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Article

Dissolution and Biological Assessment of Cancer-Targeting Nano-ZIF-8 in Zebrafish Embryos

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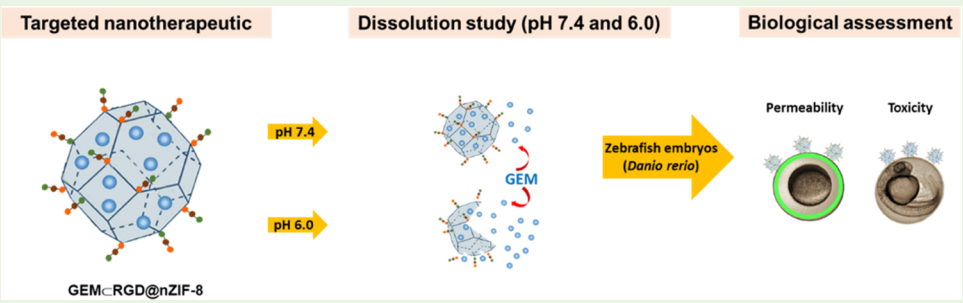

ABSTRACT: Cancer-targeting nanotherapeutics offer promising opportunities for selective delivery of cytotoxic chemotherapeutics to cancer cells. However, the understanding of dissolution behavior and safety profiles of such nanotherapeutics is scarce. In this study, we report the dissolution profile of a cancer-targeting nanotherapeutic, gemcitabine (GEM) encapsulated within RGD-functionalized zeolitic imidazolate framework-8 (GEM⊂RGD@nZIF-8), in dissolution media having pH = 6.0 and 7.4. GEM⊂RGD@nZIF-8 was not only responsive in acidic media (pH = 6.0) but also able to sustain the dissolution rate (57.6%) after 48 h compared to non-targeting nanotherapeutic GEM⊂nZIF-8 (76%). This was reflected by the f_2 value of 36.1, which indicated a difference in the dissolution behaviors of GEM⊂RGD@nZIF-8 and GEM⊂nZIF-8 in acidic media compared to those in neutral media (pH = 7.4). A dissolution kinetic study showed that the GEM release mechanism from GEM⊂RGD@nZIF-8 followed the Higuchi model. In comparison to a non-targeting nanotherapeutic, the cancer-targeting nanotherapeutic exhibited an enhanced permeability rate in healthy zebrafish embryos but did not induce lethality to 50% of the embryos (LC_{50} > 250 μg mL^{-1}) with significantly improved survivability (75%) after 96 h of incubation. Monitoring malformation showed minimal adverse effects with only 8.3% of edema at 62.5 μg mL^{-1}. This study indicates that cancer-targeting GEM⊂RGD@nZIF, with its pH-responsive behavior for sustaining chemotherapeutic dissolution in a physiologically relevant environment and its non-toxicity toward the healthy embryos within the tested concentrations, has considerable potential for use in cancer treatment.

KEYWORDS: *cancer, chemotherapy, targeting nanotherapeutics, reticular chemistry, drug delivery, zebrafish embryo, permeability, toxicity*

INTRODUCTION

Cancer is one of the leading causes of mortality with a significant number of reported global cases each year.[1] Although chemotherapy plays a vital role in cancer treatment, many non-selective chemotherapeutics are fundamentally limited by dose-dependent toxicity that leads to hair loss, diarrhea, constipation, nausea, vomiting, fatigue, skin problems, hearing loss, and low blood cell counts.[2] For this simple reason, there is an immediate need, and moral obligation, to develop more efficient, selective chemotherapeutic systems that have minimal adverse side effects. A viable strategy for minimizing adverse side effects while maintaining high efficiency and efficacy is to encapsulate the non-selective chemotherapeutics inside a biocompatible nanocarrier whose external surface is functionalized with an arsenal of ligands that are capable of selectively targeting and, thereafter, releasing the chemotherapeutics directly to cancer cells without harming normal cells.

Nanosized zeolitic imidazolate framework-8 (nZIF-8) is widely used as a nanocarrier for chemotherapeutics due to its unique properties such as high loading capacity, surface customizability, and pH-responsive nature for the desired treatment purpose.[3−8] The flexibility of nZIF-8 offers vast opportunities for chemical or ligand surface functionalization to improve chemotherapeutic nanodelivery methods, especially

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