Sustainable Synthesis of FA and *β*-Cyclodextrin functionalized GO decorated MIL-100(Fe): A Biocompatible Drug Carrier for Targeted Dual Drug Delivery

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**Abstract**

Surgery, radiation therapy and chemotherapy are some of the common cancer treatment methods of the present day. Among these, chemotherapy is the most often utilized therapeutic method. However, its effectiveness is limited by the inability to distinguish between precipitously propagating normal cells and cancer cells, escorting to severe side effects. The drawbacks of traditional drug delivery systems (DDS) are the abrupt metabolization of drugs, poor solubility, non-specific targeting, low retention effectiveness and adverse effects on normal cells. Additionally, the use of a single chemotherapeutic agent frequently fails to achieve a complete cancer regression due to the diversity of cancer cells, the emergence of drug resistance, and the adverse effects caused by high and/or repeating medication doses. Targeted drug delivery systems (DDS), utilizing advanced nanomaterials such as nanocarriers and natural/green chemotherapeutic agents like tannic acid (TA), offer a promising solution to overcome these challenges while improving the sustainable consumption of chemotherapeutic agents. The main principle of targeted DDS is to target and release the loaded drug on specific cells in a controlled manner. Moreover, combination chemotherapy, which uses multiple chemotherapeutic agents, is also prevalent. The main objective of most anti-tumour medications is to eradicate tumours by activating signalling pathways that lead to apoptosis. However, it is possible for cancer cells to avoid apoptosis and develop greater chemoresistance due to a phenomenon called multidrug resistance (MDR). The overexpression of drug efflux proteins like P-glycoprotein (P-gp) is considered to be one of the root causes of MDR. Chemosensitizers and resistance modulators, which are able to limit P-gp's ability to efflux drugs, can be used to resolve such concerns by enabling larger concentrations of medications to reach their cellular target sites. The chemical P-gp inhibitors formerly used to illustrate the MDR reversal effect are severely toxic and require higher dosages. Hence, the use of natural chemosensitizers along with commercial chemotherapeutic drugs is of great interest. In line with this, the present study focuses on the use of Tannic Acid (TA), a natural chemotherapeutic agent, along with a commercial drug, Doxorubicin (DOX), for targeted dual drug delivery. Both these drugs were loaded on a novel nanocarrier fabricated using Graphene Oxide (GO), β- Cyclodextrin (β-CD), Folic Acid (FA) and a metal-organic framework, MIL-100(Fe) (MF). The synthesis of MF and its functionalization with β-CD-GO-FA was accomplished through a one-pot, room temperature, sustainable and facile method via the HF-free route. The nano-morphology, surface chemistry, and structure of β-CD-GO-FA-MIL-100(Fe) (BGFw\_MF) nanocomposites were investigated via TEM, FESEM, FTIR, XRD, XPS, BET, Raman spectroscopy, and zeta-potential analysis. The dual drug loading efficiencies of different weight proportions (w/w) of the nanocarrier (BGF0.25\_MF, BGF0.5\_MF, BGF0.75\_MF, BGF1\_MF, BGF1.5\_MF) at pH conditions (5,7.4,10) was investigated. The nanocarrier-to-drug ratio (BGF0.5\_MF: TA\_DOX) and dual-drug ratio (TA: DOX) were also optimized for better loading efficiencies. The release behaviour at physiological pH conditions (5,7.4) was further studied using kinetic modelling. The nanocarrier obtained by the functionalization of GO, along with its impregnation in the structural cage of MF, shows a significant improvement in the loading and release behaviour for the co-delivery of TA and DOX. The findings of this work emphasized the potential of BGFw-MF nanocarriers obtained at room temperature for DOX and TA loading, release, and cytotoxicity assessment for cancer cells for DDS.

**Keywords:** *Graphene oxide; β-cyclodextrin; Tannic acid; Targeted dual drug delivery; Cancer therapeutics; Sustainable synthesis.*