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**SYNTHESIS AND SURFACE
MODIFICATION OF LIPOSOME HYBRID
MESOPOROUS SILICA NANOPARTICLES
FOR ANTI-CANCER DRUG
DOXORUBICIN DELIVERY**

DOCTORAL DISSERTATION IN MATERIALS SCIENCE

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INTRODUCTION

1. Rationale for the research: Cancer remains a prevalent disease with high mortality rates, profoundly impacting the lives, economic stability, and well-being of tens of millions of patients worldwide. Although nanomedicine platforms offer distinct advantages over traditional chemotherapy, they still face inherent limitations. The development of hybrid systems, integrating prototypical nanomaterials such as mesoporous silica nanoparticles (MSN) and liposomes (LP), has been demonstrated to significantly mitigate these drawbacks while synergistically enhancing the merits of each component, thereby improving drug delivery performance and therapeutic efficacy.

2. Objectives: This study aims to develop a multifunctional hybrid nanoplatform based on mesoporous silica nanoparticle-liposome (MSN-LP) structures, surface-functionalized with folate-conjugated biocompatible polymers, to enhance colloidal stability in physiological environments, achieve stimuli-responsive drug release, and improve anti-tumor efficacy.

3. Scientific and practical significance: The study contributes novel nanocarriers (MLBF, MLGPF, and MLCPF) characterized by superior drug retention, controlled release profiles, and enhanced cellular internalization compared to pristine MSN. These findings provide a promising foundation for the development of clinical-grade drug delivery systems for advanced cancer therapy.

4. Dissertation structure: The dissertation consists of 137 pages, organized as follows: Introduction; Chapter 1: Literature

Review; Chapter 2: Methodology; Chapter 3: Results and Discussion: 3.1. Synthesis of MSN-LP; 3.2. Synthesis of Brij-FA Coated MSN-LP; 3.3. Synthesis of Gelatin-PEG-FA Coated MSN-LP; 3.4. Synthesis of Chitosan-PEG-FA Coated MSN-LP; 3.5. Discussion; Conclusions. The work includes 3 tables, 65 figures, and 179 references.

CHAPTER 1. LITERATURE REVIEW

In the last decade, the rapid advancement of nanotechnology has pioneered a new generation of drug delivery systems with superior physicochemical properties, showing immense promise for cancer therapy. Among these, mesoporous silica nanoparticles (MSNs) and liposomes (LPs) are prominent materials that have reached clinical trials. MSNs offer high physicochemical stability, high surface area, and large pore volumes, enabling versatile drug loading and tunable morphology for optimized biodistribution. Conversely, LPs possess cell membrane-like structures, exceptional biocompatibility, and the ability to encapsulate hydrophobic drugs within their lipid bilayer while enhancing cellular interactions.

However, individual systems face inherent limitations: MSNs with open-pore structures may exhibit premature drug leakage, surface groups can cause hemolysis, and they often have short circulation half-lives. LPs, being purely organic, tend to be unstable under physiological conditions. Consequently, the MSN-LP (ML) hybrid material emerged as a strategy to integrate the strengths and mitigate the weaknesses of both components. The LP shell coating the MSN core reduces drug leakage, ensures

sustained release, enhances biocompatibility, and expands surface functionalization possibilities.

Building upon this hybrid platform, coatings of biocompatible polymers such as polyethylene glycol (PEG) or PEG-based copolymers (e.g., chitosan-PEG, gelatin-PEG) minimize opsonization and phagocytosis, improve colloidal stability, reduce aggregation, and prolong systemic circulation. Furthermore, the conjugation of folic acid (FA) as a targeting agent enables the recognition of folate receptors (FR), which are frequently overexpressed in various cancer cell lines, thereby enhancing selective cytotoxicity toward tumors. Additionally, the ML platform provides pH-responsive release control: the lipid bilayer and polymer layers can be engineered to remain stable at physiological pH (7.4) to limit premature leakage, while responding dynamically to the acidic microenvironment of tumors or intracellular compartments ($\text{pH} \approx 5.0\text{--}6.5$).

Based on these considerations, research focusing on the synthesis, surface modification of MSN-LP hybrids, coating with biocompatible polymers, and conjugation of targeting agents, alongside the evaluation of pH-sensitive release mechanisms and in vitro anticancer efficacy, holds significant scientific and practical value for the development of smart nanocarriers in oncology.

CHAPTER 2. METHODOLOGY

2.1. Synthesis methods

2.1.1. Synthesis of MSN-NH₂

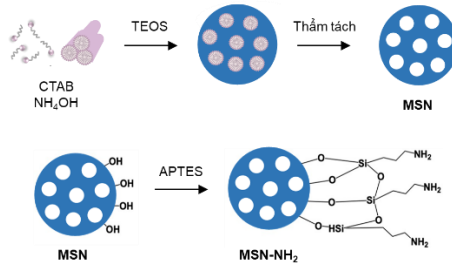


Figure 2.1. Synthesis process of MSN- NH_2

2.1.2. Synthesis of LP

Liposomes (LPs) were synthesized using the thin-film hydration method followed by ultrasonic homogenization. The LP-Brij and LP-Brij-FA systems were prepared via a similar procedure, with the addition of Brij or Brij-FA into the initial lipid formulation.

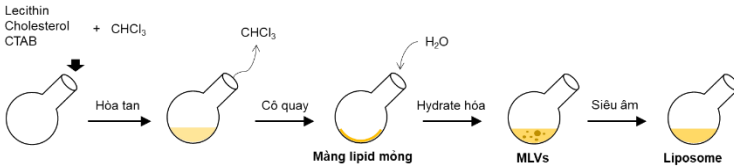


Figure 2.2. Synthesis process of LP

2.1.3. Synthesis of ML, MLB, và MLBF

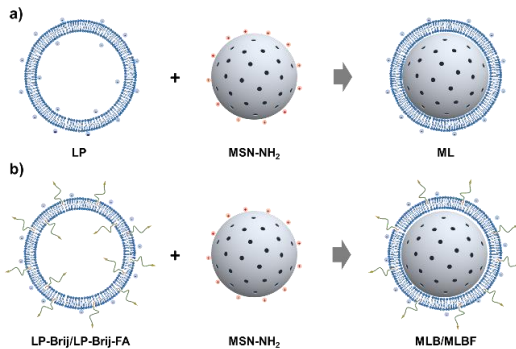


Figure 2.3. Synthesis process of ML (a), và MLB / MLBF (b)

ML, MLB, and MLBF were synthesized by combining MSN-NH₂ with LP, LP-Brij, or LP-Brij-FA (respectively), followed by magnetic stirring and ultrasonication. The resulting products were purified by centrifugation.

2.1.4. Synthesis of copolymer

2.1.4.1. Synthesis of Brij-FA

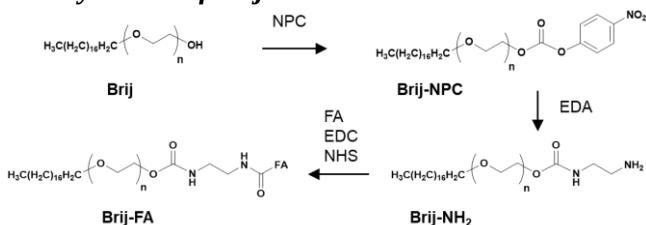


Figure 2.4. Reaction scheme for the synthesis of Brij-FA

2.1.4.2. Synthesis of Gelatin-PEG-FA

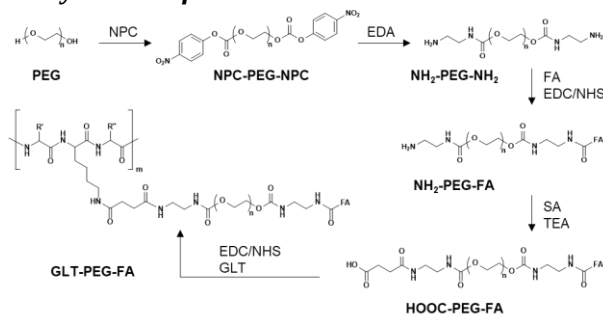


Figure 2.5. Reaction scheme for the synthesis of GLT-PEG-FA

2.1.4.3. Tổng hợp Chitosan-PEG-FA

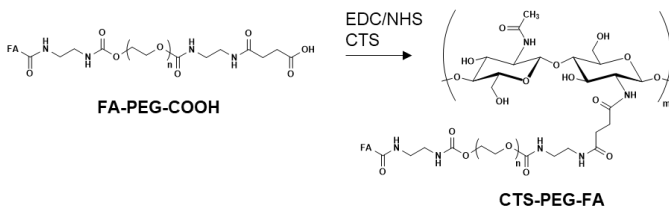


Figure 2.6. Reaction scheme for the synthesis of CTS-PEG-FA

2.1.5. Synthesis of MLGPF and MLCPF

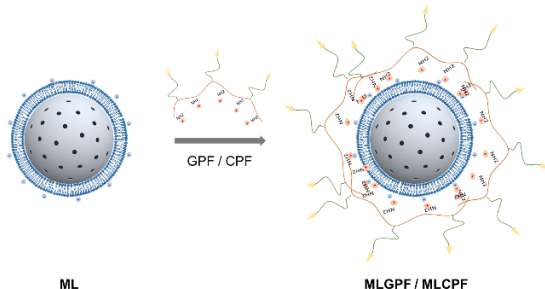


Figure 2.7. Synthesis process of MLGPF and MLCPF

2.2. Analytical Methods

The chemical structures of the copolymers were characterized using NMR and FT-IR spectroscopy. The morphology and particle size of the nanomaterials were determined via DLS, SEM, and TEM. Surface charge was evaluated by Zeta potential measurements using DLS. Elemental composition and chemical bonding were further confirmed by FT-IR and EDX spectroscopy. Thermal properties were analyzed using TGA. Drug concentrations were quantified by spectrophotometry using an ELISA plate reader.

2.3. Drug Encapsulation and Release

2.3.1. DOX Encapsulation

Doxorubicin (DOX) was loaded into MSN-NH₂ via the aqueous diffusion method. The mixture was centrifuged at 10,000 rpm for 30 minutes. The resulting supernatant was analyzed spectrophotometrically at a wavelength of 490 nm to determine the concentration of the residual drug.

2.3.2. Drug Release

Drug release profiles were evaluated using the dialysis method in two buffer systems at pH 7.4 and pH 5.5. Samples were collected to determine the drug concentration at specific time intervals: 1, 3, 6, 12, 24, 48, and 72 hours.

2.4. Cytotoxicity and Cellular Internalization

The cytotoxicity of the nanoplatforms was assessed on the HeLa human cervical cancer cell line using the MTT assay. Cellular internalization was investigated by loading the nanocarriers with fluorescent markers for imaging.

CHAPTER 3. RESULTS AND DISCUSSION

3.1. Synthesis of MSN-LP

3.1.1. Synthesis of MSN-NH₂

MSNs were successfully synthesized with a hydrodynamic size of 139.9 nm and a zeta potential of -25.9 mV. Following surface modification with APTES, the resulting MSN-NH₂ exhibited an increased hydrodynamic size of 153.2 nm. Due to the protonation of the amine functional groups, the zeta potential underwent a significant shift from -25.9 mV to +42.2 mV.

3.1.2. Synthesis of LP

The synthesized LPs displayed high monodispersity, with a hydrodynamic size of 154.8 ± 1.4 nm and a zeta potential of -63.2 ± 1.2 mV.

3.1.3. Synthesis of ML

The ML hybrid system was successfully synthesized using the mixing method combined with ultrasonication. The particle size increased from 153.2 nm to 178 nm, while the zeta potential shifted from +42.2 mV to -38.2 mV.

3.1.4. Physicochemical characterization of ML

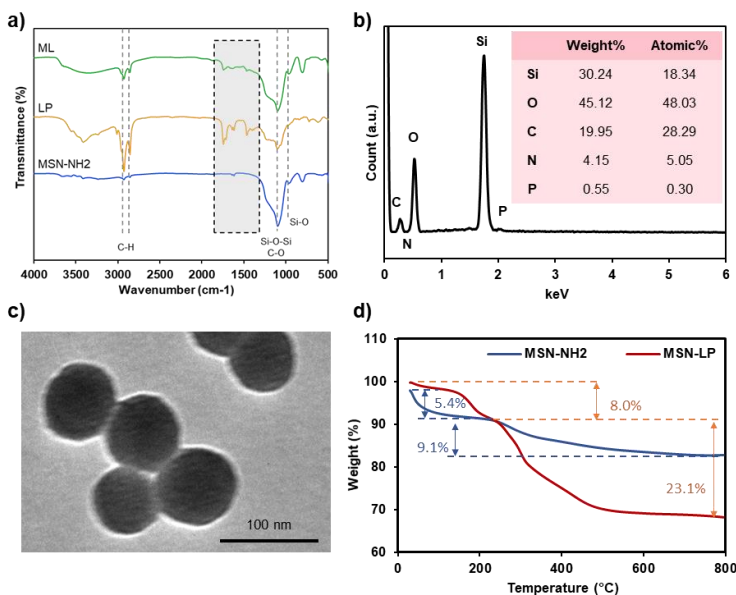


Figure 3.1. FT-IR spectra of MSN-NH₂, LP, and ML (a). EDX spectrum (b) and TEM image (c) of ML. TGA thermograms of MSN-NH₂ and ML (d)

The FT-IR spectrum of ML exhibits characteristic peaks from both MSN-NH₂ and the lipid components (**Figure 3.1a**).

The EDX spectrum of ML confirms the presence of elements constituting the surface-coating lipid bilayer, including 28.29% carbon, 48.03% oxygen, 5.05% nitrogen, and 0.30% phosphorus (**Figure 3.1b**).

In the TGA thermograms of the ML sample, an 8.0% weight loss occurred at 200 °C, similar to MSN-NH₂. The 23.1% weight loss at 800 °C is assigned to the decomposition of the coating LP layer. These results confirm the successful encapsulation of MSN particles by LP (**Figure 3.1d**).

TEM imaging reveals that the ML hybrid material possesses a spherical morphology with a uniform particle size of approximately 60-90 nm (**Figure 3.1c**).

3.1.5. Drug Loading and Release

The encapsulation efficiency (EE) and loading capacity (LC) of DOX into the ML system reached $60.3 \pm 2.5\%$ and $11.1 \pm 0.7\%$, respectively. Both MSN-NH₂ and ML exhibited higher drug release rates at pH 5.5 compared to pH 7.4. Additionally, the ML platform showed a sustained release profile with lower release rates than MSN-NH₂ at the same time intervals.

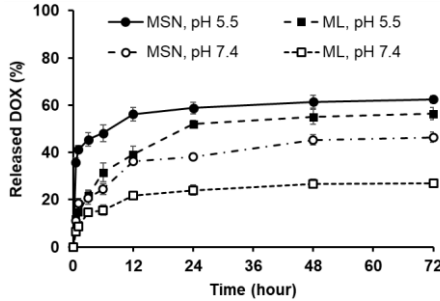


Figure 3.2. Drug release profiles of DOX@MSN-NH₂ and DOX@ML in PBS at pH 5.5 and pH 7.4

3.1.6. Cytotoxicity

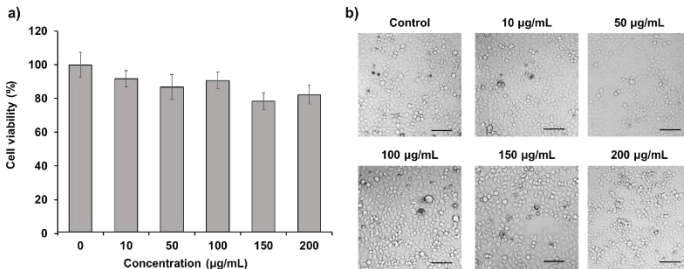


Figure 3.3. Cytotoxicity (a) and microscopic images (b) of ML.

Scale bar: 100 µm.

ML exhibited no significant toxicity toward HeLa cells at concentrations up to 200 $\mu\text{g/mL}$, with cell viability remaining above 80%.

3.2. Synthesis of Brij-FA coated MSN-LP

3.2.1. Synthesis of Brij-coated ML

Brij-coated LPs (LB) were prepared using various types and ratios of Brij, resulting in particle sizes ranging from 140 to 180 nm. LB formulations containing 5-30% Brij exhibited good stability; however, a Brij ratio of 40% led to particle aggregation.

3.2.1.1. Investigation of Brij types

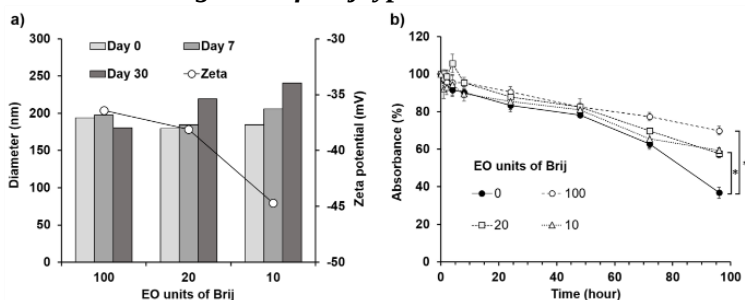


Figure 3.4. Particle size and zeta potential after 30 days of storage (a) and stability in FBS medium (b) of MLB samples using different types of Brij. (*) $p < 0.05$

Increasing Brij PEO chain length (10 to 100 units) slightly varied MLB particle size and increased zeta potential. After 30 days, MLB100 showed superior stability with minimal size changes, whereas MLB10 and MLB20 exhibited significant particle aggregation and growth.

3.2.1.2. Investigation of Brij ratios

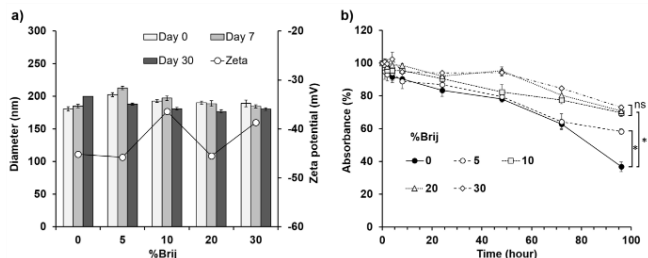


Figure 3.5. Particle size and zeta potential after 30 days of storage (a) and stability in FBS medium (b) of MLB samples using different Brij ratios. (*) $p < 0.05$

Brij incorporation initially increased MLB particle size, peaking at 5% (202.6 nm), followed by a gradual decrease at higher ratios. While Brij enhanced stability in FBS, no significant improvements occurred beyond 10%. These findings indicate that a 10% Brij ratio provides an optimal balance between size reduction and structural stability (**Figure 3.5**).

Based on these analytical results, Brij with 100 PEO units was selected for conjugation with FA.

3.2.2. Synthesis of Brij-FA

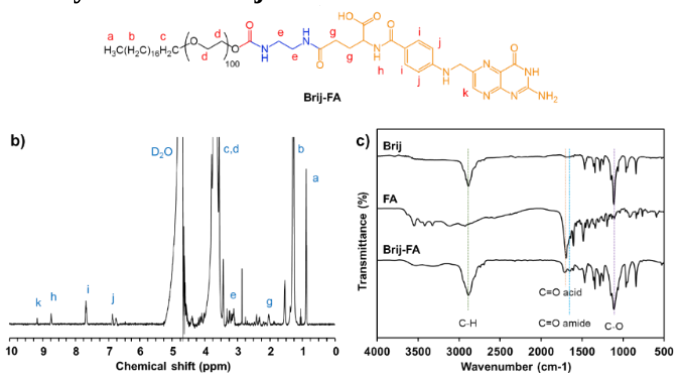


Figure 3.6. Structure of Brij-FA (a). ¹H-NMR spectrum of Brij-FA (b). FT-IR spectra of Brij, FA, and Brij-FA (c).

Brij-FA was successfully synthesized, as confirmed by the ^1H -NMR and FT-IR spectra (**Figure 3.6**).

3.2.3. Synthesis of Brij-FA coated ML

MLBF nanoparticles were successfully synthesized with a hydrodynamic diameter of 191.8 nm and a zeta potential of -24.4 mV. Characterization via SEM/TEM confirmed a spherical morphology (60-90 nm). EDX analysis showed a significant increase in carbon (37.99%) and a decrease in silicon (10.06%) compared to ML, indicating successful Brij-FA coating (**Figure 3.7a**). Furthermore, TGA revealed a higher weight loss for MLBF (34.9%) than ML (31.6%) at 800 °C, attributed to the thermal decomposition of the exterior Brij-FA shell, providing robust evidence for the successful integration of the polymer coating onto the lipid bilayer (**Figure 3.7b**).

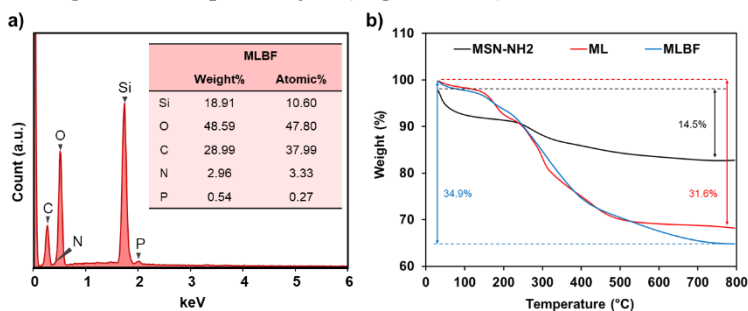


Figure 3.7. EDX spectrum of MLBF (a). TGA thermograms of MSN-NH₂, ML, and MLBF (b).

3.2.4. Drug loading and release

The DOX-loaded MLBF system achieved an EE of $58.4 \pm 2.9\%$ and an LC of $10.45 \pm 0.2\%$. MLBF exhibited pH-responsive controlled drug release, with cumulative DOX release

after 72 hours reaching only 25.26% at pH 7.4 compared to 49.74% at pH 5.5.

3.2.5. Cytotoxicity

MLBF demonstrated excellent biocompatibility and negligible cytotoxicity across a concentration range of 10-200 $\mu\text{g/mL}$, maintaining cell viability above 80%. DOX-loaded MLBF exhibited cytotoxic effects against the HeLa cancer cell line with no statistically significant difference compared to free DOX at equivalent concentrations, indicating that the MLBF nanoplatform preserves the anticancer efficacy of the free drug (Figure 3.8).

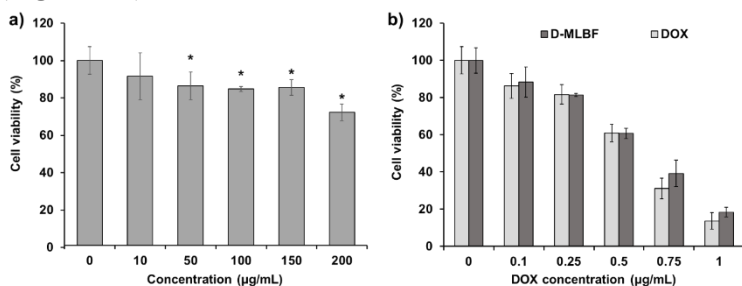


Figure 3.8. In vitro cytotoxicity of MLBF (a), free DOX, and DOX@MLBF (b) against the HeLa cell line after 48 hours

3.2.6. Cellular Uptake

Cells treated with DiO-MLBF exhibited significantly higher fluorescence intensity compared to those treated with DiO-ML, indicating that functionalization with Brij-FA substantially enhances cellular internalisation.

3.3. Synthesis of GLT-PEG-FA coated MSN-LP

3.3.1. Synthesis of GLT-PEG-FA

GPF (GLT-PEG-FA) was successfully synthesized, as evidenced by the $^1\text{H-NMR}$ and FT-IR spectral results (**Figure 3.9**).

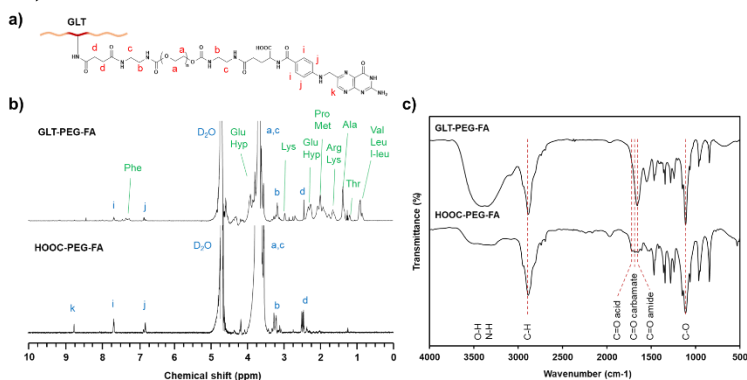


Figure 3.9. Chemical structure of GPF (a). $^1\text{H-NMR}$ (b) and FT-IR (c) spectra of HOOC-PEG-FA and GPF

3.3.2. Synthesis of GLT-PEG-FA coated ML

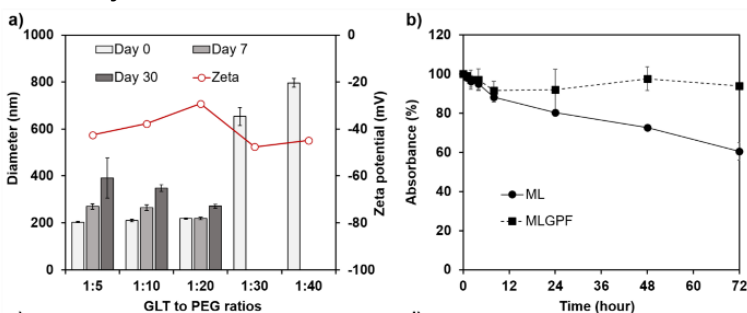


Figure 3.10. Stability of MLGPF with varying GLT:PEG ratios (a) and stability of ML and MLGPF in FBS medium (b)

The stability and particle size of MLGPF are significantly influenced by the ML:GPF ratio, GPF concentration, and PEG conjugation levels. Optimal parameters (1:3 ML:GPF and 2000 $\mu\text{g/mL}$ GPF) yielded the smallest size (218.8 nm). While high

PEG ratios ($>1:30$) caused substantial size increases (>600 nm), lower ratios ($1:5$ to $1:20$) maintained stability. Notably, the $1:20$ GPF:PEG ratio exhibited superior long-term stability after 30 days (**Figure 3.10a**). Furthermore, MLGPF demonstrated enhanced stability in FBS medium over 72 hours compared to bare ML, confirming the polymer's protective effect (**Figure 3.10b**).

3.3.3. Physicochemical properties of MLGPF

The LP and GPF coatings within the MLGPF structure were confirmed by the FT-IR signals of LP at 1747 cm^{-1} and GPF at 1654 cm^{-1} (**Figure 3.11a**).

TGA analysis at $800\text{ }^{\circ}\text{C}$ showed MLGPF had a higher weight loss (39.1%) than ML (31.5%), confirming GPF shell decomposition (**Figure 3.11b**).

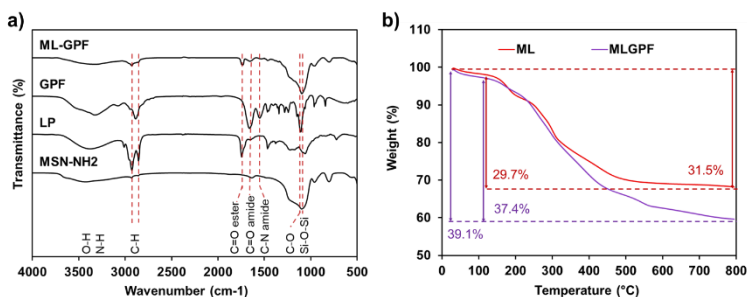


Figure 3.11. FT-IR spectra of MSN-NH₂, GPF, LP, and MLGPF (a). TGA thermograms of ML and MLGPF (b)

EDX data supported this with increased carbon (58.23%) and decreased silicon/oxygen levels (**Figure 3.12a**). TEM imaging verified a spherical morphology with sizes between 60-90 nm, successfully demonstrating the successful coating of GPF onto the ML nanostructure (**Figure 3.12b**).

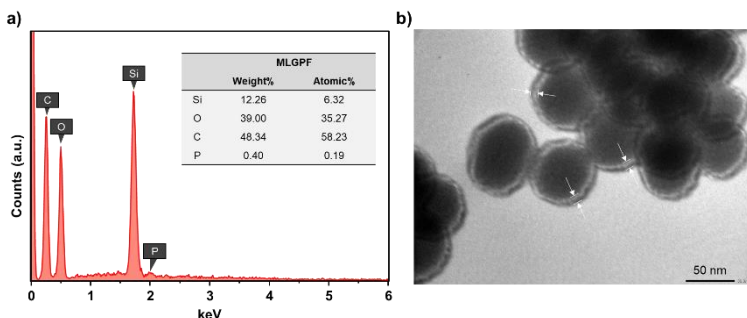


Figure 3.12. EDX spectra (a and c) and elemental mapping (b and d) of ML and MLGPF

3.3.4. Drug loading and release

The DOX-loaded MLGPF system achieved an EE of $52.5 \pm 1.6\%$ and an LC of $9.82 \pm 0.4\%$. MLGPF exhibited pH-responsive controlled drug release, with the cumulative DOX release after 72 hours reaching only 23.3% at pH 7.4, compared to 44.3% at pH 5.5.

3.3.5. Cytotoxicity

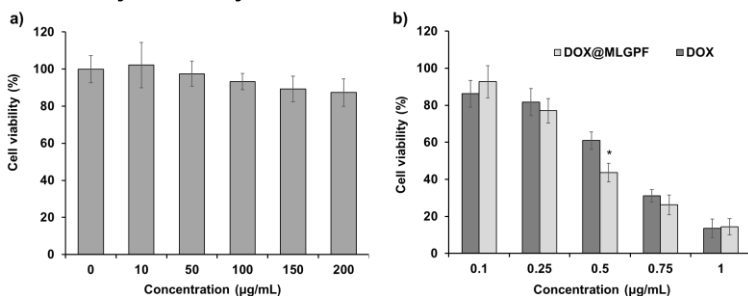


Figure 3.13. *In vitro* cytotoxicity of MLGPF (a), free DOX, and DOX@MLGPF (b) against the HeLa cell line after 48 hours

MLGPF demonstrated excellent biocompatibility and negligible cytotoxicity across a concentration range of 10-200 µg/mL, maintaining cell viability above 80%. DOX-loaded

MLGPF exhibited higher cytotoxicity against the HeLa cancer cell line compared to free DOX, with an $IC_{50} = 0.47 \mu\text{g/mL}$ versus $0.67 \mu\text{g/mL}$, respectively (**Figure 3.13**).

3.3.6. Cellular uptake

Cells treated with DiO-MLGPF exhibited significantly higher fluorescence intensity compared to those treated with DiO-ML, indicating that functionalization with GPF substantially enhances cellular internalization.

3.4. Synthesis of CTS-PEG-FA coated MSN-LP

3.4.1. Synthesis of CTS-PEG-FA

CTS-PEG-FA (CPF) was successfully synthesized, as evidenced by the $^1\text{H-NMR}$ spectral results (**Figure 3.14**).

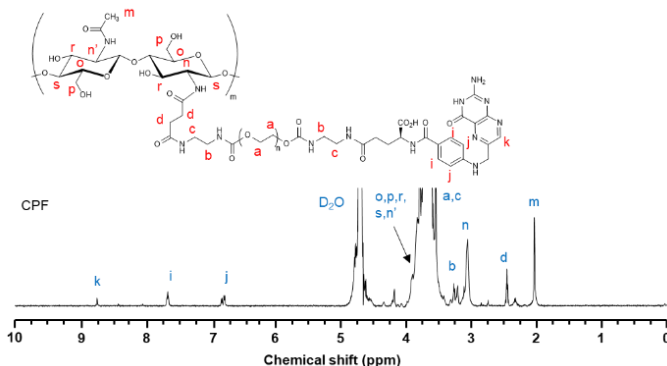


Figure 3.14. $^1\text{H-NMR}$ spectrum of CPF

3.4.2. Synthesis of CPF coated ML

Increasing the CPF ratio resulted in a slight increase in particle size and an elevated zeta potential for MLCPF (**Figure 3.15**).

The particle size of MLCPF showed negligible changes at low PEG ratios (1:5 to 1:20) but increased significantly at higher PEG

ratios (1:30 and 1:40). Conversely, the zeta potential gradually decreased as the PEG ratio increased (**Figure 3.15**).

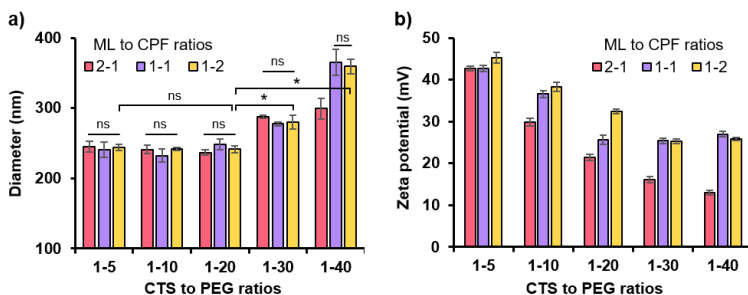


Figure 3.15. Particle size (a) and zeta potential (b) of MLCPF with varying ML:CPF and CTS:PEG ratios

After 30 days, MLCPF with a CTS:PEG ratio of 1:20 exhibited a smaller increase in size compared to the 1:5 and 1:10 ratios. Furthermore, the polymer-coated MLCPF demonstrated superior stability in FBS medium compared to ML after 72 hours (**Figure 3.16**).

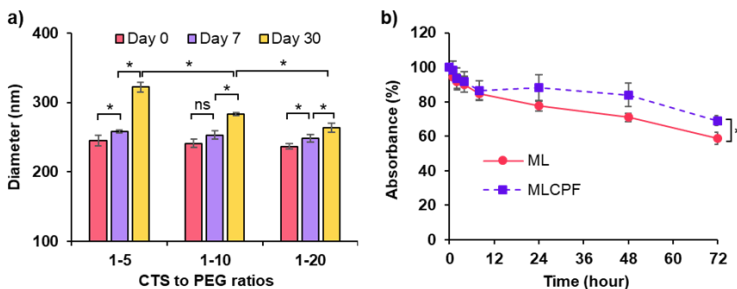


Figure 3.16. Particle size of MLCPF after 30 days (a). Stability of ML and MLCPF in FBS (b)

3.4.3. Physicochemical properties of MLCPF

The architecture of MLCPF was confirmed by FT-IR, identifying characteristic signals for LP (1743 cm^{-1}) and CPF (1631 cm^{-1}) (**Figure 3.17a**).

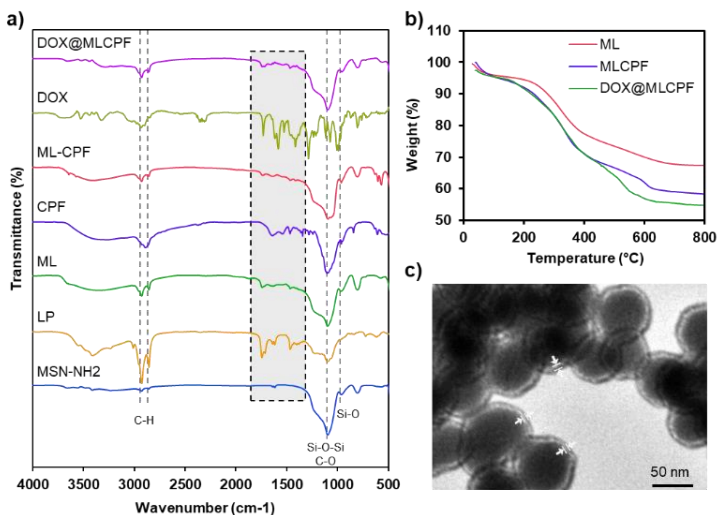


Figure 3.17. FT-IR spectra of MLCPF and its precursors (a). TGA thermograms of MLCPF and ML (b). TEM image of MLCPF (c)

TGA analysis at 800 °C showed a higher weight loss for MLCPF (41.6%) than ML (32.6%), reflecting the thermal decomposition of the exterior CPF shell (**Figure 3.17b**). TEM imaging revealed spherical nanoparticles (60-90 nm) with a distinct 5 nm thick surface layer (**Figure 3.17c**).

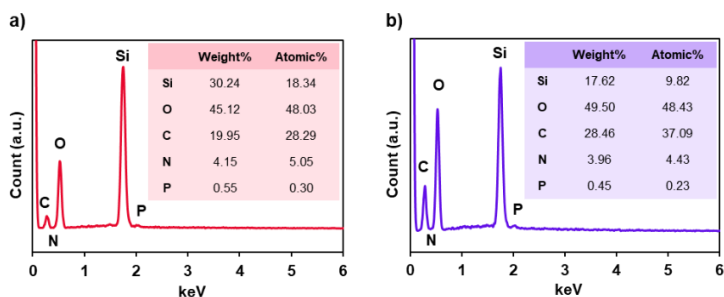


Figure 3.18. EDX spectra of ML (a) and MLCPF (b)
EDX spectra showed increased organic signals (C, O) and

reduced inorganic signals (Si) relative to ML. These consistent data points validate the successful multi-layered integration of the CPF copolymer onto the ML surface (**Figure 3.18**).

3.4.4. Drug loading and release

The DOX-loaded MLCPF system achieved an EE of 59.5% and an LC of 9.7%. MLCPF exhibited pH-responsive controlled drug release behavior.

3.4.5. Cytotoxicity

MLCPF demonstrated excellent biocompatibility and negligible cytotoxicity within the concentration range of 10-200 $\mu\text{g/mL}$, maintaining a cell viability rate above 80%. DOX-loaded MLCPF exhibited higher cytotoxicity against the HeLa cancer cell line compared to free DOX, with an IC_{50} of 0.41 $\mu\text{g/mL}$ versus 0.60 $\mu\text{g/mL}$, respectively (**Figure 3.19**).

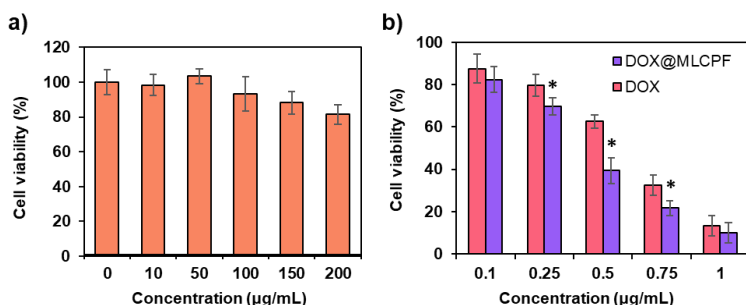


Figure 3.19. *In vitro* cytotoxicity of MLCPF (a), free DOX, and DOX@MLGPF (b) against HeLa cell lines after 48 Hours

3.4.6. Cellular Uptake

Cells treated with DiO-MLCPF exhibited significantly higher fluorescence intensity than those treated with DiO-ML, indicating that functionalization with CPF substantially enhances cellular internalization.

3.5. Discussion

3.5.1. Comparison of physicochemical properties

The hydrodynamic size of the nanoplateforms increased progressively from ML (178 nm) to MLCPF (236.7 nm), correlating with the increasing molecular weight of functionalizing agents (Brij-FA < GPF < CPF). All systems remain within the optimal range (50-300 nm) for effective cancer drug delivery. Regarding surface charge, the high negative zeta potential of ML (-38.2 mV) decreased upon functionalization with Brij-FA (-24.4 mV) and GPF (-29.2 mV) due to PEG layer shielding. Notably, MLCPF exhibited a charge reversal to +21.4 mV, confirming complete coverage by the cationic CPF layer. TGA results at 800 °C validated the multi-layered architecture, with weight loss increasing from MSN-NH₂ (7.6%) to ML (26.1%), and peaking at MLCPF (36.2%) . This rising trend, MSN-NH₂ < ML < MLBF < MLGPF < MLCPF, is fully consistent with the particle size data, rigorously confirming successful macromolecular integration onto the nanoparticle surface.

3.5.2. Drug loading and release

The ML achieved the highest encapsulation efficiency (EE = 60%) and loading capacity (LC = 11%). The polymer-functionalized systems exhibited lower EE (52-58%) due to losses during the modification steps. All hybrid systems demonstrated excellent pH responsiveness: at pH 7.4, drug leakage remained low (23-26%), whereas at pH 5.5, drug release increased sharply (50-60%) due to the structural transformation of the lipid layer. Specifically, the MLCPF system showed the

fastest release, driven by the protonation of amine groups causing the polymer shell to swell.

3.5.3. Cytotoxicity

The materials ML, MLBF, MLGPF, and MLCPF all displayed high biocompatibility, with cell viability exceeding 80% across the concentration range of 10-200 $\mu\text{g/mL}$. Cytotoxicity against cancer cells was concentration-dependent, with IC_{50} values revealing distinct differences in efficacy. DOX@MLBF ($\text{IC}_{50} = 0.625 \mu\text{g/mL}$) showed stronger activity than DOX@ML ($\text{IC}_{50} = 0.738 \mu\text{g/mL}$) due to folic acid conjugation, which enhances receptor-mediated endocytosis. Notably, DOX@MLGPF ($\text{IC}_{50} = 0.450 \mu\text{g/mL}$) and DOX@MLCPF ($\text{IC}_{50} = 0.410 \mu\text{g/mL}$) exhibited superior cell-killing efficiency compared to free DOX ($\text{IC}_{50} = 0.585 \mu\text{g/mL}$). This enhanced performance is attributed to synergistic effects: the GPF shell contains the RGD peptide sequence, which binds specifically to integrin receptors, while the positively charged CPF layer generates strong electrostatic attraction with the cell membrane. Surface modification, particularly in the MLCPF system, optimized the localized drug concentration at the target and significantly improved anti-cancer efficacy.

CONCLUSION

1. MSN-Liposome (ML) hybrid materials were successfully synthesized with a particle size of 178 nm and a zeta potential of -38.2 mV, alongside several polymer-coated ML variants including Brij-coated ML (MLB) with a size range of 188–202 nm, Brij-FA-coated ML (MLBF) characterized by a size of $191.8 \pm 3.2 \text{ nm}$ and a zeta potential of -24.4 mV, GLT-PEG-FA-

coated ML (MLGPF) at 218.6 nm with a zeta potential of -29.2 mV, and CLT-PEG-FA-coated ML (MLCPF) measuring 236.7 nm with a positive charge reversal to +21.4 mV.

2. All polymer-coated hybrid systems demonstrated pH-responsive controlled drug release, with cumulative DOX release limited to a maximum of 30% at pH 7.4 and reaching at least 44% at pH 5.5 after 72 hours.

3. Both ML and polymer-coated ML hybrids exhibited high biocompatibility. While DOX-loaded MLBF showed cytotoxicity against HeLa cancer cells comparable to free DOX, DOX-loaded MLGPF and MLCPF demonstrated significantly higher efficacy.

4. FA-functionalized polymer-coated hybrids (MLBF, MLGPF, and MLCPF) exhibited superior cellular uptake compared to the bare hybrid material (ML).

5. Among all investigated materials, MLCPF demonstrated the highest efficacy in eradicating HeLa cancer cells.

Recommendations

1. Evaluate sub-chronic toxicity, pharmacokinetics, tissue distribution, and clearance time, as well as anti-tumor efficacy in *in vivo* models, to further elucidate the therapeutic potential and clinical applicability of the developed nanocarrier systems.

2. A limitation of MSN-based hybrid materials is that the cumulative drug release rate only reaches above 50%. Therefore, further design optimization is required to enhance drug release efficiency.

3. Advance the design of hybrid nanosystems with multi-stimuli-responsive controlled release capabilities and specific targeting towards distinct tumor types.

NEW CONTRIBUTIONS OF THE DISSERTATION

1. Developed the synthesis and characterization protocols for three novel inorganic-organic hybrid nanomaterials for anti-cancer drug delivery applications: surface-modified liposome-mesoporous silica hybrid nanoparticles (ML) functionalized with Brij-FA (MLBF), Gelatin-PEG-FA (MLGPF), and Chitosan-PEG-FA (MLCPF). Demonstrated enhancements in stability, pH-responsive controlled drug release, cytotoxicity against cancer cells, and cellular internalization efficiency of the synthesized nanomaterials.

2. Provided comprehensive data on the influence of Brij ratio and PEO chain length on the properties, stability of the materials. Analyzed the effects of the ratio, concentration, and PEG content of Gelatin-PEG-FA and Chitosan-PEG-FA on the physicochemical properties and stability of the resulting nanoplateforms.

LIST OF PUBLICATIONS

1. **Nguyen-Dinh, Tien-Dung**, Ngoc Hoi Nguyen, Tan Phat Nguyen, Ngoc Thuy Trang Le, and Dai Hai Nguyen. "Enhancing Stability and Entrapment Efficiency of Liposome-Coated Mesoporous Silica Nanocarriers Using Polyoxyethylene Alkyl Ether as a Polyethylene Glycol Anchoring Agent." *ChemMedChem* 20, no. 22 (2025): e202500223. (**Q1, IF = 3.3**)

2. **Nguyen-Dinh, Tien-Dung**, Ngoc Hoi Nguyen, Pham Nguyen Dong Yen, Minh Hoang Vo Do, Dai Hai Nguyen, Ching Yern Chee, and Ngoc Thuy Trang Le. "Polymeric liposome-silica hybrid nanocarriers as stimuli-responsive systems for targeted drug delivery." *Journal of Polymers and the Environment* 33, no. 12 (2025): 5443-5459. (**Q1, IF = 6.1**)

3. **Nguyen-Dinh, Tien-Dung**, Ngoc Hoi Nguyen, Tan Phat Nguyen, Ching Yern Chee, and Dai Hai Nguyen. "Stealth Protocell System Based on Folated Poxoxyethylene Stearyl Ether-Modified Liposome-Encapsulated Mesoporous Silica for Active Tumor Targeting and pH-Responsive Releasing." *ACS Applied Engineering Materials* 4, no. 9 (2026): 5394-5406. (**Q2, IF = 3.5**)

4. **Nguyen-Dinh, Tien-Dung**, Ngoc Thuy Trang Le, Tan Phat Nguyen, Ching Yern Chee, and Dai Hai Nguyen. "Gelatin-Poly (Ethylene Glycol) Functionalized Lipid-Silica Hybrid Nanostructures With Enhanced Interfacial Properties and Colloidal Stability." *Journal of Applied Polymer Science* (2026): e71588. (**Q2, IF = 3.2**)