ZIF-8 as a pH responsive nanoplatform for 5-fluorouracil delivery in the chemotherapy of oral squamous cell carcinoma

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Introduction

- **5-fluorouracil (5-FU):** one of the most effective chemotherapy agents against oral squamous cell carcinoma (OSCC) [1].
- 5-FU is limited by poor pharmacokinetics, multidrug resistance by cancer cells, and potential toxicity to healthy tissues [2,3].
- The pH-responsive zeolite imidazolate framework-8 (ZIF-8) can ↑ efficacy of 5-FU by degrading and releasing the drug into the acidic tumor microenvironment, which ↑ cancer cell uptake and ↓ systemic toxicity without diminishing the pharmacological effect of 5-FU [Figure 1].
- ***The in vitro uptake and release of 5-FU in ZIF-8 was quantified, and ensuing results were applied to SCC7 cytotoxicity assays.***

Methods

1. Synthesis of 5-FU loaded ZIF-8

The initial absorbance of the 5-FU solution was determined by UV-vis spectroscopy at λ = 260 nm. ZIF-8 was added, and the solution was stirred for 48 h while periodically taking UV-vis measurements. The drug loading capacity was calculated using a predetermined standard plot and line of best fit [Figure 2a-c].

2. In vitro quantification of 5-FU release

5-FU@ZIF-8 were submerged into 5 mL of pH 7.4 and pH 5.5 acetate buffer and maintained at 37℃. Over 48 h, the 5-FU concentrations were determined by UV-vis [Figure 2d, 3].

3. In vitro cell compatibility studies

The *in vitro* cytotoxicity of 5-FU, ZIF-8, and 5-FU@ZIF-8 was assayed against SCC7 cells and cell viability visualized via a nuclear staining technique. Prepared SCC7 cells were passed to a 12-well tissue culture plate at a density of 8.0 x 10^5 cells per well and incubated overnight at 37°C and 5% CO_2. 5-FU, ZIF-8, and 5-FU@ZIF-8 were added to the culture medium at 25 µg/mL, 50 µg/mL, and 100 µg/mL [Figure 4]. After removing the medium at 72 hours, toluidine blue stain was added. After 8 h, the stain was removed and the wells were washed with PBS and air-dried.

Results

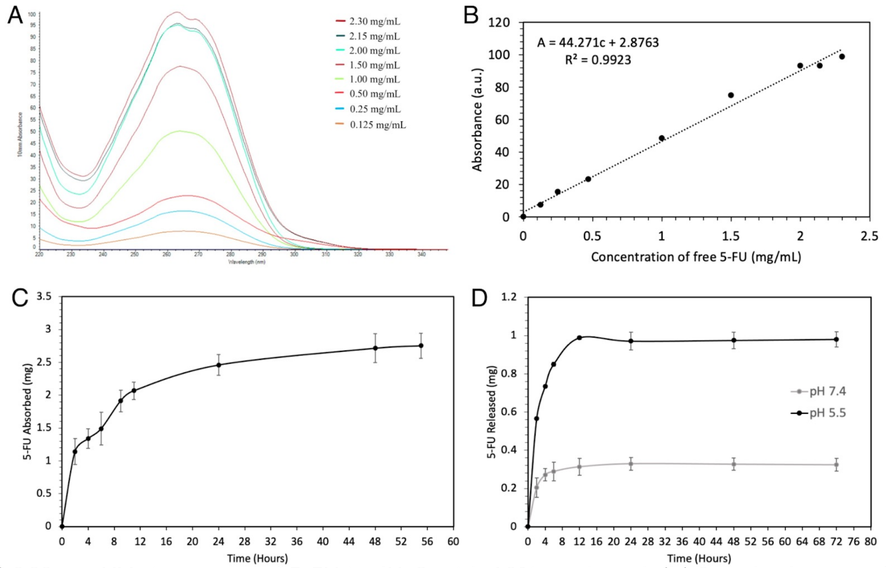

Fig. 2 (a) 260 nm UV-vis spectra of 5-FU in dH_2O with 10% methanol. (b) Standard curve of 5-FU in dH_2O with 10% methanol, as determined by UV-vis spectra. (c) The loading of 5-FU in ZIF-8 in dH_2O with 10% methanol. (d) A comparison of 5-FU delivery in various acidities of 1M acetate buffer.

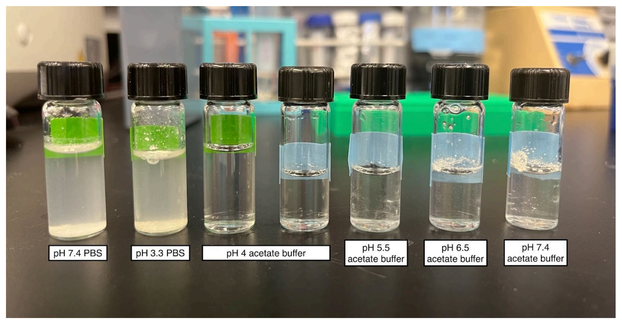

Fig. 3 Comparison of ZIF-8 dissolution within various acidities of PBS and acetate buffer solutions. Commercially available ZIF-8 can degrade in acidic acetate buffer and not acidic PBS. This characteristic may help the carrier better target cancer cells, in which upregulated *de novo* lipid synthesis increases the need for acetate as a building block.

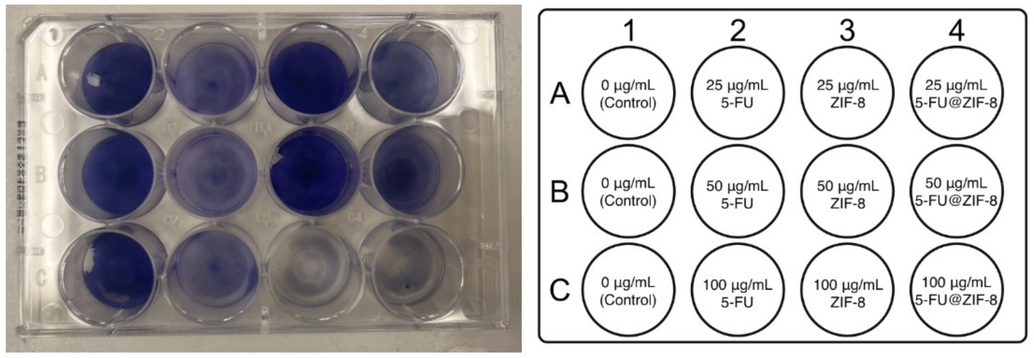

Fig. 4 Both 5-FU and 5-FU@ZIF-8 treatments had an inhibitory effect, with the 5-FU@ZIF-8 more evident at 100 µg/mL. Similarly, ZIF-8 had a cytotoxic effect towards the cells at 100 µg/mL, but did not impact the cells at lower concentrations of 50 µg/mL and 25 µg/mL.

Discussion & Conclusions

- Commercially available ZIF-8 can absorb 5-FU in a controlled manner up to 271.41 ± 21.94 mg/g.
- The release of 5-FU was medium and pH-dependent and occurred best within a pH 5.5 acetic acid buffer solution.
- ↑ *de novo* fatty acid synthesis and acidification of the tumor microenvironment may present as key targets for ZIF-8 drug delivery.

Future directions:

- Determine whether the long-term treatment of 5-FU@ZIF-8 nanoparticles can inhibit SCC7 and/or mesenchymal stromal cells (MSC) for a chronic therapeutic effect.
- Investigate the enhancement of lipogenesis, a potential target of 5-FU@ZIF-8 nanoplatforms, in SCC-associated MSCs.

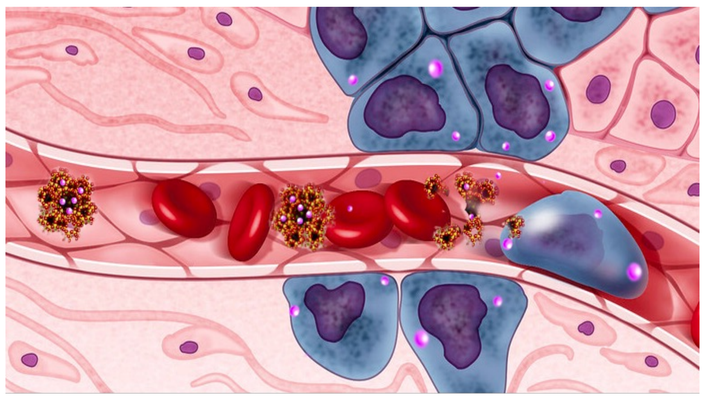

Fig. 1: The pH-sensitive zeolite can selectively release anticancer drugs into the acidic tumor microenvironment while minimally impacting normal cells.

Works Cited

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