Engineering Biocompatible Hydrogen Titanate Nanocarriers with Blood Brain Barrier (BBB) Crossing Potential for Doxorubicin Delivery to Glioma Cells

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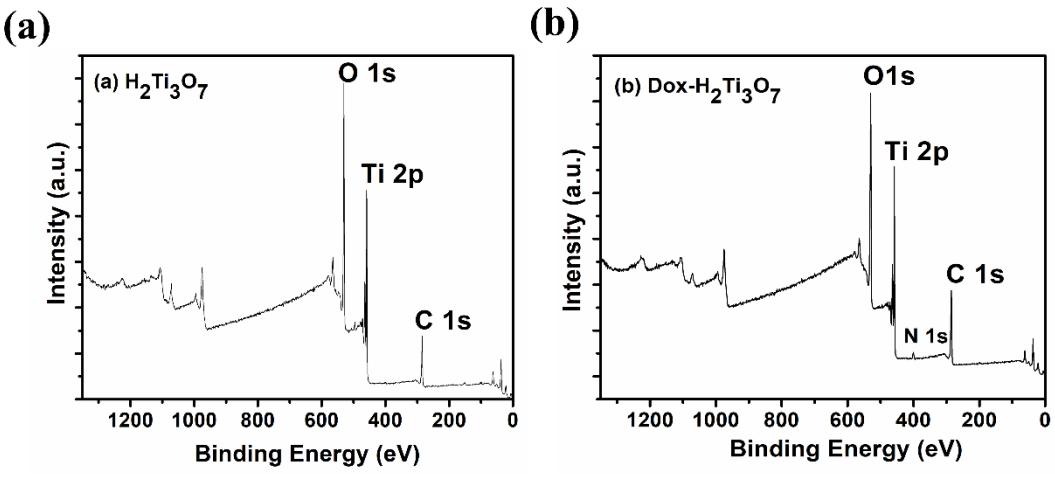

Figure S1: XPS survey spectra of (a) $H_2Ti_3O_7$ and (b) Dox-$H_2Ti_3O_7$. The spectra show characteristic peaks corresponding to O 1s, Ti 2p, and C 1s. In the Dox-loaded sample (b), an additional N 1s peak is observed, indicating the presence of doxorubicin.

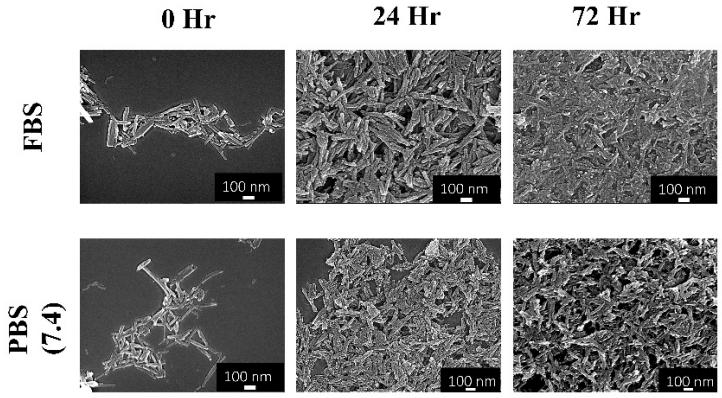

Figure S2: FESEM images illustrating the stability of Dox-$H_2Ti_3O_7$ nanotubes in FBS and PBS (pH 7.4) over time. Images show slight aggregation in FBS compared to PBS after 72 hours of interaction. (Scale bars = 100 nm)

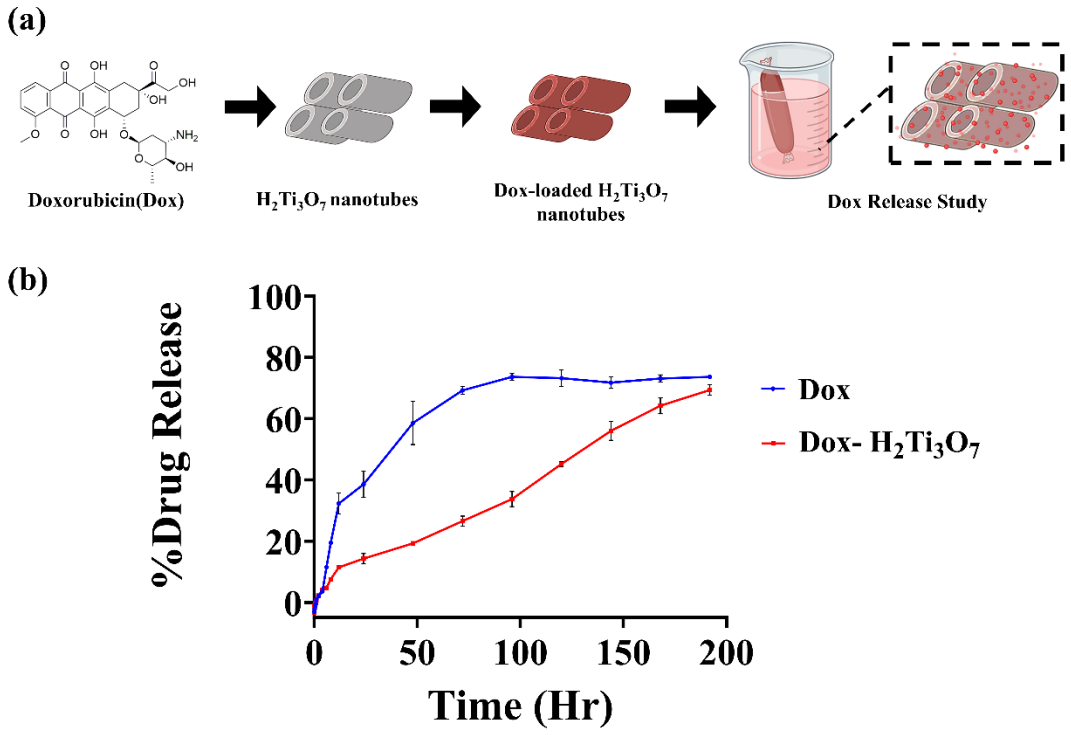

Figure S3: (a) The process of Dox loading and release from $H_2Ti_3O_7$ nanotubes. (b) Graph showing the percentage of drug release from these nanotubes after 192 hours (8 days). (Schematic representation created using Biorender.com).

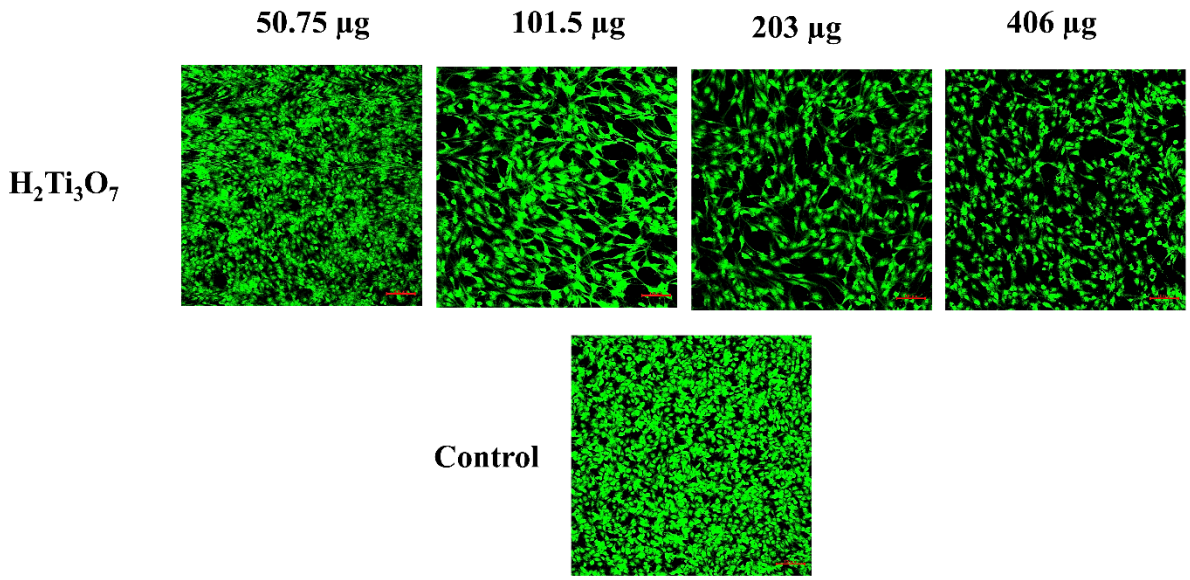

Figure S4: Calcein AM staining of C6 cells exposed to $H_2Ti_3O_7$ nanotubes of equivalent concentration present in Dox-$H_2Ti_3O_7$ nanotubes. (Scalebar:100µm).

Table 1: A comparative table highlighting the pros and cons of $H_2Ti_3O_7$ nanotubes as carrier relative to other commonly used nanocarriers in glioma and cancer therapy.

Nano Carriers	Carrier's Pros	Carrier's Cons	References
Carbon nanotubes (CNTs)	-Efficient Drug Transport: CNTs offer a high capacity for loading therapeutic agents, allowing for effective drug delivery.	**-Toxicity Risks:** Associated with the generation of reactive oxygen species (ROS) and potential neuroinflammation. **- Biodegradation**	[1] [2] [3]

	- Enhanced BBB Crossing: CNTs can achieve unique penetration across the blood-brain barrier (BBB) through surface modifications facilitating targeted delivery to the brain. -Immunomodulatory Effects: CNTs have the potential to modulate immune responses, such as delivering CpG oligonucleotides, which can stimulate immune activity against tumors.	**Issues:** Lack of biodegradability, which complicates their breakdown in biological systems. **- Environmental Challenges:** Difficulties in safe environmental disposal due to their persistence and potential ecological impact.	
Lipid nanoparticles	- Effective BBB Penetration: HFn liposomes, which efficiently cross the blood-brain barrier. - Minimal Immunogenicity: These nanoparticles tend to elicit a low immune response, reducing the risk of	- Restricted Drug Capacity: Lipid nanoparticles have a limited ability to carry therapeutic agents, which can limit their effectiveness in delivering high doses of drugs. - Storage Stability Concerns: These	[4] [5] [6]

	adverse reactions. - Scalable Manufacturing: Production can be easily scaled up, making them suitable for large-scale applications.	nanoparticles can be prone to degradation or structural changes during storage, affecting their performance over time. - Dependence on Passive Targeting: Lipid nanoparticles primarily rely on the Enhanced Permeability and Retention (EPR) effect for targeting tumors, which can be less precise and consistent than active targeting strategies.	
Polymeric nanocarriers	- Adjustable Biodegradation: Materials like chitosan and PLGA can be tailored to degrade at specific rates, allowing for controlled release profiles. - Responsive Drug Release: These polymers can be	- Solubility Issues: Chitosan, for example, exhibits limited solubility in water, which can complicate formulation and delivery. - Thrombogenic Potential: There is a risk of inducing blood clots, which	[7] [8] [9]

	engineered to release drugs in response to environmental cues such as pH changes or temperature variations. - Easy Surface Modification: The surfaces of these polymers can be easily modified with targeting ligands or other functional groups, enhancing their ability to interact with specific cells or tissues.	could lead to thrombosis. - Reproducibility Challenges: The production process can result in inconsistent quality between batches, affecting reliability and efficacy.	
$H_2Ti_3O_7$ nanotubes	- Excellent Biocompatibility and Stability: These nanotubes exhibit high compatibility in biological systems and maintain structural integrity over time. - pH-Responsive Drug Release: They can release drugs in response to changes in pH levels, which is beneficial for	- Limited in vivo distribution data: There is currently a lack of comprehensive data on how these nanotubes distribute within living organisms. - Surface modifications needed for active targeting: To enhance their ability to specifically target	[10] [11]

	targeting acidic tumor environments. - Intrinsic BBB Permeability: These nanotubes can cross the blood-brain barrier, highlighting their inherent ability to deliver therapeutic agents to the brain. - Minimal Cytotoxicity: They exhibit low toxicity to normal cells, ensuring safety in therapeutic applications.	certain cells or tissues, these nanotubes require additional surface modifications.	

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