Nanoparticle Drug Delivery System

A new cancer chemotherapeutic formulation doxorubicin nanocarrier (MIOpoly-Dox) has been designed and revealed by synchrotron X-ray/neutron scattering and absorption techniques.

The concern of drug carrier design includes toxicity, side effect, therapeutic effect, stability, price, release efficiency, surface tailoring, *etc*. Small-sized nanoparticles have efficient cellular uptake *in vitro* and the enhanced permeability and retention effect of the vasculature. Hence, they directly interact with the diseased cells at higher efficiency and reduce side effects. Several types of nanoparticles such as magnetic nanoparticles present promising opportunities in pharmaceutical and biomedical applications. For drug/gene delivery, magnetic iron oxide nanoparticles (MIOs) are extensively studied due to their non-toxicity, low-cost production, and tunable surface property. MIOs can be used for imaging, diagnostic, and therapeutic applications.[1] These MIOs have diameters ranging from 1 to 100 nm and display a core of iron oxide (Fe_3O_4) or maghemite (Fe_2O_3) or a nonstoichiometric configuration of both. MIOs are the most potent nanomaterials in nanomedicine, owing to their exceptional physicochemical characteristics and excellent biocompatibility, non-toxicity, and stability in aqueous solutions. Iron oxide nanoparticles with bare surfaces tend to aggregate because of the strong magnetic attraction between these particles.[1,2]

Kuen-Song Lin (Yuan Ze University) recently fabricated a cancer chemotherapeutic formulation DOX nanocarrier, MIOs with polymer-modified surface and doxorubicin-loaded (MIOpoly-Dox). **Figure 1** shows the synthesis process of MIOpoly-Dox. The MIOs were surface modified by crosslinking Pluronic F127 (PF127) and branched polyethylenimine (bPEI) and formed MIOpoly nanocarrier. These nanocarriers were then loaded with doxorubicin (DOX) anticancer drugs to form the MIOpoly-DOX complex.[1] Grafting of PF127/bPEI onto the surface of MIOs was able to improve stability and dispersion, prevent oxidation, increase drug loading, and avoid agglomeration of MIOs. Therefore, the polymer-grafted nanocarriers could contribute towards a more effective drug delivery system.[1–3]

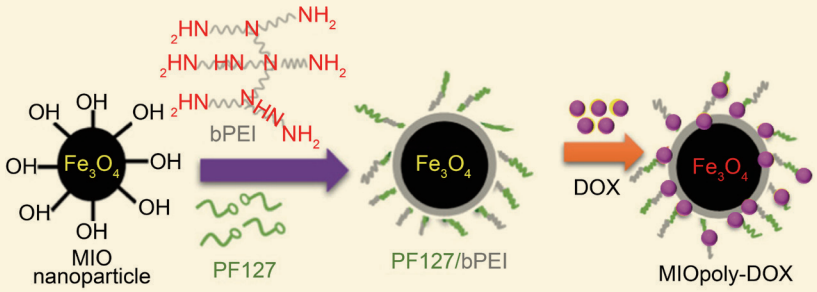

Fig. 1: Synthesis of MIOpoly-Dox. The PF127/bPEI-modified MIOs were called MIOpoly nanocarrier. DOX anticancer drugs were loaded in these nanocarriers, and then the MIOpoly-DOX complex was formed. [Reproduced from Ref. 1]

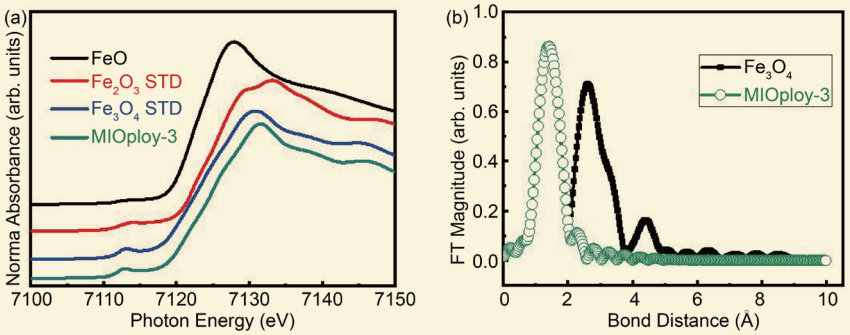

Fig. 2: (a) Fe K-edge derivative XANES spectra of FeO, Fe_2O_3, Fe_3O_4, and MIOpoly. (b) Fe K-edge EXAFS Fourier transformed spectra of MIOpoly. [Reproduced from Ref. 1]

X-ray absorption near edge fine structure (XANES)/extended X-ray absorption fine structure (EXAFS) spectra were measured in a transmission mode at **TLS 17C1**. The nature of the iron products was characterized by the XANES/EXAFS technique. The existence of Fe(III) in the prepared nanocarriers was indicated by the sharp feature observed at 7,134 eV, which occurred due to the dipole-allowed 1*s* to $4p_{xy}$ electron switch (**Fig. 2(a)**). Moreover, EXAFS can probe the critical atomic configurations, such as the type of near neighbors, interatomic distance, and numbers of inorganic nanocarriers. The fitting results indicated that the MIOpoly nanocarriers contained Fe atoms at the center that were interconnected largely by Fe–O (**Fig. 2(b)**). The distinctive Fe–O interatomic distance in MIOpoly nanocarriers was 1.96 Å with 3.95 coordination number. The nanocarriers contained a Debye–Waller factor (σ^2) of 0.0015 Å.[2] The coordination number of the neighboring oxygen shell oscillated between the MIOpoly nanocarriers and MIO nanoparticles, demonstrating the

protective role.

The thermogravimetric analysis (TGA) evaluates the weight loss of a substance at a certain temperature and can analyze the composition, percentage, or reaction of the compound (**Fig. 3(a)**). The interaction of MIO nanoparticles with PF127/bPEI polymer may lead to different microstructures. TGA results elucidated the thermal stability and proved the successful drug loading of MIOpoly nanocarriers. The surface modification of MIOs with polymers form spherical core-corona micelles in aqueous solution as evidenced using small-angle neutron scattering (SANS) from **TAIKAN** at J-PARC. Further, a distinctive increase in the scattering intensity in relation to the temperature was observed. At high Q (> 0.1 Å^{-1}), the SANS intensity of the MIOpoly nanocarriers remained unchanged at different temperatures. An increase in the structural arrangement of the nanoparticles was observed when the temperature was increased from 25 to 37°C. In contrast, upon increasing the temperature from 37 to 55°C, an insignificant increase in the structural arrangement was observed because the structure of the nanocarriers had reached their maximum capacity (**Figs. 3(b) and 3(c)**). Increasing temperature from 25 to 37°C and 55°C influenced the expansion of the core radius (R_c) and the agglomeration number (N_{agg}). The enlargement of the core radius (R_c) propels the shrinkage in the hard sphere radius of hydrophilic PF127 when temperatures increased from 25 to 57°C, suggesting the elimination of water from the corona region. This may be a result of the collapsed structure of the PF127 polymer. The team also examined drug release kinetics and cellular uptake efficiency. The Korsmeyer–Peppas and Weibull models displayed the best fit at low pH (pH 5.4) and high temperature (42°C) respectively, which suggests that the drug delivery system is pH and temperature dependent.

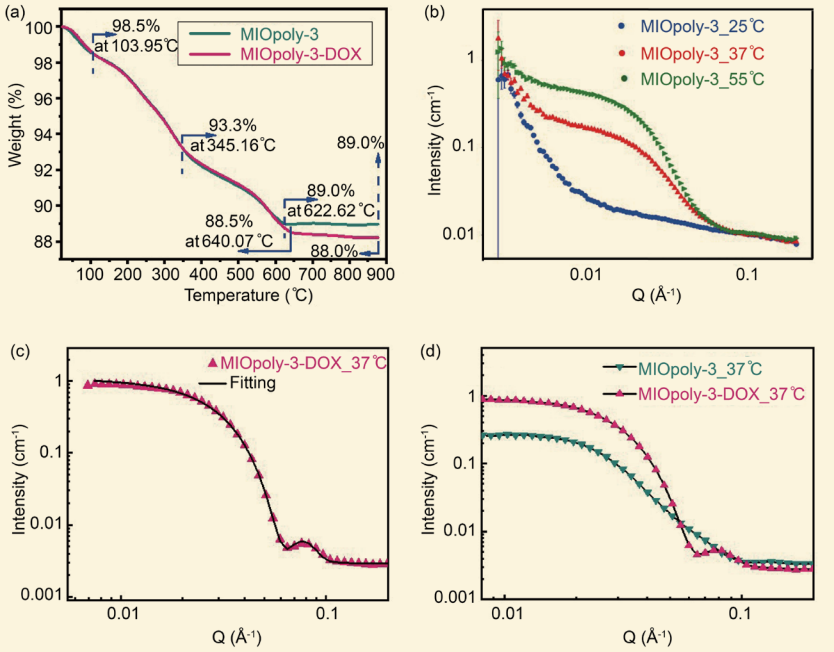

Fig. 3: (a) TGA analysis obtained from of MIOpoly nanocomposites and MIOpoly-DOX complex. SANS spectra of MIOpoly-3 (b) at different temperatures; (c) after DOX loading (37°C); and (d) before and after DOX loading at 37°C. [Reproduced from Ref. 1]

In summary, DOX-encapsulated pH-/thermo-responsive nanocarriers were successfully synthesized and characterized for their drug loading, release, and cellular uptake. (Reported by Kuen-Song Lin, Yuan Ze University)

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References

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