In vitro Drug Release Kinetics Profile

The in vitro release profiles of Cisplatin (CP) from Fe-based MOFs formulations were studied, considering both non-HA and HA systems, under different pH conditions (5.0 and 7.4), by the standard kinetic models: zero-order, first-order, Higuchi and Korsmeyer–Peppas model, as well as data analysis on the rate controlling step between free drug generation from NPs to releasing medium during CP delivery was carried out. The model that best fit to each condition was selected according to the correlation coefficient (R^2) and the n exponent of the diffusion-based models.

For HA/Fe-MOF/CP, release kinetics of the drug at physiological pH (7.4) is fitted with a value of $R^2 = 0.9402$ for Korsmeyer–Peppas model suggesting that drug release process mainly depends on the diffusion in functionalized nanocarrier system. The zero-order ($R^2 = 0.7635$) and first-order ($R^2 = 0.4916$) models have poor fitting, indicating that the release is not a constant or concentration dependent respectively. Moderate correlation of the Higuchi model ($R^2 = 0.8483$) was observed, with release exponent (n) of 0.84 indicating anomalous (non-Fickian) transport. This suggests that drug diffusion into the porous network and polymer relaxation dynamics both participate in the release process. The supported n value of 0.7635 further supports the proposition of a mixed diffusion–relaxation mechanism under physiological conditions, indicating that the release kinetics can be designed by HA functionalization combined with Fe-MOF framework for synergetic regulation.

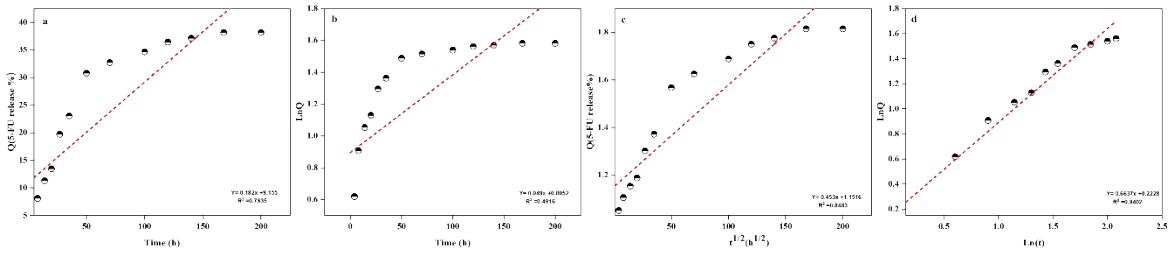

Figure S1: kinetics model at pH 7.4 of HA/Fe-MOF/CP (a) zero-order model (b) First-order model **(c)** Higuchi model (d) Korsmeyer–Peppas

The drug release from the Fe-MOF/CA at physiological pH (7.4) was most accurately modeled using the Korsmeyer-Peppas equation ($R^2 = 0.9534$) to describe the anomalous transport

mechanisms, where both Fickian diffusion and matrix relaxation are involved in the control of drug release. Additionally, there was a good fit of the data to the Higuchi equation (R^2 = 0.9064), further suggesting that diffusion (or effusion) drives the release process. Conversely, the R^2 values for the zero-order (R^2 = 0.8042) and first-order (R^2 = 0.5025) equations were less than those for the Korsmeyer-Peppas and Higuchi equations, indicating that the release does not occur by either a constant rate or simply by a function of the amount of drug available. Together, these results demonstrate that the release mechanism involves multiple factors, and can be best described as a synergistic interaction between diffusion and matrix relaxation; however, the primary factor contributing to this synergism appears to be the highly porous structure of the Fe-MOFs, which allows for controlled and sustained release of the drug.

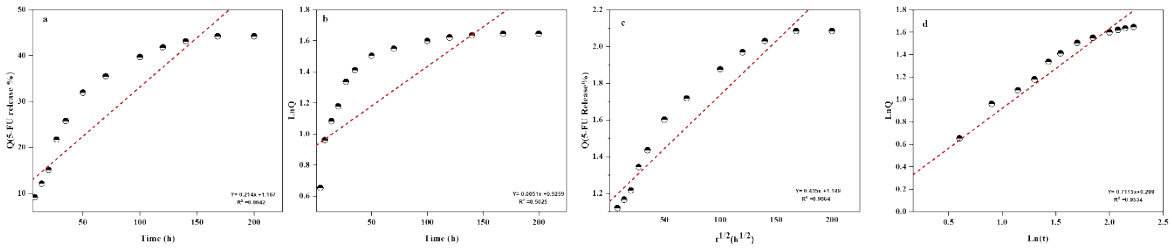

Figure S2: kinetics model at pH 7.4 of Fe-MOF/CP (a) zero-order model (b) First-order model **(c)** Higuchi model (d) Korsmeyer–Peppas

The release of Cisplatin (CP) in the form of a Fe-MOF/CP, under acidic pH 5.0, using hyaluronic acid (HA) as the functionalizing agent, predominantly uses the Higuchi model (R^2=0.9714). This means the majority of the release process of the drug occurs by diffusion, as the drug diffuses throughout the porous structure of the nanocomposite and ultimately diffuses out to the external medium. There are some anomalous (non-Fickian) transport processes occurring as indicated by the relatively good fit of the Korsmeyer-Peppas model (R^2 = 0.7355), indicating both diffusion and relaxation of the polymer matrix occur. Both the First-Order Model (R^2= 0.5352), and the Zero-Order Model (R^2= 0.5724), indicate a poorer fit than the previous models, indicating that the release is neither solely dependent on the concentration of the drug nor a constant rate over time. Therefore, under acidic pH conditions, the predominant mechanism of drug release is due to diffusion; however, the HA functionalization provides for some relaxation mechanisms that contribute to slight modifications of the overall kinetic rate of drug release.

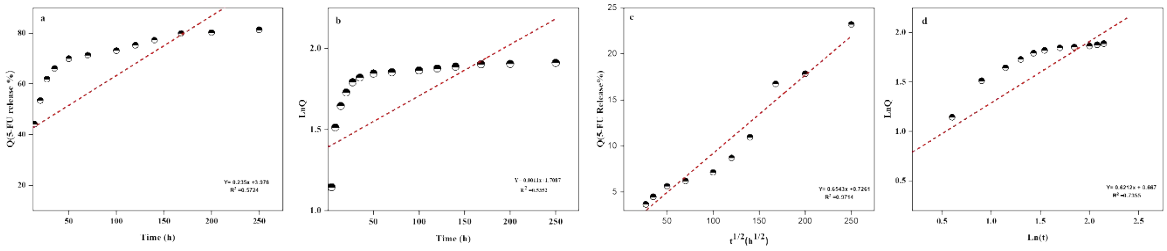

Figure S3: kinetics model at pH 5.0 of HA/Fe-MOF/CP (a) zero-order model (b) First-order model **(c)** Higuchi model (d) Korsmeyer–Peppas

With a pH lower than 5.0, the release behavior of Fe-MOF/CP is best described using the Korsmeyer-Peppas kinetic model (R^2 = 0.9495), suggesting an anomalous diffusion release mechanism; that is, a synergistic process between Fickian diffusion and relaxation of the polymer matrix controlling the release behavior. The Higuchi plot, which represents diffusion or effusion, has a high degree of fitting (R^2 = 0.8499) with the release data, thereby confirming that diffusive or effusive release is a major contributing force. On the other hand, the lower value of the R^2 coefficients corresponding to the zero-order (R^2 = 0.8986) and first-order (R^2 = 0.3618) models clearly indicates that release does not manifest in a simple zero-order or first-order-type process, respectively; that is, release is neither dependent on time nor concentration. From these findings, it could be interpreted that the release may manifest in a complex manner because of a synergistic effect between diffusive and relaxation mechanisms that could be attributed to the highly porous nature of Fe-MOFs with molecular transport enabled by the swelling dynamics of the polymer matrices.

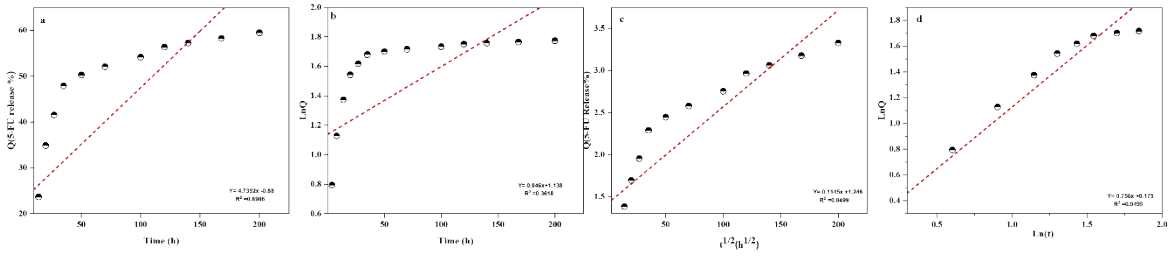

Figure S4: kinetics model at pH 5.0 of Fe-MOF/CP (a) zero-order model (b) First-order model **(c)** Higuchi model (d) Korsmeyer–Peppas