from a batch to a continuous process.

सारांश

पिछले दो दशकों में चित्ताकर्षक गुणों से युक्त और अनेकानेक अनुप्रयोगों में प्रयोज्य छिद्रमय बहुलकीय संरचनायें जैसे की छिद्रमय - खंड, छड़ें, मनकें, झिल्ली इत्यादि ने महत्वपूर्ण ध्यानाकर्षित किया है। छिद्रमय बहुलकीय संरचनायें निर्मित करनेवाली विभिन्न तकनीकों में से वैशिष्ट एकचरणीय उच्च आंतरिक प्रावस्था वाले पायसन (हाईप, आंतरिक प्रावस्था के आयतन का अंश, ≥०.७४) प्रतिरूप तकनीक बहुत ही प्रशंसनीय है क्यूंकी यह तकनीक अनुकूलित गुणधर्म और विशिष्टता से युक्त परस्पर छिद्रमय बहुलकीय संरचनाओं का निर्माण करती है। पृष्ठसक्रियकारक और/अथवा पिकरिंग स्थिरकरकों से निर्मित जलीय और अजलीय हाईप-प्रतिरूप - जल/तेल, तेल/जल और तेल/तेल का उपयोग करके संश्लेषित विविध छिद्रमय बहुलकीय संरचनायें अनेकानेक अनुप्रयोगों में जैसे कि चयनात्मक-शोषण, अधिशोषण, जल-परिष्करण, ऊतक-अभियांत्रिकी इत्यादि में उपयुक्त हैं। विभिन्न प्रकार की बहुलकीय अभिक्रियाओं में से मुक्त-मूलक प्रक्रिया का असंतृप्त एकलकों से सम्बंधित हाईप-प्रतिरूप में उच्चतम प्रयोग करके विभिन्न छिद्रमय बहुलकीय संरचानाओं का निर्माण किया गया है। अन्य बहुलकीयकरण-प्रक्रियायें जैसे कि एटम ट्रांसफर रेडिकल (एटीआर), रिवर्सिबल अडिशन-फ्रग्मेंटेशन चैन-ट्रान्स्फर (राफ्ट), रिंग-ओपनिंग मेटाथेसिस (आरओएम), स्टेप-ग्रोथ इत्याई का उपयोग अल्पनीयता में किया गया है। इसके अतिरिक्त रिंग ओपनिंग बहुलकीयकरण प्रक्रिया (आरओपी) द्वारा जैव-निम्नकारक एलीफैटिक पॉलिएस्टर विशेषतः पाली(ε-कैप्रोलैक्टोन) (पीसीएल) पर आधारित हाईप-प्रतिरूप में निर्मित छिद्रमय संरचनायें न्यूनतता में वर्णित हैं। हाईप-प्रतिरूप में निर्मित पीसीएल की छिद्रमय संरचनायें पूर्वनिर्मित उच्च अथवा निम्न परमाणुभारवाले पीसीएल बहुलक पर आधारित हैं। हाईप-प्रतिरूप में पूर्वनिर्मित उच्च और निम्न परमाणुभारवाले पीसीएल से सम्बंधित कार्यविधियाँ बहुचरणीय हैं जिसमें कार्बनिक विलायकों का उपयोग करके कम श्यानता वाले विलयन तैयार किए जाते हैं जो हाईप की

आंतरिक प्रावस्था के पायसीकरण को सुगम्य बनाते हैं। इसके अतिरिक्त हाईप-प्रतिरूप में निर्मित पीसीएल की छिद्रमय संरचनायें निर्बल भी होती हैं और विशेषतः ऊतक-अभियांत्रिकी के लिए बहुत ही सीमित रूप में उपयोगी हैं। अतः एक ऐसी एकचरणीय प्रक्रिया की अत्यधिक आवश्यकता है जिसमें एकलक, ε-कैप्रोलैक्टोन का उपयोग हाईप-प्रतिरूप की सतत प्रावस्था के रूप में करके प्रबल छिद्रमय संरचनायें निर्मित की जा सकें।

इस शोधकार्य में एक ऐसी एकचरणीय प्रक्रिया, हाईप-आरओपी विकसित की गयी है जो तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनायें निर्मित करती है। एकलक, ε-कैप्रोलैक्टोन के हाईप-प्रतिरूप के निर्माण करने और उनकें बहुलकीयकरण से सम्बंधित चुनौतियों के निवारण हेतु आंतरिक प्रावस्था - हेक्साडेकेन, अपमार्जक - प्लुरोनिक एफ-१२७, चुम्बकीय क्रियाशीलता (१५०० परिक्रमण गति प्रति मिनट) का विवेकपूर्ण तरीके से चयन किया गया। ε-कैप्रोलैक्टोन में हेक्साडेकेन के पायसीकरण से निर्मित हाईप-प्रतिरूप का १२०° सेल्सीयस तापमान पर आठ घंटे तक बहुलकीयकरण करने पर तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनायें संश्लेषित हुईं। तिर्यककारक - बिस-(ε-कैप्रोलैक्टोन-४-वाय-एल) (बीसीवाय) को ε-कैप्रोलैक्टोन में पिघलाकर तैयार किए गये विलयन का टिन-अष्टक (स्टैनस-ऑक्टोएट) द्वारा उत्प्रेरित बहुलकीयकरण करने पर पीसीएल की श्रृंखलायें तिर्यकबन्ध में समाहित हो गईं। तिर्यकबन्ध की सघनता और आंतरिक प्रावस्था के अनुपातिक आयतन में तब्दीली लाकर विभिन्न किस्म की तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनायें निर्मित की गईं। आर्द्रता-संवेदनशील एकलक और उत्प्रेरक से निहित बहुलकीयकरण प्रकिया, हाईप-आरओपी में प्राप्त बहुलक-परिमाण (>९५%) और जलैप-मान (>९८%), बहुलकीयकरण-प्राचल की प्रभाविकता का प्रतीक हैं। तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनाओं नें परस्पर-रंध्र, उच्च-सरन्ध्रता, उच्च-प्रबलता और प्रचंड तरल-अभिशोषण प्रदर्शित किया। आंतरिक प्रावस्था के उच्च आयतन और तिर्यकबन्ध की सघनता के कारण उत्पन्न द्विप्रतिरोधकता का स्पष्ट प्रभाव तिर्यकबन्धवाली पीसीएल की

श्रृंखलाओं के विगलन और स्फटिकीकरण तापमान पर दिखाई दिया। इसके अतिरिक्त हाईप-प्रतिरूप में तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनाओं के संश्लेषण के दौरान प्रयुक्त अपमार्जक की उच्च मात्रा से सम्बंधित समस्या के निवारण हेतु नैनों-ग्रेफ़ीन आक्साइड डॉट्स को पिकरिंग स्थिरकारक के रूप में हाईप की सतत प्रावस्था में समाहित किया गया। कृत्रिम परिस्थिति में किए गये कोशिका-पालन, जैविक-खनिजन और नियंत्रित जल-अपघटनीय निम्नीकरण प्रयोग, तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनाओं की ऊतक-अभियांत्रिकी में उपयोगिता को सिद्ध करते हैं। व्यापक रूप से तिर्यकबन्धवाली पीसीएल की छिद्रमय संरचनाओं की एकचरणीय बहुलकीयकरण प्रक्रिया एक ऐसी नई प्रणाली को स्थापित करती है, जिसके द्वारा हाईप-प्रतिरूप में अन्य चक्रिय-एकलक, लैक्टोन्स और लैक्टाइड्स की छिद्रमय संरचनायें विकसित की जा सकती हैं। हाईप-आरओपी संश्लेषण प्रक्रिया जो अपरिष्कृत एकलकों और अभिकर्मकों पर आधारित है, व्यावसायिक व्यवहार्ता और अनिरन्तर से निरन्तर बनने की प्रक्रिया की उच्च क्षमता रखती है।

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List of Symbols

S	Second
Min	Minute
H	Hour
M	Meter
Cm	Centimeter
Mm	Micrometer
Nm	Nanometer
G	Gauge
cm^{-1}	Centimetre inverse
L	Litre
mL	Millilitre
μL	Microlitre
mL/min	Millilitre per minute
%	Percentage
ppm	Parts per million
g	Gram
Mg	Milligram
Mol	Mole
g/mol	Gram per mole
g/cm^3	Gram per cubic centimetre
m^2/g	Square meter per gram
J/g	Joule per gram
Hz	Hertz
kHz	Kilohertz
MHz	Megahertz
kV	Kilovolt
mA	Milliampere
m/z	*Mass-to-charge* ratio
°C	Degree Celsius
T_g	Temperature of glass transition
T_m	Temperature of melting
T_c	Temperature of crystallization

H_f	Heat of fusion
H_f^0	Heat of fusion of 100% crystalline poly(ε-caprolactone) sample
H_c	Heat of crystallization
W_c	Crystallinity
π^*	Polarizability
Pa	Pascal
MPa	Mega-Pascal
ρ	Density
kN	Kilo Newton
α	Alpha
δ	Chemical shift
δ'	Solubility parameter

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
RT	Room temperature
FDA	Food and drug administration
HLB	Hydrophilic-lipophilic balance
rpm	Revolution per minute
RP	Rapid prototyping
SFF	Solid freeform fabrication
CAD	Computer aided designs
SLS	Selective laser sintering
FDM	Fused deposition modeling
TIPS	Thermally induced phase separation
wt.%	Weight percentage
w.r.t.	With respect to
X_c	Crosslink density
ϕ_d	Volume fraction of dispersed phase
w/o	Water-in-oil
o/w	Oil-in-water
o/o	Oil-in-oil
HIPE	High internal phase emulsion
PolyHIPE	Polymerized high internal phase emulsion
FRP	Free radical polymerization
RAFT	Reversible addition fragmentation chain transfer
ATRP	Atom transfer radical polymerization
AGET-ATRP	Activator generated electron transfer-atom transfer radical polymerization
ROMP	Ring opening metathesis polymerization
ROP	Ring opening polymerization
HIPE-ROP	High internal phase emulsion-ring opening polymerization
PGA	Poly(glycolic acid)
PLLA	Poly(L-lactic acid)
PDLA	Poly(D,L-lactide)
PTMC	Poly(trimethylene carbonate)

PVA	Poly(vinyl alcohol)
PEO	Poly(ethylene oxide)
PPO	Poly(propylene oxide)
PCL	Poly(ε-caprolactone)
4-PCLMA	4-arm PCL methacrylate
PEGDMA	Poly(ethylene glycol) dimethacrylate
MPS	Methacryloxypropyltrimethoxysilane
AA	Acrylic acid
AM	Acrylamide
LA	Lauryl acrylate
MMA	Methyl methacrylate
SMA	Stearyl methacrylate
HEMA	2-Hydroxyethyl methacrylate
GMA	Glycidyl methacrylate
DXO	1,5-dioxepan-2-one
PDL	Pentadecanolide
CL	ε-Caprolactone
CL-HIPE	High internal phase emulsion of ε-caprolactone
BCY	Bis(ε-caprolactone-4-yl)
MBA	N,N′- methylene bisacrylamide
DVB	Divinyl benzene
VBC	4-Vinylbenzyl chloride
EHA	2-Ethylhexyl acrylate
BDA	1,4-Butanediol diacrylate
EGDMA	Ethylene glycol dimethacrylate
KPS	Potassium persulphate
AIBN	2,2'-Azobisisobutyronitrile
APS	Ammonium persulfate
TEMED	N,N,N′,N′-Tetramethylethylendiamine
$Sn(Oct)_2$	Stannous octoate
MSA	Methane sulphonic acid
m-CPBA	m-Chloroperbenzoic acid
ECM	Extracellular matrix

SBF	Simulated body fluid
PBS	Phosphate-buffered saline
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyl tetrazolium bromide
TPO	Trimethylbenzoyldiphenyl phosphine oxide
SSNa	4-Vinylbenzenesulfonic acid sodium salt
LiTFSI	Bis(trifluoromethane) sulfonimide lithium salt
CTAB	Cetyl trimethyl ammonium bromide
P123	Pluronic P-123
F108	Pluronic F-108
F127	Pluronic F-127
CNC	Cellulose nanocrystals
GO	Graphene oxide
nGO	Nano-graphene oxide dots
mSiNP	Hydrophobically modified silica nanoparticles
nHAp	Hydroxyapatite nano particles
MMT	Montmorillonite nanoclay
Ca/P	Calcium to phosphate ratio
CO_2	Carbon dioxide
$scCO_2$	Super critical carbon dioxide
DCM	Dichloromethane
$CDCl_3$	Deuterated chloroform
DES	Deep eutectic solvent
THF	Tetrahydrofuran
DMF	N,N'-Dimethyl formamide
DMSO	Dimethyl sulfoxide
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
SEM	Scanning electron microscopy
FE-SEM	Field emission-scanning electron microscopy
TEM	Transmission electron microscopy
SAED	Selected area electron diffraction
WAXD	Wide angle X-ray diffraction
EDS	Energy dispersive X-ray spectroscopy
FTIR	Fourier transform infrared spectroscopy

ATR	Attenuated Total Reflectance
DSC	Differential scanning calorimetry
TGA	Thermogravimetric analyzer
LDI-MS	Laser desorption ionization-mass spectrometry
TOF	Time-of-flight
Cu	Copper
K	Potassium
Hg	Mercury
HCl	Hydrochloric acid
NaOH	Sodium hydroxide
NaCl	Sodium chloride
KCl	Potassium chloride
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium hydrogen carbonate
$CaCl_2.6H_2O$	Calcium hexahydrate
$CaCl_2.2H_2O$	Calcium chloride dihydrate
$K_2HPO_4.3H_2O$	Dipotassium hydrogen orthophosphate trihydrate
$MgCl_2.6H_2O$	Magnesium chloride hexahydrate