GLYCEROL- AND DIGLYCEROL-BASED POLYESTERS: EVALUATION OF BACKBONE ALTERATIONS UPON NANO-FORMULATION PERFORMANCE

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Background: Despite the success of polyethylene glycol-based (PEGylated) polyesters in the drug delivery and biomedical fields, concerns have arisen regarding PEG's immunogenicity and limited biodegradability. In addition, inherent limitations, including limited chemical handles as well as highly hydrophobic nature, can restrict their effectiveness in the physiological conditions of the polyester counterpart. To address these matters, an increasing amount of research has been focused towards identifying alternatives to PEG. One promising strategy involves the use of bio-derived polyols, such as glycerol. In particular, glycerol is a hydrophilic, non-toxic, untapped waste resource and as other polyols, can be incorporated into polyesters via enzymatic catalysis routes.

Methods: In this work, the effects of purification steps and variations in the stoichiometry of monomer feed ratio on the amphiphilicity balance of glycerol/diglycerol-based polyester backbones were investigated. The polymers were prepared using a one-pot, one-step enzymatic polycondensation process and were characterized for their physiochemical properties. More specifically, a systematic screening is conducted focusing on the incorporation of 1,6-hexanediol (Hex) (hydrophobic diol) into both poly(glycerol adipate) (PGA) and poly(diglycerol adipate) (PDGA) at different (di)glycerol:hex ratios (30:70; 50:50 and 70:30 mol/mol). We examined their impact not only on their physiochemical properties, but also on nanoparticle properties, including nanoparticle formation, stability, drug encapsulation, and cell uptake.

Results: It was found that by changing the (hydrophilic) polyol: (hydrophobic) diol feed ratio, polymers with different properties could be prepared in mild and sustainable conditions. By varying the amphiphilicity of the backbone, we demonstrated that minor adjustments influence the NPs formation, NPs stability, drug encapsulation, cell uptake, and degradation of these polymers, despite the high chemical similarity. Moreover, the best-performing materials have shown good biocompatibility in both in vitro and in vivo (whole organism) tests. As preliminary result, the sample containing diglycerol and Hex in a 70:30 ratio, named as PDGA-Hex 30%, has shown to be the most promising candidate in this small library analysed. It demonstrated comparable stability to the glycerol-based samples in various media but exhibited superior encapsulation efficiency and enhanced cellular uptake of a model hydrophobic dye.

Conclusions: The variation of the chain amphiphilicity allows the fine-tuning of NPs stability in biologically relevant media, as well as drug encapsulation efficiency. Combined with the assessed biodegradability and the absence of cytotoxicity in vitro experiments as well as in vivo whole organism models, this work shows promising potential for further screening of these polymers and new variations as nano-drug delivery carriers. This in-depth investigation provides these new insights into the design and modification of biodegradable (di)glycerol-based polyesters, potentially paving the way for more effective and sustainable PEG-free drug delivery nano-systems in biomedical fields.