Hybrid Silica Nanocarriers with Lipid and PLGA Coatings for Dual Drug Loading and Enzyme-Responsive Chemotherapeutic Delivery

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"The knowledge of anything, since the things have causes,
is not acquired or complete unless it is known by its causes."

— Ibn Sina (Avicenna)

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Abstract

The therapeutic index of anticancer drugs is generally limited by their poor solubility, instability in biological fluids, and uncontrolled release, which calls for advanced drug administration approaches enabling an efficient uptake and reducing systemic toxicity. Nanocarriers such as mesoporous silica nanoparticles ($mSiO_2$ NPs) and liposomes offer potential solutions towards targeted drug delivery, but each has inherent shortcomings. While mesoporous silica provides a stable inorganic scaffold with high surface area and tunable porosity, its hydrophilic surface results in weak retention of hydrophilic drugs and poor loading of hydrophobic ones. Liposomes, in contrast, can efficiently encapsulate hydrophobic agents but are prone to premature drug leakage and limited stability under physiological conditions. To overcome these challenges, this thesis presents a series of core-shell hybrid nanocarriers that combine the structural stability of $[\text{-Si-O-Si-}]_n$ framework with the biocompatibility of lipid bilayers or polymeric shells.

In the first part of the thesis, to promote encapsulation of poorly water-soluble drugs, the surface of silica nanocarriers was modified with a hydrophobic linker, followed by coating with a lipid bilayer acting as a gatekeeper. This design prevented premature drug-leaching at neutral pH and enabled pH-responsive release in acidic, tumor-like environments. In an acidic environment, protonation destabilizes the lipid bilayer and weakens linker–drug interactions, thereby enhancing membrane permeability and facilitating controlled drug diffusion. The role of NP morphology (spherical, ellipsoidal, and cube-shaped) was studied, demonstrating how surface curvature and pore accessibility influence drug encapsulation, release profile, and overall biocompatibility of nanocarriers.

For an elaborate understanding of the effect of surface chemistry, nanocarriers were modified by grafting small-molecule linkers (3-aminopropyl)trimethoxysilane and cationic polymers such as polyethylenimine (PEI). In addition, mannose (a monosaccharide sugar molecule) was conjugated to the surface to suppress the inherent toxic nature of PEI and to enable receptor-mediated uptake, demonstrating how monosaccharide conjugation can balance stability and biological compatibility.

Building on these findings, a dual-drug delivery approach was explored, since simultaneous delivery of two drugs is known to provide superior tumor control compared with single-drug carriers or free drug cocktails. To address the challenges of co-loading, two hybrid systems were developed by combining amphiphilic polymers, such as poly(lactic-co-glycolic acid) (PLGA),

with hydrophilic $mSiO_2$ and lipid bilayer with an aqueous core. In liposomes, tamoxifen (a hydrophobic anticancer drug) was incorporated into the lipid bilayer while doxorubicin (DOX, a hydrophilic chemotherapeutic agent) was actively loaded into the aqueous core, resulting in a biphasic release profile. In PLGA-coated silica nanocarriers, TAM was incorporated within the PLGA shell while DOX was confined to the $mSiO_2$ core, producing complementary and pH-sensitive release kinetics. Without these protective layers (i.e., in bare silica), complete drug release occurred within 6 hours, whereas both PLGA coating and liposomal encapsulation prolonged the release, enabling controlled and sustained delivery over a period of three weeks, required for enhanced cancer therapy. In the case of liposomes, the release was characterized by an initial abrupt burst followed by a sustained drug release as acidic conditions protonated the lipid head groups and disrupted bilayer packing, thereby enhancing membrane permeability. For PLGA-coated carriers, the acidic microenvironment accelerated the hydrolytic degradation of ester linkages in the polymer backbone, which in turn facilitated gradual drug diffusion from the polymer matrix resulting in controlled drug release. This hybrid design enabled the efficient encapsulation of both hydrophobic and hydrophilic drugs in a single compartmentalized nanocarrier. The distinct release profiles from hydrophobic and hydrophilic shells generated complementary kinetics that were found to enhance combinatorial therapeutic outcomes.

Despite these modifications, a common limitation observed throughout the studies was partial release of drugs under normal physiological pH. To address this, an enzyme-responsive strategy was developed by covalently linking doxorubicin (a chemotherapeutic agent) to $mSiO_2$ NPs through a cathepsin B-cleavable Val–Cit–PAB–PNP linker. This approach provides control over drug release by restricting it specifically under enzymatic activation in the tumor microenvironment, thereby reducing nonspecific, premature leakage and improving tumor selectivity. Although coupling efficiency was modest, the results demonstrate a promising route toward protease-activated nanocarriers and highlight enzyme-responsive chemistry as a key step toward clinically translatable precision drug delivery.

Kurzzausammenfassung

Die therapeutische Breite von Krebsmedikamenten ist im Allgemeinen durch ihre geringe Löslichkeit, Instabilität in biologischen Flüssigkeiten und unkontrollierte Freisetzung begrenzt. Dies erfordert fortschrittliche Ansätze der Arzneimittelverabreichung, die eine effiziente Aufnahme ermöglichen und die systemische Toxizität verringern. Nanoträger wie mesoporöse Silica-Nanopartikel ($mSiO_2$-NPs) und Liposomen bieten potenzielle Lösungen für den gezielten Wirkstofftransport, weisen jedoch jeweils inhärente Nachteile auf. Während mesoporöses Silica ein stabiles, anorganisches Gerüst mit hoher Oberfläche und einstellbarer Porosität bereitstellt, führt seine hydrophile Oberfläche zu einer geringen Retention hydrophiler Wirkstoffe und einer schwachen Beladung hydrophober Substanzen. Liposomen hingegen können hydrophobe Wirkstoffe effizient verkapseln, sind jedoch anfällig für vorzeitige Leckage und eingeschränkte Stabilität unter physiologischen Bedingungen. Um diese Herausforderungen zu überwinden, präsentiert diese Dissertation eine Reihe von Kern–Schale-Hybridnanoträgern, die die strukturelle Stabilität des $[\text{-Si-O-Si-}]_n$-Gerüstes mit der Biokompatibilität von Lipid-Doppelschichten oder polymeren Hüllen kombinieren.

Im ersten Teil wurde die Oberfläche von Silica-Nanoträgern mit einem hydrophoben Linker modifiziert, um die Verkapselung schlecht wasserlöslicher Arzneistoffe zu fördern. Anschließend erfolgte die Beschichtung mit einer Lipid-Doppelschicht, die als „Torwächter“ fungierte. Dieses Design verhinderte ein vorzeitiges Austreten des Wirkstoffs bei neutralem pH-Wert und ermöglichte eine pH-responsive Freisetzung in sauren, tumorähnlichen Umgebungen, in denen die Protonierung die Lipid-Doppelschicht destabilisiert und die Linker–Wirkstoff-Interaktionen schwächt, wodurch die Membranpermeabilität erhöht und eine kontrollierte Diffusion erleichtert wird. Die Rolle der NP-Morphologie (sphärisch, ellipsoid und würfelförmig) wurde untersucht und zeigte, wie Oberflächenkrümmung und Porenzugänglichkeit die Wirkstoffverkapselung, das Freisetzungsprofil und die Biokompatibilität der Nanoträger beeinflussen.

Zum vertieften Verständnis des Einflusses der Oberflächenchemie wurden Nanoträger durch Anbindung von Kleinmolekül-Linkern wie (3-Aminopropyl)trimethoxysilan sowie kationischen Polymeren wie Polyethylenimin (PEI) modifiziert. Zusätzlich wurde Mannose (ein Monosaccharid) an die Oberfläche konjugiert, um die inhärente Toxizität von PEI zu unterdrücken und eine rezeptorvermittelte Aufnahme zu ermöglichen. Dies demonstrierte, wie die Konjugation von Monosacchariden Stabilität und biologische Verträglichkeit in Einklang brin-

gen kann.

Aufbauend auf diesen Erkenntnissen wurde ein Ansatz zur dualen Arzneimittelabgabe untersucht, da die gleichzeitige Verabreichung zweier Wirkstoffe eine bessere Tumorkontrolle ermöglicht als Einzelwirkstoffträger oder freie Wirkstoffcocktails. Um die Herausforderungen der Ko-Beladung zu bewältigen, wurden zwei Hybridsysteme entwickelt: Kombination amphiphiler Polymere wie Poly(lactid-co-glycolid) (PLGA) mit hydrophilem $mSiO_2$ sowie Lipid-Doppelschichten mit wässrigem Kern. In Liposomen wurde Tamoxifen (ein hydrophober Krebswirkstoff) in die Lipid-Doppelschicht eingebettet, während Doxorubicin (DOX, ein hydrophiler Chemotherapeutikum) aktiv in den wässrigen Kern geladen wurde, was zu einem biphasischen Freisetzungsprofil führte. In PLGA-beschichteten Silica-Nanoträgern war TAM in der PLGA-Schale verteilt, während DOX im $mSiO_2$-Kern zurückgehalten wurde, was komplementäre und pH-sensitive Freisetzungskinetiken erzeugte. Ohne diese Schutzschichten (d.h. in nacktem Silica) erfolgte die vollständige Wirkstofffreisetzung innerhalb von 6 Stunden, wohingegen sowohl PLGA-Beschichtung als auch Liposomenverkapselung die Freisetzung verlängerten und eine kontrollierte, nachhaltige Abgabe über drei Wochen ermöglichten. Bei Liposomen war die Freisetzung durch einen anfänglichen abrupten Burst gekennzeichnet, gefolgt von einer kontinuierlichen Abgabe, da saure Bedingungen die Lipid-Kopfgruppen protonierten und die Packung der Doppelschicht störten, wodurch die Membranpermeabilität erhöht wurde. Bei PLGA-beschichteten Trägern beschleunigte das saure Milieu den hydrolytischen Abbau der Esterbindungen im Polymergerüst, was wiederum eine allmähliche Wirkstoffdiffusion aus der Polymermatrix erleichterte. Dieses Hybriddesign ermöglichte die effiziente Verkapselung sowohl hydrophober als auch hydrophiler Arzneistoffe in einem einzigen, kompartmentalisierten Nanoträger. Die unterschiedlichen Freisetzungsprofile aus hydrophoben und hydrophilen Hüllen erzeugten komplementäre Kinetiken, die zu verbesserten kombinatorischen therapeutischen Ergebnissen führten.

Trotz dieser Modifikationen zeigte sich in allen Studien eine teilweise Wirkstofffreisetzung unter physiologischem pH. Um dies zu adressieren, wurde eine enzym-responsive Strategie entwickelt, bei der Doxorubicin (ein Chemotherapeutikum) kovalent an $mSiO_2$-NPs über einen Cathepsin-B-spaltbaren Val–Cit–PAB–PNP-Linker gekoppelt wurde. Dieser Ansatz gewährleistete eine kontrollierte Freisetzung ausschließlich unter enzymatischer Aktivierung im Tumormikromilieu, reduzierte unspezifische, vorzeitige Leckage und verbesserte die Tumorselektivität. Obwohl die Kopplungseffizienz moderat war, zeigen die Ergebnisse einen vielver-

sprechenden Weg zu protease-aktivierten Nanoträgern auf und unterstreichen die Bedeutung enzym-responsiver Chemie als entscheidenden Schritt hin zur klinisch übertragbaren, präzisen Arzneimittelverabreichung.

Diese Arbeit etabliert einen umfassenden Rahmen für das rationale Design von Lipid–Silica- und Polymer–Silica-Hybridnanoträgern. Die Ergebnisse liefern grundlegende Erkenntnisse und praktische Ansätze für die Entwicklung von Nanoträgern der nächsten Generation mit verbesserter Stabilität, Selektivität und therapeutischem Potenzial in der Krebstherapie.