Journal of Pharmaceutical Sciences 105 (2016) 293–300

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutical Nanotechnology

The Pharmacokinetics and Biodistribution of a 64 kDa PolyPEG Star Polymer After Subcutaneous and Pulmonary Administration to Rats

Song Yang Khor [1, 2], Jinming Hu [1, 2], Victoria M. McLeod [2], John F. Quinn [1, 2], Christopher J.H. Porter [1, 2], Michael R. Whittaker [1, 2, *], Lisa M. Kaminskas [2, *], Thomas P. Davis [1, 2, 3, *]

[1] *ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia, 3052*
[2] *Drug Delivery Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia, 3052*
[3] *Department of Chemistry, University of Warwick, Coventry, ULCV4 7AL, UK*

ARTICLE INFO

Article history:
Received 5 October 2015
Revised 16 November 2015
Accepted 17 November 2015

Keywords:
nanoparticles
star polymers
PEG
pharmacokinetics
biodistribution
bioavailability
subcutaneous
pulmonary

ABSTRACT

PolyPEG star polymers have potential utility as cost-effective polymeric drug delivery vehicles, and as such, it is important to develop an understanding of their biopharmaceutical behavior. Moreover, although a number of studies have evaluated the utility of PolyPEG stars *in vitro*, investigation of these novel materials *in vivo* has been limited. Herein, we evaluated the pharmacokinetics of a 64 kDa tritiated PEG-based star polymer after subcutaneous and pulmonary administration in rats. After subcutaneous administration, the star polymer showed near complete bioavailability (~80%) and a similar organ biodistribution profile to the polymer after intravenous administration. After intratracheal instillation to the lungs, the star polymer showed limited bioavailability (~3%), and most of the administered radiolabel was recovered in lung tissue and feces after 6 d. The data reported here suggest that star polymers display similar pharmaceutical behavior to PEGylated dendrimers after subcutaneous and inhaled delivery and may therefore be used as similar, but more cost-effective drug delivery vehicles.

Introduction

Aside from destroying rapidly dividing cancer cells, anticancer drugs also attack healthy proliferative cells in the gastrointestinal tract, bone marrow, and hair follicles, resulting in adverse side effects such as inflammation and ulceration of the gastrointestinal tract, nausea, and alopecia.[1,2] Nanotechnology promises to circumvent such undesirable adverse side effects by providing functional nanoparticle platforms that deliver therapeutic agent(s) to the desired target and enable controlled and potentially site-specific drug liberation. To achieve this outcome, nanoparticle platforms require stability in the systemic circulation and at the site of administration, biocompatibility, and the ability to accumulate at the target site. The biocompatibility and plasma exposure of nanoparticle and polymer-based drug delivery vectors can be improved via surface coverage with polyethylene glycol (PEG), which inhibits plasma protein binding and subsequent sequestration by macrophages of the mononuclear phagocyte system.[3,4] Importantly, prolonging plasma circulation times promotes passive uptake of the nanoparticle into solid tumors via the enhanced permeation and retention effect.[5] In addition, there may be some advantage to using smaller (10-20 nm) nanoparticles as tumor-targeted drug delivery vectors as opposed to larger (typically >100 nm) systems, because smaller particles have enhanced motility at the site of extravasation in a solid tumor to enable access to more drug-resistant cells in hypoxic regions of the tumor microenvironment.[6-8]

A number of different nanoparticle formulations have been developed to exploit the enhanced permeation and retention effect, and it is generally accepted that nanoparticles <100 nm are the most optimal for accumulation.[9] Owing to their precise molecular structure and surface functionalities, significant interest has been focused on dendrimers for drug delivery applications.[10-12] However, dendrimer production is expensive (especially for

* *Correspondence to*: Thomas P. Davis (Telephone: +61-3-9903-9260; Fax: +61-3-9903-9583); Michael R. Whittaker (Telephone: +61-3-9903-9266; Fax: +61-3-9903-9583); and Lisa M. Kaminskas (Telephone: +61-3-9903-9522; Fax: +61-3-9903-9583).
E-mail addresses: Michael.whittaker@monash.edu (M.R. Whittaker), Lisa.kaminskas@monash.edu (L.M. Kaminskas), thomas.p.davis@monash.edu (T.P. Davis).

http://dx.doi.org/10.1016/j.xphs.2015.11.038
0022-3549/

higher order structures where higher molecular sizes are desired) due to the repeated nature of their synthesis, and increased production costs may hinder their successful clinical translation and market performance. It is therefore important to explore other potential alternatives that display the same benefits of dendrimers, but with greater synthetic simplicity.

Star polymers possess many of the characteristics of dendrimers with the significant advantage that it is easier to tune their size. Star polymers have versatile design characteristics and can be synthesized using relatively simple techniques. The star polymers are assembled by cross-linking linear polymer chains to form a star-shaped polymer. This simple yet versatile construction enables easy transition to large scale production and thus reduces overall production costs. Synthesis and postmodification of star polymers with low polydispersity (PDI < 1.2) and tunable physiochemical properties using arm-first reversible addition-fragmentation chain transfer (RAFT) polymerization has previously been demonstrated.[1,13,14] The flexibility of the RAFT-derived platform was exhibited by pH-stimulated intracellular delivery of both doxorubicin and heat shock protein Hsp90 inhibitor in mammalian cancer cell lines.[15,16] Moreover, star polymers have shown promise as theranostic vectors, particularly with magnetic resonance imaging contrast imaging techniques.[17-21]

Recently, we also characterized the impact of molecular weight (hydrodynamic volume) on the pharmacokinetics of intravenously (IV) delivered ^{3}H-labeled star polymers in rats and tumor-bearing nude mice.[22] The stars were synthesized by cross-linking poly (oligoethylene glycol) acrylate arms to form a star-shaped polymer (Fig. 1). Additionally, the stars were constructed with vinyl dimethyl oxazolone functional groups in the core. The vinyl dimethyl oxazolone groups in the core were then exploited to attach tritiated ethanolamine via amide bonds and yield ^{3}H-labeled star polymers. The polymer remained intact in circulation, enabling pharmacokinetic calculations based on radioactivity detected in plasma samples at varying time points. In general, as the molecular weight of star polymers was increased, plasma exposure and tumor biodistribution increased. This correlation between molecular weight and systemic disposition after intravenous administration in rats can also be found for polylysine dendrimers with different PEG chain lengths.[23] Owing to the similarities in biopharmaceutical behavior between star polymers and dendrimers described so far, further comparisons should be conducted to test the capabilities of star polymers as a viable alternative to dendrimers.

Targeting is a significant challenge in nanomedicine and in a recent review Cheng et al.[24] emphasized the advantage of using a holistic approach to polymer nanoparticle design to couple the molecular design characteristics with a specific mode of delivery. Although IV administration is the most direct route for delivering nanoparticles to the bloodstream (and also the conventional route for the administration of chemotherapeutic drugs and nanomedicines), other routes of administration offer specific advantages over conventional IV delivery. Subcutaneous (SC) delivery, for instance, can allow self-administration without the need for trained medical personnel to administer the dose. Maximal plasma concentrations are also reduced when compared with IV administration which may limit systemic side effects. In addition, SC administration may allow the site-specific targeting and controlled release of the therapeutic payload in lymph nodes draining the injection site, providing an opportunity to target lymph node metastases downstream from a primary tumor.[25] However, the main drawback of SC delivery is the potential for incomplete absorption and drug liberation at the injection site which can cause localized toxicity. This can be limited, nonetheless, via optimization of the polymers physicochemical properties and drug linker chemistry to facilitate efficient absorption and drug-polymer stability at the injection site.

Another attractive route of administration is inhaled delivery to the lungs, which can provide a needle-free means of delivering nanomedicines to the systemic circulation or allow direct access of associated drugs to lung-resident diseases (such as lung cancer, chronic obstructive pulmonary disease and lung infections) while limiting the systemic exposure of potentially toxic drugs.[26-28]

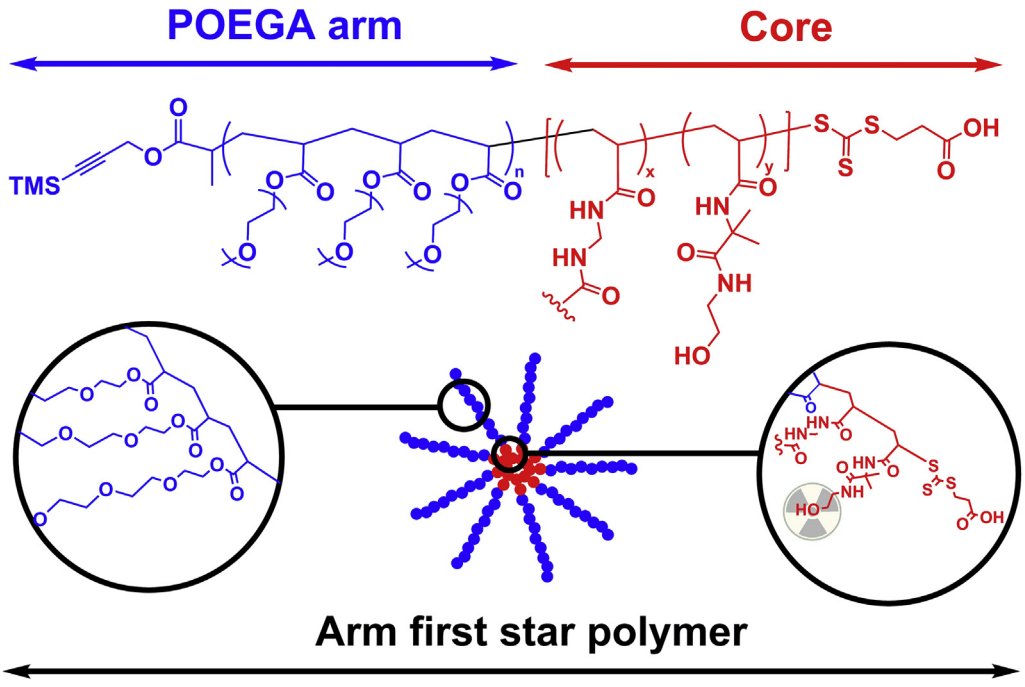

Figure 1. Chemical structure of arm-first star polymer consisting of POEGA arm and core. The radiation symbol depicts the approximate location of the core confined ^{3}H radiolabel. POEGA, poly(oligoethylene glycol) acrylate.