

Surface modification of doxorubicin-loaded niosomes for targeting HER2-positive breast cancer

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ABSTRACT

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Targeted drug delivery enhances cancer treatment by improving efficacy and reducing side effects. Niosomes can encapsulate hydrophilic drugs efficiently within their aqueous core for improved stability and controlled release, while their lipid bilayer enhances the solubility and sustained delivery of hydrophobic drugs. However, their limited specificity can result in off-target effects. Carbon dots (CDs) offer tunable surface modifications for precise targeting, strong fluorescence and biocompatibility. This study aimed to modify the niosome surface through electrostatic condensation of trastuzumab-conjugated nitrogen-doped CDs (TCDs) onto negatively charged, doxorubicin-loaded niosomes (DNio) for targeting HER2-positive BT-474 breast cancer cells. Therefore, the ratios of DNio-TCD complexes were varied, and the changes in size and zeta potential were analyzed by dynamic light scattering. Furthermore, the biological effects, including cytotoxicity assays of the DNio-TCD complex, were assessed in BT-474 cells. The optimized complexes were achieved at a 1:24 ratio (DNio:TCD), which exhibited a size of 458 ± 16.64 nm, a positive charge of 32.18 ± 0.34 mV, and a polydispersity index of 0.30 ± 0.06 . The results showed that the DNio-TCD complex enhanced cytotoxicity by approximately 2-fold, compared to DNio alone. Overall, these findings indicate that the DNio-TCD complex could offer promising applications in targeted drug delivery for HER2-positive breast cancer cells.

Keywords: carbon dots; niosomes; electrostatic condensation; drug delivery; cytotoxicity

1. INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of mortality among women. According to GLOBOCAN 2020, breast cancer

accounted for 684,996 deaths, representing one in six cancer-related fatalities, with a global incidence of 2.3 million new cases in the same year (Sung et al., 2021). These statistics underscore the ongoing public health challenge posed by breast cancer. Based on gene

expression profiles and biological markers, breast cancer is categorized into four molecular subtypes: Luminal A, Luminal B, HER2-enriched, and Basal-like (Cheng, 2024; Sitia et al., 2022). HER2-positive instances account for roughly 20–25% of all cases. In addition, HER2-positive cancers demonstrate aggressive proliferation, heightened metastatic capability, and resistance to standard treatment, requiring specialized and highly effective therapeutic strategies (Sitia et al., 2022). Trastuzumab (Tmab), a monoclonal antibody approved for treating HER2-positive breast cancer and metastatic gastric cancer, exerts its anticancer activity by binding to HER2 to prevent dimerization and inhibiting cell proliferation and migration. Moreover, its use alongside chemotherapy has greatly improved patient outcomes (Cruz & Kayser, 2019; Vaidya et al., 2018).

Currently, nanocarriers have emerged as an approach to enhance the targeted accumulation of chemotherapeutic agents in cancer tissues, while minimizing off-target damage (Murugan et al., 2016; Sun et al., 2023; Xia et al., 2021). Niosomes are self-assembled bilayer vesicular structures, which are composed of non-ionic surfactants, cholesterol, and charge-inducing agents. They possess desirable properties such as biocompatibility, stability, and the ability to encapsulate a variety of hydrophilic, hydrophobic, and amphiphilic compounds. Furthermore, in comparison to liposomes, niosomes exhibit greater structural stability, prolonged circulation time, and lower production costs, making them attractive for therapeutic application (Liga et al., 2024; Witika et al., 2022). To improve the targeting ability of niosomes, surface modification is required to enhance their efficiency in delivering drugs directly to cancer cells (Priya et al., 2023).

The main challenge with conventional niosomes is their lack of inherent targeting ability, which results in reduced accumulation in HER2-overexpressing cancer cells (Fobian et al., 2022). To overcome this challenge, functionalizing niosomes with targeting ligands, including Tmab, is necessary. This approach would improve receptor-mediated endocytosis, consequently increasing drug retention in HER2-positive cells (Sitia et al., 2022). Therefore, developing a stable and efficient Tmab-functionalized niosome system is crucial for optimizing HER2-targeted drug delivery (Moammeri et al., 2023; Momekova et al., 2021).

Among the numerous novel nanomaterials carbon dots (CDs) are unique candidates for theragnostic applications, such as drug delivery and imaging, due to their biocompatibility, low toxicity, tunable surface chemistry, and strong fluorescence (Ullah et al., 2025). Consequently, positively charged Tmab-conjugated CDs (TCD) could be used to modify the negatively charged niosome surface through electrostatic self-assembly to enhance HER2-targeting while preserving the integrity and efficiency of the niosomes (Moammeri et al., 2023).

In this study, doxorubicin (DOX) was used as the model drug for encapsulation within niosomes. DOX is an anthracycline chemotherapy agent commonly used because of its proven effectiveness in breast cancer treatment (Shafei et al., 2017). The incorporation of TCD onto the DOX-loaded niosome (DNio) surface could enhance the efficacy of drug delivery, resulting in increased selective cytotoxicity against HER2-positive breast cancer cells. This study aimed to use electrostatic

interaction to complex the positively charged TCD with the negatively charged DNio to create targeting niosomes (DNio-TCD). Physicochemical characterization was conducted using dynamic light scattering (DLS) to measure particle size, zeta potential, and polydispersity (PDI) to observe the condensation, uniformity, and surface charge of the complexes, which is an essential parameter for their effective application. Moreover, evaluating the cytotoxicity of DNio-TCD in BT-474 cells was necessary to assess the biocompatibility of TCD and the therapeutic efficacy of the complexes compared to non-targeted DNio. Electrostatic interaction-based TCD modification is expected to enhance the targeting efficiency of DNio by improving cytotoxicity in HER2-positive cells as BT-474 cells. The findings of this study contribute to the ongoing development of smart, multifunctional drug delivery systems with enhanced precision and therapeutic outcomes.

2. MATERIALS AND METHODS

2.1 Materials

DOX hydrochloride, and chitosan (low molecular weight of 50–190 kDa; 75%–85% deacetylated), were acquired from Sigma Aldrich (St. Louis, MO, USA). Cholesterol (Chol) was acquired from Carlo Erba Reagents (Cornaredo, MI, Italy). Span20 (Sp20), oleic acid (OA) were purchased from Sigma Aldrich® St. Louis (MO, USA). Methanol was acquired from Honeywell International Inc. (North Carolina, USA). Cell culture media including Roswell Park Memorial Institute Medium (RPMI 1640), fetal bovine serum (FBS), penicillin-streptomycin, and trypsin-EDTA were obtained from Gibco BRL (Rockville, MD, USA). The BT-474 cell lines were obtained from the American Type Culture Collection (Manassas, VA, USA).

2.2 Preparation of DOX-loaded niosomes

Niosomes were prepared using the thin-film hydration method. Sp20, Chol and OA at a molar ratio of 3:1:1 (mM) were dissolved in a solvent mixture of chloroform and methanol at a ratio of 2:1 v/v, and the solvent was evaporated under N₂ gas, and the thin film was placed in desiccator chamber at room temperature overnight. The thin lipid film was subsequently hydrated with PBS containing 0.2 mM DOX. The niosomes were sonicated to achieve a small and uniform size distribution. Niosome size, zeta potential, and PDI were determined using DLS.

To quantify DOX, DNios samples were filtered to remove free DOX using a 3-kDa centrifugal filter and centrifuged at 15,000 rpm for 30 min. The filtrate was collected to determine the drug concentration. DOX levels were measured by UV spectrophotometry at 480 nm using a standard curve ranging from 0.02 to 5 mM, with blank niosomes serving as the control. All measurements were performed in triplicate. Encapsulation efficiency (EE) and drug loading capacity (LC) were calculated using Equations (1) and (2), respectively.

$$\%EE = \frac{\text{Total drug } (\mu\text{Mol}) - \text{Free drug } (\mu\text{Mol})}{\text{Total drug } (\mu\text{Mol})} \times 100 \quad (1)$$

$$LC = \frac{\text{Total drug} - \text{Free drug } (\mu\text{Mol})}{\text{Total amount of lipid } (\mu\text{Mol})} \quad (2)$$

2.3 TCD preparation

CDs were synthesized using a microwave-assisted method (Discover SP, CEM Corporation, USA). *o*-Phenylenediamine and chitosan were selected as precursors to produce CDs with amine-functionalized surfaces. The amine groups on the CDs facilitated electrostatic interactions with the negatively charged niosomes, enabling effective binding for targeted delivery to HER2-positive breast cancer cells. TCDs were synthesized by initially activating Tmab with EDC (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide) and NHS (N-hydroxysuccinimide) in PBS at pH 5.5 for 30 min, followed by the addition of CDs at a mass ratio of 1:40 (Tmab: CD). The mixture was stirred overnight in the dark, and subsequently centrifuged using a 50-kDa centrifugal filter at 12,000 rpm for 15 min to remove unreacted Tmab. Following synthesis, the physicochemical properties of the CDs, including particle size, surface charge (zeta potential) and PDI, were characterized using DLS. Moreover, Trastuzumab (Tmab) conjugation efficiency was determined by high-performance liquid chromatography (HPLC) using gel permeation chromatography (GPC). Briefly, Tmab-conjugated carbon dots (TCD) and blank carbon dots (CDs) were analyzed on a Shodex OHpak SB-804 HQ column using ultrapure water as the mobile phase at a flow rate of 0.5 mL/min. A Tmab standard curve (0–5 mg/mL) was constructed, and the conjugation efficiency was calculated using the following equation: (Kumar et al., 2024):

$$\text{Tmab conjugation} = \frac{\text{Initial Tmab } (\mu\text{Mol}) - \text{Free Tmab } (\mu\text{Mol})}{\text{Initial Tmab } (\mu\text{Mol})} \times 100\% \quad (3)$$

2.4 DNio-TCD complex formation

Niosomes and CDs were combined in different mass ratios (1:4, 1:8, 1:12, 1:16, 1:20, and 1:24) to determine the optimal formulation. The mixtures were incubated overnight at room temperature using the ELMI Intelli-Mixers™ at a speed of 30 rpm to ensure uniform interaction between the components. After incubation, the resulting DNio-TCD complexes were analyzed for their physicochemical properties, including particle size, polydispersity index, and zeta potential, using DLS.

2.5 Cell culture

BT-474 cells, which overexpress the human epidermal growth factor receptor 2 (HER2), were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin under standard cell culture conditions at 37°C in a humidified atmosphere with 5% CO₂. The cells were grown in a 25-cm² flasks until reaching 80–90% confluence. Once the desired cell density was achieved, the cells were harvested and seeded into 96-well plates at a density of 7 × 10³ cells per well. The seeded cells were then incubated for 24 h to allow cell attachment and growth before further experimentation.

2.6 Cytotoxicity assay

Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl trazolium bromide (MTT) assay to evaluate the cytotoxic effects of the DNio-TCD complex. BT-474 cells were treated with various formulations, including DNio-TCD complex at a ratio of 1:24 (DNio:TCD), individual DNio, TCDs, and a combination of DOX with Tmab (DOX+Tmab). The

treatments were incubated for 24 h. Following the incubation period, 25 µL of MTT reagent was added to each well, to achieve a final concentration of 1 mg/mL, allowing enzymatic reduction of MTT by metabolically active cells into insoluble formazan crystal. The plates were then incubated further to facilitate formazan crystal formation. Subsequently, dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan, ensuring a homogenous solution for accurate absorbance measurement. The optical density was measured at 550 nm using a microplate reader. Cell viability was calculated using the following Equation:

$$\% \text{ Cell viability} = \frac{\text{OD}_s - \text{OD}_B}{\text{OD}_c - \text{OD}_B} \times 100\% \quad (4)$$

where OD_c is the optical density of the control (untreated cells), OD_s is the optical density of the samples (the cells that were treated with DNio-TCD complex at a ratio of 1:24, DNio, TCDs, and DOX+Tmab), and OD_B is the optical density of the blank.

2.7 Statistical analysis

Statistical analysis was performed using Excel 2019, with all measurements conducted in triplicate and presented as the mean ± standard deviation (SD). Significant differences between groups were determined using one-way analysis of variance (ANOVA), followed by Tukey's HSD post hoc test for pairwise comparisons. A significance level of *p* < 0.05 was considered statistically significant. All analyses were conducted using SPSS software version 17.0.

3. RESULTS

3.1 DNio-TCD complex formation

DNios were successfully prepared using the thin-film hydration method, resulting in a light red colloidal solution. The size, zeta potential, and PDI of DNios, as measured by DLS, are summarized in Table 1. In addition, Table 1 presents the characteristics of CD and TCD. To enhance HER2 targeting, DNios were electrostatically complex with TCD, allowing Tmab to be displayed on the niosome surface for improved specificity.

After incubating DNio and TCD for 24 h to facilitate electrostatic complexation, the DNio-TCD complexes exhibited noticeable changes in size compared to bare niosomes. The extent of size variation depended on the ratio of niosomes to CDs; an initial fluctuation in particle size was observed as the complexation process progressed. However, once binding was complete at a ratio of 1:24, the complex size stabilized, as illustrated in Figure 1.

Simultaneously, zeta potential measurements revealed a shift toward more positive values, indicating successful electrostatic interactions between the positively charged carbon dots and the negatively charged niosomes. This shift confirmed the effective surface modification of the DNios by TCD, ensuring stable complex formation. These changes in size and surface charge, shown in Figure 1, further support the successful formation of DNio-TCD complexes, enhancing their potential for HER2-targeted delivery.



Table 1. The characteristics of DNio, CD, and TCD

	Particle size (nm)	Zeta potential (mV)	PDI	EE (%)	LC ($\mu\text{Mol}/\mu\text{Mol}$)	Tmab conjugation (%)
DNio	142.1 $\pm$ 0.25	-68.99 $\pm$ 1.82	0.15 $\pm$ 0.02	55.70 $\pm$ 1.50	0.02 $\pm$ 0.01	-
CD	410.93 $\pm$ 2.20	30.57 $\pm$ 1.18	0.13 $\pm$ 0.03	-	-	-
TCD	657 $\pm$ 58.76	15.33 $\pm$ 5.79	0.26 $\pm$ 0.03	-	-	56.63 $\pm$ 6.27

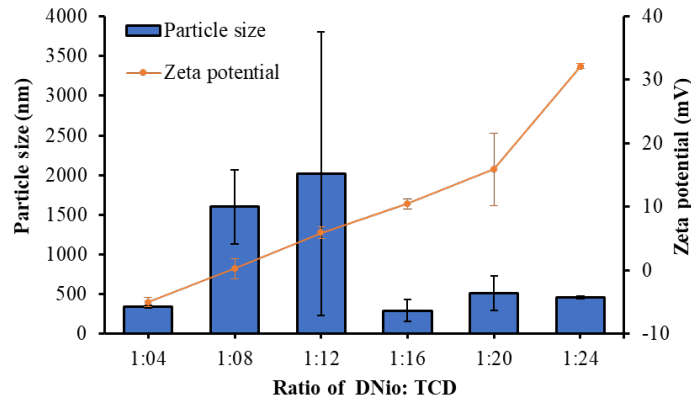


Figure 1. The particle size (nm) and zeta potential (mV) of DNio: TCD complex at various mass ratios. Note. Data are presented as the mean $\pm$ SD (n=3)

3.2 Cytotoxicity

The MTT assay results demonstrated that BT-474 cells exhibited no significant cytotoxicity when treated with TCDs at concentrations ranging from 0.09 to 1.50 mg/mL, as shown in Figure 2. Across this broad concentration range, TCDs exhibited low toxicity and did not cause

significant cell death. Due to their minimal toxicity, TCDs serve as ideal surface modification agent for niosomes, allowing for selective engagement with HER2-overexpressing breast cancer cells. This specific approach enhance the potential of niosomes for treating HER2-positive breast cancer.

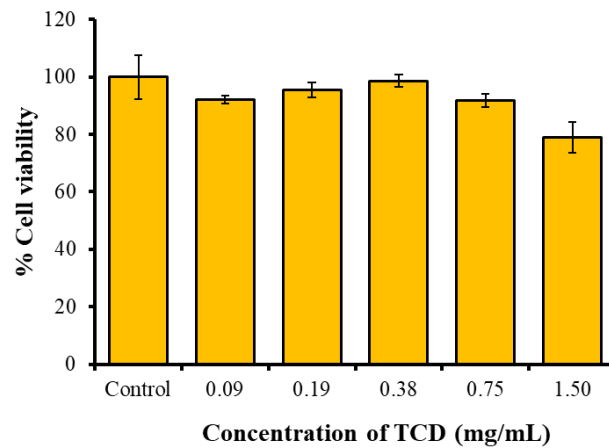


Figure 2. The cytotoxicity of TCD on BT-474 cells

Furthermore, the DNio-TCD complex (1:24 ratio), which exhibited a distinctly positive surface charge, was assessed for its cytotoxic effects on BT-474 cells. After 24 h of incubation, the cytotoxicity of the DNio-TCD complex were evaluated and compared to DNio alone and the DOX+Tmab combination. The findings indicate that at DOX concentrations of 4.16 and 8.32 μM , the 1:24 complex significantly reduced cell viability compared to both DNio

and the DOX+Tmab mixture. This suggests a superior cytotoxicity of the 1:24 complex. Among the tested samples, the 1:24 complex showed the most potent cytotoxic activity, as illustrated in Figure 3. These findings suggest that complexation with TCDs enhances the therapeutic efficiency of DNio, likely due to improved receptor-mediated targeting in Her-2 positive BT-474 cells.

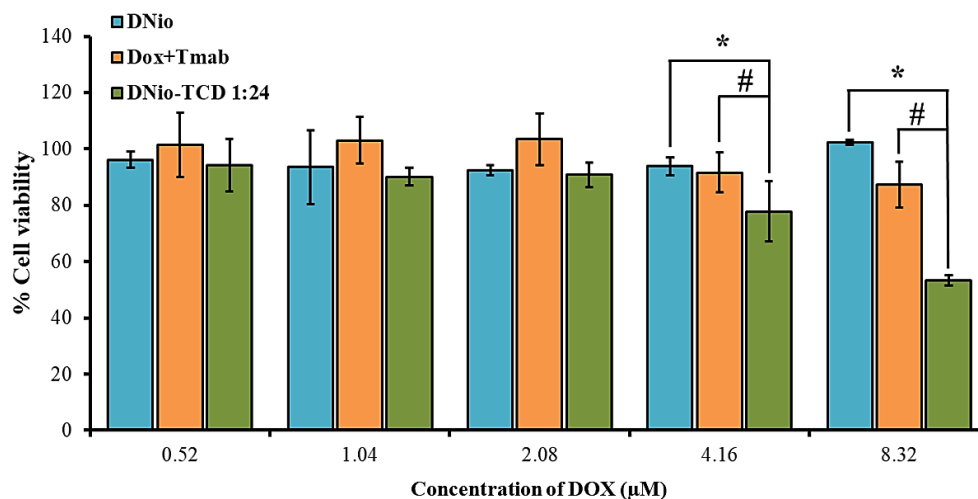


Figure 3. Comparative cytotoxicity of DNio, DOX+Tmab, and DNio-TCD complex (1:24 ratio) in BT-474 cells.

Note. Data represent cell viability following 24 h of treatment. The symbols * and # denote significant differences ($p < 0.05$) compared to DNio and DOX+Tmab, respectively.

4. DISCUSSION

This research successfully modified the surface of DNios with TCDs to enhance targeted drug delivery for HER2-positive breast cancer treatment. The DNio formulation, prepared using the thin-film hydration technique, presented as a light red colloidal solution. As shown in Table 1, DOX was successfully encapsulated in the niosome system. Particle size, zeta potential, and PDI, critical factors for nanocarrier-mediated delivery, were characterized via DLS (Liga et al., 2024; Moammeri et al., 2023). Following the conjugation of Tmab on the carbon dot surface, we observed an increase in particle size and a reduction in zeta potential. These changes are consistent with previous reports, where antibody conjugation results in steric enlargement and reduced surface charge due to protein masking of surface functional groups (Kumar et al., 2024). The incorporation of TCD onto the DNio resulted in distinct physicochemical change. At the optimized ratio of 1:24, the particle size stabilized, suggesting successful complex formation. The electrostatic interactions between the positively charged TCDs and negatively charged DNios were confirmed by a shift in zeta potential toward positive values, indicating that Tmab effectively coated the niosome surface. Such modifications are known to enhance the stability of nanocarriers and improve their targeting capabilities (Momekova et al., 2021; Sitia et al., 2022).

To evaluate the biocompatibility of TCD, an MTT assay was conducted using BT-474 cells. As shown in Figure 2, cell viability remained relatively high across the concentration range of 0.09–1.50 mg/mL, suggesting that TCD modifications does not cause significant cellular harm. These results are consistent with previous findings indicating that carbon dots exhibit minimally toxic at therapeutic levels (Ullah et al., 2025). The mild cytotoxic effects observed are likely attributable to the presence of Tmab within the TCD conjugate. Tmab specifically binds to HER2 receptors, which are overexpressed in BT474 cells, leading to inhibition of key proliferative signaling pathways. By disrupting HER2 dimerization, Tmab blocks downstream pathways such as PI3K/AKT and MAPK

pathways. Consequently, TCDs demonstrate promising biocompatibility and targeted cell death through HER2-mediated signal suppression (Fatima et al., 2021).

The cytotoxicity of DNio-TCD complex was further assessed, revealing that the complex significantly improved DOX delivery to HER2-positive cells. Notably, the 1:24 DNio-TCD complex showed strong cytotoxic effects, as illustrated in Figure 3. At DOX concentrations of 4.16 and 8.32 μM, the complex resulted in greater reduction in cell viability compared to DNio alone. These findings reveal that Tmab-functionalized niosomes improve drug internalization via receptor-mediated endocytosis, supporting previous study which indicate that HER2-targeted nanoparticles enhance cytotoxicity by increasing drug retention in breast cancer cells (White et al., 2020).

Moreover, this enhanced cytotoxicity is attributed to a two-step targeted delivery mechanism. First, the Tmab-functionalized nanocarriers bind specifically to HER2 receptors. Second, the carriers form clusters on the cell surface, facilitating receptor-mediated endocytosis, and promoting intracellular drug accumulation. This approach enhances cytotoxicity while reducing off-target effects (Cruz & Kayser, 2019; Hapuarachchige et al., 2014; Truffi et al., 2018; White et al., 2020).

Despite these promising findings, challenges remain before clinical application. Further investigations into drug release kinetics under physiological conditions are required to ensure sustained release. Moreover, further research is needed to evaluate biological activities, such as cell binding, uptake, and apoptosis induction. Finally, *in vivo* studies are essential to assess pharmacokinetics, biodistribution, and tumor-targeting efficacy (Liu & Shen, 2024).

5. CONCLUSION

Electrostatic condensation between DNio and TCD successfully formed a uniform complex with positive surface charge. Biological evaluation showed that the TCD modified surface significantly increased cytotoxicity in

BT474 cells, likely due to enhanced DOX accumulation. Further assessments, including cellular uptake, apoptosis assays, and *in vivo* testing, and long-term stability study, are required to confirm the DNio-TCd complex as a viable strategy for targeted cancer therapy.

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AUTHOR CONTRIBUTIONS

S.P. and P.O. conceived and designed the study. S.S., K.D., and C.P. developed the methodology. S.S., K.D., and B.P. carried out the investigation. S.S. and C.P. performed the formal analysis, while S.S. and K.D. conducted data curation. T.R., T.C., and T.K. provided resources for the study. S.S. prepared the original draft of the manuscript. S.P. and P.O. reviewed and edited the manuscript. S.P. supervised the project. All authors have read and agreed to the published version of the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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