

D-GALACTOSE AND PIPERAZINE DERIVED
BIODEGRADABLE AND BIOCOMPATIBLE POLYMERS
AND THEIR APPLICATIONS

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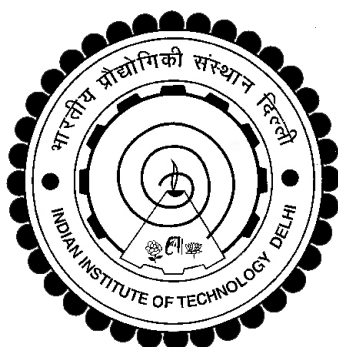
SHUBHRA GOEL

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Submitted

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

to the



Indian Institute of Technology Delhi

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Dedicated to my

Grandparents

Parents

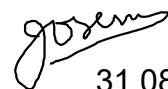
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Bhavik

CERTIFICATE

This is to certify that the thesis entitled “**D-galactose and piperazine derived biodegradable and biocompatible polymers and their applications**” being submitted by **Mrs. Shubhra Goel** to the Indian Institute of Technology Delhi, New Delhi, for the award of degree of **Doctor of Philosophy** is a record of bonafide research work carried out by her. **Mrs. Shubhra Goel** has worked under my guidance and supervision and has fulfilled the requirements for the submission of her 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 University or Institute for the award of any other degree or diploma.



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(SHUBHRA GOEL)

ABSTRACT

Adsorption is the most efficient, affordable, and environmentally beneficial approach for dye removal. Polymeric materials are developing as a new class of effective adsorbents. Natural and synthetic glycopolymers have been extensively researched to generate diverse architectures, including linear chain polymers and crosslinked gels. The compelling properties of D-galactose and its ability of protection-deprotection makes it attractive towards the synthesis of organic solvent-soluble polymers, as well as organogel and hydrogel utilizing the same monomeric unit. Although crosslinking of hydroxyl groups using diisocyanates have been reported earlier, its utility in hydrogel synthesis has been less explored.

Apart from glycopolymers, aliphatic polyesters, such as poly(lactic acid) (PLA), poly(ϵ -caprolactone) (PCL) and poly(butylene succinate) (PBS) are well established biodegradable polyesters utilized in biomedical sector. However, these hydrophobic polyesters lack reactive sites, limiting their biodegradability and so their use in few of the biomedical applications. Enhancing their hydrophilicity can improve biodegradation and widen their scope for use. Several literatures have reported on biodegradable polymers with pendant functionalities like hydroxyl, amino, carboxyl etc., they still suffer from longer degradation time. Thus, it is necessary to design and produce biodegradable polymers that degrade faster. Although incorporating ionomeric moieties as pendant units to accelerate degradation has been reported, their influence on the polymer backbone has been less explored, including cationic aliphatic polyesters as an interesting area of current research. The unique biological and physicochemical properties of piperazine moiety along with its stimuli-responsive pH sensitivity and its capability to impart antibacterial properties, provides it a huge potential as a precursor for the development of antimicrobial polyesters with enhanced biodegradability.

Therefore, this research focuses on development of biocompatible D-galactose based crosslinked polymers exploring dye sequestration, phase-selective organogelation, and drug

release applications. Additionally, a series of biodegradable piperazine-derived polyesters and copolyesters has been developed to overcome the degradability challenge.

In the first section, D-galactose has been utilized to synthesize acrylate-based monomer (**MAIpGal**) bearing isopropylidene moieties that led to organic solvent solubility. Based on the optimized parameters for linear polymer, the novel chemically crosslinked polymers (**OG10**, **OG15** and **OG20**) were prepared in good yields by varying the crosslinker amount as 10, 15 and 20 wt%, respectively, to evaluate the effect of crosslinker content on structural properties. The materials were designed with the objective of toxic dye sequestration and phase-selective organogelation from organic-aqueous solvent mixtures. The polymeric gel marked its capability to selectively adsorb cationic dyes, like ~85% of RhB dye from a mixture of RhB/MO from the water within 6 h. Also, **OG10** was found to be a suitable polymeric material for selective removal of organic solvents from their oil/water mixture by phase-selective organogelation, and showed nearly 100% absorption of toluene and chloroform from water.

In the next section, the same monomer was also utilized to develop a glutaraldehyde-free strategy to produce the novel glycomeric hydrogels. The pendant hydroxyl groups were condensed with different ratio of diisocyanate to produce macroporous novel crosslinked polymers (**HG5**, **HG2.5** and **HG1**) in good yields, utilizing 5, 2.5 and 1 wt% crosslinker content respectively. The swelling and morphological studies revealed the formation of macropores in the polymer matrix with 16-20 μm pore size and maximum swelling up to 526% in **HG1**. Due to their tunable porosity and cytocompatibility with the cells, the material was evaluated for drug load and release studies. The drug release took place through a simple diffusion mechanism and the trend correlates well with the decreased crosslinking density, larger pore size and thereby, comparatively faster drug release through **HG1** matrix (~92% in 72 h).

In the subsequent sections of this work, aliphatic polyesters and copolyesters were synthesized from piperazine-derived diester utilizing step polycondensation method. In the first part, polymers were synthesized using dimethyl 2,2'-(piperazin-1,4-diyl)diacetate (**M1**) with a series of alkane diols (C4 to C10) and characterized. An N-alkylation and protonation approach were adopted to tune their crystallinity and hydrophilicity so as to enhance the biodegradability. Significant changes in structural and thermal properties were observed after quaternization with methyl iodide, including reduced crystallinity and improved hydrophilicity. The T_g of polyesters varied from -19.3 to 30.4 °C, which decreased with alkyl chain length and increased with protonation/N-alkylation. Furthermore, the hydrolytic and microbial degradation studies were conducted to evaluate the biodegradability of the synthesized polyesters. In the second part, the incorporation of charged units utilizing the feasible copolymerization approach was carried out, to broaden the scope of hydrophobic polymers and achieve materials with tailored properties. A series of synthesized copolyesters own tunable hydrophilicity and crystallinity by charge modulation at N-atoms. Zeta potential measurements showed the pH-responsiveness of the polyesters and copolyesters. Further, the cytocompatibility with U2OS cells and antibacterial studies were performed against *E. coli* and *S. aureus* bacterial strains, to establish their suitability as potential antibacterial agents.

डाई हटाने के लिए ऐडजोर्पेशन सबसे कुशल, सस्ता और पर्यावरण की दृष्टि से लाभकारी तरीका है। पॉलिमरिक सामग्री प्रभावी ऐडजोर्बेंट्स के एक नए वर्ग के रूप में विकसित हो रही है। रैखिक श्रृंखला पॉलिमर और क्रॉसलिंकड जेल सहित विविध आर्किटेक्चर उत्पन्न करने के लिए प्राकृतिक और सिंथेटिक ग्लाइकोपॉलिमर पर बड़े पैमाने पर शोध किया गया है। डी-गैलेक्टोज के सम्मोहक गुण और प्रोटेक्शन-डीप्रोटेक्शन की इसकी अनूठी क्षमता इसे आर्गेनिक सॉल्वेंट सॉल्युबल पॉलिमर के संश्लेषण के साथ-साथ एक ही मोनोमरिक इकाई का उपयोग करने वाले ऑरगेनोजेल और हाइड्रोजेल के लिए आकर्षक बनाती है। हालाँकि डाईआईसोसियानेट्स का उपयोग करने वाले हाइड्रॉक्सिल समूहों के क्रॉसलिंग को पहले बताया गया है, हाइड्रोजेल संश्लेषण में इसकी उपयोगिता कम खोजी गई है।

ग्लाइकोपॉलिमर के अलावा, पॉलि(लैक्टिक एसिड) (PLA), पॉलि(ε-कैप्रोलैक्टोन) (PCL) और पॉलि(ब्यूटाईलीन सकसिनेट) (PBS) जैसे ऐलिफैटिक पॉलीएस्टर बायोमेडिकल क्षेत्र में उपयोग किए जाने वाले बायोडिग्रेडेबल पॉलीएस्टर हैं। हालांकि, इन हाइड्रोफोबिक पॉलीएस्टर में प्रतिक्रियाशील साइटों की कमी होती है, जिससे उनकी बायोडिग्रेडेबिलिटी और इसलिए कुछ ही बायोमेडिकल अनुप्रयोगों में उनका उपयोग होता है। उनकी हाइड्रोफिलिसिटी को बढ़ाने से बायोडिग्रेडेशन में सुधार हो सकता है और उपयोग के लिए उनके दायरे का विस्तार हो सकता है। कई लिटरेचर्स ने बायोडिग्रेडेबल पॉलिमर पर पेंडेंट फंक्शनैलिटीज जैसे हाइड्रोक्साइल, अमीनो, कार्बोक्सिल आदि के बारे में बताया है, वे अभी भी लंबे समय तक डिग्रेड होते हैं। इसलिए, ऐसे बायोडिग्रेडेबल पॉलिमर का डिजाइन और उत्पादन करना आवश्यक है जो तेजी से डिग्रेड हो सकते हैं। हालांकि डिग्रेडेशन में तेजी लाने के लिए आयनोमेरिक मोइटीज़ को पेंडेंट इकाइयों के रूप में शामिल किया गया है, परन्तु पॉलीमर बैकबोन पर उनके प्रभाव का कम पता लगाया गया है। पॉलीमर बैकबोन के साथ वितरित आवेशित इकाइयों से युक्त कैटआयनिक ऐलिफैटिक पॉलीएस्टर्स वर्तमान शोध के एक दिलचस्प क्षेत्र के रूप में उभरे हैं। पिपराज़ीन की मात्रा के

अद्वितीय जैविक और भौतिक-रासायनिक गुणों के साथ स्टिमुलाई-रेस्पॉन्सिव pH-सेंसिटिविटी और एंटीमाइक्रोबियल गुण इसे बायोडिग्रेडेबिलिटी एंटीमाइक्रोबियल पॉलीएस्टर बनने की क्षमता रखता है।

इसलिए, यह शोध बायोकंपैटिबल डी-गैलेक्टोज आधारित क्रॉसलिंकड पॉलिमर के विकास पर केंद्रित है, जो डाई सीकेस्ट्रेशन, फेज-सेलेक्टिव ऑर्गेनेलेशन और ड्रग रिलीज़ एप्लिकेशन की खोज करता है। इसके अतिरिक्त, डिग्रेडेशन की चुनौती को दूर करने के लिए बायोडिग्रेडेबल पिपराज़ीन-डिराइव्ड पॉलीएस्टर और कोपोलीएस्टर्स की एक श्रृंखला विकसित की गई है।

पहले खंड में, डी-गैलेक्टोज का उपयोग एक्राईलेट-आधारित मोनोमर (MAIpGal) को संश्लेषित करने के लिए किया गया है, जो आइसोप्रोपाइलिडीन मोइटीज़ को प्रभावित करता है जिससे आर्गेनिक सॉल्वेंट सोल्युबिलिटी पैदा होती है। लिनियर पॉलिमर के अनुकूलित मापदंडों के आधार पर, संरचनात्मक गुणों पर क्रॉसलिंकर सामग्री के प्रभाव का मूल्यांकन करने के लिए, रासायनिक रूप से क्रॉसलिंक किए गए पॉलिमर (**OG10**, **OG15** और **OG20**) को क्रॉसलिंकर राशि को क्रमशः 10, 15 और 20 wt% के रूप में बदलकर अच्छी यील्ड में तैयार किया गया था। पॉलिमर को आर्गेनिक-एक्स सॉल्वेंट से टॉक्सिक डाई सीकेस्ट्रेशन और फेज़-सेलेक्टिव ऑर्गेनोजेलेशन के उद्देश्य से डिजाइन किया गया था। पॉलिमरिक जेल ने चुनिंदा रूप से कैटायनिक डाईयों को एडसोर्ब करने की अपनी क्षमता को चिह्नित किया, जैसे कि 6 घंटे के भीतर RhB/MO के मिश्रण से ~ 85% RhB डाई अलग हुई। इसके अलावा, OG10 को फेज़-सेलेक्टिव ऑर्गेनोजेलेशन द्वारा उनके तेल/पानी के मिश्रण से आर्गेनिक सॉल्वेंट्स के चयनात्मक हटाने के लिए एक उपयुक्त पॉलिमरिक सामग्री के रूप में पाया गया, और पानी से टोल्यूईन और क्लोरोफॉर्म का लगभग 100% अवशोषण देखा गया।

अगले खंड में, उसी मोनोमर का उपयोग नॉवल ग्लाइकोमेरिक हाइड्रोजेल के उत्पादन के लिए ग्लूटाराल्डिहाइड-मुक्त रणनीति विकसित करने के लिए भी किया गया था। पेंडेंट हाइड्रॉक्सिल समूहों को डायसोसायनेट के विभिन्न अनुपात के साथ कंडेन्स किया गया था ताकि अच्छी यील्ड में मैक्रोपोरस नॉवल क्रॉसलिंकड पॉलिमर (**HG5**, **HG2.5** और **HG1**) का उत्पादन किया जा सके, जो क्रमशः 5, 2.5 और 1

wt% क्रॉसलिंगर कंटेंट का उपयोग करते हैं। स्वेलिंग और मॉर्फोलॉजिकल स्टडीज में पाया गया कि पॉलीमर मैट्रिक्स में मैक्रोप्रोर्स का गठन 16-20 माइक्रोन पोर साइज़ और 526% तक अधिकतम स्वेलिंग HG1 में है। पॉलीमर की ट्यूनेबल पोरसिटी और कोशिकाओं के साथ साइटोकम्पैटिबिलिटी के कारण, ड्रग लोड और रिलीज अध्ययन के लिए मूल्यांकन किया गया। घटती हुई क्रॉसलिंग डेंसिटी और बढ़ते हुए पोर साइज़ के साथ साथ ड्रग रिलीज सिंपल डिफ्यूजन मैकेनिज्म के माध्यम से हुआ, तथा सबसे तेज़ ड्रग रिलीज HG1 मैट्रिक्स (72 घंटे में ~ 92%) के द्वारा देखा गया।

इसके बाद के खंडों में, ऐलिफैटिक पोलीएस्टर्स और कोपोलीएस्टर्स को स्टेप पोलीकॉन्डेंसेशन मेथड का उपयोग करके पिपराज़ीन डिराइव्ड डाईएस्टर से संश्लेषित किया गया। पहले भाग में, पॉलिमर को डाइमिथाइल 2,2'- (पिपराज़ीन-1,4- डाईऑल) डाईऐसीटेट (M1) का उपयोग करके ऐलकेन डाईऑलज़ (C4 से C10) की एक श्रृंखला के साथ संश्लेषित एवं कैरेक्टराइज़ किया गया। पोलीएस्टर्स की क्रिस्टलैनीटी और हाइड्रोफिलिसिटी को ट्यून करने के लिए एन-एल्काइलेशन और प्रोटोनेशन दृष्टिकोण अपनाया गया ताकि बायोडिग्रेडेबिलिटी को बढ़ाया जा सके। मिथाइल आयोडाइड के साथ क्राटरनाइजेशन के बाद संरचनात्मक और थर्मल गुणों में महत्वपूर्ण परिवर्तन देखे गए, बेहतर हाइड्रोफिलिसिटी के साथ। इसके अतिरिक्त क्रिस्टलैनीटी में महत्वपूर्ण रिडक्शन देखि गयी। पॉलीएस्टर का T_g 19.3 से 30.4 °C तक भिन्न होता है, जो अल्काइल श्रृंखला की लंबाई के साथ कम हो जाता है और प्रोटोनेशन / एन-एल्काइलेशन के साथ बढ़ जाता है। इसके अलावा, संश्लेषित पॉलीएस्टर की बायोडिग्रेडेबिलिटी का मूल्यांकन करने के लिए हाइड्रोलाइटिक और माइक्रोबियल डिग्रेडेशन अध्ययन किए गए। दूसरे भाग में, हाइड्रोफोबिक पॉलिमर के दायरे को व्यापक बनाने और अनुरूप गुणों के साथ सामग्री प्राप्त करने के लिए व्यवहार्य कोपोलीमराइजेशन दृष्टिकोण का उपयोग करने वाली चार्ज इकाइयों का समावेश किया गया था। संश्लेषित कॉपोलिस्टर की एक श्रृंखला N-atoms पर चार्ज मॉड्यूलेशन द्वारा ट्यून करने योग्य हाइड्रोफिलिसिटी और क्रिस्टलीयता का मालिक है। ये संश्लेषित कोपोलीएस्टर्स एन- ऐटम्स पर चार्ज मॉड्यूलेशन द्वारा ट्यून करने योग्य हाइड्रोफिलिसिटी और क्रिस्टलैनीटी प्रदान करते हैं। जीटा पोटेंशियल

मैज़रमेन्ट्स ने पोलिएस्टर्स और कोपोलीएस्टर्स की pH- रेसपौनसिवनेस को दिखाया। इसके अलावा, संभावित जीवाणुरोधी एजेंटों के रूप में उनकी उपयुक्तता स्थापित करने के लिए, U2OS कोशिकाओं के साथ साइटोकोमपैटिबिलिटी एवं *E. coli* एवं *S. aureus* जीवाणु उपभेदों के खिलाफ एंटीबैक्टेरियल अध्ययन किये गए।

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LIST OF ABBREVIATIONS

PBS	Poly (butylene succinate)
PESu	Poly (ethylene succinate)
PLA	Poly (lactic acid)
PEG	Poly (ethylene glycol)
PLGA	Poly (lactic-co-glycolic acid)
PCL	Poly (ϵ -caprolactone)
PBSA	Poly (butylene succinate-co-butylene adipate)
PDMAEMA	Poly ((2-dimethylamino)ethyl methacrylate)
AIBN	2,2'-azobis(2-methylpropionitrile)
BPO	Benzoyl peroxide
EGDMA	Ethylene glycol dimethacrylate
HEMA	2-Hydroxyethyl methacrylate
PVA	Polyvinyl alcohol
LMWGs	Low-molecular-weight gelators
MB	Methylene blue
RhB	Rhodamine B
MO	Methyl orange
CV	Crystal violet
Quats	Quaternary ammonium salts
PI	Propidium iodide
MTT	3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide
NMGDMA	Nonamethylene glycol dimethacrylate
MAIpGal	6-O-methacryloyl-1,2;3,4-di-O-isopropylidene-D-galactose

PMAIpGal	Poly (6-O-methacryloyl-1,2;3,4-di-O-isopropylidene-D-galactose)
NMR	Nuclear Magnetic Resonance
FTIR	Fourier-transform infrared
GPC	Gel permeation chromatography
XRD	X-ray diffraction
DSC	Differential scanning calorimetry
TGA	Thermogravimetric Analysis
MACl	Methacryloyl chloride
DCC	N,N'-dicyclohexylcarbodiimide
TEA	Triethylamine
THF	Tetrahydrofuran
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
FESEM	Field Emission Scanning Electron Microscope
DLS	Dynamic light scattering
TLC	Thin-layer chromatography
PMAGal	Poly (6-O-Methacryloyl-D-galactose)
HMDI	Hexamethylene diisocyanate
GM	Gentamicin
FBS	Fetal bovine serum
DMEM	Dulbecco's Modified Eagle's Medium

LIST OF CHEMICAL FORMULAE

H ₂ O	Water
CO ₂	Carbon-dioxide
(NH ₄) ₂ S ₂ O ₈	Ammonium persulphate
P ₂ O ₅	Phosphorus pentoxide
ZnCl ₂	Zinc chloride
H ₂ SO ₄	Sulfuric acid
CDCl ₃	Deuterated chloroform
Na ₂ CO ₃	Sodium carbonate
Na ₂ SO ₄	Sodium sulphate
HCl	Hydrochloric acid
NaOH	Sodium hydroxide
NaHCO ₃	Sodium bicarbonate
K ₂ HPO ₄	Dipotassium hydrogen phosphate
KH ₂ PO ₄	Potassium dihydrogen phosphate
NH ₄ NO ₃	Ammonium nitrate
MgSO ₄ ·7H ₂ O	Hydrous magnesium sulphate
FeSO ₄ ·7H ₂ O	Hydrous ferrous sulphate
MnSO ₄ ·4–6H ₂ O	Manganese(II) sulphate hexahydrate
ZnSO ₄ ·7H ₂ O	Zinc sulphate heptahydrate
CuSO ₄ ·7H ₂ O	Copper sulphate heptahydrate

