Chain length impact on the retro Diels-Alder mediated release of gemcitabine from hybrid nanoparticles

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Background: Pancreatic cancer is the 5th most common cause of cancer related death in the UK. As the 10th most common type of cancer, with a 10-year survival rate of only 5%, it is disproportionately also the deadliest type of malignant carcinoma. A previous study demonstrated a 56% improvement in tumour retardation with a novel formulation consisting of gold coated iron oxide nanoparticles (Au-IONP's) covalently surface conjugated with gemcitabine via a thermally labile Diels-Alder linker when compared to gemcitabine alone only after heat-mediated release of gemcitabine caused by the retro Diels-Alder reaction[1,2]. This study's objective is to investigate how the Diels-Alder linker alkyl chain length affects the heat-mediated process of drug release.

Methods: Synthesis of the different chain length analogues of the gemcitabine-linker conjugate was based on a protocol by Oluwasanmi et al[1]. Au-IONP's at 1mg/mL (based on Fe conc) were loaded in a 5:1 ratio of gemcitabine linker:Au-IONP's and magnetically separated from unbound gemcitabine-linker supernatant. The extent of drug loading was determined by HPLC analysis of the gemcitabine-linker supernatant. Drug release studies were carried out in triplicate at 20, 37, 45 and 60 ˚C to determine the extent of drug release.

Results: Synthesis of the gemcitabine-linker was determined by ^{1}H NMR and their drug release was approximately 95 – 100% via HPLC for all three gemcitabine-linker analogues. Drug release was negligible for all 3 formulations at 20 ˚C, with a sharp release profile observed at 37, 45 and 60 ˚C, with the total release correlating with higher temperatures. Longer chain length led to lower total drug release rates, demonstrating the effect of proximity to the gold shell on the heat-mediated retro Diels-Alder.

Conclusions: Release studies of all three formulations demonstrated their stability at 20 ˚C and a positive correlation between total release and temperature, with an increased rate of release as chain length decreased.