Gemcitabine-loaded metal-organic frameworks for pancreatic cancer

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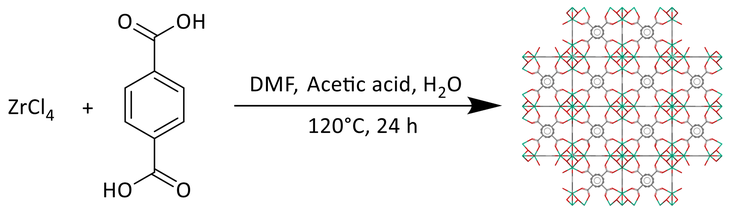
Introduction

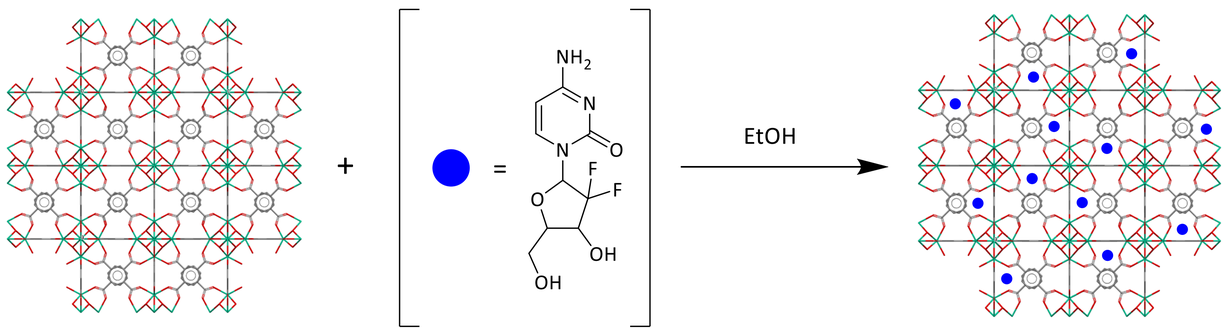
Pancreatic cancer (PC), despite its relatively low incidence rate, is fast becoming the leading cause of cancer-related death on a global scale according to estimates.[1,2] Gemcitabine (Gem) is used clinically as a treatment for PC, but recently has faced issues with resistance hence its use is limited.[3,4] Metal-organic frameworks (MOFs) are self-assembled structures containing metal centres joined together by organic linkers. These porous, stable and crystalline materials can be easily functionalised for a variety of applications such as drug delivery, hence this project aims to incorporate gemcitabine into or onto MOFs to generate a drug delivery system for PC.

UiO-66 Synthesis[5]



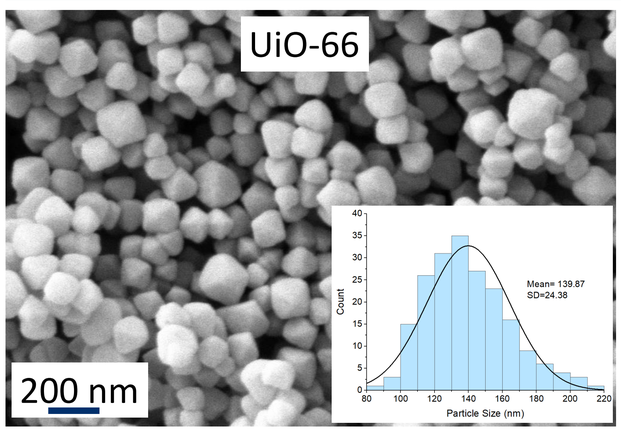
Drug Loading and Quantification

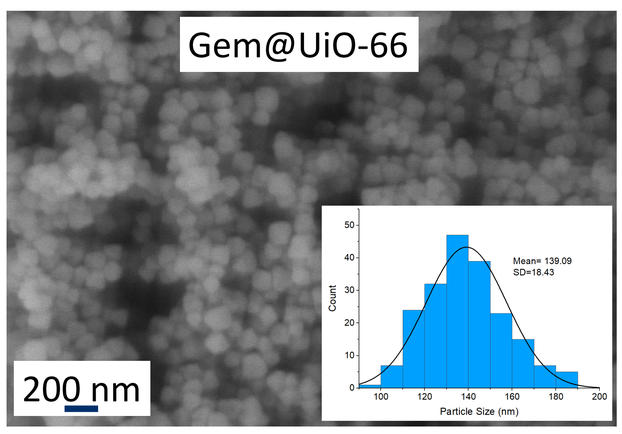
Drug loading of Gem in UiO-66 was determined by degradation of samples in pH 7.4 phosphate buffered saline, analysed by HPLC to gain the Gem concentration. A fake loading protocol, in which the MOFs were stirred in solution without Gem, was also completed to see any solvent effects of MOF structure and porosity. Drug loading was concluded to be 0.039 ± 0.007 µg/mg MOF.

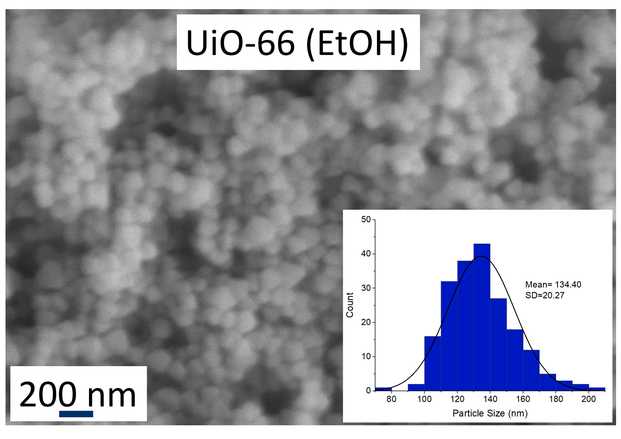


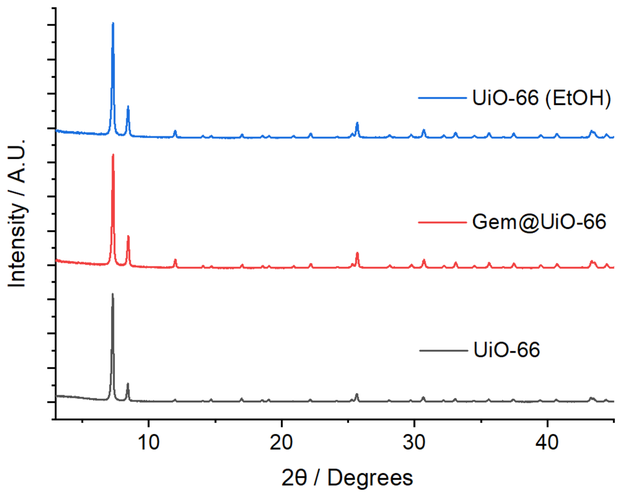
Characterisation

MOF morphology and crystallinity pre- and post-loading were determined using scanning electron microscopy (SEM) and powder X-ray diffraction. The SEM images show UiO-66, Gem loaded UiO-66 (Gem@UiO-66), and fake loaded UiO-66 (UiO-66 (EtOH)).

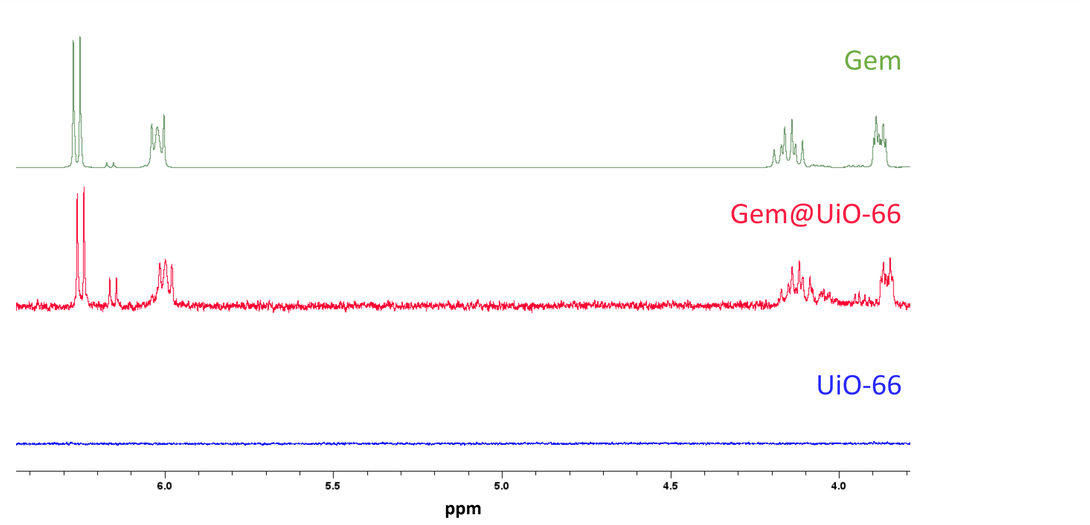


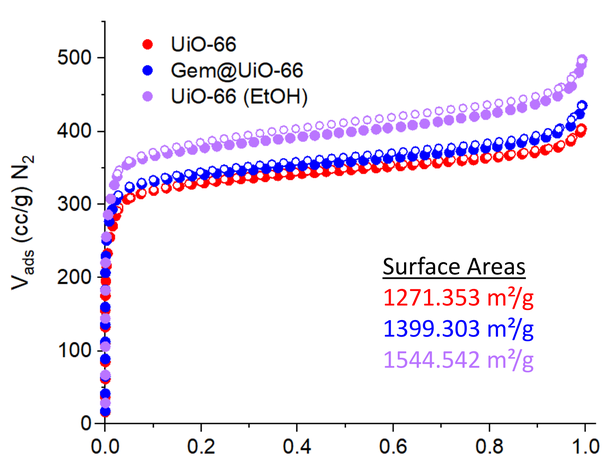


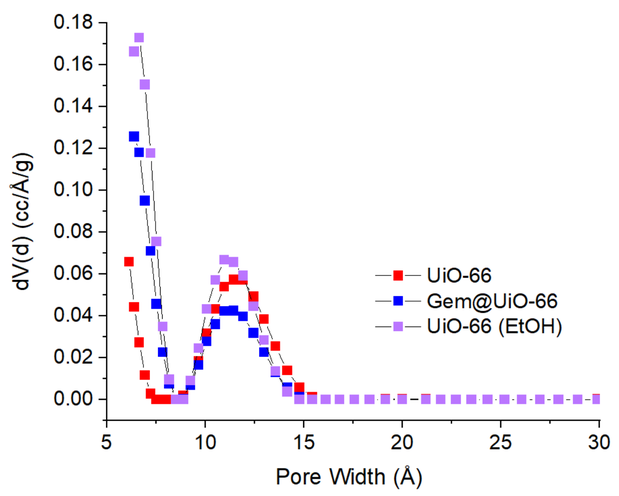




Proton NMR by acid digestion and N_2 gas adsorption have also been used to confirm Gem loading in UiO-66.

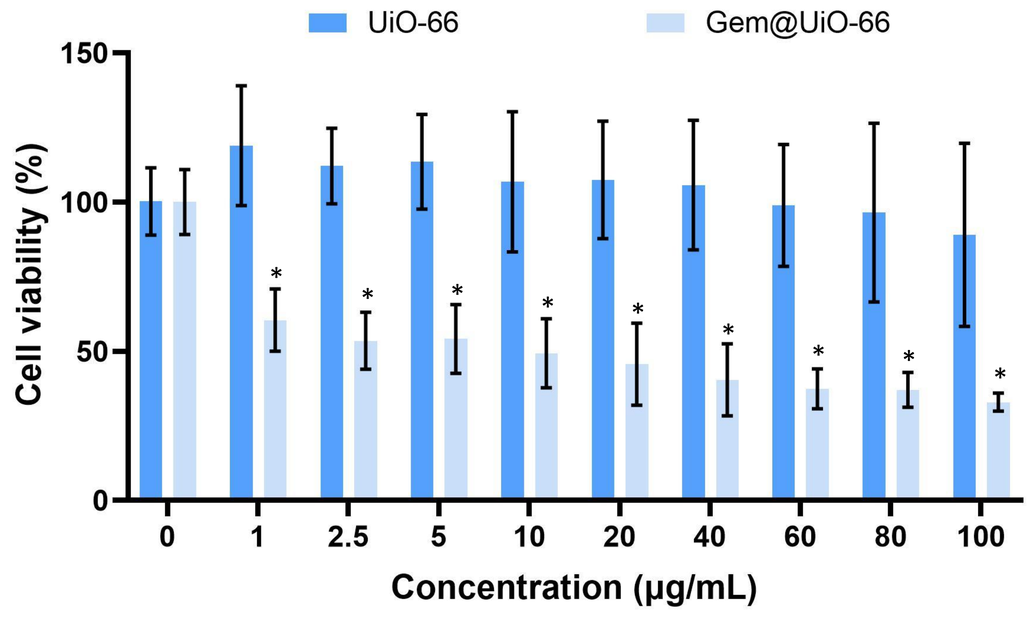






Preliminary Cytotoxicity Assay

Gem@UiO-66 has been tested for its toxicity using the Alamar blue assay in the PANC-1 (pancreatic adenocarcinoma) cell line, with an apparent concentration-dependent effect. Cells were incubated with UiO-66 and Gem@UiO-66 for 72 hours. There was no statistically significant difference in the control values between the two experiments, and no statistically significant difference between all UiO-66 concentrations and the control. Gem@UiO-66 concentrations were all statistically significantly different to the control (* = $p<0.05$).



Conclusions and Future Work

Overall, the loading of Gem into UiO-66 was successful, with preliminary evidence of a cytotoxic effect noticeable in the PANC-1 cell line and no notable toxicity of the carrier itself. Future work for this project will compare the effects of free Gem versus the Gem@UiO-66 using PANC-1 and other PC cell lines, including BxPC-3 and MiaPaCa-2, and release profiles will be collected. Furthermore, co-loading of drugs will also be attempted and any synergistic effects determined.

References

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