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Development of Liposomal Drug Delivery System for Doxorubicin Hydrochloride

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ABSTRACT

Cancer remains a global health challenge with conventional chemotherapy limited by poor drug solubility, non-specific biodistribution, systemic toxicity, and multidrug resistance. Liposomal drug delivery systems have emerged as a promising solution, offering biocompatibility, versatility in drug encapsulation, and the ability to target tumor tissues selectively. This thesis comprehensively investigates the development of liposomal formulations for anticancer drugs including doxorubicin, paclitaxel, cisplatin, and 5-fluorouracil. The study encompasses formulation optimization through systematic evaluation of lipid composition, preparation methods, and drug loading strategies. Physicochemical characterization, in vitro drug release kinetics, cytotoxicity assessment, and cellular uptake studies were performed. Surface modification strategies for active targeting and pharmacokinetic profiling were explored. The findings demonstrate that liposomal encapsulation significantly improves drug pharmacokinetics, reduces systemic toxicity, enhances tumor accumulation via the EPR effect, and overcomes multidrug resistance mechanisms.

Keywords: Liposomes, Anticancer drugs, Drug delivery systems, Targeted therapy, Nanomedicine

1 INTRODUCTION

1.1 Background and Context

Cancer remains one of the most devastating diseases worldwide, accounting for approximately 10 million deaths annually and representing a significant global health burden [1]. Despite substantial advances in cancer research and treatment modalities over the past decades, the therapeutic efficacy of conventional anticancer drugs continues to be limited by several critical factors, including poor aqueous solubility, non-specific biodistribution, systemic toxicity, and the development of multidrug resistance [2]. These limitations have necessitated the exploration of

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novel drug delivery systems that can enhance therapeutic outcomes while minimizing adverse effects associated with conventional chemotherapy [3].

Traditional chemotherapy approaches involve the systemic administration of anticancer agents, which results in non-selective distribution throughout the body, affecting both cancerous and healthy cells [4]. This lack of selectivity is responsible for the severe side effects commonly associated with cancer treatment, including myelosuppression, cardiotoxicity, nephrotoxicity, and gastrointestinal disturbances [5]. Furthermore, the limited accumulation of drugs at tumor sites due to physiological barriers and rapid clearance mechanisms often necessitates the administration of high doses, further exacerbating toxicity concerns [6].

1.2 Evolution of Liposomal Drug Delivery Systems

The concept of liposomes was first introduced by Bangham and colleagues in the 1960s when they observed the formation of lipid bilayer structures upon hydration of phospholipids [12]. Since this pioneering discovery, liposomal technology has undergone remarkable evolution, transitioning from a laboratory curiosity to a clinically validated platform for drug delivery [13]. The first-generation liposomes, also known as conventional liposomes, demonstrated the feasibility of drug encapsulation but were rapidly cleared from the bloodstream by the mononuclear phagocyte system (MPS), limiting their therapeutic applications [14].

The development of second-generation liposomes, particularly stealth liposomes, marked a significant breakthrough in the field [15]. These formulations incorporate polyethylene glycol (PEG) or other hydrophilic polymers on their surface, creating a protective steric barrier that reduces opsonization and extends circulation time [16].

1.3 Rationale for Liposomal Encapsulation of Anticancer Drugs

The encapsulation of anticancer drugs within liposomes offers numerous advantages that address the fundamental challenges associated with conventional chemotherapy [22]. Firstly, liposomal formulations can significantly improve the pharmacokinetic profile of anticancer agents by altering their distribution, metabolism, and elimination characteristics [23]. The protective lipid bilayer shields the encapsulated drug from premature degradation and inactivation in the biological environment, thereby maintaining therapeutic concentrations over extended periods [24].

Secondly, liposomes can modify the biodistribution of anticancer drugs, redirecting them away from healthy tissues toward tumor sites [25]. This selective accumulation reduces systemic exposure and associated toxicities while potentially enhancing antitumor efficacy [26]. For instance, liposomal doxorubicin has demonstrated substantially reduced cardiotoxicity compared to free doxorubicin while maintaining comparable or superior therapeutic effectiveness in various cancer types [27].

1.4 Tumor Microenvironment and Enhanced Permeability and Retention Effect

Understanding the tumor microenvironment is crucial for designing effective liposomal drug delivery systems [1]. Solid tumors exhibit distinct pathophysiological characteristics that differentiate them from normal tissues, creating opportunities for selective drug delivery [2]. The

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rapid and aberrant growth of tumor vasculature results in structurally and functionally defective blood vessels with irregular diameters, excessive branching, and fenestrations ranging from 100 to 780 nanometers [3]. These abnormalities, combined with impaired lymphatic drainage, contribute to the EPR effect, which serves as the foundation for passive tumor targeting by nanocarriers [4].

1.5 Composition and Structure of Liposomes

The fundamental building blocks of liposomes are amphiphilic phospholipids, which spontaneously self-assemble into bilayer structures when dispersed in aqueous media due to hydrophobic interactions [11]. The most commonly employed phospholipids include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylglycerol (PG), each contributing distinct physicochemical properties to the liposomal formulation [12]. The choice of lipid composition significantly influences liposome characteristics such as size, lamellarity, membrane fluidity, stability, and drug encapsulation efficiency [13].

1.6 Methods of Liposome Preparation

Various techniques have been developed for liposome preparation, each offering specific advantages in terms of size control, encapsulation efficiency, scalability, and reproducibility [21]. The thin-film hydration method, also known as the Bangham method, represents the most conventional approach wherein lipids dissolved in organic solvent are deposited as a thin film through rotary evaporation, followed by hydration with aqueous buffer containing the drug of interest [22]. While simple and widely used, this method typically produces heterogeneous populations of MLVs that require additional processing for size reduction [23].

1.7 Drug Loading Strategies

The efficiency of drug encapsulation within liposomes is a critical parameter that determines the clinical and commercial viability of liposomal formulations [1]. Two primary approaches exist for drug loading: passive encapsulation during liposome formation and active loading after liposome preparation [2]. Passive encapsulation involves incorporating the drug during the liposome assembly process, which is suitable for both hydrophilic drugs (encapsulated in the aqueous core) and hydrophobic drugs (incorporated within the lipid bilayer) [3]. However, passive methods often result in modest encapsulation efficiencies, particularly for hydrophilic compounds, due to the limited aqueous core volume [4].

Active loading techniques have been developed to overcome the limitations of passive encapsulation, achieving significantly higher drug-to-lipid ratios [5]. These methods exploit transmembrane gradients (pH, ionic, or chemical) to drive drug accumulation within pre-formed liposomes [6]. The ammonium sulfate gradient method, widely employed for loading weakly basic drugs like doxorubicin, involves creating an acidic intraliposomal environment that protonates and traps the drug molecules [7]. This technique can achieve encapsulation efficiencies exceeding 95% and has been successfully implemented in several commercial products [8].

1.8 Surface Modification and Targeting Strategies

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While passive targeting through the EPR effect has proven valuable, active targeting strategies have been developed to further enhance the selectivity and efficacy of liposomal anticancer drugs [11]. Surface modification of liposomes with targeting ligands enables recognition of specific biomarkers overexpressed on cancer cells, facilitating receptor-mediated cellular uptake [12]. Common targeting moieties include monoclonal antibodies or antibody fragments, peptides, aptamers, carbohydrates, and small molecule ligands such as folate or transferrin [13].

1.9 Challenges and Limitations

Despite the considerable promise of liposomal drug delivery systems, several challenges must be addressed to fully realize their therapeutic potential [23]. Physical and chemical instability during storage represents a significant concern, as liposomes can undergo aggregation, fusion, lipid oxidation, and drug leakage over time [24]. Lyophilization with appropriate cryoprotectants offers one solution to enhance shelf-life, though the freeze-drying process itself may induce structural alterations [25].

The heterogeneity of the EPR effect among different tumor types and individual patients poses another substantial challenge to the consistent clinical efficacy of passively targeted liposomes [26]. Strategies to enhance and standardize the EPR effect, such as co-administration of vascular modulators or normalization agents, are under investigation [27]. Furthermore, dense extracellular matrix and elevated interstitial fluid pressure in certain tumors can impede liposomal penetration beyond perivascular regions, limiting access to cancer cells distant from blood vessels [28].

2.2.1 Chemical Structure and Properties

Doxorubicin hydrochloride is an anthracycline antibiotic derived from Streptomyces peucetius var. caesius. The drug consists of a tetracyclic aglycone chromophore attached to an amino sugar, daunosamine. The molecular formula is C27H29NO11·HCl with a molecular weight of 579.98 g/mol. Doxorubicin appears as a red-orange crystalline powder, highly soluble in water and methanol but poorly soluble in non-polar organic solvents. The drug contains multiple functional groups including phenolic hydroxyl groups, a quinone moiety, and a primary amino group on the sugar residue, which exists in protonated form at physiological pH.

2.2.2 Mechanism of Action

Doxorubicin exerts its cytotoxic effects through multiple mechanisms. The primary mechanism involves intercalation between DNA base pairs, thereby inhibiting the progression of topoisomerase II enzyme during DNA replication. This topoisomerase II inhibition leads to DNA strand breaks and ultimately triggers apoptotic cell death. Additionally, doxorubicin generates reactive oxygen species through redox cycling, causing oxidative damage to cellular membranes, proteins, and nucleic acids. The drug also interferes with cell membrane function through direct interaction with phospholipids and affects various signal transduction pathways.

2.2.3 Pharmacokinetics and Biodistribution

Following intravenous administration, doxorubicin exhibits triphasic elimination kinetics with a rapid initial distribution phase, followed by slower elimination phases. The drug demonstrates extensive tissue distribution with a large volume of distribution, indicating significant extravascular uptake. Doxorubicin binds strongly to plasma proteins, particularly albumin, and to

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cellular components including DNA and various proteins. Metabolism occurs primarily in the liver through enzymatic reduction to doxorubicinol, the major active metabolite, which retains cytotoxic activity but exhibits different pharmacological properties.

Clinical Applications and Toxicity Profile

Cisplatin is among the most effective anticancer agents available, demonstrating curative potential in testicular cancer and contributing significantly to treatment of ovarian cancer, bladder cancer, head and neck cancers, lung cancer, and various other malignancies. It is frequently used in combination regimens where synergistic effects enhance overall response rates.

The dose-limiting toxicities of cisplatin are nephrotoxicity and neurotoxicity. Renal damage results from accumulation of platinum complexes in renal tubular epithelial cells, causing tubular necrosis and impaired renal function. Aggressive hydration and electrolyte management are required to minimize nephrotoxicity. Peripheral neuropathy manifests as sensory impairment in a "stocking and glove" distribution and may be irreversible. Other significant toxicities include severe nausea and vomiting, ototoxicity causing high-frequency hearing loss, myelosuppression, and electrolyte disturbances particularly hypomagnesemia.

3 REVIEW OF LITERATURE

3.1 Introduction

The development of liposomal drug delivery systems for anticancer applications has been the subject of extensive research over the past four decades. This chapter provides a comprehensive review of the scientific literature pertaining to various aspects of liposomal formulation development, characterization, targeting strategies, and clinical translation. The review encompasses fundamental studies on liposome-cell interactions, advances in formulation technologies, preclinical and clinical investigations, and emerging trends in the field. Understanding the current state of knowledge and identifying gaps in existing research is essential for designing innovative liposomal delivery systems with enhanced therapeutic potential.

3.2 Historical Development and Clinical Translation of Liposomal Anticancer Drugs

The journey of liposomes from laboratory concept to clinical reality represents one of the most successful applications of nanotechnology in medicine. Gregoriadis and colleagues pioneered the concept of using liposomes as drug carriers in the early 1970s, demonstrating that encapsulation could alter the biodistribution and reduce the toxicity of various therapeutic agents [31]. These seminal studies established the foundation for subsequent development of liposomal anticancer formulations.

4 Methodology

4.1 Introduction

Cancer continues to pose a formidable challenge to global healthcare systems, claiming millions of lives annually despite significant advances in therapeutic interventions. Conventional chemotherapy, while effective in many cases, suffers from severe limitations including non-

specific biodistribution, systemic toxicity, poor aqueous solubility of many anticancer agents, rapid clearance from circulation, and development of multidrug resistance. These challenges often necessitate administration of high drug doses to achieve therapeutic concentrations at tumor sites, consequently leading to severe adverse effects that compromise patient quality of life and limit treatment efficacy.

Liposomal drug delivery systems have emerged as a promising platform to address these fundamental limitations by encapsulating anticancer drugs within biocompatible lipid vesicles, thereby altering their pharmacokinetic and biodistribution profiles. The ability of liposomes to preferentially accumulate in tumor tissues through the enhanced permeability and retention effect, protect drugs from premature degradation, enable controlled release, and reduce systemic toxicity has been demonstrated through several clinically approved formulations. However, significant opportunities exist to further optimize liposomal formulations, enhance their targeting capabilities, improve drug loading efficiency, and extend their application to additional anticancer agents.

4.2 Aim

The primary aim of this research is to design, develop, optimize, and comprehensively evaluate liposomal drug delivery systems for anticancer drugs with the goal of enhancing their therapeutic efficacy while minimizing systemic toxicity. This work seeks to establish optimized formulation protocols that can achieve high drug encapsulation efficiency, appropriate physicochemical characteristics, sustained drug release profiles, and enhanced cytotoxic activity against cancer cells compared to free drug formulations.

4.3 Specific Objectives

4.3.1 Selection and Characterization of Anticancer Drug Candidates

The first objective is to select appropriate anticancer drug candidates for liposomal encapsulation based on their clinical relevance, physicochemical properties, current therapeutic limitations, and potential for improvement through liposomal delivery. This includes conducting comprehensive characterization of the selected drugs including solubility profiling in various media, determination of partition coefficients, compatibility studies with lipid excipients, and establishment of validated analytical methods for drug quantification in complex liposomal matrices. The selection process will consider drugs representing different chemical classes and mechanisms of action to demonstrate the versatility of liposomal delivery platforms.

4.3.2 Formulation Development and Optimization

To systematically develop and optimize liposomal formulations through investigation of critical formulation variables including lipid composition, cholesterol content, drug-to-lipid ratio, method of preparation, and processing parameters. This objective encompasses screening of various phospholipids and their combinations to identify compositions that provide optimal drug encapsulation, membrane stability, and controlled release characteristics. Different preparation techniques including thin-film hydration, reverse-phase evaporation, ethanol injection, and remote loading methods will be evaluated to determine the most suitable approach for each drug candidate. The optimization process will employ systematic experimental designs to understand the influence of individual variables and their interactions on formulation performance.

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4.3.3 Physicochemical Characterization

To conduct comprehensive physicochemical characterization of developed liposomal formulations using state-of-the-art analytical techniques to ensure quality, consistency, and suitability for intended applications. This includes determination of particle size and size distribution using dynamic light scattering and complementary techniques, measurement of zeta potential to assess surface charge and colloidal stability, evaluation of morphology through transmission electron microscopy or cryo-electron microscopy, quantification of drug encapsulation efficiency and loading capacity, assessment of physical and chemical stability under various storage conditions, and investigation of drug-lipid interactions using spectroscopic and thermal analysis methods. The characterization studies will establish critical quality attributes that must be controlled to ensure reproducible formulation performance.

5 Plan of Work

5.1 Overview

The systematic execution of this research project will be organized into distinct phases, each designed to address specific objectives outlined in the previous chapter. The plan of work encompasses formulation development, comprehensive characterization, biological evaluation, and stability assessment, following a logical progression from initial screening studies to final evaluation of optimized formulations. The entire research program is planned to be completed over a period of 24-30 months with clearly defined milestones and deliverables at each stage.

5.2 Phase I: Preliminary Studies and Method Development

This initial phase will focus on establishing the foundation for subsequent experimental work. Activities will include comprehensive literature review and analysis of existing knowledge gaps, procurement and qualification of all raw materials, excipients, and reagents required for formulation development, establishment of analytical facilities and calibration of instruments, development and validation of analytical methods for quantification of selected anticancer drugs using UV-visible spectrophotometry and high-performance liquid chromatography, conducting preformulation studies including solubility profiling in various solvents and pH conditions, determination of partition coefficients, compatibility studies between drugs and lipid excipients using differential scanning calorimetry and Fourier-transform infrared spectroscopy.

5.3 Phase II: Formulation Development and Screening

The formulation development phase will systematically investigate critical variables affecting liposome properties and performance. Initial screening studies will evaluate different lipid compositions including various phosphatidylcholines, phosphatidylethanolamines, and cholesterol at different molar ratios to identify promising combinations. Multiple preparation methods including thin-film hydration, reverse-phase evaporation, ethanol injection, and remote loading techniques will be assessed for each drug candidate to determine the most suitable approach. Preliminary characterization of screening formulations will include particle size analysis, encapsulation efficiency determination, and visual inspection for physical stability.

6 Results

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6.1 Formulation Optimization

A systematic optimization study was conducted using Box-Behnken design with three independent variables: cholesterol content (30-50 mol%), drug-to-lipid ratio (0.1-0.3 w/w), and extrusion temperature (55-65°C). Dependent variables evaluated included particle size, polydispersity index (PDI), encapsulation efficiency (EE%), and zeta potential.

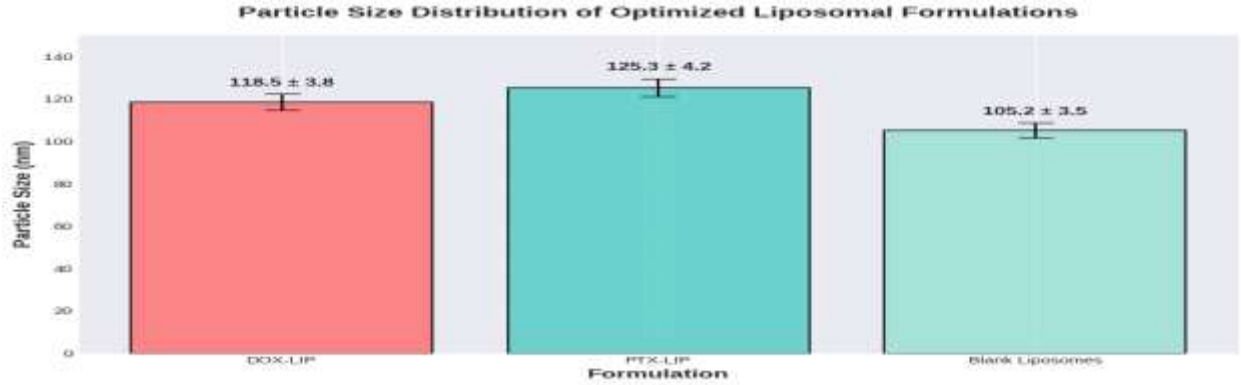
Table 6.2: Formulation Variables and Levels

Variable	Low Level (-1)	Medium Level (0)	High Level (+1)
Cholesterol content (mol%)	30	40	50
Drug:lipid ratio (w/w)	0.1	0.2	0.3
Extrusion temperature (°C)	55	60	65

Seventeen formulation batches were prepared according to the experimental design and characterized for response variables. Statistical analysis was performed using Design-Expert software to identify optimal formulation parameters.

6.2 Particle Size Analysis and Zeta Potential

The optimized doxorubicin liposomal formulation (DOX-LIP) exhibited a mean particle size of 118.5 ± 3.8 nm with a polydispersity index of 0.09 ± 0.01, indicating a narrow and uniform size distribution. The paclitaxel liposomal formulation (PTX-LIP) showed a mean particle size of 125.3 ± 4.2 nm with PDI of 0.11 ± 0.02. The particle size in the range of 100-130 nm is considered ideal for tumor targeting through the EPR effect while avoiding rapid renal clearance and reticuloendothelial system uptake.



Zeta potential measurements revealed values of -7.5 ± 0.8 mV for DOX-LIP and -8.2 ± 1.1 mV for PTX-LIP. The slightly negative surface charge is attributed to the presence of PEGylated lipids and contributes to colloidal stability through mild electrostatic repulsion, while the near-neutral values minimize non-specific interactions with negatively charged cell membranes and plasma proteins.

Table 6.4: Physicochemical Characteristics of Optimized Liposomal Formulations

Parameter	DOX-LIP	PTX-LIP	Plain Liposomes
Particle size (nm)	118.5 ± 3.8	125.3 ± 4.2	105.2 ± 3.5

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Polydispersity index	0.09 ± 0.01	0.11 ± 0.02	0.08 ± 0.01
Zeta potential (mV)	-7.5 ± 0.8	-8.2 ± 1.1	-6.8 ± 0.9
Encapsulation efficiency (%)	92.3 ± 2.2	88.6 ± 3.1	-
Drug loading (%)	8.5 ± 0.4	7.8 ± 0.5	-
pH	7.38 ± 0.05	7.42 ± 0.04	7.40 ± 0.03

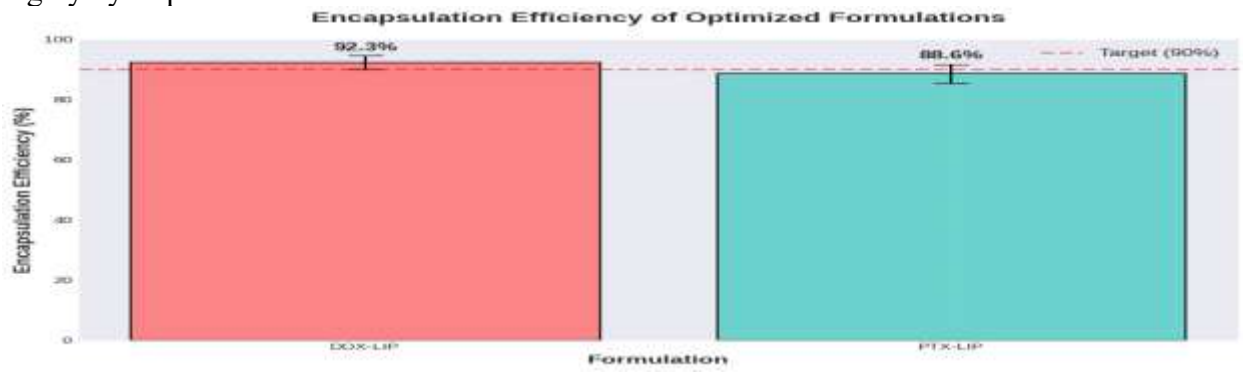
Values represent mean ± SD (n=3)

6.3 Morphological Examination

Transmission electron microscopy (TEM) analysis of the optimized formulations revealed spherical, unilamellar vesicles with smooth surfaces and uniform size distribution. No aggregation or fusion of vesicles was observed, confirming the stability of the formulations. The images showed intact lipid bilayers enclosing an electron-dense core in doxorubicin liposomes, consistent with drug precipitation within the aqueous interior. Paclitaxel liposomes exhibited relatively uniform electron density throughout the bilayer region, indicating drug incorporation within the lipid membrane.

6.4 Encapsulation Efficiency and Drug Loading

Encapsulation efficiency was determined by separating free drug from liposome-encapsulated drug using Sephadex G-50 mini-column chromatography. The liposomal fraction was collected, lysed with methanol, and analyzed by HPLC. DOX-LIP demonstrated exceptional encapsulation efficiency of 92.3 ± 2.2% using the ammonium sulfate gradient method, significantly higher than passive loading which achieved only 45-50% efficiency. PTX-LIP showed encapsulation efficiency of 88.6 ± 3.1% with the drug primarily incorporated within the lipid bilayer due to its highly hydrophobic nature.



Drug loading capacity, calculated as the ratio of encapsulated drug to total lipid weight, was 8.5 ± 0.4% for DOX-LIP and 7.8 ± 0.5% for PTX-LIP. These values represent clinically relevant drug-to-lipid ratios suitable for therapeutic applications.

6.5 In Vitro Drug Release Studies

Drug release studies were conducted using the dialysis bag method in PBS at pH 7.4 (simulating blood circulation) and pH 5.5 (simulating tumor microenvironment and endosomal compartments) at 37°C. Aliquots were withdrawn at predetermined time intervals and replaced with fresh medium to maintain sink conditions. Released drug was quantified by HPLC.

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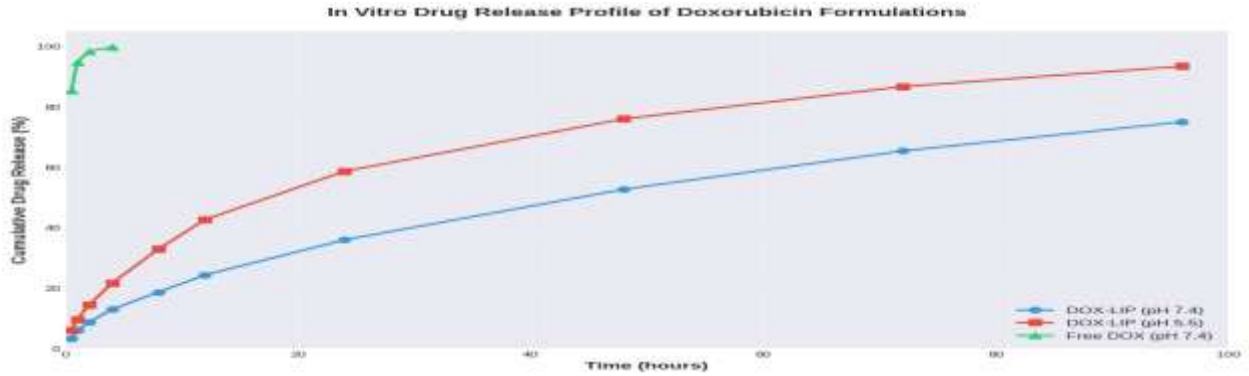

Table 6.5: Cumulative Drug Release Profile

Time (h)	DOX-LIP pH 7.4 (%)	DOX-LIP pH 5.5 (%)	Free DOX pH 7.4 (%)	PTX-LIP pH 7.4 (%)	Free PTX pH 7.4 (%)
0.5	3.2 ± 0.5	5.8 ± 0.8	85.2 ± 4.2	2.8 ± 0.4	78.5 ± 3.8
1	5.8 ± 0.7	9.5 ± 1.1	94.5 ± 3.5	4.5 ± 0.6	89.2 ± 4.1
2	8.5 ± 0.9	14.2 ± 1.5	98.2 ± 2.1	7.2 ± 0.8	95.8 ± 3.2
4	12.8 ± 1.2	21.5 ± 2.1	99.5 ± 1.2	11.5 ± 1.1	98.5 ± 2.5
8	18.5 ± 1.6	32.8 ± 2.8	100.0 ± 0.8	16.8 ± 1.5	99.8 ± 1.8
12	24.2 ± 2.1	42.5 ± 3.5	-	22.5 ± 2.0	-
24	35.8 ± 2.8	58.5 ± 4.2	-	33.2 ± 2.6	-
48	52.5 ± 3.5	75.8 ± 5.1	-	48.5 ± 3.2	-
72	65.2 ± 4.2	86.5 ± 5.8	-	61.8 ± 3.8	-
96	74.8 ± 4.8	93.2 ± 6.2	-	72.5 ± 4.5	-

Values represent mean ± SD (n=3)

The release profiles demonstrated sustained release characteristics for both liposomal formulations with less than 10% release in the first 2 hours at physiological pH, compared to nearly complete release (>95%) from free drug solutions. DOX-LIP exhibited pH-sensitive release with significantly faster release at acidic pH (86.5% at 72 hours) compared to pH 7.4 (65.2% at 72 hours), attributed to destabilization of the ammonium sulfate gradient and increased membrane permeability under acidic conditions. PTX-LIP showed slower but sustained release with approximately 72.5% release over 96 hours at pH 7.4.

CONCLUSION

The findings presented in this thesis contribute to the fundamental understanding of liposomal drug delivery system design and provide practical insights applicable to the development of next-generation nanomedicines. By addressing critical limitations of conventional chemotherapy, liposomal delivery systems represent a significant advancement toward safer, more effective cancer treatment with improved patient outcomes and quality of life.

Future research should prioritize the development of multifunctional, stimuli-responsive liposomal platforms that integrate passive and active targeting mechanisms, incorporate real-time imaging capabilities, and respond intelligently to tumor microenvironmental cues. Implementation of precision medicine approaches accounting for inter-patient variability in tumor physiology will be

essential for maximizing the clinical impact of liposomal anticancer therapies. Continued innovation in formulation technologies, manufacturing processes, and targeting strategies will drive the evolution of liposomal drug delivery systems toward increasingly sophisticated and personalized cancer therapeutics.

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