Novel Iron Oxide-Gold Nanohybrids with Heat Triggered Surface Manipulation

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INTRODUCTION

Iron oxide-gold nanohybrids (HNPs) are core-shell nanoparticles whose properties include inherent magnetism from the iron oxide core and surface plasmon resonance (SPR) from the gold shell [1,2]. Laser irradiation of these HNPs triggers SPR resulting in localised heating to around 45°C, which can be used for thermal manipulation.

In order to facilitate the transport of cytotoxic drugs, a thermally-labile linker has been developed to attach the cytotoxic drugs to the HNP surfaces.

MATERIALS AND METHODS

The synthesis of a thiolated cycloadduct with gemcitabine was achieved by boc protection of 2-furanmethane thiol, followed by a Diels Alder reaction with 4-maleimidobutyric acid n-hydroxysuccinimide ester, forming a Diels Alder cycloadduct. This adduct was used to perform an amide coupling with previously boc protected gemcitabine, before an acid wash deprotection of the boc groups, yielded our gemcitabine cycloadduct linker.

The rate of the retro Diels Alder reaction was monitored using 1H NMR spectroscopy. Attachment of the modified gemcitabine onto the HNP and release studies at varied temperatures was quantified by HPLC. In vitro cytotoxicity was determined using MTT assay on BxPC-3 cell lines.

RESULTS AND DISCUSSION

The thiolated cycloadduct successfully underwent the retro Diels Alder reaction at 37, 45 and 70°C, with measurable levels of starting material being detected after the first 5 mins. However, no breakdown occurred at room temperature. Up to 4 mgmL-1 gemcitabine was capable of conjugation onto the HNPs and the release profile was in agreement with the NMR data showing temperature and time dependant drug release.

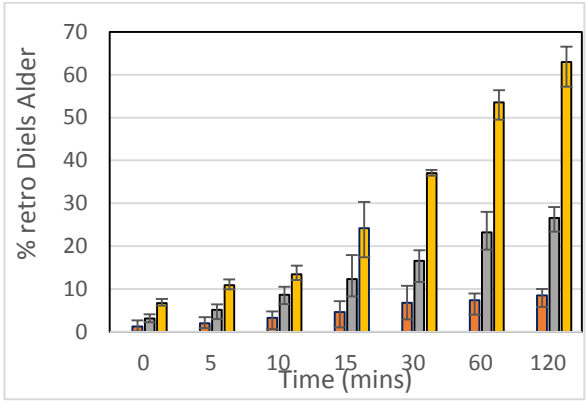

Fig. 1 Retro Diels Alder % conversion of thiolated adduct back into starting materials

In vitro cytotoxicity studies indicated that the gemcitabine-HNP formulation was more toxic than the unbound drug. Further investigation is required in order to determine mechanism of formulation uptake.

CONCLUSIONS

These studies highlight the potential of exploitation of retro Diels Alder linkers for the reversible binding of drug molecules to HNPs in pancreatic cancer therapy. Further in vitro and in vivo studies are required in order to elucidate the full clinical potential.

REFERENCES

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