Polymer Nanoparticles for Drug Delivery – Synthetic *vs.* Biopolymers?

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Nanoparticles have a great prospect for therapeutic applications. They can protect drugs under physiological conditions and act as a matrix for directed delivery of drugs, *e.g.*, to a specific tissue or cell type. Polymer-based nanomaterials are considered as highly effective in this regard. Their properties can be tailored to meet specific demands for given therapeutic purposes. Considering the high-quality standards placed on medical products, the question arises: Which type of polymer material should be employed? One might select synthetic polymer compounds, which are highly diverse in terms of the molecular structures and supramolecular architectures that can be created, or biopolymers such as polysaccharides that are renowned for their native biocompatibility.

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Nanocarriers for Targeted Drug Delivery

Nanoparticles (NPs) are considered here as particles having at least one dimension in the nanoscale (around 1 to 1000 nm). They are characterized by unique physical, chemical, and biological properties that are neither shown by the individual molecules nor the macroscopic bulk materials. In addition to many other fields of applications, the use of NPs in drug delivery has been studied intensively. Due to their size, NPs of various types are able to penetrate cellular membranes, circulate in the blood stream, and/or accumulate selectively in specific tissues, cells, or cellular compartments. They possess a high specific surface area for covalent immobilization of drugs and/or provide a matrix for physical entrapment of drugs, preferably in an amorphous state. Research activities in this area aim for a rational design of the nanomaterials, in particular regarding their morphology (*e.g.*, size, shape, architecture) and surface chemistry (*e.g.*, hydrophilicity/hydrophobicity, functional groups, bioaffinity ligands).

Self-assembling of polymers is a particularly viable bottom-up approach for the preparation of highly functional NPs for drug delivery. By designing the molecular structure of the macromolecules, it is possible to tailor NP features such as size, shape, surface chemistry, and charge, which in return will have an impact on the final application performance, *e.g.*, drug loading and release kinetics, cellular uptake, cytotoxicity, and biodegradability. General approaches for the preparation of synthetic polymers focus on the synthesis and subsequent polymerization of ever more complex monomer compounds. Modern polymer chemistry provides a plethora of options to design tailored nanomaterials. These include a broad diversity of polymer backbones, variable chain lengths, multi-block copolymers with defined alignment of functional segments, and complex architectures of macromolecule chains (*e.g.*, branched, star-shaped, grafted). Thus, it is possible to create

libraries of synthetic polymer nanomaterials for screening optimal structural features for specific drug delivery tasks.

When nanoformulations are administered to the human body, *e.g.*, orally, transdermal, or by injection, they should be nontoxic, biocompatible, and preferably biodegradable. Synthetic polymer-based nanomaterials frequently struggle in these areas because the polymers itself, their biodegradation products and/or impurities from the synthesis (*e.g.*, residual monomers, catalysts) can induce unfavorable bioresponses. Quite often, it is required to compromise therapeutic efficiency for increased biocompatibility. Moreover, layers of "stealth polymers" are introduced to mask the toxic nature of a particular nanoformulation or to achieve cellular uptake.

Polysaccharides as Ideal Candidates for Biomedical Applications?

Polysaccharides (PS) are ubiquitous in nature, in which they play vital roles as structure polymers and/or energy storages for microorganisms, plants, animals, and humans alike. By design, biopolymers such as starch, cellulose, and dextran are inherently biocompatible and non-toxic. Thus, PS-based nanomaterials are generally considered as highly promising candidates for drug delivery applications. Different top-down and bottom-up procedures can be used to prepare PS-NPs having specific properties. Furthermore, coating of organic and inorganic NPs with an outer PS layer is feasible. An approach that is easy to perform and broadly applicable is self-assembling of hydrophobically modified PS derivatives by nanoprecipitation. It has been demonstrated that these types of PS-NPs are non-cytotoxic and taken up by cells. Both features are vital for therapeutic applications in human health care.

Despite their inherent advantages, however, PS are certainly not the sole solution for everything when it comes to the development of nanomaterials for drug delivery purposes. They are produced by living organisms and need to be extracted from complex biocomposites. A typical example in this context is wood (source for cellulose and hemicelluloses), a complex material composed of different polymers that is designed by nature to withstand harsh environmental conditions for decades. Thus, the composition and molecular structure of PS might change (*e.g.*, depending on the species, season, isolation process), which is less of an issue for synthetic polymers of high grade. The molecular structure of synthetic polymers can be tuned in various ways, which is the basis for the development of task-specific NPs for drug delivery. The possibilities for chemically modified PS derivatives are more restricted in this regard. They are only accessible by polymer analogue derivatization of the native biopolymers, which can be a challenging task compared to the vast possibilities of classical monomer synthesis. Thus, modern PS research constantly aims to develop new selective synthesis methods. Many aspects related to the preparation and application of PS-NPs are, however, still not fully understood, such as the specific role of the polymer backbone on the nano-self-assembling process.

Concluding Remarks and Future Opportunities

Polymer-based NPs have demonstrated their vast potential as tunable drug delivery agents in many academic studies. Knowledge transfer into commercial applications is the next development step for many potential candidates. Rather than focusing on either synthetic or biobased polymers, both should be integrated and combined into future R&D strategies. As an example, development of novel technical procedures for preparation of NPs in a commercially attractive scale is crucial for a transition from academia to actual

applications. Synthetic polymer nanomaterials are at the forefront of these developments due to availability and the possibilities for property tuning. Biobased PS-NPs can greatly benefit from these applied studies. Likewise, the inherent beneficial features of PS and other biopolymers can be exploited to improve the therapeutic performance of synthetic polymer-based NPs, *e.g*., by incorporating layers of PS or by selective surface modification with mono- and oligosaccharide motives. A key issue in this regard is to address research activities from multiple angles in an interdisciplinary and comprehensive approach. The *Collaborative Research Center 1278* POLYTARGET ("Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies") was established in this spirit at the *Friedrich-Schiller-University* of Jena in July 2017 with a grant from the German Research Council (DFG). During the first funding period, the research groups involved in this program have achieved major contributions in diverse fields ranging from polymer synthesis and characterization over nanomaterial development and design to pharmaceutical/medical studies and theoretical structure-property-relationship evaluations. Plans for the second phase application are currently in the pipeline.