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Dhaka University Nanotechnology Center (DUNC)
University of Dhaka

INCEPTION REPORT

Title of the Research Project:
Polymeric Nanocarriers for Targeted and Sustained Drug delivery in Cancer Therapy for Diabetic Patients

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Submitted by
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Project Inception Report for 2025-26

Title of the Proposed Research Project: Polymeric Nanocarriers for Targeted and Sustained Drug delivery in Cancer Therapy for Diabetic Patients
(Development of PLGA/Chitosan-Liposome Hybrid Nanoparticles for Co-delivery of Pioglitazone and Doxorubicin: A novel strategy for improved targeted therapy in Diabetes-linked Cancer)

1. **Name of the Project Supervisor/Supervisors with affiliation:**
Amina Alam Kotha, Lecturer, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka

2. **Place where the work will be performed:**
Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka.

3. **Outline of the project with background information:**
Diabetes mellitus is a global metabolic disorder often associated with multiple complications, including an increased risk of cancer. Also, Cancer therapy in diabetic patients presents unique challenges, including altered pharmacokinetics, systemic toxicity, and limited efficacy of conventional chemotherapeutics. Recent research has shown that several antidiabetic drugs, possess potential anticancer properties through mechanisms involving AMPK activation and modulation of cell proliferation pathways. However, their therapeutic potential is limited by poor bioavailability and non-specific distribution.
Pioglitazone (a Thiazolidinedione, PPAR-γ agonist) induces apoptosis and cell-cycle arrest via PPAR-γ activation. Inhibits angiogenesis and tumor cell proliferation and modulates tumor microenvironment and reduces inflammation. Pioglitazone-loaded PLGA/Chitosan nanoparticles and liposomes have been tested for improved bioavailability and targeted delivery in breast and colon cancer models (J Control Release, 2019 – Pioglitazone nanoparticles enhanced cytotoxicity in MCF-7 cells).
Doxorubicin, a widely used anthracycline anticancer drug, is highly effective against a broad spectrum of cancers; however, its clinical utility is restricted due to cardiotoxicity and resistance mediated by efflux transporters and tumor microenvironment (TME) barriers.
Nanotechnology-based drug delivery systems offer a promising approach to overcome these limitations by enhancing targeted delivery, sustained release, and improved pharmacokinetic profiles. Polymeric nanocarriers have emerged as versatile platforms for targeted drug delivery, capable of improving therapeutic index, sustaining release, and minimizing off-target effects. By engineering nanoparticles with biocompatible polymers such as PLGA or Chitosan, drug accumulation at the tumor site can be enhanced, while controlled release mechanisms reduce systemic exposure. This project aims to develop and characterize polymeric nanocarriers encapsulating selected antidiabetic and anticancer agents using biocompatible materials such as

PLGA/Chitosan and evaluate their physicochemical and biological performance.
Therefore, this project proposes the development and evaluation of hybrid nanoparticles co-loaded with Pioglitazone (PIO) and Doxorubicin (DOX) for enhanced cancer therapy. Pioglitazone, a PPAR-γ agonist, can reprogram tumor stroma, mitigate drug resistance, and reduce DOX-induced toxicity. The co-delivery system aims to synchronize pharmacokinetics, improve tumor penetration, and lower systemic toxicity. PLGA/Chitosan-liposome hybrid nanoparticles will be formulated, characterized, and evaluated in vitro and in vivo to determine synergistic efficacy and safety in breast cancer models.

4. Background & Rationale of the project:

The growing global prevalence of diabetes and cancer demands innovative therapeutic approaches that maximize efficacy while minimizing systemic side effects. Conventional anticancer therapy often fails due to poor drug bioavailability, rapid clearance, and multidrug resistance. Nanocarriers can overcome these limitations through:

• Targeted delivery to tumor microenvironments via passive (EPR effect) or active targeting mechanisms.

• Sustained and pH-sensitive release of drugs to improve intratumoral drug concentration.

• Potential co-delivery of modulators that can enhance therapeutic efficacy or overcome resistance.

Metabolic reprogramming and stromal desmoplasia contribute to chemoresistance in cancer. Pioglitazone, beyond its antidiabetic role, exhibits anticancer potential through PPAR-γ activation and stroma modulation. Co-delivery with Doxorubicin in a nanocarrier can enhance tumor penetration and minimize systemic toxicity. Hybrid PLGA/Chitosan-liposome systems offer controlled release and prolonged circulation. Recent studies show Pioglitazone nanoparticles improving Doxorubicin efficacy and reducing adverse effects This research will strengthen the nanotechnology-based pharmaceutical research capacity at the University of Dhaka and may open avenues for translational research in drug delivery and formulation development in Bangladesh.

Primary Objective:

- To formulate and optimize PLGA/Chitosan-liposome hybrid nanoparticles co-loaded with Pioglitazone and Doxorubicin.

Secondary Objectives:

- To characterize the physicochemical properties of the developed nanoparticles, including particle size, zeta potential, morphology, encapsulation efficiency, and release kinetics.
- To evaluate in vitro cytotoxicity, apoptosis, cellular uptake, and synergistic anticancer activity in breast cancer cell lines.
- To assess in vivo pharmacokinetics, biodistribution, therapeutic efficacy, and systemic toxicity in suitable animal models.

5. Scope of the Study:

This project will focus on:

- Nanoformulation development using biocompatible materials
- In vitro biological evaluation using established breast cancer cell lines
- In vivo assessment within ethical and financial constraints
- Generation of data suitable for future translational research and publications

The study is designed to be completed within **6months** under the funding framework of **DUNC (50,000 BDT).**

6. Methodology:

6.1 Study Design Overview:

This experimental study involved the formulation, optimization, characterization, and biological evaluation of PLGA–liposome hybrid nanoparticles co-loaded with pioglitazone (PIO) and doxorubicin (DOX). The work will be conducted in four sequential phases:

1. Nanoparticle formulation and optimization
2. Physicochemical characterization
3. In vitro biological evaluation
4. In vivo pharmacokinetic, efficacy, and toxicity assessment

6.2 Materials Selection and Preparation

- Pioglitazone (lipophilic) will be used as a PPAR-γ agonist and chemosensitizer.
- Doxorubicin hydrochloride (hydrophilic) will serve as the model chemotherapeutic agent.
- PLGA (50:50) will be selected for its biodegradability, controlled release properties, and FDA approval.
- Phospholipids (DSPC) and cholesterol will form the liposomal shell to enhance stability and biocompatibility.

All chemicals will be of analytical or research grade.

6.3 Formulation of PLGA/Chitosan–Liposome Hybrid Nanoparticles

6.3.1 Preparation of Pioglitazone-Loaded PLGA/Chitosan Core

- PLGA/Chitosan and pioglitazone will be dissolved in an organic solvent (dichloromethane or ethyl acetate).
- The organic phase will be emulsified into an aqueous PVA solution using probe sonication.
- Solvent evaporation will yield pioglitazone-loaded PLGA/Chitosan nanoparticles.
- Nanoparticles will be collected by centrifugation and washed to remove free drug and surfactant.

6.3.2 Liposome Coating and Doxorubicin Loading

- Lipids (DSPC, cholesterol ± DSPE-PEG2000) will be dissolved in chloroform and dried to form a thin lipid film.
- The film will be hydrated with ammonium sulfate solution.
- Pioglitazone- PLGA/Chitosan nanoparticles will be added during hydration to allow liposome coating.
- Doxorubicin will be actively loaded using an ammonium sulfate gradient method.
- Unencapsulated drug will be removed by dialysis or centrifugation.

6.3.3 Optimization Parameters

Formulation variables to be optimized:

- PLGA : lipid ratio
- Drug : polymer ratio
- Sonication time and power
- Surfactant concentration

6.4 Physicochemical Characterization

Parameter Method	Parameter Method
Particle size & PDI	Dynamic Light Scattering (DLS)
Zeta potential	Electrophoretic mobility
Morphology	TEM / SEM
Drug loading & EE%	HPLC
Physical stability	Size & EE% over 30 days
In-vitro drug release	Dialysis method at pH 7.4 and pH 5.5

Release kinetics will be analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

6.5 In Vitro Biological Evaluation

6.5.1 Cell Culture

- MCF-7 and MDA-MB-231 breast cancer cell lines will be cultured in DMEM/RPMI supplemented with FBS and antibiotics.
- Normal fibroblast cells (L929) will be used for cytotoxicity comparison.

6.5.2 Cytotoxicity Assay

- MTT assay will be conducted to determine IC_{50} values of:
  - Free DOX
  - Free PIO
  - Free DOX + PIO
  - PIO-NPs
  - DOX-NPs
  - PIO-DOX hybrid NPs

6.6 In Vivo Evaluation

6.6.1 Animal Model

- Female BALB/c nude mice will be used.
- Tumors will be induced by subcutaneous injection of breast cancer cells.

6.6.2 Pharmacokinetic and Biodistribution Study

- Blood samples collected at predetermined time points.
- DOX and PIO quantified using HPLC.
- Tissue distribution assessed in tumor, liver, kidney, heart, and spleen.

6.6.3 Antitumor Efficacy

- Tumor volume and body weight monitored regularly.
- Tumor growth inhibition compared across treatment groups.

6.6.4 Toxicity Assessment

- Serum biochemical markers (ALT, AST, BUN, creatinine)
- Histopathological examination of major organs

6.7 Data Analysis

- Results expressed as mean ± SD.
- Statistical analysis using ANOVA followed by post hoc tests.
- Significance set at $p < 0.05$

Drug Selection
(Pioglitazone + Doxorubicin)
↓
PLGA Core Preparation
(Solvent Evaporation Method)
↓
Liposome Film Formation
(Thin-Film Hydration)
↓
Hybrid Nanoparticle Assembly
(PLGA Core + Liposome Shell)
↓
Remote Loading of Doxorubicin
(Ammonium Sulfate Gradient)
↓
Physicochemical Characterization
(Size, Zeta, Morphology, EE%)
↓
In Vitro Evaluation
(Cytotoxicity, Apoptosis, Uptake, Synergy)
↓
In Vivo Studies
(PK, Biodistribution, Efficacy, Toxicity)
↓
Data Analysis & Reporting

7. Expected Outcomes:

- Development of stable PLGA–liposome hybrid nanoparticles (80–180 nm, EE > 60%)
- Enhanced intracellular accumulation of doxorubicin
- Reversal of chemoresistance through pioglitazone-mediated modulation
- Reduced systemic toxicity compared to free drug administration
- Strengthening of nanotechnology research capacity at the University of Dhaka

8. Significance of the Study:

This project integrates nanotechnology, oncology, and metabolic pharmacology to address a clinically relevant problem—chemoresistance in cancer, particularly in diabetes-associated conditions. The findings are expected to contribute to:

- Improved therapeutic strategies for resistant cancers
- Advancement of nano-drug delivery research in Bangladesh
- Future translational and collaborative research opportunities