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| **Poly(diglycerol adipate) variants as enhanced nanocarrier replacements in drug delivery systems** |
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| **Background:** Sustainably derived poly(glycerol adipate) (PGA) is considered to deliver all the desirable features expected in a polymeric scaffold for drug-delivery. It is biodegradable, biocompatible, capable of self-assembly into nanoparticles (NPs) and has a functionalisable pendant group. Despite exhibiting these advantages over commercial alkyl polyesters, PGA suffers from a series of key drawbacks caused by poor amphiphilic balance. This leads to weak drug-polymer interactions, low drug-loading in NPs and NPs stability. To overcome this, in the present work, we have applied a significant variation of the polyester backbone while maintaining mild and sustainable polymerisation conditions. |
| **Methods:** PGA and variants thereof have been characterised using 1H NMR spectroscopy, GPC, DSC and water contact angle measurements. Nanoparticles were synthesised by nanoprecipitation and were characterised by DLS and zeta-potential measurements. Nanoencapsulation of coumarins was determined by measuring ΔA% using UV-vis spectrometry. Polymers were tested for *in vitro* cytotoxicity using a Presto Blue cell viability assay on human carcinoma colon epithelial cells. *In vivo* cytotoxicity and uptake were investigated by challenging *C. elegans* nematodes to polymers. |
| **Results:** PGA, its diglycerol counterparts poly(diglycerol adiapte) (PDGA), and variants of both including a 1:1 ratio of (di)glycerol:1,6-*n*-hexanediol (PGAHex and PDGAHex) were successfully synthesised via a mild enzymatic polymerisation. All polymers self-assembled into NPs of ~150 nm in size and with PGAHex and PDGAHex demonstrating excellent stability in bovine serum albumin up to 24 h. PDGA NPs had low stability, however the polymer demonstrated improved water solubility. All polymers were tested for their ability to encode enhanced drug loading with both hydrophobic and more hydrophilic coumarin compounds. Both classes of coumarin were successfully encapsulated, with the more hydrophobic coumarin (coumarin-6) displaying significantly enhanced apparent water solubility compared to its unformulated state. Furthermore, all polymers demonstrated good biocompatibility in both *in vitro* and *in vivo* (whole organism) experiments. Coumarin-6 encapsulated PDGAHex NPs were used to track uptake *in vivo* in nematodes, showing successful coloured NPs delivering across the *C. elegans* intestinal membrane. (P. L. Jacob *et al,*, J. Colloid Interface Sci., 2023, **641**, 1043–1057) |
| **Conclusions:** Enzymatic polycondensation has been exploited as a more sustainable, one-pot tool to produce new functional polyesters. In-depth physico-chemical and biological screenings have been adopted to study the behavior of the materials. Of the newly synthesised polymers, the hexanediol modifications demonstrated excellent stability and an improved ability to encapsulate hydrophobic compounds. This has been rationalised by an improvement in the amphiphilic balance between the hexanediol-adipic hydrophobic portion within the polymer backbone as well as the additional, stabilising hydroxyl functionalities provided by the diglycerol moiety. The discovered synergistic relationship between the hydrophilic and hydrophobic backbone segments renders this novel material highly suited to pharmaceutical and biomedical applications. |

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