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Development of a Novel Self-Immolative System Activated by DT-diaphorase for Hypoxic Environments

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Summary:
In this work, a total synthesis of a self-immolative material has been done. Firstly, MCM-41 nanoparticles were synthesized, after that, they were loaded with a fluorophore, and finally the pores were capped with an azo-based molecule. The aim of this work is to detect hypoxic environments based on the overexpression of DT-diaphorase, leading to the breakdown of the azo bond and the releasing of the fluorophore.

Keywords: hypoxia, nanotechnology, DT-diaphorase, MCM-41

Background, Motivation an Objective

Cancer remains a persistent challenge in contemporary healthcare, despite advancements in chemotherapy. By identifying cancer before it spreads, patients often undergo less aggressive therapies with fewer side effects, preserving their quality of life. Moreover, early detection increases the likelihood of successful treatment outcomes and long-term survival. Therefore, investing in methods and technologies for early cancer detection is crucial in improving patient outcomes and reducing the burden of cancer-related treatments [1].

Solid tumors frequently thrive in hypoxic environments, decreasing the amount of oxygen available, and increasing the resistance of the tumor to radiotherapy treatments due to the lack of oxygen-free radicals, required to induce DNA damage; they are also resistant to chemotherapy, due to the ineffectiveness of the drugs to reach these environments via the circulation [2]. Notably, these environments exhibit heightened levels of reductase enzymes like DT-diaphorase, azoreductase and nitroreductase [3].

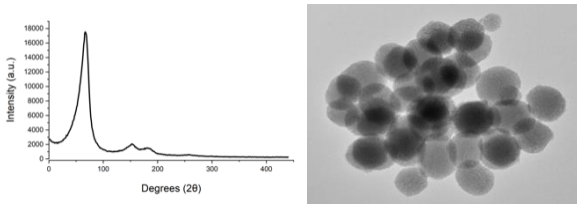
The aim of this study is to synthesize a novel self-immolative gate responsive to the presence of DT-diaphorase, facilitating a controlled release of the fluorophore encapsulated within the MCM-41 nanoparticle pores. This approach aims to trigger fluorophore liberation upon enzymatic activation, offering a potential avenue for diagnostic applications.

Description of the New Method or System

Within the context of this study, a novel molecule featuring an azo bond has been synthesized. This molecule has the particularity of breaking in the presence of DT-diaphorase, an enzyme commonly overexpressed in hypoxic environments characteristic of solid tumors. Serving as a cap for the MCM-41, retaining the fluorophore from spreading. When DT-diaphorase is in the media, the azo bond undergoes cleavage, facilitating the release of fluorophore.

Results

Throughout this investigation, MCM-41 nanoparticles have been synthesized and characterized by X-ray powder diffraction (XRD) and transmission electron microscopy (TEM).



(A) DOI:

Fig. 1. (A) XRD pattern for MCM-41 and, (B) TEM image of empty MCM-41.

Upon successful synthesis of MCM-41, the nanoparticle pores were loaded with rhodamine B, and subsequently capped with the synthesized gate as depicted in Figure 2. This gate is the product of a three-step synthesis process.

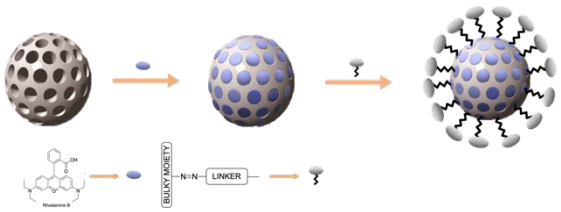


Fig. 2. Representation of the MCM-41 gated nanomaterial loaded with Rhodamine B.

Thereafter, the nanomaterial is exposed to DT-diaphorase, allowing for the measurement of fluorophore release upon enzymatic cleavage of the azo bond. This release was quantified by monitoring the increase in fluorescence intensity exhibited by rhodamine B.

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