Poly(ester amide) nanoparticles with covalently-conjugated drugs for drug delivery

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Poly(ester amide)s (PEAs) (Fig a) are promising materials for a wide range of biomedical applications including tissue engineering and drug delivery, as they combine the degradability of esters with the favourable mechanical properties of polyamides. The choice of dicarboxylic acid, diol, and α-amino acid can be used to tune the polymer properties and degradability. The incorporation of α-amino acids with pendant functional groups such as carboxylic acids or amines can provide sites for further PEA functionalization to conjugate cell signalling molecules, drugs, or targeting moieties for biomedical applications. Here we describe the development of PEA nanoparticles with a covalently immobilized anti-cancer drug floxuridine. Covalent attachment of the drug should provide a slow and controlled release in comparison to physical encapsulation strategies, which typically result in a rapid, burst release of a large fraction of the drug.

First, a functionalized PEA containing 10% of a *L*-aspartic acid-based monomer was successfully synthesized, and protecting groups were removed from the amino acid to provide pendant carboxylic acid groups. Floxuridine was then conjugated via an ester linkage to afford the PEA-drug conjugate. Next, the conditions were optimized to prepare nanometer-sized particles based on this drug conjugate. This was achieved using an emulsification-diffusion method with poly(vinyl alcohol) (PVA) as a surfactant. Freeze-dried particles were characterized by dynamic light scattering (DLS) and scanning electron microscopy (SEM). These results suggested that the particles had an average diameter of ~200 nm. The release of floxuridine from the nanoparticles was studied *in vitro*. It was found that ~6% of the drug was release rapidly during the first several hours, but the remainder of the drug exhibited a slow release, likely due to the requirement for ester hydrolysis to occur within the hydrophobic core of the particles. This nanoparticle-based prodrug approach may therefore reduce the toxicity of this chemotherapeutic and reduce the frequency required for its administration.

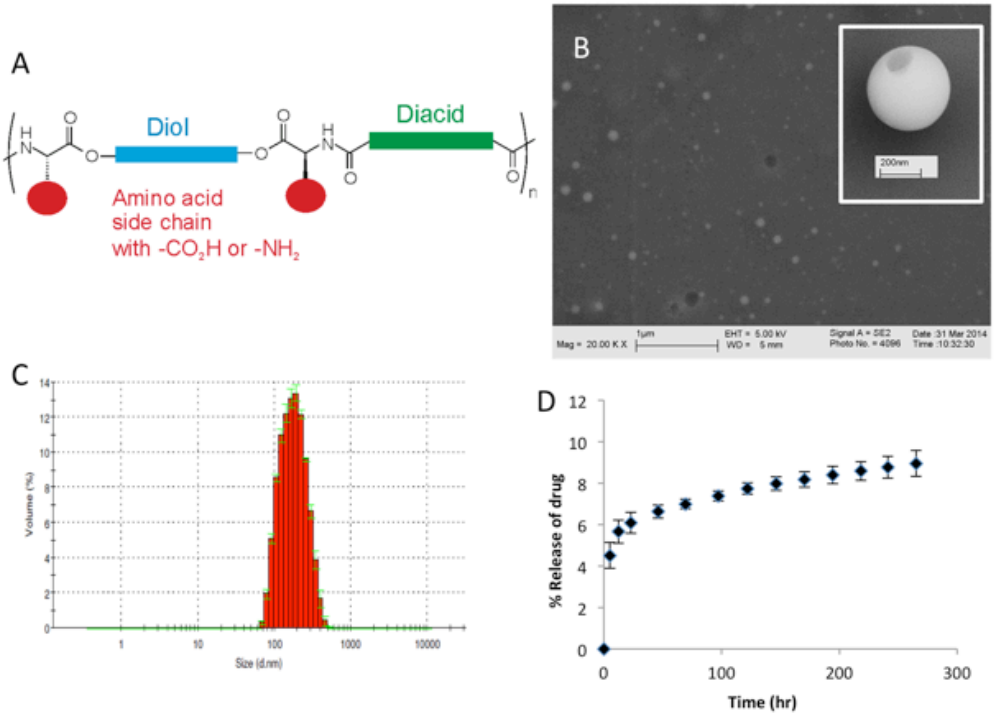

Figure: A) Chemical structure of PEA; B) SEM images of PEA nanoparticles; C) DLS trace for PEA nanoparticles; D) Release rate of the covalently immobilized anti-cancer drug floxuridine from PEA nanoparticles.

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