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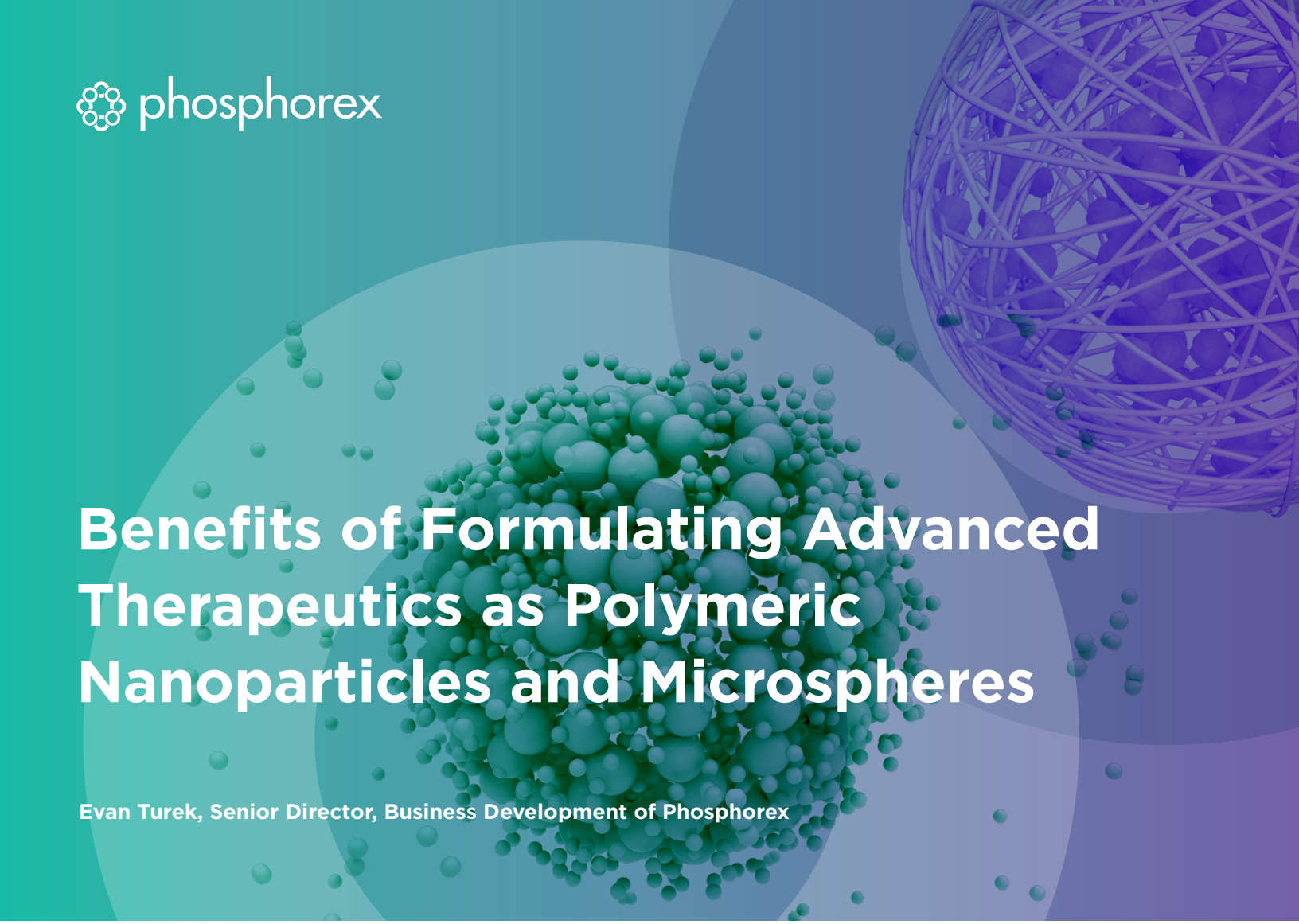

Benefits of Formulating Advanced Therapeutics as Polymeric Nanoparticles and Microspheres

Evan Turek, Senior Director, Business Development of Phosphorex

Polymeric nanoparticles (PNPs) are a game-changing solution for delivering therapeutic agents, including small molecules, peptides, proteins, and nucleic acids. By encapsulating active pharmaceutical ingredients in biodegradable polymer nanoparticles, it is possible to protect them from degradation, thereby extending their time in the bloodstream; improving their bioavailability; enhancing their cellular uptake; and, in many cases, achieving targeted delivery through careful particle design and surface modification. Fluorescent labeling techniques also enable the use of polymeric particles in diagnostic applications.

Polymeric microsphere (PMP) formulations, when delivered subcutaneously (SC) or intramuscularly (IM), can dramatically reduce dosing frequency, increase patient convenience, and improve medication adherence.

Successful development of therapeutic and diagnostic PNPs or PMPs requires optimal particle design, which in turn necessitates selection of the most appropriate biodegradable polymers for a given drug substance and target product profile, choosing the best surface ligands and conjugation methods for active targeting, development of consistent, scalable manufacturing processes, and establishment of phase-appropriate analytical methods that ensure comprehensive analysis of both encapsulated payloads and the particulate vehicle.

Distinguishing Polymeric Nanoparticles and Microspheres

Polymeric nanoparticles and microspheres are typically distinguished by their sizes. There can be some confusion, however, as different organizations define nanoparticles differently. Literature publications often consider polymeric nanoparticles to have dimensions ranging from 1 to 1000 nm.[1,2] The US Food and Drug Administration (FDA) defines nanomaterials as materials that have been engineered to have one or more dimensions within the nanoscale range, which, although most commonly pertains to average diameters around 100 nm, is considered to include diameters up to 1000 nm by regulatory definition.[3]

In 2017, an FDA study found that of more than 350 drugs containing nanomaterials submitted to the agency, the majority contained engineered nanomaterials with dimensions under 300 nm. Phosphorex considers polymeric particles with diameters < 500 nm to justify the polymeric nanoparticle (PNP) title, and those that are larger to be characterized as polymeric microspheres (PMPs).

There are three other important distinctions between PNPs and PMPs. First, PNPs can be leveraged to facilitate non-viral intracellular delivery of nucleic acid cargoes, whereas microspheres are not well suited for nucleic acid cargoes due to a considerably limited potential for intracellular uptake. Second, PNPs and PMPs exhibit very different pharmacokinetics. The *in vivo* half-lives of active pharmaceutical ingredients (APIs) delivered by PNPs and PMPs are influenced by particle size, with larger particles providing longer durations of API release.

Finally, the manufacturing operations applied for polymeric nanoparticle and microsphere production are quite different. Nanoparticle vehicles are typically filtered through commonly used 0.2-micron sterile filters prior to fill-and-finish; whereas microspheres, are too large to be filtered in this manner, and thus require terminal sterilization or fully aseptic processing within a controlled, sterile environment, depending on the cargo.

Many Benefits of Polymeric Delivery Vehicles

Polymeric nanoparticles and microspheres represent alternative methods for delivering diagnostic and therapeutic agents. Incorporation of APIs into biodegradable polymer particles offers numerous benefits, including protection against degradation, extended drug release, and improved bioavailability.

Polymeric particles can also enable conversion of some injectables to oral formulations, enhance cellular uptake, and facilitate targeted delivery. Compared to lipid nanoparticles (LNPs) in particular, PNPs offer extended half-lives because they do not exhibit the burst-release profile common to liposomes or LNPs. Furthermore, polymeric nanoparticles can be better suited for alternative administration route strategies that liposomes or LNPs may struggle to support, provided there is sufficient formulation, process development, and chemistry, manufacturing, and controls (CMC) expertise to manage and scale these intricate systems.

Polymeric microspheres, meanwhile, provide a means to achieve true long-acting release for molecules with sufficient potency to support long-term doses in a single injection volume. Formulations requiring administration only twice per year are possible and can often be self-injected at home, dramatically increasing patient convenience and resulting in greater medication adherence. Other important benefits of formulating sustained-release products such as polymeric microspheres includes the potential to reduce systemic exposure, resulting in decreased side effects and the ability to enhance the therapeutic index.

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Developing complex polymeric delivery systems, however, requires specialized expertise in formulation development and optimization, as the relationships among API and polymer chemistries, the target product profile, and the processing techniques required must be carefully considered. With the right expertise and capabilities, though, polymeric systems can be leveraged to improve patient convenience and compliance, enhance tolerability, capture new IP space, and even harness safer materials and more economical distribution logistics.

Choosing Nanoparticles vs. Microspheres: The What and the Why

When deciding whether to formulate a novel drug substance as a polymeric nanoparticle or microsphere, it is important to consider the delivery problem statement, as both technologies can be used to incorporate a wide variety of API formats. The particle class and API class are not typically mutually exclusive. Each approach has its own strengths, and thus, the delivery problem statement should drive the drug product selection.

The key is to determine whether a micro- or a nanoparticle is the better option given the desired physiological target and dose. It is then important to empirically determine the chemistry and particle characteristics that provide optimal performance.

For instance, peptides are often more difficult to encapsulate in polymeric particles than small molecules, which are typically more hydrophobic. Clever strategies may be needed to achieve sufficient loading of a nominated peptide or hydrophilic small-molecule API into the desired type of polymeric particle, while achieving the target product profile. Such strategies must leverage the physicochemical properties of API and marry them to the polymers and processing techniques. For polymeric microspheres and nanoparticles to be formulated as suspensions for subcutaneous (SC) or intramuscular (IM) injection, specialty formulation expertise is often required to achieve a loading capacity sufficient to meet dose requirements while maintaining injection volume limits that support safe administration.

The potential application of PNPs or even PMPs for oral delivery is an important

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area of research. The focus is on developing PNPs that can induce relevant uptake mechanisms within the gastrointestinal (GI) tract. Even for biologics, PNPs have been shown to protect the payload and facilitate targeted delivery by providing sufficient stability in the GI tract. However, transport across the gut or intestinal wall remains challenging for many applications and will continue to be modeled and empirically investigated to realize fuller potential.

Polymeric microspheres have already been proven in commercial sustained-release products. ZILRETTA® (triamcinolone acetonide extended-release injectable suspension, Pacira Biosciences) for the treatment of osteoarthritis knee pain is formulated in biodegradable poly(lactic-co-glycolic acid) (PLGA) microparticles and is widely considered the gold standard in the field.

Polymer Chemistry Matters

The materials used to produce polymeric nanoparticles and microspheres for drug delivery consist primarily of biocompatible polymers containing hydrolysable esters for biodegradation. The fine-tuning of these polymer structures by expert formulators can be employed to improve drug loading, drug release, or the manufacturability of the target product profile. Polymer selection can also facilitate the conjugation of targeting ligands to the surface of polymeric particles.

Key attributes for selecting a specific polymer or polymer mix for any given application include the chemical structure and molecular weight of the polymer(s). These properties are tuned to facilitate critical quality attributes such as particle size, drug loading, encapsulation efficiency, and stability, as well as favorable process conditions such as solvent selection, and required solvent volumes, which can be critical for scalable manufacturing.

Generally, for encapsulation of small molecules and peptides, PLGA and polylactic acid (PLA)-derived polymers are preferred because they often provide the necessary balance of API loading, tunable release rate, and manufacturability (including favorable organic solvent solubility). Tuning the specific properties is achieved, for instance, by adjusting the polymer MW and/or the ratio of lactide to glycolide (LA/GA) in the polymer.

Polymers used in PNP formulations are often modified with polyethylene glycol (PEG), which lead to smaller particles and provide sites for the attachment of surface ligands, such as antibodies and other molecules that support active targeted delivery.

Polymeric microspheres can be produced using a diverse range of biodegradable polymers, including not only PLGA and PLA but also polycaprolactone (PCL), polyanhydrides, and poly(ortho esters), with the specific choice based on the desired therapeutic effects, the desired sustained-release time frame, and the ability to reduce side effects.

In addition to these polymers, which have been used in numerous food and pharmaceutical applications with some having "Generally Recognized as Safe", or GRAS, status, several novel cationic polymer excipients with attractive properties for encapsulation of nucleic acids into PNPs for nonviral intracellular delivery are currently being developed.

These polymers have not only hydrolysable ester groups but also accompanying cationic moieties, typically via tertiary amine groups. The cationic charges enable them to bind to negatively charged nucleic acids, pass through cell membranes, and disrupt endosomes. The most promising examples are poly(beta-amino esters) (PBAEs), which have been shown to condense and deliver nucleic acid cargoes intracellularly with minimal systemic toxicity risk (e.g., lower than widely explored polyethyleneimine).

Research is now focused on identifying PBAEs and other polyamino-based block polymers with optimized transfection efficiencies versus prior generations. Interest in this approach to nonviral gene therapies is rising in response to updates to the FDA's guidance and acceptance framework to promote the rapid development of personalized medicines and gene therapies[4], which opens the door for PNPs designed to excel at nucleic acid delivery.

Achieving Targeted Delivery with Multiple Approaches

The ability to modify the surfaces of polymer nanoparticles enables targeted delivery beyond lipid-based approaches, and their extended half-life can be advantageous for improving target uptake. Additional phenomena, such as the enhanced permeability and retention (EPR) effect, can be leveraged with polymeric nanoparticles at solid tumor target sites. With this approach, particles within the appropriate size range preferentially accumulate (passive targeting) in solid tumors due to the presence of leaky, abnormal vasculature and poor lymphatic drainage. The key to success in this approach is determining the optimal size, duration of drug release, and surface chemistry for the tumor environment of interest.

With active targeting, ligands (e.g., antibody fragments, nanobodies, peptides, small molecules, etc.) are chemically conjugated to the surfaces of drug-loaded PNPs.

By designing delivery systems with scalability, reproducibility, and regulatory expectations in mind from the start, Phosphorex addresses the process translation gap and enables partners to maintain delivery performance while de-risking the development path from candidate selection to IND filing.

Ligand conjugation to the nanoparticle surface is typically achieved using either maleimide bioconjugation or copper-free click chemistry approaches. The specific ligand is chosen based on its ability to selectively bind to the target cell or tissue. This approach enhances the drug's potential to reach its intended destination while shielding it from degradation until release. Fluorescent dyes and imaging agents can also be conjugated to and/or encapsulated within PNPs for *in vivo* imaging applications.

Investing in Optimal Analytics Early in Development Pays Dividends

Polymeric nanoparticles and microspheres are complex systems. It is important to perform intentional, well-structured experiments from the outset of a development project to establish a deep understanding of the critical design characteristics that impact loading capacity, release rate, targeting ability, and manufacturability.

Powerful analytical methods that utilize high-performance liquid chromatography (HPLC) provide better characterization of discovery prototypes than simpler plate-based methods, leading to better candidate nomination. These techniques can, once a development candidate demonstrates full scalability potential, be further developed as stability-indicating methods for IND-enabling studies and IND filings. Additionally, with the expertise described above, it is possible to identify manufacturability issues before candidates are nominated, allowing selected candidates to move forward through development without the risk of redesign or repeated development.

Overcoming Translational Gaps

In fact, the inherent complexity of PNPs and polymeric microspheres often leads to large translational gaps when moving from preclinical to clinical development, particularly in achieving effective, economical, and scalable, clinically relevant production operations. Use of polymeric particles as drug delivery vehicles adds significant manufacturing complexity, and many manufacturers lack the expertise required for GMP production of these complex systems. In some cases, novel vehicles are developed on the benchtop only to reach a moment of truth: the technology transfer of this science to scalable, clinically relevant unit operations is not trivial. Even large contract development and manufacturing organizations (CDMOs) with experience in the production of traditional four-component lipid nanoparticle (LNP) formulations lack expertise to address critical process development and formulation optimization challenges associated with polymeric particles.

Phosphorex has focused on polymeric delivery vehicles since its founding over 20 years ago. Today, we help clients evaluate the potential of both polymeric and lipidic targeted nanoparticle delivery systems in parallel. As a specialized partner, we guide innovators through small-scale feasibility testing and formulation optimization to ensure a balance of physical and chemical properties in the target product profile, resulting in reproducible *in vivo* performance and successful scale-up. We also know how to minimize process volumes and hold times to develop an economical process that can be efficiently tech-transferred for clinical drug product manufacturing.

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Solving Delivery Challenges for Highly Potent APIs and Nucleic Acids

The unique properties of polymeric nanoparticles make them attractive as delivery vehicles for two challenging applications – highly potent compounds (HPAPIs) and nonviral delivery of nucleic acids. For HPAPIs, PNPs, by encapsulating the drug substance, protect the body from systemic toxicity, while the active targeting capability of ligand-modified PNPs promotes selective delivery to the target site (such as solid tumors) to mitigate off-target effects.

For nucleic acids, while LNPs will remain the predominant solution for nonviral delivery, there are certain instances where lipidic vehicles fall short. In cases where extended half-life is advantageous for targeted gene therapy or there are tolerability challenges LNPs can't avoid, PNPs can emerge as an important part of the delivery toolkit. PNPs, for example, also hold the potential to unlock improved stability characteristics for more reliable targeting and streamlined distribution logistics. Finally, PNPs also have the potential to improve nuclear transport inefficiencies in non-viral gene-editing therapies.

Combined, the safety, tolerability, manufacturing stability, less saturated IP, and some differentiated performance properties of polymeric nanoparticles make them an exciting technology worth further investigation and investment. Indeed, the few examples presented herein highlight only some of the ways in which PNPs may help drug developers harness the full potential of non-lipidic nanoparticles and microparticles to treat highly sought-after indications with open demand for solutions.

REFERENCES

1. Aleksandra Zielińska et al., "Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology," Molecules. 2020 Aug 15;25(16):3731. Doi: 10.3390/molecules25163731

2. Hemant K.S. Yadav, Aiah A. Almo dad, Sumia I.M. shaluf, Manar S. Debe, "Polymer-Based Nanomaterials for Drug-Delivery Carriers" in *Nanocarriers for Drug Delivery* Ed. Shyam S. Mohapatra et al., Elsevier 2019. DOI: 10.1016/C2017-0-00199-4

3. FDA, Considerations for Drug Products that Contain Nanomaterials, CDER Small Business and Industry Assistance Chronicles, 05/15/2024 https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/considerations-drug-products-contain-nanomaterials

4. FDA, Draft Guidance for Industry: Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause. February 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-plausible-mechanism-framework-develop-individualized-therapies-target-specific

Evan Turek
Senior Director of Business Development

LinkedIn: www.linkedin.com/in/evan-turek-b9178a64