Novel Synthesis of Iron-based Metal-Organic Framework for Site-specific Doxorubicin Delivery

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Statement of Purpose: Although Doxorubicin (DOX) is used effectively to treat several cancers, yet, it has low tumor targetability resulting in adverse side effects including acute vomiting and nausea, gastrointestinal problems, baldness, and cardiotoxicity (C. F. Thorn, C. Oshiro, S. Marsh, T. Hernandez-Boussard, H. McLeod, T. E. Klein and R. B. Altman. Pharmacogenet Genomics. 2011; 21:440-446, C. Carvalho, R. X. Santos, S. Cardoso, S. Correia, P. J. Oliveira. M. S. Santos and P. I. Moreira. Curr. Med. Chem. 2009; 16:3267-3285). Recently, a new class of porous nanomaterials, namely metal-organic frameworks (MOFs), has attracted tremendous attention as promising nanocarriers to encapsulate DOX. Herein, we report the green microwave synthesis of a new 3-D MOF (Fe@2,6-NDC) from iron nitrate and 2,6-naphthalene dicarboxylic acid. Fe@2,6-NDC particles had diameters ranging between 50 and 80 nm and length span of 300-450 nm with an average pore diameter of 148.551 Å. The synthesized MOF showed high cell viability (more than 85%) when tested against the MCF-7 cell line and succeeded in encapsulating DOX with a loading efficiency and capacity of 67.5% and 11.9 wt.%, respectively.

Methods: All chemicals were used without further purification as obtained from LABCO (the official Sigma-Aldrich distributor in the United Arab Emirates). The MOF was synthesized using iron(III) nitrate nonahydrate ($Fe(NO_3)_3.9H_2O$, ACS reagent, ≥98%) and 2,6-naphthalene dicarboxylic acid (2,6-NDC, 99%). Approximately, 0.2307 mmol of iron(III) nitrate nonahydrate and 0.2307 mmol of 2,6- naphthalene dicarboxylic acid were dissolved in 10 ml of N,N-dimethylformamide (DMF, ReagentPlus®, ≥99%). Then, the solution was transferred into a 23-ml Teflon autoclave bomb (model 4781 microwave acid digestion vessel, Parr Instrument Company, USA) and heated in a microwave oven (model RCMT5088W, Frigidaire Company, USA) at 160 W for 5 min. The resulting MOF particles were separated from the mixture by centrifugation (5,500 rpm, 30 min) using an EB Series centrifuge (Centurion Scientific Ltd, UK). The collected particles were washed with DMF and dried. The morphology of MOF was determined using scanning electron microscopy (SEM) (model MIRA3 XMU, Tescan Orsay Holding Company, Czech Republic) and the porosity was measured using a TriStar II 3020 micromeritics instrument (Micromeritics Instrument Corporation, USA). *In vitro* cytotoxicity experiments were carried out by incubating different concentrations of Fe@2,6-NDC (12.5, 25, 50, 100, and 200 μg/ml) with the breast cancer MCF-7 cell line and the viability was measured using flow cytometry (CYTOMICS FC 500, Beckman Coulter, Inc., USA). The drug loading was performed as follows: 100 mg of the MOF were stirred with 10 ml of Doxorubicin hydrochloride (DOX.HCl) dissolved in methanol for 72 h. The loaded particles were separated by centrifugation, washed, and dried. The fluorescence values before and after loading were measured using fluorescence spectroscopy (QuantaMaster™ 30 System, Photon Technology International, Inc., USA).

Results: The morphology of Fe@2,6-NDC particles is shown in Figure 1. The Fe@2,6-NDC particles have a rod-like shape with diameters ranged between 50-80 nm and a length of 300-450 nm. Figure 2 represents the cell viability of the MCF-7 cell line incubated with Fe@2,6-NDC after 24 h. The cell viability percentages were very high (approximately 96, 94, 94, 91, and 85%) at the corresponding concentrations (12.5, 25, 50, 100, and 200 μg/ml) of the MOF (Figure 2), indicating excellent biocompatibility of Fe@2,6-NDC. Finally, the DOX loading efficiency and capacity were calculated to be 67.5% and 11.9 wt.%, respectively

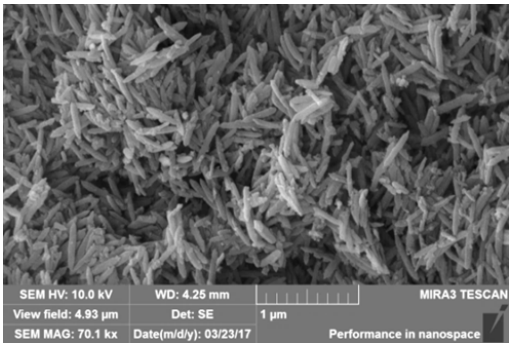

Figure 1. The SEM images of Fe@2,6-NDC

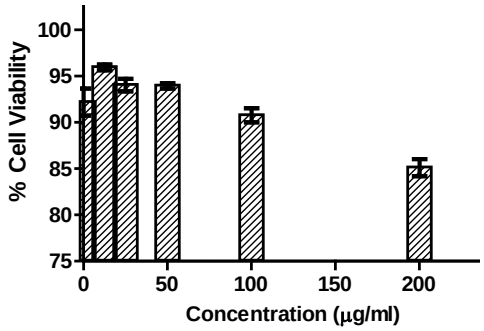

Figure 2. Cell viability of MCF-7 cell line incubated with Fe@2,6-NDC for 24 h.

Conclusions: The new metal-organic framework (Fe@2,6-NDC) was successfully synthesized using a green facile microwave irradiation technique in 5 min. The resultant, MOFs particles had shown promising structural and physical properties as new drug nanocarriers including small particles size, large pore size, and a high degree of compatibility. Further experiments arising from these findings include: coating the MOF with a hydrophilic polymer to increase the blood circulation half-life, conjugating targeting moieties to the MOF surface (active-targeting), and conducting *in vitro* and *in vivo* cytotoxicity studies.