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Lipid-based nanoparticles and their recent advances

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Abstract

Lipid-based nanoparticles hold great potential for drug delivery, providing biocompatibility and the ability to encapsulate both hydrophilic and hydrophobic drugs. However, there are certain challenges associated with small molecules, such as leakage and premature release, which can compromise their effectiveness. Despite these challenges, lipid nanoparticles offer advantages in terms of solubility, stability, and targeted delivery, thereby reducing side effects. Additionally, they can be customized for specific molecules, ensuring biocompatibility and biodegradability. While complications may arise, lipid nanoparticles offer numerous benefits for loading biomolecules, improving pharmacokinetics, and enhancing therapeutic effects. It is important to address stability and loading challenges when encapsulating biomolecules and consider potential immunogenic responses that may impact biocompatibility and safety.

Keywords: Nanoparticles; Drug delivery; Lipid-based nanoparticles; Solubility

1. Introduction

1.1. Lipid-Based Nanoparticles

Lipid-based nanoparticles are a versatile class of drug-delivery systems that have garnered significant attention due to their unique properties. They can encapsulate a broad range of hydrophilic and hydrophobic drugs, facilitating enhanced drug delivery and improve therapeutic outcomes [1].

There are several types of lipid-based nanoparticles, categorized based on their specific molecular arrangement [2]:

Liposomes: These are spherical vesicles with one or more lipid bilayers. The unique structure of liposomes—an aqueous core surrounded by a lipid bilayer—allows them to encapsulate both hydrophilic and hydrophobic drugs.

Solid Lipid Nanoparticles (SLNs) are composed of solid lipids, either pure triglycerides or a blend of triglycerides and complex glyceride mixtures. They offer high drug stability, controlled drug release, and a good tolerability profile. However, they suffer from limitations such as low drug loading capacity and the risk of drug expulsion during storage due to the crystallization of the lipid matrix.

Nanostructured Lipid Carriers (NLCs) were developed to overcome the shortcomings of SLNs. They are comprised of a blend of solid and liquid lipids, which forms an imperfect matrix structure that can accommodate more drug molecules, thereby improving the drug-loading capacity. This imperfect matrix structure also minimizes the risk of drug expulsion during storage.

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Lipid Drug Conjugates (LDCs): In LDCs, the drug molecule is chemically bound to the lipid carrier. This modification improves drug stability and controls drug release.

Lipid-based nanoparticles offer remarkable benefits in formulating, targeting, and preserving small molecules. These nanoparticles possess self-emulsifying properties that allow for the encapsulation of both hydrophilic and hydrophobic drugs, thereby improving the solubility of poorly water-soluble drugs and enhancing bioavailability [3]. Furthermore, lipid-based nanoparticles can be customized to specific molecules based on their physicochemical characteristics [4]. In terms of targeting, these nanoparticles selectively deliver drugs to specific tissues or cells within the body [5]. This is achieved through surface modifications using ligands or antibodies that bind to target cell receptors [6]. Such targeted delivery minimizes the risk of systemic side effects and enhances therapeutic efficacy [7]. Storage-wise, lipid-based nanoparticles exhibit superior stability compared to other drug delivery systems [8]. They can withstand temperature and pH variations, ensuring sustained drug efficiency over time [9]. Additionally, lipid-based nanoparticles are biodegradable and biocompatible, enabling safe metabolism within the body without adverse effects [10]. In conclusion, lipid-based nanoparticles offer significant advantages in formulating, targeting, and storing small molecules, making them a promising tool in drug delivery [11]. However, it is important to acknowledge the associated challenges. Achieving uniform size distribution and consistent drug loading during formulation can be demanding [12]. Oxidation susceptibility may impact drug stability [13]. Modifying lipid-based nanoparticle surfaces with ligands or antibodies without compromising physical properties or eliciting unintended immune responses can be complex [14]. Long-term storage may lead to aggregation or sedimentation, affecting drug quality and efficacy [15]. Careful consideration and addressing of these challenges are crucial in designing and implementing lipid-based nanoparticle-based drug delivery systems.

1.2. Complications concerning encapsulation

Loading hydrophilic small molecules into lipid-based nanoparticles poses unique challenges. The inherent hydrophobicity of lipid nanoparticles can result in inefficient encapsulation of hydrophilic drugs, leading to poor loading efficiency [16]. Additionally, due to the lipophilic nature of these nanoparticles, there is a tendency for premature release of the hydrophilic drug into the surrounding aqueous environment during circulation [17]. Various strategies have been explored to overcome these challenges. For example, the use of mixed micelles composed of lipids and surfactants has been investigated. These mixed micelles enable the inclusion of hydrophilic drugs in their hydrophilic core, thereby improving loading efficiency [18]. Another strategy involves the use of specific lipids, such as phospholipids, that can form a hydrophilic layer around the nanoparticle, facilitating the encapsulation of hydrophilic drugs [19]. Despite these strategies, further research is necessary to optimize the encapsulation process and address the challenges associated with loading hydrophilic small molecule drugs into lipid-based nanoparticles [20-24].

When it comes to loading hydrophobic small molecules into lipid-based nanoparticles, there are both complications and advantages. On one hand, the hydrophobic nature of these molecules aligns with the lipophilic environment of lipid-based nanoparticles, facilitating encapsulation and minimizing premature release [25]. This characteristic can enhance loading efficiency and extend the circulation time of hydrophobic drugs, thereby enhancing their therapeutic efficacy [26]. However, there are certain challenges to consider. Hydrophobic drugs often exhibit poor water solubility, resulting in low bioavailability and limited therapeutic effects [27]. Additionally, the high affinity of hydrophobic drugs for the lipid environment can potentially lead to particle overload, affecting nanoparticle stability and causing uncontrolled drug release [28]. Despite these challenges, strategies such as co-encapsulation with hydrophilic substances or surface modification with hydrophilic polymers have been employed to improve the water solubility and bioavailability of hydrophobic drugs [29]. In conclusion, while loading hydrophobic small molecules into lipid-based nanoparticles presents certain complications, the advantages offered by this approach, such as enhanced loading efficiency and therapeutic efficacy, make it a promising strategy in drug delivery [30].

Loading biomolecules into lipid-based nanoparticles introduces its own set of challenges and advantages. Biomolecules, including proteins, DNA, and RNA, have complex structures and are often larger than traditional small-molecule drugs. This complexity can pose difficulties in encapsulation and stability within lipid-based nanoparticles [31]. For instance, mRNA vaccines, such as those developed for COVID-19 by Pfizer-BioNTech and Moderna, utilize lipid-based nanoparticles to protect the mRNA and facilitate its delivery into cells [32]. However, the encapsulation process must be carefully controlled to prevent disruption of the mRNA structure, which could render the vaccine ineffective [33]. Moreover, the large size of these biomolecules can result in inefficient loading into lipid-based nanoparticles and premature release [34-40].

Despite these complications, several strategies have been explored to improve biomolecule loading into lipid-based nanoparticles. Modifying the lipid composition of the nanoparticle can create a more favorable environment for

biomolecule encapsulation. In the case of mRNA vaccines, the use of ionizable lipids, which carry positive charges, promotes encapsulation and stability of the negatively charged mRNA [41]. Another strategy involves co-encapsulation with stabilizing agents, such as polyethylene glycol, which enhances the stability of biomolecules within the nanoparticle and prevents premature release [42]. These examples illustrate the potential of lipid-based nanoparticles in delivering biomolecules, despite the associated challenges. However, ongoing research is crucial to optimize these techniques and further enhance the efficiency and effectiveness of biomolecule delivery via lipid-based nanoparticles [43].

1.3. Complications concerning targeting

The delivery of small molecules and biomolecules using lipid-based nanoparticles poses significant challenges. The primary hurdle is ensuring targeted delivery without interference from the immune system. The foreign nature of the nanoparticles can lead to rapid recognition and clearance by the mononuclear phagocyte system (MPS), reducing their therapeutic effect [44]. Furthermore, the navigation of nanoparticles through the complex biological environment presents obstacles. In solid tumors, the dense extracellular matrix can impede nanoparticle penetration, hindering their ability to reach tumor cells [45]. To overcome these barriers, researchers have explored surface modification of nanoparticles with targeting ligands, such as antibodies or peptides that bind specifically to receptors on target cells. However, maintaining the stability of these ligands during circulation and ensuring their proper orientation on the nanoparticle surface for effective binding is a complex task [46].

In the context of biomolecule delivery, endosomal escape is another challenge. Nanoparticles often get trapped in endosomes and degraded in lysosomes after cellular uptake, resulting in a loss of encapsulated biomolecules before their therapeutic effects can be exerted [47]. Various strategies, including the incorporation of pH-sensitive lipids that destabilize the endosomal membrane, are being investigated to enhance endosomal escape [48]. Lastly, achieving controlled release is a common hurdle for both small-molecule and biomolecule delivery. The release rate of therapeutic agents encapsulated within nanoparticles must be carefully controlled to maintain therapeutic drug concentrations and minimize side effects. However, this is challenging due to factors such as the drug's characteristics, the lipid composition of the nanoparticle, and the physiological conditions where the release occurs [49]. In conclusion, while lipid-based nanoparticles hold promise for the delivery of small molecules and biomolecules, addressing these significant hurdles is crucial to fully realize their potential in targeted therapy [50].

1.4. Complications concerning industry scalability and storage

Scaling up lipid nanoparticle production for industrial use poses unique challenges. Consistent quality and uniformity of nanoparticle size during large-scale production is difficult to maintain. The lipid nanoparticles must have a consistent size to effectively encapsulate therapeutic agents and be efficiently taken up by cells. Any size deviation could affect biodistribution and therapeutic efficacy [51]. Large-scale lipid nanoparticle production requires specialized equipment and skilled personnel, adding costs. The use of organic solvents in fabrication raises environmental and safety concerns, requiring solvent recovery systems [52].

Storage presents significant issues for lipid nanoparticles. They can be unstable under certain conditions, leading to changes in physical properties over time, and potentially affecting therapeutic efficacy. Lipid nanoparticles typically need specific temperature-controlled storage, increasing costs and logistical challenges, especially for global distribution [53]. Freeze-thaw cycles compromise lipid nanoparticle stability, resulting in size changes and drug leakage, reducing therapeutic effectiveness [54]. For biomolecules, like mRNA, storage concerns arise. mRNA stability is sensitive to temperature. For example, the Pfizer-BioNTech COVID-19 vaccine, which uses lipid nanoparticles, requires ultra-low temperature storage (-70°C) for stability. This requirement poses challenges, especially where ultra-cold storage facilities are not available [55]. In conclusion, lipid nanoparticles show promise for encapsulating and delivering molecules. However, industry scalability and storage pose challenges. Research and innovation are needed to address these issues and optimize lipid nanoparticle use in drug delivery [56].

1.5. Future direction

The future of lipid nanoparticles in the delivery of small molecules and biologics holds immense potential [57]. One key area of exploration is the development of novel lipid materials that can further improve stability, control drug release, and enhance targeting [58]. Advances in nanotechnology could facilitate the creation of multifunctional lipid nanoparticles, where different therapeutic agents are encapsulated within a single nanoparticle, enabling combination therapy [59-62]. Furthermore, the application of machine learning and artificial intelligence in the design of lipid nanoparticles could revolutionize the field [63]. These technologies could provide insights into complex relationships

between lipid nanoparticle characteristics and their therapeutic efficacy, ultimately enabling the design of optimized drug delivery systems [63].

In the context of biologics delivery, researchers are exploring strategies to enhance endosomal escape and improve the delivery efficiency of biomolecules [64]. For instance, novel materials that can respond to specific stimuli within the body, like changes in pH or temperature, to trigger endosomal escape are under investigation [64]. In terms of production and storage, innovations in manufacturing processes and storage solutions are expected [65]. Efforts are being made to develop more efficient, cost-effective production processes that minimize the environmental impact [65]. Meanwhile, research is underway to find ways to improve lipid nanoparticle stability at higher temperatures, reducing the dependency on ultra-cold storage [65].

Lastly, regulatory considerations will also play a crucial role in the future of lipid nanoparticles [66]. As these systems become more complex and multifunctional, regulatory bodies will need to adapt their guidelines to ensure safety and efficacy [66-71].

2. Conclusion

In conclusion, the future direction of lipid nanoparticles in drug delivery is likely to be influenced by advances in materials science, nanotechnology, computational modeling, and regulatory science, all of which will shape the path toward their successful clinical translation.

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