International Journal of
Biological and Chemical Research

ScienceAssist International

Commentary | Open Access

Perspectives of Polysaccharide Nanoparticles in Advanced Biomedical Applications: A Commentary on Emerging Technologies in Polysaccharide Research

Martin Gericke*, Thomas Heinze*

Department of Organic Chemistry and Macromolecular Chemistry, Friedrich-Schiller-University of Jena, Jena, Germany

***Correspondence:** Dr. Martin Gericke, Department of Organic Chemistry and Macromolecular Chemistry, Friedrich-Schiller-University of Jena, Jena, Germany, E-mail: martin.gericke@uni-jena.de

Prof. Dr. Thomas Heinze, Department of Organic Chemistry and Macromolecular Chemistry, Friedrich-Schiller-University of Jena, Jena, Germany, E-mail: thomas.heinze@uni-jena.de

Received: September 15, 2020; Accepted: October 09, 2020; Published: October 16, 2020

Abstract

Polysaccharide (PS) based nanoparticles (NP) are of increasing interest in biological and chemical research. They can circumvent many of the drawbacks of nanomaterials derived from inorganic compounds and synthetic polymers with respect to toxicity, biodegradability, and sustainability. PS have a huge potential in this context as abundant bio-resources that can be tailored in their properties by advanced chemical modification. This commentary provides an introduction into an advancing research field; PS-NP that are prepared by self-assembling of hydrophobically modified PS derivatives. These PS derivatives are easy to prepare, can be obtained with a broad variety of functionalities, and possess great application potential in biomedical areas such as drug delivery and sensing.

Keywords: Polysaccharides; Nanoparticles; Self-assembling; Drug delivery; Sensing; Stimuli-responsiveness

INTRODUCTION

Many nanomaterials are used in commercialized applications ranging from every-day products to high-value products. In recent research and application studies, nanoparticles (NP) are of particular interest. Characteristic features of NP are their nm-scaled size (1-1000 nm in one or more dimensions) and their unique physical, chemical, and/or biological properties that are significantly different from both the macroscopic bulk material and the individual molecules [1-3]. NP can be derived from different materials and by different bottom-up- and top-down approaches. Inorganic NP, which are usually considered as “hard” nanomaterials, are composed of metals, metal oxides, silica, carbon, or mixtures therefrom [4,5]. Organic NP are considered as “soft” materials because their particle surface is less defined by comparison [6]. Various types of synthetic polymers and oligomers as well as biopolymers (e.g., proteins, nucleic acid aggregates, polysaccharides/PS) have been employed to obtain organic NP with tailored properties [5-7].

NP are intensively studied as materials for advanced biomedical applications. Due to their size, they can enter cells and specific organs via different transport mechanism (e.g. endocytosis), which is a desired property for drug delivery purposes. Moreover, NP are investigated as labels for sensing and catch-and-release applications because they can carry a large density of functionalities (e.g., dyes, affinity groups, antibodies) due to their high surface-to-volume-ratio [8,9].

PS based nanomaterials possess significant advantages over those prepared from synthetic polymers or inorganic compounds. PS such as cellulose, starch, dextran, chitosan, and alginate are inherently non-cytotoxic and biocompatible by nature’s design. Native PS and many chemically modified PS derivatives are also biodegradable, which is a sought after trait for NP that could cause undesired interaction and safety issues when they persist in nature or within the human body [10].

PS based nanomaterials (i.e., cellulose nanocrystals, nanofibrilated cellulose) can be prepared in top-down approaches by chemical and/or mechanical treatment

of PS biomass [11,12]. Frequently employed bottom-up methods towards PS-NP include the directed chemical or electrostatic cross-linking of hydrophilic PS (or chemically modified PS derivatives) [13-15]. Moreover, hybrid nanomaterials can be assembled by coating NP cores with an outer PS layer [16,17]. A viable and facile approach that received increasing interest in recent years is the self-assembling of PS derivatives into spherical NP with specific common features (Figure 1) [18].

SELF-ASSEMBLING OF POLYSACCHARIDE DERIVATIVES INTO NANOPARTICLES

Native PS are hydrophilic compounds due to the abundancy of hydroxyl group as well as in some cases amino-, carboxyl-, and sulfate groups. However, the properties of these biopolymers can be tailored by chemical modification with a vast variety of substituents [25]. Of particular interest in the context of PS-NP are short chain (e.g., acetate, propionate, butyrate) and long chain carbocyclic acid esters (e.g., decanoate, laurate, stearate) as well as ethers like ethyl- and trimethylsilyl ethers. With increasing degree of substitution (DS), the PS derivatives become increasingly amphiphilic and finally hydrophobic, which renders the compounds soluble in dipolar aprotic solvents (e.g., dimethyl sulfoxide, *N,N*-dimethyl acetamide) and even in non-polar solvents like tetrahydrofuran and chloroform. At the same time, the PS derivatives no longer dissolve or swell in water. This solubility behavior can be exploited to induce self-assembling of the hydrophobic PS derivatives into NP by a controlled displacement of the solvent against the non-solvent water ("nano-precipitation"), which can be achieved through a dialysis process [26,27]. The solubility of the PS-NP is successively decreased, which results in a self-aggregation of the polymer chains into spherical NP. A similar effect is achieved by slowly dropping water into a polymer solution or *vice versa* the polymer solution into water [28,29]. Another technique for the preparation of PS-NP, which uses the same type of hydrophobic polymers, is based on the ultrasound assisted formation nano emulsions [30]. Therein, the PS derivatives are dissolved in a non-polar, water immiscible solvent like chloroform together with a surfactant and an o/w-emulsion with nm-sized droplets is formed by ultra-sonication. After removal of the organic solvent be evaporation, PS-NP with a rather narrow size distribution are obtained [19].

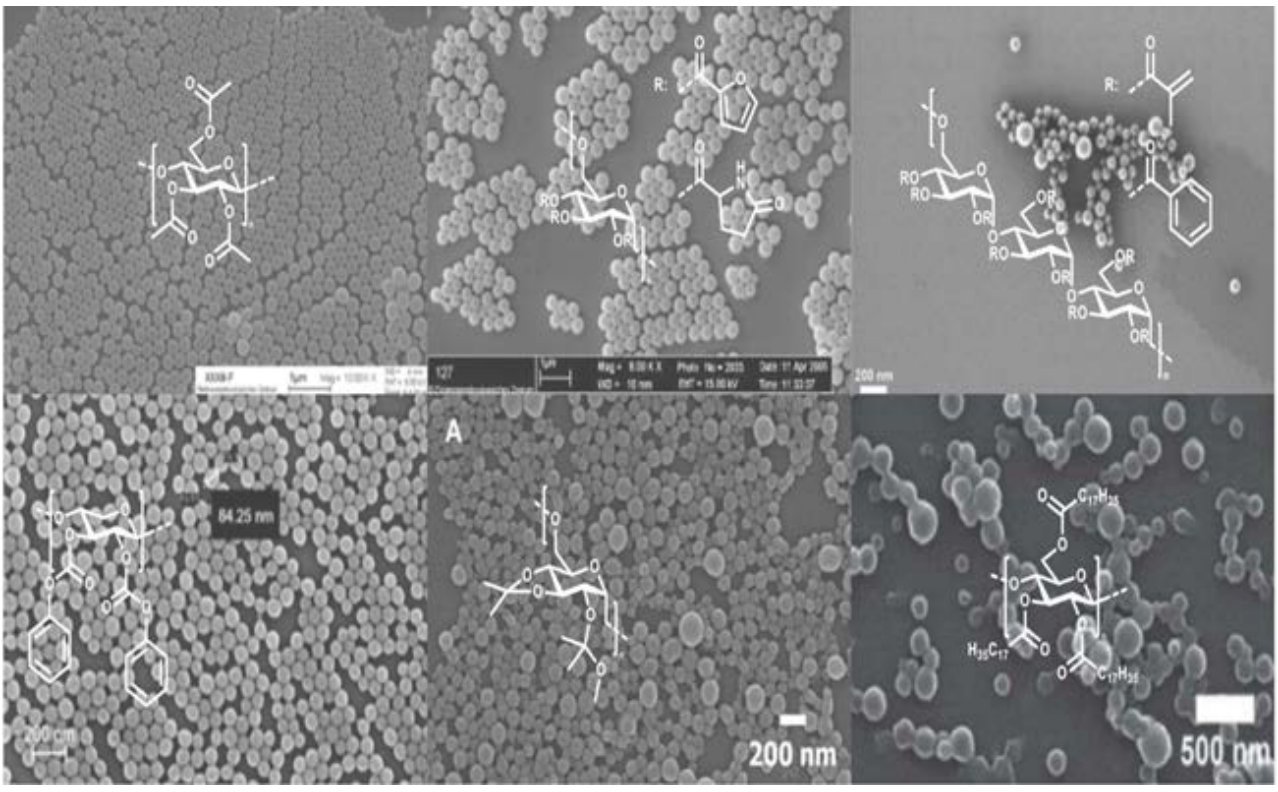

Figure 1: Scanning electron microscopy images of nanoparticles prepared by self-assembling of hydrophobic polysaccharide derivatives, adapted from literature [19-24].

A broad variety of hydrophobic PS derivatives, most notably cellulose- and dextran esters and mixed esters has been employed to prepare PS-NP by self-assembling [19,21,31,32]. These particles with well-defined spherical shape possess a size usually in the range of about 100 to 500 nm, depending on the substituent (type, DS), the PS backbone, and the preparation conditions [18].

APPLICATIONS IN DRUG DELIVERY AND SENSING

It has been proven for several examples that PS-NP prepared by self-assembling of hydrophobic PS derivatives can be considered as biocompatible and non-cytotoxic [33,34]. Moreover, cells take up these particles (Figure 2), which opens ways for using them for *in vitro* or *in vivo* applications. Drugs can be entrapped physically within PS-NP. In this case, the release at a specific target site or cellular compartment is mostly controlled by diffusion from the hydrophobic particles [35]. Another approach is the covalent immobilization of drugs on the PS backbone [36]. Release of the drugs requires cleavage from the prodrug conjugate, e.g., by hydrolysis at certain pH-values or the action of specific enzymes, which might depend on the specific target location within the body.

Stimuli-responsive PS-NP are highly desired in the context of drug release because they feature a drastic change in properties (in particular the size) that could release drugs by specific internal or external triggers (e.g., irradiation, change of pH-value or temperature) [37,38]. As an example, dextran acetals can form PS-NP that are stable at a physiological pH value of 7.4. but disintegrate under mildly acidic conditions (e.g., found in tumor tissue, sites of inflammation, endocytic vesicles; Figure 2) [23, 39]. The therapeutic payload is released in this process and dextran is liberated, which is non-cytotoxic and biodegradable.

PS-NP can be modified with dye molecules (UV/Vis, fluorescent dye etc.) by covalent fixation (either to the NP forming PS derivative or the PS-NP) or by physical entrapment during the self-assembling step [34,40,41]. These materials have been employed to study the uptake of PS-NP within specific tissue or cellular compartments [33,34]. Moreover, these PS-NP are suited for *in vitro* sensing applications if a dye is chosen that is sensitive to specific conditions (e.g., pH value, concentration of physiological analytes) [42]. Ideally, a second dye whose optical properties are not dependent on the respective parameter is incorporated as an internal reference standard. Due to their high specific surface area that allows for the immobilization of dyes and receptor ligands (e.g., antibodies, metal chelators) in combination with a low non-specific binding affinity, PS-NP are also of great interest for *ex vivo* sensing applications [43]. They can be incorporated into lateral flow immunoassays as highly sensitive nano labels for the detection of clinically relevant antigens [41]. Of particular interest in this context are reactive PS-NP that can easily be functionalized with different dyes and affinity ligands [8,44].

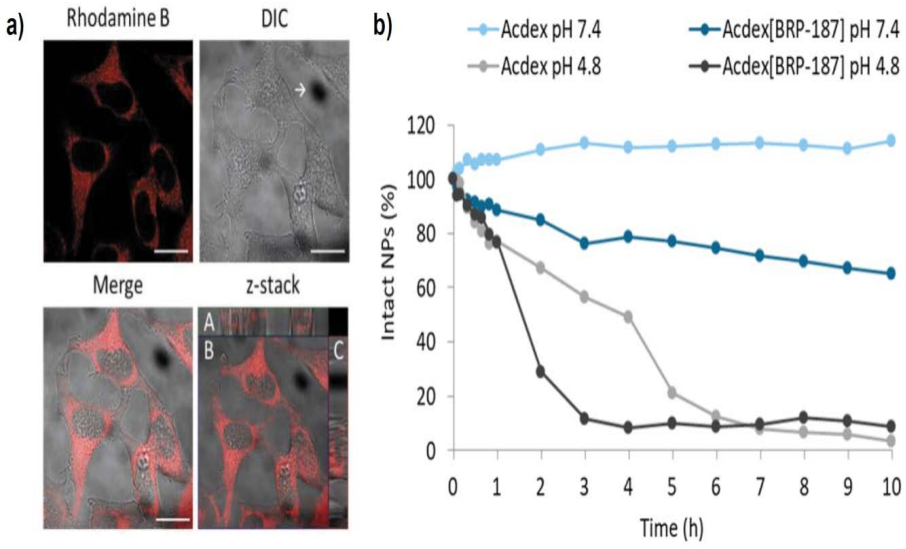

Figure 2: (a) Confocal microscopy images of HeLa cells after incubation with rhodamine B labeled nanoparticles derived from cellulose valproate, adapted from [36]. (b) Degradation profile of nanoparticles derived from dextran acetals (Acdex) with and without the inhibitor BRP-187, adapted from [23].

CONCLUSION

PS-NP are readily accessible by self-assembling of hydrophobically modified PS derivatives. These nanomaterials can be tailored by using different types of PS, substituents, and preparation techniques. The application potential in biomedical areas such as drug delivery and *in vivo*/*ex vivo* sensing has been demonstrated. Innovations can be expected in this emerging field through a combination of modern organic chemistry, PS research, advanced materials design, and application focused product development. A big hurdle is the upscaling of the currently employed lab-scale procedures for particle formation that needs to be addressed in order to establish commercialized applications. Novel reactive and/or multifunctional PS-NP that can be employed for different purposes are highly desired in this context.

AUTHOR'S CONTRIBUTION

Both authors contributed equally to the present work.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

FUNDING

This work was financially supported by the DFG-funded Collaborative Research Centre PolyTarget (SFB 1278, project A02).

REFERENCES

1. Letchford K, Burt HA. Review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: Micelles, nanospheres, nanocapsules and polymersomes. Europ J Pharma Biopharma. 2007;65(3):259-269.
2. Maysinger D. Nanoparticles and cells: Good companions and doomed partnerships. Org Biomol Chem. 2007;5(15):2335-2342.
3. Roduner E. Size matters: Why nanomaterials are different. Chem Soc Rev. 2006;35(7):583-592.
4. Boles MA, Engel M, Talapin DV. Self-assembly of colloidal nanocrystals: From intricate structures to functional materials. Chem Rev. 2016;116(18):11220-11289.
5. Tomalia DA. In quest of a systematic framework for unifying and defining nanoscience. J Nano Res. 2009;11(6):1251-1310.
6. Delgado AV, González-Caballero F, Hunter RJ, Koopal LK, Lyklema J. Measurement and interpretation of electro-kinetic phenomena (IUPAC Technical Report). Pure Appl Chem. 2005; 77:1753-1805.
7. Zhang L, Gu F, Chan J, Wang A, Langer R, Farokhzad O. Nanoparticles in medicine: Therapeutic applications and developments. Clin Pharma Ther. 2008;83(5):761-769.
8. Schulze P, Gericke M, Heinze T. Reactive nanoparticles with activated ester moieties from cellulose acetate phthalate derivatives. Cellulose. 2019;26:475-490.
9. Fidale, LC, Nikolajski M, Rudolph T, Dutz S, Schacher FH, Heinze T. Hybrid Fe_3O_4@amino cellulose nanoparticles in organic media-heterogeneous ligands for atom transfer radical polymerizations. J Col Interface Sci. 2013;390(1):25-33.
10. Krug HF. Nanosafety research-are we on the right track? Angew Chem Intern Edit. 2014;53(46):12304-12319.
11. Eyley S, Thielemans W. Surface modification of cellulose nanocrystals. Nanoscale. 2014;6(14):7764-7779.
12. Nechyporchuk O, Belgacem MN, Bras J. Production of cellulose nanofibrils: A review of recent advances. Ind Crop Prod. 2016;93:2-25.
13. Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z. Polysaccharides-based nanoparticles as drug delivery systems. Adv Drug Deliv Rev. 2008;60(15):1650-1662.
14. Quiñones JP, Peniche H, Peniche C. Chitosan based self-assembled nanoparticles in drug delivery. Polymers. 2018;10(3):235.
15. Paques JP, van der Linden E, van Rijn CJM, Sagis LMC. Preparation methods of alginate nanoparticles. Adv Col Interface Sci. 2014;209:163-171.
16. Uthaman S, Lee SJ, Cherukula K, Cho CS, Park IK. Polysaccharide-coated magnetic nanoparticles for imaging and gene therapy. BioMed Res Internat. 2015;2015:14.
17. Facchi DP, Cruz JAD, Bonafé EG, Pereira AGB, Fajardo AR, Venter SAS, et al. Polysaccharide-based materials associated with or coordinated to gold nanoparticles: Synthesis and medical application. Curr Med Chem. 2017;24(25):2701-2735.
18. Gericke M, Schulze P, Heinze T. Nanoparticles based on hydrophobic polysaccharide derivatives - Formation principles, characterization techniques, and biomedical applications. Macromol Biosci. 2020;20(4):e1900415.
19. Wondraczek H, Petzold-Welcke K, Fardim P, Heinze T. Nanoparticles from conventional cellulose esters: Evaluation of preparation methods. Cellulose. 2013;20:751-760.
20. Hornig S, Heinze T, Hesse S, Liebert T. Novel nanoparticles based on dextran esters with unsaturated moieties. Macromol Rapid Commun. 2005;26(24):1908-1912.
21. Aschenbrenner E, Bley K, Koynov K, Makowski M, Kappl M, Landfester K, et al. Using the polymeric ouzo effect for the preparation of polysaccharide-based nanoparticles. Langmuir. 2013;29(28):8845-8855.
22. Gericke, M, Gabriel L, Geitel K, Benndorf S, Trivedi P, Fardim P, et al. Synthesis of xylan carbonates-An approach towards reactive polysaccharide derivatives showing self-assembling into nanoparticles. Carbohydr Polym. 2018;193:45-53.
23. Shkodra-Pula B, Kretzer C, Jordan PM, Klemm P, Koeberle A, Pretzel D, et al. Encapsulation of the dual FLAP/mPEGS-1 inhibitor BRP-187 into acetalated dextran and PLGA nanoparticles improves its cellular bioactivity. J Nanobiotechnol. 2020;18(1):73.
24. Zhang K, Geissler A, Heinze T. Reversibly crystalline nanoparticles from cellulose alkyl esters via nanoprecipitation. Part Part Syst Charact. 2015;32(2):258-266.
25. Heinze T, El Seoud OA, Koschella A. Cellulose derivatives synthesis, structure, and properties. Springer Nature Switzerland AG. 2018.
26. Schubert S, Delaney JJT, Schubert US. Nanoprecipitation and nanoformulation of polymers: From history to powerful possibilities beyond poly(lactic acid). Soft Matter. 2011;7(5):1581-1588.
27. Chronopoulou L, Fratoddi I, Palocci C, Venditti I, Russo MV. Osmosis based method drives the self-assembly of polymeric chains into micro and nanostructures. Langmuir. 2009;25(19):11940-11946.

28. Aubry J, Ganachaud F, Cohen Addad JP, Cabane B. Nanoprecipitation of polymethylmethacrylate by solvent shifting:1. Boundaries. Langmuir. 2009;25(4):1970-1979.

29. Hornig S, Heinze T. Efficient approach to design stable water-dispersible nanoparticles of hydrophobic cellulose esters. Biomacromolecules. 2008;9(5):1487-1492.

30. Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates-A review. J Control Release. 2008;128(3):185-199.

31. Hornig S, Heinze T. Nanoscale structures of dextran esters. Carbohydr Polym. 2007;68(2):280-286.

32. Geissler A, Biesalski M, Heinze T, Zhang K. Formation of nanostructured cellulose stearoyl esters via nanoprecipitation. J Mater Chem A. 2014;2(4):1107-1116.

33. Ernsting MJ, Tang WL, MacCallum N, Li SD. Synthetic modification of carboxymethylcellulose and use thereof to prepare a nanoparticle forming conjugate of docetaxel for enhanced cytotoxicity against cancer cells. Biocon Chem. 2011;22(12):2474-2486.

34. Nikolajski M, Wotschadlo J, Clement JH, Heinze T. Amino-functionalized cellulose nanoparticles: Preparation, characterization, and interactions with living cells. Macromol Biosci. 2012;12(7):920-925.

35. Han F, Gao C, Liu M. Fabrication and characterization of size-controlled starch-based nanoparticles as hydrophobic drug carriers. J Nanosci Nanotechnol. 2013;13(10):6996-7007.

36. Lindemann H, Kühne M, Grune C, Warncke P, Hofmann S, Koschella A, et al. Polysaccharide nanoparticles bearing HDAC inhibitor as nontoxic nanocarrier for drug delivery. Macromol Biosci. 2020;20(6):e2000039.

37. Wang Y, Heinze T, Zhang K. Stimuli-responsive nanoparticles from ionic cellulose derivatives. Nanoscale. 2016;8(1):648-657.

38. Wang Y, Liu Y, Liu Y, Wang Y, Wu J, Li R, et al. pH-sensitive pullulan-based nanoparticles for intracellular drug delivery. Polym Chem. 2014;5(2):423-432.

39. Bachelder EM, Beaudette TT, Broaders KE, Dashe J, Fréchet JMJ. Acetal-derivatized dextran: An acid-responsive biodegradable material for therapeutic applications. J Am Chem Soc. 2008;130(32):10494-10495.

40. Li Y, Tan Y, Ning Z, Sun S, Gao Y, Wang P. Design and fabrication of fluorescein-labeled starch-based nanospheres. Carbohydr Polym. 2011;86(1):291-295.

41. Schulze P, Gericke M, Scholz F, Wondraczek H, Miethe P, Heinze T. Incorporation of hydrophobic dyes within cellulose acetate and acetate phthalate based nanoparticles. Macromol Chem Phys. 2016;217(16):1823-1833.

42. Hornig S, Biskup C, Grafe A, Wotschadlo J, Liebert T, Mohr GJ, et al. Biocompatible fluorescent nanoparticles for pH-sensoring. Soft Matter. 2008;4(6):1169-1172.

43. Pei X, Zhang B, Tang J, Liu B, Lai W, Tang D. Sandwich-type immunosensors and immunoassays exploiting nanostructure labels: A review. Anal Chim Acta. 2013;758:1-18.

44. Cui L, Cohen JA, Broaders KE, Beaudette TT, Fréchet JMJ. Mannosylated dextran nanoparticles: A pH-sensitive system engineered for immunomodulation through mannose targeting. Biocon Chem. 2011;22(5):949-957.