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| **Chain length impact on the retro Diels-Alder mediated release of gemcitabine**  **from hybrid nanoparticles towards pancreatic cancer therapy** |
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| **Background:** Pancreatic cancer, also known as pancreatic ductal adenocarcinoma (PDAC) is the deadliest type of malignant carcinoma with a 10-year survival rate of only 5%. Disproportionately, it is the 5th most common cause of cancer related death in the UK, while being the 10% most common type of cancer, demonstrating its abysmal survival rate. A previous study investigated the design and synthesis of a novel drug delivery formulation, wherein gemcitabine was conjugated to the surface of gold coated iron oxide nanoparticles (Au-IONP’s) via a 4-carbon thermally labile Diels-Alder based linker (TTLD4). Overall, with the aid of this Diels-Alder linker, the formulation was 56% more effective at tumor retardation in pancreatic models than gemcitabine alone. This study’s objective is to investigate whether the alkyl chain length of the Diels-Alder influences temperature of activation of drug release. |
| **Methods:** Synthesis of structural analogues of these linkers, was achieved by changing the 4-maleimidobutyric acid, with 3 and 6-length analogues via the EDC/NHS coupling reaction. A 5mL suspension of 5mg/mL drug-linker with 1mg/mL Au-IONP’s (based on Fe conc) was stirred at room temperature for 2h, to form a 5:1 ratio of drug-linker to Au-IONP’s. The drug conjugated Au-IONP’s were magnetically separated, with the supernatant analyzed using high performance liquid chromatography (HPLC). The three formulations were suspended within dialysis membranes at room temperature, 37 and 45 ˚C to determine drug release over time. |
| **Results:** Heat-mediated release of gemcitabine at 45 ˚C over 180 min from these formulations was confirmed to be based on linker length, which was 94%, 76% and 45% for TTLD3, TTLD4 and TTLD6, respectively. Drug loading of the Diels-Alder linkers in a 5:1 Drug/Au-IONP w/w ratio appears to favor those containing an even number of carbons TTLD4 (76%) & TTLD6 (57%) over TTLD3 (25%), possibly due to the linker likely being positioned perpendicular to the Au-IONP surface because of the 120˚ C-C bond. |
| **Conclusions:** The differences in the release of gemcitabine, based on variations in TTLD-(Au-IONP) linker length offer additional opportunities to further control the overall retro Diels-Alder mediated release of gemcitabine from Au-IONP surfaces. This includes the possibility of generating TTLD-(Au-IONP) formulations comprised of a blend of different TTLD linkers to fine tune the overall rate of retro Diels-Alder mediated drug release. |