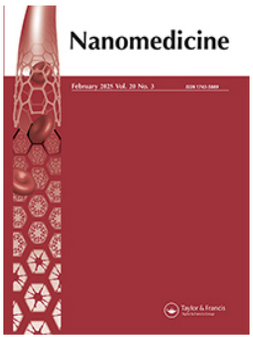

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EDITORIAL

Advantages and challenges of polymer-lipid hybrid nanoparticles for the delivery of biotech drugs

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In the last few years, the research regarding the use of nanoparticles (NPs) for medical use, often referred to as nanomedicine, has been growing faster than ever before, especially after the development and approval of mRNA-based vaccines against COVID-19, which exploited the potential of lipid NPs [1]. The great success of those innovative drug delivery systems put the spotlight on the advantages of NPs and their use to deliver biotech drugs, such as proteins, enzymes and genetic materials, not only for genetic diseases but also for the prevention and treatment of several other pathologies [2]. This led several scholars to join the research on NPs, also supported by the rapid diffusion of accessible microfluidic-based instruments that can produce a vast range of different formulations in a very short time, making it possible to quickly test the impact of a large number of technological parameters on the final product [3,4].

In such a crowded and competitive landscape, the major player is represented by fully lipidic NPs, which tend to be more investigated thanks to their well-known biomimetic composition, biocompatibility, and straightforward optimization. Lipidic NPs, however, might suffer from some limitations, especially when applied to the delivery of large hydrophilic molecules such as biotech drugs, that can be overcome using polymers: thus, polymer-lipid hybrid NPs (HNPs) can represent an interesting tool to face the challenges posed by a fully lipidic NP. The encapsulation of biotech drugs requires the design of NPs that are highly efficient in protecting the payload from mechanical, chemical and biological stress, which is possible with polymeric NPs, while at the same time high biocompatibility, as granted by the use of biomimetic lipids, is always preferred. Therefore, HNPs have begun to increase in popularity thanks to the possibility of combining the higher stability of polymeric NPs with the biocompatibility of lipids [5]. These HNPs have the potential to be produced using various bench-top technologies, including solvent displacement and microfluidic methods. These techniques allow for precise control over the size and morphology of the nanoparticles. In the case of microfluidic technologies, it's essential to assess the compatibility of the organic solvents with the materials used in the microfluidic systems. Ensuring this compatibility is vital to prevent any adverse reactions that could affect the production process and the quality of the HNPs.

The root concept of HPNs can be found in research studies of the late 1990s and early 2000s, when researchers synthesized conjugates between a lipidic portion and a polyethylene glycol (PEG) chain [6]: PEGylated lipids were destined to be part of NP research up to this day, and PEGylated NPs might be considered the first example of HNPs. The use of this conjugate was essential to improve the circulation time of nanosystems, allowing for a reduced clearance and therefore an increased therapeutic efficiency.

Nowadays, the ability to combine the mechanical stability of polymers, along with the vast array of synthesized polymers having varying sensibilities, with the biocompatible nature of lipids is showing great promise in the nanomedical field, especially when it comes to gene therapy.

One of the major aims and challenges linked to the use of siRNA as therapeutic molecules using NPs as non-viral vectors is their protection against degradation. In this scenario, the use of HNPs is a winning strategy that can combine a protective environment, stimuli-responsive behaviors, controlled and prolonged release, and mechanical stability. This is particularly evident when designing nanoparticles for topical delivery, where the shear forces during skin permeation could cause degradation of the particle and the payload, but also a certain degree of flexibility is required. In their proof-of-concept study, de Araujo et al. demonstrated the possibility of delivering functional siRNA to epidermal cells after topical application, thanks to the optimization of a hybrid nanoparticle composed of Compritol 888 and polyethylenimine (PEI). While PEI was used to promote the interaction with the siRNA, Compritol was added to exploit its ability to be highly biocompatible, flexible, and adhesive to the skin surface, resulting in efficient transfection in keratinocytes and fibroblasts [7]. Cancer treatment is another field where tissue penetration is crucial for an efficient therapy. In fact, one of the most challenging aspects of the use of nanoparticles is extravasation: while this first step is generally possible for NPs in the size range <200 nm, especially when they are decorated with specific targeting ligands, NP distribution within the organ parenchyma might be limited to the area surrounding the capillaries. This limited penetration in deeper tissues was efficiently overcome in a recent study by Phungh et al, where

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authors used hybrid poly lactic-co-glycolic acid (PLGA) and distearoyl-phosphatidylethanolamine (PLGA/DSPE) NPs, modified with an RGD peptide, to deliver an siRNA against TGF-β1 in tumor-bearing mice. This approach allowed for a wide distribution of NPs in the tumor tissues, leading to inhibition of tumor growth and prolonged survival rate [8].

Looking at the general structure of these polymer-lipid HNPs, the most common composition seems to be made of PLGA, although with different characteristics such as the L:G ratio or molecular weight, and one or two phospholipids. This approach is generally preferred due to the high biocompatibility, low cost, and market availability of phospholipids, such as DOTAP or DOPE, and their spontaneous formation of a lipid bilayer. Rinaldi et al for example screened the use of two cationic lipids, i.e., DOTAP and DC-Cholesterol, to produce siRNA-loaded hybrid NPs against Glioblastoma, showing a different silencing efficiency of DOTAP compared to DC-Cholesterol [9]. In a similar work about triple negative breast cancer, Mehta et al. reported the use of PLGA as a core to be mixed with DOTAP and DSPE-PEG to formulate hybrid NPs [10].

Following the most common composition of PLGA and a lipid, the group of Dr. Foged actually did a step forward by using a newly synthesized lipidic molecule, called L5N12. In their study, they investigated the use of this custom molecule to formulate, along with PLGA, HNPs with the microfluidic technique (MF). In their system, the siRNA was located at the interface between the PLGA core and the outer lipidoid layer, allowing for its protection during pulmonary delivery [11,12]. Moreover, thanks to the use of the MF, authors were able to evaluate the different biodistribution *in vivo* of hybrid NPs depending on the size of the NPs, which is easily controllable by using this formulation method. Another interesting application of the MF to the formulation of siRNA-loaded HNPs was recently published by Wang and collaborators. A common approach when using a microfluidic chip for this purpose, independent of the chip geometry or instrument used, is to solubilize the core materials (e.g., polymers and lipids) in the organic phase and the siRNA with eventual surfactants in the aqueous phase. With this approach, the nucleation of the polymeric and lipidic fraction happens at the same time as the complexation with the genetic material, with the final production of siRNA HNPs. In this work instead, authors first formed a DOTAP/DOPE liposome to be complexed with siRNA to form a lipoplex, and the lipoplex suspension was then used as an aqueous phase to be fed to the MF chip against an organic polymeric phase. This strategy allowed for the evaluation of the different lipid:polymer ratio on the rigidity, highlighting the crucial role of the polymeric fraction in determining the mechanical stability of the resulting NP [13]. Although overall this formulation strategy might seem long and complex due to the several steps involved, the fragmentation of the process might actually be beneficial to a thorough characterization of the resulting product. In fact, the main limitation to NP approval by regulatory agencies currently lies in the lack of full characterization and therefore reproducibility, enhanced by the lack of standardized procedures to obtain these data. To overcome this limitation, Figueroa-Espada reported an interesting method that involved the chemical conjugation between a selected lipid and PEI polymer. The new molecule comprised all the features of the two precursors and was then formulated via a MF chip to complex siRNA by self-assembling into HNPs. This led to a faster characterization of the nanosystems, as they were technically composed of only one macromolecule, along with a high transfection efficacy and low toxicity on cells [14].

To summarize, in the last 20 years we have witnessed the rise of HNPs as incredibly promising tools to protect and deliver siRNA to target cells, by combining the mechanical protection of the polymeric fraction with the biomimetic behavior of the lipids; we were then caught into the high complexity of these systems, that require such an extensive characterization that might hamper their translation in the clinics. Eventually, we found that chemical conjugates that self-assemble into HNPs might be the right answer to bring the advantages of HNPs into the clinics. In the end, after 30 years of research we are going back to the same idea that generated PEGylated lipids, further evidence that the simplest solution is always the best.

To thoroughly analyze the advances and challenges in the field of nanomedicines utilizing hybrid material compositions, we have identified several advantages associated with polymer/lipid formulations. However, researchers must recognize the limitations and potential opportunities of each approach as it is essential to incorporate a well-structured experimental design. This foundational step not only enhances the reliability of the outcomes but also ensures the alignment of the nanoparticles with the intended therapeutic applications.

A critical aspect of this process is the rational design of nanomedicines, which involves tailoring the nanoparticles based on the specific drugs intended for encapsulation. The properties of the drug, such as its solubility, stability, and release profile, directly influence how the nanoparticles are formulated. Moreover, the design of the experiment should encompass rigorous characterization techniques to evaluate the physical and chemical properties of the nanoparticles produced. Parameters such as size, shape, surface charge, and drug loading efficiency are crucial in determining the performance of the nanomedicine. Advanced characterization methods, including dynamic light scattering (DLS), electron microscopy, and zeta potential analysis, can provide vital insights into these properties.

Finally, the integration of a design rationale that incorporates both theoretical frameworks and empirical data can significantly contribute to the success of HNPs in nanomedicine. By understanding how different formulation strategies impact drug encapsulation and release dynamics, researchers can develop nanocarrier systems that are not only effective but also safe for clinical applications. This approach will not only facilitate the production of efficacious therapies but also enhance their translational potential in clinical settings.

Particular attention should be directed toward the factors influencing the future development of nanomedicine prototypes for industrial and clinical applications. This includes a detailed examination of production feasibility at a large scale and the standardization of essential properties in accordance with regulatory guidelines. In this context, hybrid nanomedicines may present certain challenges compared to fully polymeric or lipid-based drug delivery systems, necessitating further analysis and investigation to address these issues effectively.

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Author contributions statement

Ilaria Ottonelli – Writing; Conceptualization
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Barbara Ruozi – Supervision
Maria Angela – Vandelli Validation; Supervision
Giovanni Tosi – Conceptualization; Writing; Review & Editing; Supervision
Jason T. Duskey – Conceptualization; Writing; Review & Editing

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