Late-Stage Development and Manufacturing of Novel Excipients for Precision Nanomedicines and Targeted Therapies

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Medication formulations vary widely in their administration routes, but they all contain the Active Pharmaceutical Ingredient (API) and excipients, with some incorporating novel excipients. Since novel excipients are assessed by authorities at the same level as the API, developing a robust control strategy for their GMP manufacturing is essential. Examples are provided, illustrating the development and manufacturing of two novel excipients and the expertise involved in progressing from early to late stage development.

Introduction

Over the years, drug product formulation has undergone significant advancements. From simple tablets, where an active pharmaceutical ingredient (API) is blended with magnesium stearate [17] and compressed into a tablet, to sophisticated systems such as long-acting parenteral formulations [1], pharmaceutical technology has evolved considerably. Today, tens of thousands of drug formulations are available on the market [2], each requiring specific excipients depending on the formulation type. Excipients serve multiple functions, including long-term stabilization, bulking up solid formulations containing highly potent active ingredients in small quantities (often referred to as "bulking agents," "fillers," or "diluents"), and enhancing the therapeutic properties of the API in the final dosage form. They can improve drug absorption, reduce viscosity, or enhance solubility [3, 4].

While excipients were once considered "inactive" ingredients, it is now recognized that they can be "a key determinant of dosage form performance" [5]. As a result, both the API and excipients must meet strict safety and efficacy requirements [6]. This is particularly critical when developing a novel excipient, as regulatory authorities assess it with the same rigor applied to APIs. The approval process follows a stringent development pathway, requiring a full regulatory submission.

One class of drug product formulations that has gained significant attention in recent years is nanoparticle-based drug delivery systems, also known as

nanomedicines. A key advantage of utilizing nanoscale technologies in medicine is that smaller carriers are less invasive and can be administered within the body or intravenously, as demonstrated by the thermosensitive liposome developed by Thermosome. These carriers offer greater precision and sensitivity compared to conventional drug delivery methods [7]. Lipid- or polymer-based nanoparticles can be specifically designed to enhance the pharmacokinetics and biodistribution of the drug [8-11].

At Ardena, we provide a fully integrated approach to nanomedicine development, covering everything from payloads and building blocks to novel excipients, nanoparticle manufacturing, fill & finish, and bioanalysis. Our seamless workflow ensures efficient, tailored, and successful project outcomes. This approach is supported by the development and manufacturing of novel excipients essential for nanoparticle preparation. In this white paper, we highlight our capabilities in developing a novel excipient for (phospho) lipid-based lipid nanoparticles, including liposomes, LNPs, and lipid micelles. Additionally, we present an example of a novel excipient designed for an oncology treatment.

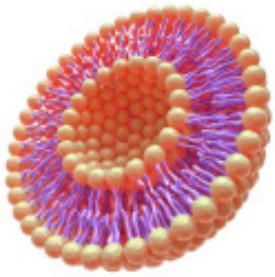


Figure 1: Schematic picture of a liposome.

Phospholipids for Constructing Lipid-Based Nanoparticles

Liposomes have garnered significant attention over the past two decades and have achieved notable clinical success, starting with the approval of Doxil in 1995. Since then, several liposome-based formulations have been approved for clinical use, demonstrating their unique advantages over other drug delivery systems [12]. A liposome is a small, spherical artificial vesicle with at least one lipid bilayer [13]. Due to their amphiphilic structure, biocompatibility, particle size, and other beneficial properties, liposomes are ideal for use as drug delivery vehicles for pharmaceutical applications [18]. Phospholipids are the most common components of liposomes [19].

The molecule developed for our client, Thermosome, as part of our CDMO services is shown in Figure 2.

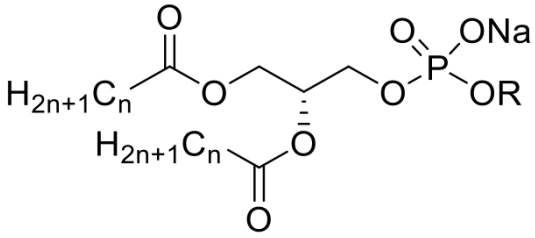


Figure 2: Phospholipid applied to construct thermosensitive liposomes.

The molecule has been anonymized to respect intellectual property confidentiality, though its phospholipid nature is clear. Throughout process development, several improvements were identified and implemented. For example, during one step, a critical byproduct was formed.

Through extensive process development, a quenching step was designed to replace an additional hydrogenation step, allowing an aqueous workup procedure to effectively remove the byproduct.

Procedures such as isolations, extensive extractions, evaporation to dryness, column chromatography, and drying with magnesium sulfate are commonly used in medicinal chemistry routes. However, these methods are often not scalable. In this case, telescoping and final crystallization were applied, streamlining the process and optimizing throughput.

An essential aspect of process R&D is the thorough review of chemicals and catalysts used in the synthesis, particularly as many modern synthetic routes involve transition metal-catalyzed cross-coupling reactions, such as Suzuki couplings [14], Sonogashira couplings [15], or hydrogenations involving various palladium catalysts [16]. The review process also includes evaluating the commercial availability of chemicals and catalysts, as well as the stoichiometry employed. For this particular synthesis, an alternative palladium catalyst was selected, leading to cost optimization.

Based on these advancements, the synthesis route is now ready for future scale-up. The phospholipid developed will be used to realize a new thermosensitive liposome bulk drug product and develop the manufacturing process at Ardena, in close collaboration with Thermosome.

Novel Excipient for Oncology Treatment

The molecule developed for our client is shown in Figure 3.

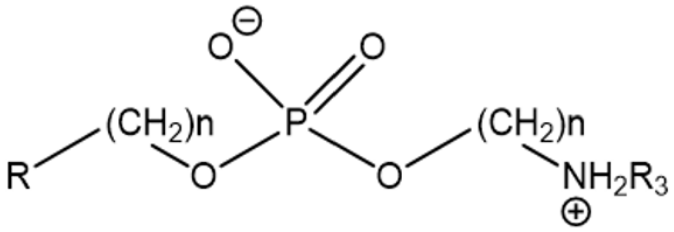


Figure 3: Cationic phospholipid applied as a novel excipient.

In line with intellectual property confidentiality, the molecule has been anonymized, though its cationic phospholipid structure is apparent. It is synthesized through approximately 10 chemical conversion steps starting from a fatty acid, with key steps including halogenation, phosphorylation, and amination.

At the beginning of the synthesis route, conversions could not be monitored by HPLC due to the nature of the molecules (lipids). To overcome this, we developed an alternative method using GC-MS and 1H NMR to track conversions and assess purity. Purifications were optimized by using crystallization methods, replacing several column purifications without compromising the purging power.

To provide our customer with a batch suitable for clinical Phase 3 studies, Late Stage Development was required.

A significant challenge during this stage was sourcing suitable GMP suppliers for several critical (regulatory) starting materials. This is particularly challenging as the lipids used in the production of the phospholipids can contain impurities that are difficult to remove during upstream processes. Several Critical Material Attributes (CMAs) were identified, highlighting the importance of carefully selecting starting materials to ensure a robust control strategy.

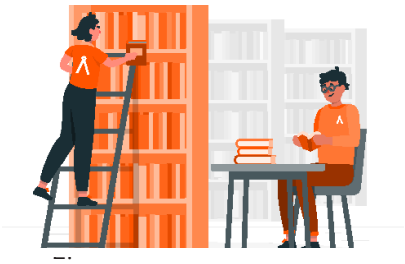
A key part of the control strategy involved a spike, fate, and purge study, for which an LC-MS method was developed. Through process development—such as modifying a quench step and changing solvents—and analytical sciences, several Critical Process Parameters (CPPs) were identified in relation to the Critical Quality Attributes (CQAs). This sometimes required trade-offs in yield optimization. Proper analysis of intermediates and the final compound using the correct wavelength and detection methods (e.g., CAD detectors) in HPLC analysis proved crucial, an aspect often overlooked in early development.

Conclusion

Innovation in drug product formulation continues to advance, with an increasing number of novel excipients being developed. Additionally, the field of nanomedicines is expanding rapidly. This paper outlined the late-stage development of two phospholipids, which serve as novel excipients in oncology treatments and thermosensitive liposome applications.

Ardena brings extensive expertise in navigating the delicate balance between EHS considerations, regulatory requirements, early clinical trial entry, and rapid patient access. Our dedicated manufacturing and analytical facilities, alongside experienced, well-trained teams and established, rational risk-based approaches, provide an integrated platform for synthesis and drug product manufacturing, bridging the critical transition from pre-clinical to clinical stages.

On behalf of Ardena, the author would like to express gratitude to our customers for their consent to publish this work. Special thanks to Thermosome for their collaboration in the development and manufacturing of the phospholipid and corresponding thermosensitive liposome.



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