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Engineering Polymeric Particles for Sustained Release of Small-Molecule Therapeutics

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Small-molecule drugs too often stumble in development or fail to reach their full potential, not because a compound lacks therapeutic benefit, but because of ineffective drug delivery and biodistribution. Polymeric drug delivery platforms, including nanoparticles and microspheres made from biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), add powerful tools to the drug developers' toolbox. By encapsulating the drug within a polymer matrix, these systems control how quickly the drug is released and how long it actively circulates in the bloodstream.

Polymeric nanoparticles are well-suited to solve three distinct delivery challenges. First, they can be engineered to overcome various biological barriers, such as penetration of the mucosal surfaces of the eye and the lining of the GI tract. This physiology is cleverly designed to prevent unwanted viruses, bacteria, and other contaminants from penetrating these surfaces. However, this protection also complicates drug delivery across these surfaces. A nanoparticle that can reside on the ocular surface longer than a standard eyedrop or survive transit through the GI tract long enough to reach its absorption site, can deliver more drug to its target.

The second benefit is the ability to control the release rate to eliminate dose-limiting side effects. Many small molecules are therapeutically effective but suffer dose-limiting toxicities due to lack of target specificity, rapid systemic clearance, and off-target tissue accumulation. However, encapsulation slows release, reduces peak exposure, and keeps drug levels within a window the body can tolerate. The third advantage polymeric nanoparticles provide is improving drug biodistribution to target tissues and cell types. Nanoparticles with appropriate size and surface chemistry can circulate in the bloodstream long enough to accumulate at designated targets, such as solid tumors, via the enhanced permeability and retention effect, without requiring active targeting mechanisms.

Polymeric microspheres solve a different problem. Delivered subcutaneously or intramuscularly, they enable true long-acting release. A single injection can maintain therapeutic drug levels for weeks or months. This reduces dosing frequency, improves pharmacokinetic consistency, and meaningfully increases patient adherence, particularly for chronic conditions where daily medication is a compliance burden.

Commercial and Clinical Success of Polymeric Drug Delivery Systems

The successful commercial track record of polymeric drug delivery belongs to microspheres. There are currently 15 FDA-approved polymeric microsphere-based therapeutics,[1] including Risperdal Consta (risperidone), which delivers a sustained-release antipsychotic via intramuscular injection, eliminating the need for daily dosing in schizophrenia patients, a significant compliance advantage for a patient population where medication adherence is a persistent clinical problem. Other approved PLGA microsphere products follow the same logic: leuprolide acetate (Lupron Depot) for prostate cancer and endometriosis, naltrexone (Vivitrol) for alcohol and opioid dependence, octreotide (Sandostatin LAR) for acromegaly, and triptorelin (Trelstar) for prostate cancer. Each encapsulates a small molecule or peptide in PLGA, injects subcutaneously or intramuscularly, and releases the drug over weeks to months.

The story of polymeric nanoparticles is more complex, with several innovative platforms in late stages of clinical development. The first targeted polymeric nanomedicine to enter clinical studies, BIND-014, was a prostate-specific membrane antigen (PSMA) targeted polymeric nanoparticle encapsulating docetaxel, which produced meaningful clinical responses across multiple tumor types in Phase I and a promising response rate in metastatic castration-resistant prostate cancer in Phase II, with manageable tolerability. Unfortunately, additional clinical testing of BIND-014 was ceased. However, BIND Therapeutic's second-generation formulations (e.g., AZD2811) demonstrated even greater clinical promise, benefiting from hydrophobic ion pairing to achieve slower drug release rates and improved encapsulation efficiencies. Based on this work, an ongoing Phase II study is evaluating AZD2811 (an Aurora B kinase inhibitor) in combination with the immunotherapy drug durvalumab as maintenance therapy after induction with platinum-based chemotherapy plus durvalumab, for the first-line treatment of patients with extensive-stage small-cell lung cancer.[2]

Why Polymeric Nanoparticle Formulations Are Attractive

The appeal of polymeric nanoparticles starts with compounds that display therapeutic benefits but are not tolerable when administered to patients. For example, kinase inhibitors are often highly effective at shutting down the cellular pathways that drive cancer, but these on-target effects also negatively impact healthy cells and tissues. Encapsulating kinase inhibitors in a polymeric nanoparticle slows release, reduces peak concentrations, and brings toxicity down to a level the body can tolerate without compromising therapeutic effect. In animal studies, slow-releasing formulations consistently produced the best tolerability and the strongest long-term efficacy.[3]

The benefits extend well beyond toxicity management. PLGA nanoparticles protect drug payloads from enzymatic degradation and from physiological conditions that would otherwise diminish potency, which is particularly relevant for oral delivery, where the GI tract presents a hostile environment for many therapeutic compounds. For pediatric formulations, encapsulation solves a different problem entirely: a bitter drug sealed inside a polymer particle never reaches the taste receptors, with direct implications for compliance in a population where palatability determines whether a medication is taken at all.

Surface modification with PEG extends circulation time by reducing opsonization and immune recognition, thereby giving particles more time to reach their target. That extended half-life creates a meaningful advantage over lipid nanoparticles, which tend to clear more rapidly from the bloodstream, opening delivery opportunities to extrahepatic tissues.

Broad Applications for Polymeric Nanoparticles

When applied to mucosal surfaces such as the ocular surface, nanoparticles can remain longer than conventional eye drops, delivering more drug before blinking clears them away. For solid tumor applications, appropriately sized nanoparticles exploit the enhanced permeability and retention effect, passively accumulating within the tumor without requiring active targeting mechanisms. Surfaces can also be functionalized with ligands, antibodies, or peptides for receptor-mediated targeting when passive accumulation isn't sufficient.

Finally, there is a commercial logic to this platform that drug developers are beginning to recognize. Reformulating a known molecule into a polymeric nanoparticle system opens new patent space, a meaningful incentive when the underlying active ingredient is mature and the IP landscape around the molecule itself is crowded. The platform doesn't change the drug. It changes what the drug can do, who can tolerate it, and in many cases, whether it reaches patients at all.

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Challenges Commercializing Polymeric Nanoparticles

The science of polymeric nanoparticles is well ahead of the commercial reality, and while there are several polymeric microsphere products on the market, there is no approved therapeutic utilizing a polymeric nanoparticle delivery system. The primary barriers are formulation and manufacturing. From a manufacturing perspective, translating a nanoparticle formulation from lab-scale production to an industrially viable, reproducible GMP process while maintaining proper characterization and quality is complex and challenging.

The formulation complexity compounds the problem. Solvent selection, co-solubilization of polymer, drug, and excipients, emulsion stability over longer processing times at larger volumes, purification, and burst-release control each require specialized expertise that few innovators or CDMOs possess. The result is a field with strong preclinical data but no approved products. Closing that translational gap requires close collaboration between manufacturing science and formulation science.

Polymer Selection: Starting with What Works

For most small-molecule applications, polymer selection begins and often ends with PLGA. The reasons are practical. PLGA is biodegradable, breaking down into lactic acid and glycolic acid, both naturally occurring metabolites the body handles without difficulty. It has an extensive history of use in FDA-approved drug products, which means its behavior is well characterized and its regulatory standing is established, reducing regulatory risks.

Importantly, PLGA isn't a single material. The ratio of lactic acid to glycolic acid in the polymer chain can be adjusted to tune degradation rates and, by extension, the drug release profile. For example, higher glycolic acid content accelerates degradation, whereas higher lactic acid content slows it. Molecular weight is another lever: low-molecular-weight polymers degrade faster than high-molecular-weight versions. Polycaprolactone and polyanhydrides are available for applications requiring different release windows or degradation characteristics, but PLGA/PLA remains the default starting point for sustained release of small molecules precisely because so much is already known about its behavior.

Drug Encapsulation Strategies: Nanoemulsion and Nanoprecipitation

Once the polymer is selected, the next decision is how to incorporate the drug. The two primary manufacturing pathways are nanoemulsion and nanoprecipitation. The choice between these two approaches comes down to one practical question: which solvent(s) effectively solubilize the drug and polymer?

Nanoemulsions use water-immiscible solvents; ethyl acetate and benzyl alcohol are common examples. The polymer and drug are co-dissolved in the organic phase, then dispersed into water, essentially a controlled version of salad dressing, with small oil droplets suspended in water, each containing polymer and drug. High-pressure homogenization reduces the droplets to the 100-nanometer range, the solvent is extracted, and the drug becomes encapsulated in the solidified particle. With straightforward formulations, drug loading typically lands in the 5–9% range by weight.

Nanoprecipitation uses water-miscible solvents instead; acetonitrile and tetrahydrofuran (THF) are two examples compatible with PLGA. There is no emulsion step; as the organic and aqueous phases are mixed, the solvent diffuses out, leaving behind precipitates in the form of polymeric nanoparticles.

Both processes require the drug and polymer to be co-soluble in the chosen solvent system, a requirement that becomes significantly more complex when additional excipients are added to the formulation.

Hydrophobic Ion Pairing: The Advanced Tool

Many small molecules (e.g., kinase inhibitors) have tertiary amine groups built into their chemical structure that create pH-dependent solubility. At high pH, the drug behaves as its most hydrophobic form (free base); upon shifting to acidic conditions, those amines become protonated, resulting in more polar, more hydrophilic behavior. Since PLGA is itself hydrophobic, encapsulation works best when the drug shares that character. By formulating at a high pH, a kinase inhibitor can be encapsulated efficiently in its freebase form, but hydrophobic ion pairing takes this further.

The strategy pairs the drug with a hydrophobic counterion (an acid in the case of a basic drug), forming an electrostatic complex that co-encapsulates within the PLGA particle far more efficiently than the drug alone. Counterion selection drives two outcomes: encapsulation efficiency and release rate.

A 1:1 molar ratio is typically optimal, but an excess of counterion can drive drug encapsulation toward 100% efficiency. Importantly, the hydrophobic ion pairing approach often reduces the extent of drug burst release, a reduction that must be avoided to maintain tolerability. Furthermore, the properties of the hydrophobic counterion (e.g., acidity, molecular weight, and lipophilicity) significantly affect the drug release rate, with formulations prepared using oleic, cholic, and pamoic acids achieving progressively longer release durations, ranging from three to over ten days, based on *in vitro* analysis.[3]

Hydrophobic ion pairing can also be used to encapsulate water-soluble payloads, such as nucleic acids, peptides and proteins, into hydrophobic polymeric matrices. The approach is similar to the use of ionizable/cationic lipids in lipid nanoparticles (LNPs), where nucleic acid-based cargo (e.g., mRNA, DNA) is encapsulated within the LNP during particle fabrication via electrostatic interactions between positively charged lipid species and negatively charged nucleic acids under acidic mixing conditions. This approach vastly expands the range of active pharmaceutical ingredients (APIs) that can be encapsulated within polymeric systems, a capability that was historically limited to hydrophobic APIs.

Phosphorex guides drug developers through the full development pathway for both polymeric nanoparticles and microspheres, with the specialized expertise to de-risk the science, close the translational gap, and move programs forward with confidence.

Overcoming Polymeric Nanoparticle Manufacturing Challenges

The formulation science behind polymeric nanoparticles is well understood. Getting that science to behave reliably at manufacturing scale is a different problem, and it has been the barrier to commercializing polymeric nanoparticle therapeutics.

Controlling Burst Release

Burst release, the rapid spike in drug concentration at the start of a release profile, results from drug adhering to the particle surface or from free drug that precipitated during manufacturing and wasn't fully removed during purification. Either way, that drug dissolves immediately upon administration, producing the peak concentrations the formulation was designed to prevent.

Tangential flow filtration (TFF) removes free drug from the nanoparticle suspension, but residual drug must be fully dissolved in solution to pass through the membrane. Any precipitated drug re-circulates with the drug product instead of passing through the TFF membrane. Where surface-bound drug remains a problem after standard purification, a 'conditioning' step can help: temporarily heating the formulation above PLGA's glass transition temperature of approximately 37°C dislodges the drug from the surface, and then a subsequent TFF step removes it from the drug product suspension. Phosphorex has extensive experience in employing the appropriate scale-able downstream processing as well as hydrophobic ion pairing strategies for minimizing API burst release.

Solving Co-Solubilization

Typical formulations using hydrophobic ion pairing require that the polymer, drug, and counterion be dissolved into a single solvent system before particle formation can begin. The physicochemical properties of the API and counterion can pose challenges during this step; aromatic structures and highly hydrophobic species are prone to precipitating out of solution, and the resulting precipitates are difficult to remove during downstream purification and also present potential in-process stability concerns that worsen at larger volumes and longer processing times. Phosphorex's solution is co-solvent development: identifying a solvent blend in which all components remain stably dissolved throughout the hold times required for manufacturing. There is no universal answer, so the right system must be found empirically for each drug and counter-ion combination.

Maintaining Stability at Scale

At the bench scale, an emulsion can be processed before instability develops. At manufacturing scale, the same formulation must remain stable over longer hold times and larger volumes. Therefore, emulsion stability should be considered from the start of development to avoid costly delays at later stages, when the stakes are higher. Through careful excipient selection (e.g., surfactants), co-solvent systems, and solid content, scalable emulsion-based formulations can be identified and considered for selection as lead formulation candidates.

Address Therapeutic Index Challenges & Extend Intellectual Property

Polymeric nanoparticles and microspheres represent one of the most technically demanding areas of pharmaceutical development, but there is a tremendous commercial opportunity. For small-molecule drugs that have stalled due to tolerability problems, the right polymeric formulation can be the difference between a shelved candidate and a viable commercial product. Additionally, polymeric microsphere or nanoparticle delivery systems might be ideal for extending therapeutic patent life and creating new areas of intellectual property.

Also, programs that reformulate utilizing a polymeric strategy may offer meaningful regulatory advantages as existing safety data on the active pharmaceutical ingredient can often be leveraged, de-risking and potentially accelerating the development timeline compared to a novel chemical entity.

However, the expertise required to navigate the complexities of polymeric therapeutic development is rare. Phosphorex has spent over two decades building this capability. From initial feasibility through formulation optimization, process development, and IND-enabling studies, Phosphorex guides drug developers through the full development pathway for both polymeric nanoparticles and microspheres, with the specialized expertise to de-risk the science, close the translational gap, and move programs forward with confidence.

For developers exploring polymeric delivery for the first time, or revisiting candidates that deserve a second look, Phosphorex is the partner built for this work.

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