



# Single-chain polymer nanoparticles in controlled drug delivery and targeted imaging

A. Pia P. Kröger<sup>a</sup>, Jos M.J. Paulusse<sup>a,b,\*</sup>

<sup>a</sup> Department of Biomolecular Nanotechnology, MESA+ Institute for Nanotechnology and TechMed Institute for Health and Biomedical Technologies, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

<sup>b</sup> Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, P.O. Box 30.001, 9700 RB, Groningen, The Netherlands

## ARTICLE INFO

### Keywords:

Single chain polymer nanoparticles  
Intramolecular cross-linking  
Biomedical applications  
Targeted imaging  
Controlled drug delivery

## ABSTRACT

As a relatively new class of materials, single-chain polymer nanoparticles (SCNPs) just entered the field of (biomedical) applications, with recent advances in polymer science enabling the formation of bio-inspired nanosized architectures. Exclusive intramolecular collapse of individual polymer chains results in individual nanoparticles. With sizes an order of magnitude smaller than conventional polymer nanoparticles, SCNPs are in the size regime of many proteins and viruses (1–20 nm). Multifaceted syntheses and design strategies give access to a wide set of highly modular SCNP materials. This review describes how SCNPs have been rendered water-soluble and highlights ongoing research efforts towards biocompatible SCNPs with tunable properties for controlled drug delivery, targeted imaging and protein mimicry.

## 1. Introduction

Polymer nanoparticles based on individual polymer chains, coined Single-Chain Polymer Nanoparticles (SCNPs) have been developed over the past two decades [1–4]. SCNPs are accomplished by exclusive intramolecularly collapsing/folding of the polymer, which leads to exceptionally small polymer nanoparticles in the sub-20 nm size range. The collapse is either achieved by self-assembly or by covalent cross-linking of functional groups on the precursor polymer or rather mediated by external cross-linkers [1]. SCNPs have been prepared via multiple ways, including via irreversible and dynamic covalent cross-linking reactions such as thermal cycloaddition [5, 6], Cu(I)-mediated click chemistry [7–9], olefin metathesis [10], disulfide [11] and hydrazone [12] formation as well as via non-covalent cross-linking interactions, including hydrogen-bonding motifs and metal coordination, which have been comprehensively reviewed earlier [1–4, 13–18]. Whereas SCNP formation was originally carried out under very harsh conditions [5, 19], orthogonal and click-chemistry techniques allowed mild reaction conditions, complex design strategies and upscaling of the synthesis [20–22]. Furthermore, a variety of single-chain architectures has been introduced from single block and multiblock to star particles, hairpins and tadpole molecules, in part aimed at approaching naturally occurring materials, such as proteins [23–26].

Proteins occur in biological organisms and display a wide variety of

functions including for example structural support, transport, and catalysis. Proteins in nature are directly translated from the corresponding RNA, one amino acid after another, by ribosomes resulting in perfectly defined structures (PDI = 1) with exquisite control over composition and (dynamic) function. In situ synthesis of proteins is limited by the number of amino acids, sequence length and/or maintained function of the proteins [27]. Therefore, not only synthetic proteins, but also protein-like materials are highly sought after, for example aiming at increasing biocompatibility of materials. Moreover, the substrate specificity of proteins is not surpassed by synthetic means and is therefore of great interest in catalysis applications or in cell targeting. To achieve such functions, cooperative binding effects are pivotal, which may be provided by synthetic polymer analogues.

A wide range of design strategies for SCNPs has been developed to adjust the properties of polymers and particles. Next to broadening the synthetic toolbox and achieving control over size and SCNP folding, recent work has focused on designing SCNPs towards (biomedical) applications. In particular their small size can be expected to cause unusual biodistribution behavior [28]. For nanoparticles below 6 nm, full renal clearance is to be expected, which would certainly increase biocompatibility, but also limit their potential to short-time applications [29]. When regarding distribution studies of nanomaterials in general, size plays a major role. Whereas liposomes of < 200 nm have been reported to accumulate in the spleen, liposomes below 70 nm are

\* Corresponding author at: Department of Biomolecular Nanotechnology, MESA+ Institute for Nanotechnology and TechMed Institute for Health and Biomedical Technologies, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands.

E-mail address: [j.m.j.paulusse@utwente.nl](mailto:j.m.j.paulusse@utwente.nl) (J.M.J. Paulusse).

<https://doi.org/10.1016/j.jconrel.2018.07.041>

Received 13 June 2018; Received in revised form 17 July 2018; Accepted 27 July 2018

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predominantly found in the liver after IV administration to mice [30]. For gold nanoparticles, series of differently sized nanoparticles (10–250 nm [31] and 15–200 nm [32]) were intravenously administered to mice and rats respectively and only the smallest species (10 nm and 15 nm respectively) were detected in the rodents' brains [31, 32]. Further, 15–100-nm-sized gold nanoparticles were also evaluated in terms of tumor uptake and penetration depth *in vitro* and *in vivo*, and accompanied by simulations, showing increased tumor penetration depths for smaller nanoparticles with increased tumor tissue size [33]. In general, size plays a central role in the biodistribution and lifetime in the body of nanomaterials [28]. The exact size of polyamidoamine dendrimers has for example been demonstrated to play a crucial role in their cell uptake and blood-circulation times [34]. Whereas dendrimers of 6.7 nm accumulated in the brains of dogs, dendrimers of 4.3 nm were undetectable. Consequently, proper size determination and tuning is crucial for *in vivo* analysis.

The intramolecular interactions in SCNPs, which establish their 3D-structure, and the exceptionally small sizes of SCNPs, may give unique advantages in these biomedical applications, in particular in targeting elusive or difficult to reach tissues, such as the brain or dense tumors, while harnessing a therapeutic cargo. This review focuses on the design parameters for SCNPs to ready them for biomedical applications, such as protein mimicry, controlled drug delivery, and targeted imaging applications.

## 2. Characterization of SCNPs

The unusually small size of SCNPs may complicate their characterization. However, a combination of characterization techniques ranging from size exclusion chromatography (SEC), to light scattering and NMR techniques, have been successfully used to determine SCNP sizes, their size reduction and the particles' morphologies.

The relative size reduction from polymer to collapsed SCNP is typically observed by SEC as an apparent size reduction due to the reduced hydrodynamic radius of SCNPs [35]. Additionally, SEC coupled detectors such as refractive index (RI), UV-vis, multi-angle light scattering (MALS)/static light scattering (SLS), fluorescence and viscometers can provide further information about the SCNPs. Self-assembled SCNP structures can be even more challenging to analyze via chromatography methods, as supramolecular interactions are concentration and solvent dependent and comparable reference polymers are not always available. Berda and co-workers demonstrated the usefulness of a SEC coupled MALS detector, which was sensitive to multi-chain aggregates, which were not detectable with an RI detector [11, 36]. MALS analysis further confirms a preserved (absolute) molecular weight of polymer and SCNP, despite differing elution times/hydrodynamic radii. The SCNP radius of gyration ( $R_g$ ) cannot be determined by MALS as SCNPs are usually smaller than 10 nm. Instead, intrinsic viscosity ( $[\eta]$ ) obtained by a SEC coupled viscometer reveals  $R_H$ , which should be in line with the elution order from the column. Additionally, viscometric data yield the Mark–Houwink–Sakurada parameter  $\alpha$ , which is related to the excluded volume parameter or scaling exponent ( $\nu$ ) from the Flory mean field theory of a self-avoiding polymer chain [37]. Both parameters provide information on the coiling degree of the polymer or SCNP and can also be estimated in the bulk [37–39].

Commonly, sizes of polymers and nanoparticles in solution are obtained from dynamic light scattering (DLS) based on their diffusion in solution, which influences the fluctuation in scattering intensity. Intensity of the scattered light is dependent on particle radius to the 6th power, and hence more sensitive for larger particles. To circumvent this influence of bigger structures on scattering intensity, DLS in material science is often transported to number or even volume plots under the assumption of the Mie theory, which makes the distribution more error-prone and larger particles are neglected [40, 41]. As these assumptions are not necessarily fulfilled for SCNPs, one must make careful use of such plots and only as complementary information. Similar to DLS,

diffusion ordered spectroscopy (DOSY) NMR determines sizes based on the diffusion of particles, and hence, can be used by to verify DLS data without the influence of scattering [16, 42]. Additionally, viscometric measurements provide also the hydrodynamic radius ( $R_H$ ), as well as  $[\eta]$ , which drops in case of merely intramolecular cross-linking.

In contrast to MALS, small-angle neutron scattering (SANS) and small-angle X-ray scattering (SAXS) measurements can provide  $R_g$  also for structures < 10 nm. Additionally,  $\nu$  is obtained via the form factor [38]. Fitting of theoretical form factors can attribute geometrical shapes, such as coils and spheres, to the SCNP structure and emerging minima in the intensity profile gives further information about how monodisperse and defined the SCNP structure is [43–47]. However, access to small angle facilities and instruments limits the practicality for routine experiments of this approach.

High resolution imaging techniques, such as atomic force microscopy (AFM) and transmission electron microscopy (TEM), have enabled detailed imaging of SCNPs. However, these methods image the particles in the dry state and are usually at their resolution limits for such small particles, and therefore only of limited use in determining size differences. Nonetheless, AFM was successfully applied to support SCNP size differences observed by other methods such as SEC and DLS and is even suitable for dynamic systems [13, 42, 48–51]. For this purpose, the measured height and radius of the particle can be used to deduce sizes of spherical particles, assuming globular particles in solution.

Conventionally, SCNP formation is conducted under ultra-high dilution conditions ( $\ll 1$  mg/mL) to avoid multi-chain constructs. However, this technique limits the feasibility of SCNP formation in particular with regard to scalability for industrial applications. Hawker and coworkers introduced the continuous addition technique for SCNP preparation, where the polymer is slowly added to a solution suitable for cross-linking [5, 20]. In this procedure, the polymer is collapsed upon an external stimuli, such as temperature or a cross-linker molecule and the slow addition allows a low local concentration in the moment of cross-linking, enabling much higher concentrations in total (up to 10 mg/mL) [52–54]. Essential for this approach is a fast, efficient and stable cross-linking technique and it is hence, not applicable for dynamic or self-assembled systems. Alternatively, application of bulky, shielding polymer moieties, such as PEG, allowed SCNP formation at up to 100 mg/mL for both cross-linked [55, 56] and self-assembled systems [16, 57, 58]. Both approaches allow SCNPs in gram-scale, as long as the nanoparticles itself are stable.

## 3. Design of SCNPs as biomaterials

Selection of the polymer precursor determines the majority of the final SCNP properties and is therefore crucial in its design as biomaterial. A thermoresponsive polymer will result in a thermoresponsive SCNP [42]. Moreover, size and density of SCNPs are defined by the length of the polymer and its degree of collapsing as will be discussed in Section 3.3. Consequently, control over the properties of the precursor polymer results in control over the SCNPs. For this reason, living/controlled polymerizations, such as reversible addition – fragmentation chain-transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), ring-opening metathesis polymerization (ROMP), nitroxide-mediated polymerization (NMP) are most commonly employed in precursor polymer synthesis. Furthermore, controlled polymerization techniques provide control over composition, e.g. random vs. multiblock vs. gradient copolymers. However, biosynthetic polymers based on dextran [52] and poly( $\gamma$ -glutamic acid) ( $\gamma$ -PGA) [43, 59, 60] have also been successfully utilized as SCNP precursors. Such well-established and approved biological precursors introduce naturally occurring motifs to the particles and increase adoption of biocompatible SCNPs. Another way of resembling naturally occurring motifs has been recently approached by equipping SCNPs with synthetic sugar moieties – either by employing carbohydrate glycomonomers for the precursor

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