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Influence of architecture of high molecular weight linear and branched polyglycerols on their biocompatibility and biodistribution

Muhammad Imran ul-haq [a], Benjamin F.L. Lai [a], Rafi Chapanian [a], Jayachandran N. Kizhakkedathu [a,b,*]

[a] Centre for Blood Research, Department of Pathology and Laboratory Medicine, The University of British Columbia, Life Sciences Centre, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada
[b] Department of Chemistry, The University of British Columbia, Life Sciences Centre, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada

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ABSTRACT

The availability of long circulating, multifunctional polymers is critical to the development of drug delivery systems and bioconjugates. The ease of synthesis and functionalization make linear polymers attractive but their rapid clearance from circulation compared to their branched or cyclic counterparts, and their high solution viscosities restrict their applications in certain settings. Herein, we report the unusual compact nature of high molecular weight (HMW) linear polyglycerols (LPGs) (LPG – 100; M_n – 104 kg mol^{-1}, M_w/M_n – 1.15) in aqueous solutions and its impact on its solution properties, blood compatibility, cell compatibility, *in vivo* circulation, biodistribution and renal clearance. The properties of LPG have been compared with hyperbranched polyglycerol (HPG) (HPG-100), linear polyethylene glycol (PEG) with similar MWs. The hydrodynamic size and the intrinsic viscosity of LPG-100 in water were considerably lower compared to PEG. The Mark–Houwink parameter of LPG was almost 10-fold lower than that of PEG. LPG and HPG demonstrated excellent blood and cell compatibilities. Unlike LPG and HPG, HMW PEG showed dose dependent activation of blood coagulation, platelets and complement system, severe red blood cell aggregation and hemolysis, and cell toxicity. The long blood circulation of LPG-100 ($t_{1/2\beta}$, 31.8 ± 4 h) was demonstrated in mice; however, it was shorter compared to HPG-100 ($t_{1/2\beta}$, 39.2 ± 8 h). The shorter circulation half life of LPG-100 was correlated with its higher renal clearance and deformability. Relatively lower organ accumulation was observed for LPG-100 and HPG-100 with some influence of on the architecture of the polymers. Since LPG showed better biocompatibility profiles, longer *in vivo* circulation time compared to PEG and other linear drug carrier polymers, and has multiple functionalities for conjugation, makes it a potential candidate for developing long circulating multifunctional drug delivery systems similar to HPG.

1. Introduction

Development of multifunctional and long circulating polymers is critical to the development of drug delivery vehicles, imaging agents and conjugates for the treatment of various diseases including cancer [1–8]. Polymer conjugation to drugs is an effective method to prolong their circulation half-life as well as it gives favorable effects on their tissue distribution. For instance, the conjugation of anticancer drugs to long circulating polymers has shown enhanced accumulation in tumor tissues due to their increased permeability to the leaky tumor vasculature and limited lymphatic drainage owing to enhanced permeation and retention (EPR) effect [1,9,10]. As highlighted recently, there is a need for long circulating multifunctional polymers [1,5,7,11] and mutlifunctionality is critical for the conjugation of drug molecules, targeting moieties and imaging agents [4,12,13]. Dendrimers and branched polymers have many of these advantages but their synthesis some times requires many steps and is laborious. In the case of branched polymers most often heterogeneous distribution of molecular weights are reported [14].

It has been shown that the size, shape, deformability and charge of the macromolecules can influence their glomerular filtration and blood circulation [15–17]. In the case of polymeric systems, as highlighted recently by Szoka and Frechet, the optimization of size and topology of the polymer structure is critical in the design of long circulating polymeric systems [15,18]. It has been

* Corresponding author. Department of Chemistry, The University of British Columbia, Life Sciences Centre, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada. Tel.: +1 604 822 7085; fax: +1 604 822 7742.
E-mail address: jay@pathology.ubc.ca (J.N. Kizhakkedathu).

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