BIODEGRADABLE POLYMERIC NANOPARTICLES MEDIATED STIMULI-RESPONSIVE DELIVERY OF CHEMOTHERAPEUTIC AGENTS FOR BREAST CANCER THERAPY

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by

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Submitted

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

to the

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Dedicated to My Family….

CERTIFICATE

This is to certify that the thesis entitled **"BIODEGRADABLE POLYMERIC NANOPARTCILES MEDIATED STIMULI-RESPONSIVE DELIVERY OF CHEMOTHERAPEUTIC AGENTS FOR BREAST CANCER THERAPY"** submitted by **Ms. PRIYA GUPTA** to **Indian Institute of Technology Delhi** for the award of degree of Doctor of Philosophy in Biomedical Engineering is a record of bona fide research work carried out by her. Ms**. Priya Gupta** has worked under my supervision and has fulfilled the requirements for the submission of this thesis.

The results contained in this thesis are original and have not been submitted partially or fully to any other university or institute for the award of any degree or diploma.

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PRIYA GUPTA

ABSTRACT

According to World Health Organization, cancer remains the second leading cause of mortality worldwide, accounting for approximately 10 million deaths in 2020. Among various cancer types, breast cancer has consistently been the most frequently diagnosed malignancy in women and a leading cause of female cancer related deaths, with an estimated 2.3 million new cases and 685,000 deaths reported globally in 2020. Conventional treatment strategies for solid breast tumors rely heavily on surgery, radiation therapy and chemotherapy. Among chemotherapeutic agents, anthracyclines, particularly Doxorubicin (Dox), have been widely employed due to their broad-spectrum anti-cancer activity. However, the clinical utility of Dox is significantly limited by its dose-dependent cardiotoxicity and multidrug resistance. Pirarubicin (Pira), a semi-synthetic analogue of Dox with a tetrahydropyranyl (THP) substitution at the 4-O position, has emerged as a promising alternative due to its enhanced cellular uptake, reduced cardiotoxicity and efficacy in Dox-resistant tumor models. Combination chemotherapy remains a cornerstone strategy for overcoming drug resistance and achieving synergistic therapeutic effects by attacking cancer cells via multiple mechanisms. However, challenges such as mismatched pharmacokinetics of individual drugs and increased systemic toxicity hinder its clinical effectiveness. Nanotechnology based drug delivery platforms offer a promising solution by enabling site-specific drug accumulation through the enhanced permeability and retention (EPR) effect. In this context, polymeric nanoparticles have gained particular attention due to their tunability, biodegradability and ability to respond to tumor-specific stimuli such as pH or redox conditions. In the first phase of this research, Pirarubicin and Gemcitabine (Gem), an FDA-approved antimetabolite with limited therapeutic efficacy due to rapid deamination and systemic toxicity, were conjugated to an amphiphilic block copolymer (mPEG-b-PLA) via a Schiff base linker (Levulinic acid) to formulate pH-sensitive dual-drug-loaded nanoparticles. The resulting polymeric nanoparticle system exhibited uniform size distribution, low

polydispersity and favourable biocompatibility profiles. *In-vitro* release studies demonstrated accelerated drug release in acidic environments, corresponding to the tumor microenvironment. Furthermore, cellular uptake assays revealed enhanced internalization, while cytotoxicity studies indicated a synergistic effect of the Pira-Gem combination in some breast cancer cell lines. However, two critical limitations were encountered (i) The nanoformulation exhibited low drug-loading efficiency, attributed to the limited number of available conjugation sites on the polymer backbone, thereby necessitating a higher polymer-to-drug ratio, which poses potential concerns regarding systemic safety (ii) The observed therapeutic synergy between the drug combination was inconsistent across different breast cancer cell lines, underscoring the need for broader validation to establish universal applicability. To overcome these issues, a second nanoparticle system was designed using polyethyleneimine (PEI), a branched polyamine polymer known for its high density of functional groups. Polyethyleneimine (PEI) was used to form Schiff base linkages with both Pirarubicin (Pira) and Salinomycin (Sal). Sal is an ionophore antibiotic known for its strong ability to target and eliminate cancer stem cells (CSCs), which are major drivers of tumor recurrence and resistance. It was strategically combined with Pirarubicin to achieve a more potent and synergistic anticancer response. The resulting PEI-Pira/Sal conjugates were encapsulated within mPEG-b-PLA to improve biocompatibility and systemic circulation. The dual-loaded nanoparticles achieved a significantly higher drug loading (~90%) compared to the initial system and maintained excellent colloidal stability while retaining a moderately negative surface charge. *In-vitro* studies confirmed the enhanced cytotoxicity, synergistic therapeutic effects and effective CSC inhibition by Pira–Sal co-loaded nanoparticles across various drug ratios (1:1, 3:1, 1:3) and multiple breast cancer cell lines. The Pira–Sal (3:1) co-loaded nanoparticles showed the highest synergy and was selected for *in-vivo* evaluation. In syngeneic EAC tumor-bearing Balb/c mice, these nanoparticles led to ~95% tumor regression after biweekly intravenous injections. However, the survival analysis showed signs of systemic toxicity, as

most mice in both the single and dual-loaded nanoparticles treatment groups did not survive until the end of the study. This was likely caused by the release of free polyethyleneimine (PEI) upon degradation of the nanoparticle matrix, which is known to be toxic in its unbound form. These findings prompted the exploration of a safer, yet equally effective, alternative strategy. In the final phase of this work, a folic acid (FA)-conjugated, redox-responsive block copolymer system $[S\text{-}(PLA\text{-}b\text{-}PEG\text{-}CONH)]_2$, was developed to achieve active targeting and controlled drug release. Folic acid was employed as a targeting ligand to exploit the overexpression of folate receptors on various breast cancer subtypes, enhancing cellular uptake and tumor-specific accumulation. The copolymer, $[S\text{-}(PLA\text{-}b\text{-}PEG\text{-}CONH)]_2$, was synthesized through a multistep process and characterized by ^1H NMR spectroscopy and gel permeation chromatography (GPC). The number average (Mn) and weight average molecular weights (Mw) were determined to be 27,726 g/mol and 38,386 g/mol, respectively, with a polydispersity index of 1.384. Dual-loaded nanoparticles incorporating Pira and Sal in varying ratios (1:1, 3:1, 1:3) were formulated using the FA-conjugated redox-responsive polymer. The nanoparticles demonstrated excellent physicochemical stability, enhanced drug loading and prominent biocompatibility under physiological conditions. *In-vitro* assays showed significant improvements in cellular uptake in both 2D monolayer cultures and 3D tumor spheroids. The redox-sensitive disulfide bonds facilitated drug release in glutathione-rich environments typical of tumor intracellular conditions, while maintaining drug integrity under normal physiological conditions. Cytotoxicity and proliferation inhibition studies indicated that the Pira/Sal dual-loaded nanoparticles were significantly more effective than either free drug or singly-loaded nanoparticles. Moreover, the combination index (CI) analysis revealed consistent synergy across all tested ratios and folate receptor-positive breast cancer cell lines. The Pira/Sal (3:1) formulation was again selected for *in-vivo* evaluation due to its superior *in-vitro* performance. *In-vivo* studies in EAC tumor-bearing mice involved biweekly tail vein injections for 3 weeks, followed by monitoring for 60 days. The FA-

conjugated redox-responsive nanoparticles achieved nearly complete tumor regression with no observable tumor recurrence during the study duration. Importantly, there was no significant body weight loss in treated mice and histopathological evaluation of major organs revealed no signs of notable toxicity. These findings confirmed the *in-vivo* safety and therapeutic effectiveness of the formulation, in clear contrast to the earlier PEI-based system, which exhibited prominent toxicity. In conclusion, this work presents a comprehensive comparison of multiple polymeric nanoparticle-based strategies for combination chemotherapy in breast cancer. FA-conjugated, redox-responsive polymeric nanoparticles co-loaded with Pirarubicin and Salinomycin not only resolved critical limitations of previous formulations such as low drug loading, systemic toxicity and variable therapeutic responses but also demonstrated exceptional *in-vivo* compatibility and anti-tumor efficacy. This dual-targeted nanoformulation emerges as a potent and safe candidate for breast cancer therapy, with potential for clinical translation. Future investigations will focus on validation in higher animal models and advancement toward clinical trials.

सारांश

विश्व स्वास्थ्य संगठन के अनुसार, कैंसर अब भी वैश्विक स्तर पर मृत्यु का दूसरा सबसे बड़ा कारण बना हुआ है, और वर्ष 2020 में लगभग 1 करोड़ लोगों की मृत्यु कैंसर के कारण हुई। विभिन्न प्रकार के कैंसर में स्तन कैंसर महिलाओं में सबसे अधिक निदान किया जाने वाला कैंसर है और महिला कैंसर-जनित मृत्यु का एक प्रमुख कारण है, जिसके वर्ष 2020 में लगभग 2.3 मिलियन नए मामले और 6.85 लाख मौतें दर्ज की गईं। ठोस स्तन ट्यूमर के पारंपरिक उपचार में शल्य चिकित्सा, विकिरण चिकित्सा और कीमोथेरेपी शामिल हैं। कीमोथेरेपी एजेंट्स में, विशेष रूप से एंथ्रासाइक्लिन्स जैसे डॉक्सोरूबिसिन (Dox) का उपयोग व्यापक रूप से हुआ है। हालांकि, Dox की खुराक-निर्भर हृदय विषाक्तता और बहु-दवा प्रतिरोध इसके नैदानिक उपयोग को सीमित कर देते हैं। डॉक्सोरूबिसिन का एक अर्ध-प्राकृतिक एनालॉग पिरारूबिसिन (Pira), 4-O पोजीशन पर टेट्राहाइड्रोपायनिल (THP) प्रतिस्थापन के कारण, बेहतर कोशिकीय अवशोषण, कम हृदय विषाक्तता और Dox-प्रतिरोधी ट्यूमर मॉडलों में प्रभावशीलता के कारण एक आशाजनक विकल्प बन कर उभरा है। संयोजन कीमोथेरेपी, कैंसर कोशिकाओं पर विभिन्न जैविक मार्गों के माध्यम से हमला कर, दवा प्रतिरोध को दूर करने और संयुक्त चिकित्सीय प्रभाव प्राप्त करने की एक प्रमुख रणनीति है। हालांकि, व्यक्तिगत दवाओं की असंगत फार्माकोकाइनेटिक्स और बढ़ी हुई प्रणालीगत विषाक्तता इसकी नैदानिक प्रभावशीलता को बाधित करते हैं। नैनोटेक्नोलॉजी आधारित ड्रग डिलीवरी प्लेटफॉर्म, ट्यूमर स्थल पर लक्षित दवा संचय को EPR (Enhanced Permeability and Retention) प्रभाव के माध्यम से संभव बना कर इस चुनौती का समाधान प्रदान करते हैं। इस संदर्भ में, पॉलीमर नैनोपार्टिकल्स अपनी अनुकूलनशीलता, बायोडिग्रेडेबिलिटी और ट्यूमर-विशिष्ट उत्तेजनाओं (जैसे pH या रेडॉक्स स्थितियाँ) के प्रति उत्तरदायी होने के कारण विशेष ध्यान आकर्षित करते हैं। इस शोध के पहले चरण में, पिरारूबिसिन और जेमसिटाबीन (Gem) — एक FDA अनुमोदित एंटीमेटाबोलाइट जिसे तीव्र डीअमीनेशन और प्रणालीगत विषाक्तता के कारण सीमित प्रभावशीलता मिलती है — को एक अम्फीफिलिक ब्लॉक कोपॉलीमर (mPEG-b-PLA) से लेवुलिनिक एसिड आधारित शिफ बेस लिंकर्स के माध्यम

से जोड़ा गया ताकि pH-संवेदनशील द्वैत्य-दवा-युक्त नैनोपार्टिकल्स तैयार किए जा सकें। ये नैनोकण समान आकार वितरण, कम पॉलीडिस्पर्सिटी और बेहतर बायोअनुकूलता दर्शाते हैं। इन विट्रो रिलीज़ अध्ययनों ने अम्लीय वातावरण (जैसे ट्यूमर माइक्रोइनवायरनमेंट) में तेजी से दवा रिलीज़ को दिखाया। सेलुलर अवशोषण परीक्षणों से यह स्पष्ट हुआ कि इन नैनोकणों का अंतर्ग्रहण अधिक था, और साइटोटॉक्सिसिटी अध्ययनों ने कुछ स्तन कैंसर सेल लाइनों में Pira-Gem संयोजन के सहयोगी प्रभाव को दर्शाया। हालांकि, दो महत्वपूर्ण सीमाएँ सामने आईं — (i) नैनोफॉर्मुलेशन में सीमित संयोजन स्थलों के कारण कम दवा-लोडिंग क्षमता पाई गई, जिससे अधिक पॉलीमर-से-दवा अनुपात की आवश्यकता हुई, जिससे प्रणालीगत सुरक्षा पर प्रभाव पड़ा, (ii) विभिन्न स्तन कैंसर सेल लाइनों और दवा अनुपातों में चिकित्सीय समन्वय में असंगति देखी गई, जिससे इसकी सार्वभौमिकता पर प्रश्नचिह्न लगा। इन समस्याओं से निपटने के लिए, दूसरे चरण में पॉलीइथाइलीनइमीन (PEI) आधारित नैनोपार्टिकल सिस्टम को डिजाइन किया गया, जो एक शाखित पॉलीअमाइन है और इसकी उच्च कार्यात्मक समूह घनता के लिए जाना जाता है। PEI को पिरारूबिसिन (Pira) और सैलिनोमाइसिन (Sal) — एक आयोनोफोर एंटीबायोटिक जो कैंसर स्टेम कोशिकाओं (CSCs) को लक्षित करने और समाप्त करने में सक्षम है — दोनों से शिफ बेस लिंकर्स के माध्यम से जोड़ा गया। सैलिनोमाइसिन को पिरारूबिसिन के साथ संयोजन में इस उद्देश्य से चुना गया कि मिलकर वे अधिक शक्तिशाली और सहयोगी कैंसर-रोधी प्रभाव उत्पन्न करें। इन PEI-आधारित यौगिकों को mPEG-b-PLA से लपेटा गया ताकि उनकी बायोअनुकूलता और रक्त में स्थायित्व में सुधार हो। इस प्रणाली ने पहले की तुलना में ~90% तक उच्च दवा-लोडिंग और उत्कृष्ट कोलॉइडल स्थिरता दिखाई। इन विट्रो अध्ययनों में विभिन्न अनुपातों (1:1, 3:1, 1:3) और विभिन्न स्तन कैंसर सेल लाइनों में Pira–Sal युक्त नैनोकणों ने प्रभावशाली साइटोटॉक्सिसिटी, सहयोगी प्रभाव और CSCs को दबाने की क्षमता प्रदर्शित की। इनमें से Pira–Sal (3:1) संयोजन सर्वश्रेष्ठ परिणाम देने वाला पाया गया और इसे इन विवो परीक्षण के लिए चुना गया। Balb/c माइस में EAC ट्यूमर मॉडल पर यह प्रणाली ~95% ट्यूमर प्रतिगमन तक पहुँची। हालांकि, पशुओं की उत्तरजीविता विश्लेषण में यह सामने

आया कि अधिकांश माइस अध्ययन की समाप्ति से पहले ही मर गए, संभवतः फ्री PEI के कारण हुई विषाक्तता की वजह से। इसने एक अधिक सुरक्षित और प्रभावशाली वैकल्पिक रणनीति की आवश्यकता को जन्म दिया। तीसरे और अंतिम चरण में, एक फोलिक एसिड (FA)-संयुग्मित रेडॉक्स-संवेदनशील ब्लॉक कोपॉलीमर सिस्टम विकसित किया गया, जिसका उद्देश्य सक्रिय लक्ष्यीकरण और नियंत्रित दवा रिलीज़ प्राप्त करना था। FA को एक लक्ष्यीकरण लिगैंड के रूप में उपयोग किया गया ताकि स्तन कैंसर उपप्रकारों में अधिक व्यक्त फोलेट रिसेप्टर्स का लाभ उठाया जा सके, जिससे कोशिकीय अवशोषण और ट्यूमर-विशिष्ट संचय को बढ़ावा मिले। बहु-चरणीय संश्लेषण प्रक्रिया द्वारा तैयार इस [S-(PLA-b-PEG-CONH)]$_2$ को ^{1}H NMR और GPC के माध्यम से विशेषता प्रदान की गई। इसका Mn और Mw क्रमशः 27,726 g/mol और 38,386 g/mol पाया गया, और polydispersity index 1.384 था, जो एक समान पॉलीमर वितरण को दर्शाता है। Pira और Sal को विभिन्न अनुपातों (1:1, 3:1, 1:3) में FA-युक्त रेडॉक्स-संवेदनशील पॉलीमर से लोड किया गया। नैनोकणों ने उत्कृष्ट स्थायित्व, बेहतर दवा लोडिंग और उत्कृष्ट जैव-अनुकूलता प्रदर्शित की। इन विट्रो अध्ययनों में 2D और 3D कैंसर मॉडल में बेहतर कोशिकीय अंतर्ग्रहण देखा गया। GSH-समृद्ध ट्यूमर वातावरण में मौजूद रेडॉक्स-संवेदनशील डिसल्फाइड बॉन्ड्स ने लक्षित दवा रिलीज़ सुनिश्चित की, जबकि सामान्य शारीरिक स्थितियों में दवा की स्थिरता बनी रही। साइटोटॉक्सिसिटी और सेल प्रसार अवरोधन अध्ययनों में यह देखा गया कि यह द्वैत्य-दवा युक्त प्रणाली मुक्त दवाओं या एकल-दवा युक्त नैनोकणों की तुलना में कहीं अधिक प्रभावशाली थी। संयोजन सूचकांक विश्लेषण ने सभी अनुपातों और FA-रेसेप्टर पॉजिटिव स्तन कैंसर कोशिकाओं में लगातार सहयोगी प्रभाव दिखाया। श्रेष्ठ प्रदर्शन वाले Pira/Sal (3:1) फॉर्मुलेशन को इन विवो परीक्षण के लिए फिर से चुना गया। EAC ट्यूमर-बेयरिंग माइस में 3 सप्ताह तक बायवीकली इंजेक्शन के बाद 60 दिनों तक मॉनिटरिंग की गई। इस सिस्टम ने ट्यूमर के लगभग पूर्ण प्रतिगमन को सुनिश्चित किया और अध्ययन अवधि में कोई पुनरावृत्ति नहीं हुई। शरीर के वजन में कोई महत्वपूर्ण गिरावट नहीं देखी गई और अंगों की हिस्टोपैथोलॉजिकल जांच में कोई विषाक्तता नहीं पाई गई। इन परिणामों ने पहले के विषाक्त PEI आधारित सिस्टम की तुलना में इस प्रणाली की सुरक्षा और प्रभावशीलता

को प्रमाणित किया। निष्कर्षतः, यह कार्य स्तन कैंसर की संयोजन कीमोथेरेपी के लिए विभिन्न नैनोपार्टिकल आधारित रणनीतियों की एक समग्र तुलना प्रस्तुत करता है। FA-संयुग्मित, रेडॉक्स-संवेदनशील पॉलीमर नैनोकणों ने पिरारूबिसिन और सैलिनोमाइसिन के साथ मिलकर पूर्ववर्ती फॉर्मुलेशनों की सीमाओं — जैसे कम दवा लोडिंग, प्रणालीगत विषाक्तता और असंगत चिकित्सीय प्रतिक्रियाओं — को सफलतापूर्वक हल किया और असाधारण जैव-संगतता व ट्यूमररोधी प्रभावशीलता दिखाई। यह द्वैत्य लक्षित प्रणाली स्तन कैंसर उपचार के लिए एक शक्तिशाली और सुरक्षित उम्मीदवार के रूप में उभरती है, जिसके नैदानिक अनुवाद की प्रबल संभावनाएं हैं। भविष्य के अध्ययनों में इसे उच्च स्तरीय प्राणी मॉडल में सत्यापित करना और नैदानिक परीक्षण की दिशा में अग्रसर होना प्रस्तावित है।

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GLOSSARY OF SYMBOLS AND ABBREVIATION

g	gram
mg	Milligram
kg	Kilogram
V	Volume
W	Weight
L	Liter
M	Molar
N	Normal
v/v	Volume/Volume
w/v	Weight/volume
m/z	Mass/charge
eV	Electron volt
cm	Centimeter
mm	millimeter
dl	Deciliter
dm	Decimeter
m	Meter
%	Percentage
~	Approximately
µ	micro

±	Plus-minus sign
ºC	Degree centigrade
@	At a rate of
≤	Less than equals to
≥	Greater than equals to
λ	Lambda
µg	Microgram
µL	Microliter
µM	Micromolar
nM	Nanomolar
ng	Nanogram
P	Probability
hr	Hour
Hz	Hertz
kDa	Kilodalton
Da	Dalton
mm^3	Millimeter cube
mmol	millimolar
mol	molar
min	minutes
rpm	Rotation per minute
Rf	Retention factor
e.g.	For example

i.e.	That is
Et. al	And others
DCM	Dichloromethane
DMF	N,N Dimethyl formamide
DMAP	Dimethyl amino pyridine
Py	Pyridine
R.T.	Room temperature
$CHCl_3$	Chloroform
MeOH	Methanol
DMSO	Dimethyl sulphoxide
Mn	Number average molecular weight
Mw	Weight average molecular weight
SD	Standard deviation
PSD	Particle size distribution
PLA	Poly lactic acid
LA	Lactic acid
PEG	Polyethylene glycol
mPEG	Methoxy polyethylene glycol
TEM	Transmission electron microscopy
SEM	Scanning electron microscopy
CLSM	Confocal laser scanning microscope
RhoB	Rhodamine B
C6	Coumarin 6

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
DAPI	4',6-diamidino-2-phenylindole
DMEM	Dulbecco's modified eagle medium
RPMI	Roswell park memorial institute
EGF	Epidermal growth factor
bFGF	Basic fibroblast growth factor
DNA	Deoxy ribonucleic acid
DDS	Drug delivery system
FBS	Fetal bovine serum
EAC	Ehrlich ascites carcinoma
EDTA	Ethylene diamine tetra acetic acid
RBC	Red blood cell
WBC	White blood cell
EPR	Enhanced permeability and retention
FDA	Food and drug administration
GPC	Gel permeation chromatography
HPLC	High performance liquid chromatography
FTIR	Fourier transform infrared spectroscopy
NMR	Nuclear magnetic resonance
RALLS	Right angle laser light scattering
LALLS	Low angle laser light scattering
DLS	Dynamic light scattering

H&E	Hematoxylin and Eosin
ANOVA	Analysis of variance
MWCO	Molecular weight cut-off
CSC	Cancer stem cell
IC_{50}	Half maximal inhibitory concentration
Np	nanoparticle
IP	Intraperitoneal
IT	Intratumorally
IV	Intravenous
TNBC	Triple negative breast cancer
pH	Potential of hydrogen
MDR	Multi-drug resistance
EMT	Epithelial to mesenchymal transition
PBS	Phosphate buffered saline