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Improved plasma stability and sustained release profile of gemcitabine via polypeptide conjugation

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Abstract

To enhance the stability of the anticancer drug gemcitabine (2'-deoxy-2',2'-difluorocytidine), it was conjugated to poly-l-glutamic acid (PG-H) via a carbodiimide reaction. The synthesised poly-l-glutamic acid-gemcitabine (PG-G) was purified and characterised by using SDS-PAGE to estimate its molecular weight, HPLC to determine its purity and degree of drug loading, and NMR to elucidate the structure. In vitro aqueous hydrolytic studies showed that the gemcitabine release from the polymeric drug conjugate was pH dependent, and that the conjugation to PG-H improved its stability in human plasma. The release of the bound gemcitabine from PG-G in plasma was mediated by a hydrolytic process. It began with a lag phase, followed by linear release between 12 and 48h, and reached equilibrium at 72h with 51% of the gemcitabine released. In vitro cytotoxicity studies using MCF-7 and MDA-MB-231 human mammary cancer cells, as well as human dermal fibroblasts (HDF), showed that PG-G displayed a lower dose dependent cytotoxic effect with respect to the parent drug gemcitabine. On the other hand, in 4T1 mouse mammary tumour cells, PG-G and gemcitabine showed similar toxicities. Gemcitabine was more than likely released hydrolytically from PG-G and taken up by MCF-7, MDA-MB-231 and HDF, whereas both released gemcitabine and PG-G were taken up by 4T1 to mediate the observed cytotoxicities. The improved stability and extended sustained release profile may render PG-G a potential anticancer prodrug.

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