Mini Review: Advances, Challenges, and Future Directions for Lipid Nanoparticles and Vesicular Nanoparticles as Emerging Nanocarrier Systems for Enhanced Drug Delivery

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Mini Review: Advances, Challenges, and Future Directions for Lipid Nanoparticles and Vesicular Nanoparticles as Emerging Nanocarrier Systems for Enhanced Drug Delivery

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Abstract: *Lipid-based nanocarrier systems, including lipid nanoparticles [LNP], liposomes, solid lipid nanoparticles [SLNs], and nanostructured lipid carriers [NLCs], have emerged as promising platforms for drug delivery across biomedical and cosmetic fields. These carriers offer significant advantages such as improved drug solubility, enhanced bioavailability, targeted delivery, and controlled release. This mini review provides an overview of the structural characteristics and mechanisms underlying drug encapsulation and drug release mechanisms in lipid and vesicular nanoparticles. Key biomedical applications are discussed, including cancer therapy, transdermal delivery, vaccine development, and central nervous system targeting. Despite their potential, several limitations hinder clinical translation, such as stability issues, toxicity, and regulatory barriers. Recent advances in smart nanoparticles, various nanosystems, personalized nanomedicine, and chemical synthesis approaches are shaping the future landscape of nanomedicine delivery technologies. By addressing these challenges through interdisciplinary innovation, lipid-based nanoparticles hold strong potential for next-generation therapeutics and diagnostics.*

Keywords: nanoparticles; therapeutics; nanotechnology; drug delivery

1. INTRODUCTION

Over four millennia ago, ancient Egyptian physicians began employing pharmaceutical preparations such as pills, ointments, and salves for the treatment of various ailments. The first documented intravenous injection in humans was performed in 1665, followed by the introduction of subcutaneous injections in 1853 [1]. The modern hypodermic syringe was subsequently developed in 1884. Present-day methods of drug administration retain many similarities with these early approaches, with minimal changes over the years. While many current methods remain similar, evolving techniques now offer added benefits such as improved UV protection, skin penetration, and anti-aging effects for specific drugs or conditions [2–4]. Conventional delivery methods often struggle with poor solubility, rapid degradation, and non-specific targeting, reducing efficacy and increasing toxicity [5,6]. As a result, global research is accelerating the development of innovative, cost-effective drug delivery systems [7].

In response to this demand, many established drugs are being formulated into advanced delivery systems to improve their efficiency and benefits. This nanoscience approach focuses on creating nanoscale platforms for the targeted delivery of therapeutic genes and small molecules [8]. Nanoparticles, in particular, have shown great promise for transporting drugs directly to specific sites within the body [9]. With typically size of 10–1000 nm, they can encapsulate, protect, and deliver active compounds with enhanced precision. The size of nanoparticles significantly influences various pharmacokinetic and pharmacodynamic parameters, including toxicological responses, circulatory half-life, tumor localization and penetration, cellular uptake, and the efficacy of targeted drug delivery [10,11]. Their ability to regulate drug release, enhance solubility, and improve cellular uptake has made them a central focus of pharmaceutical and biomedical research [12,13]. A study by A. Abdirashit et al., 2024 demonstrated the green synthesis of nanoparticles using walnut waste extracts which highlights the potential of nanoparticles being combined with various ingredients, including metals, organic materials, and natural products [14].

2. NANOPARTICLES AS THERAPEUTIC DELIVERY

Nanotechnology offers vast potential in drug delivery by enabling precise interactions with subcellular compartments in the body, thus enhancing therapeutic outcomes [3]. Nanoscale units like viruses and ribosomes naturally perform critical biological functions [15], and nanoparticles can mimic this behavior to target and activate intracellular processes, improving treatment efficacy [16].

Nanocarrier-based drug delivery systems are increasingly favored over conventional methods due to their many advantages [17]. Since the term 'nanoparticles' emerged in the 1970s, functional nanosystems have attracted strong research interest in the interdisciplinary field of nanoscience [18–21]. Their high surface-to-volume ratio enables more effective drug delivery at lower doses, reducing side effects and toxicity [15,22]. Additionally, tunable surface chemistry allows for customization to different drugs and targeting molecules, enabling sustained release, improved bioavailability, and prolonged circulation times [15].

Nanoparticles offer flexibility in drug administration through various routes, with uptake determined by their surface characteristics, often involving the liver, spleen, and reticuloendothelial system [23,24]. Controlled drug delivery systems enhance therapeutic efficacy by directing drugs to specific targets while minimizing side effects. Beyond medical applications, the unique

physicochemical properties of nanoparticles support their growing use in diverse fields.

Nanocarrier-based drug delivery systems are being actively explored for cancer treatment, vaccines, diagnostics, and theranostics. Unlike conventional therapies, they offer targeted delivery, minimizing side effects and improving drug efficacy, especially for poorly water-soluble drugs [25,26]. Commonly studied nanocarriers include lipid-based systems (SLNs, NLCs), vesicular carriers (liposomes, niosomes, transfersomes, ethosomes], polymeric nanoparticles, micelles, dendrimers, and others. These systems enhance skin penetration, stability, and bioavailability, with future research expected to expand their clinical and therapeutic applications [19].

This short review focuses on two key categories of nanocarriers for drug delivery: lipid-based and vesicular nanoparticles. It highlights solid lipid nanoparticles (SLNs] and nanostructured lipid carriers (NLCs) for their biocompatibility, enhanced drug stability, and controlled release, making them ideal for transdermal and targeted delivery. Vesicular systems such as liposomes, niosomes, transfersomes, and ethosomes are also discussed for their ability to improve drug solubility, skin permeability, and site-specific delivery. By comparing their structures, preparation methods, and therapeutic advantages, this review offers insights into their roles in modern drug delivery. Figure 1 presents a schematic of commonly used nanoparticles, including polymeric, lipid, vesicular systems, micelles, metallic nanoparticles, quantum dots, and dendrimers.

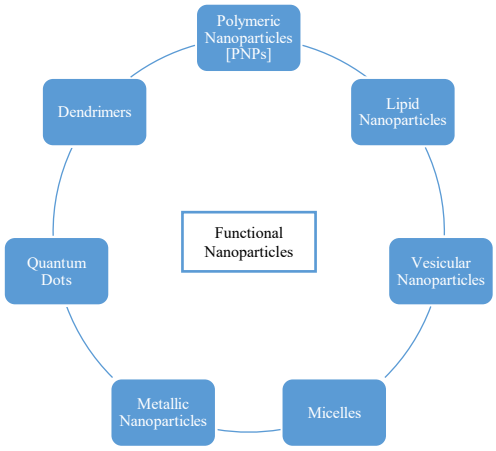

Fig. 1. Schematic illustration of functional nanoparticles. Adapted from L. Liu et al., 2023.

3. TYPES OF NANOPARTICLES

3.1 Lipid Nanoparticles (LNP)

3.1.1 Solid-Lipid Nanoparticles (SLN)

A range of lipid-based nanosystems which including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and vesicular nanocarriers have been developed to facilitate drug delivery mechanism. Solid lipid nanoparticles (SLNs), composed of physiological and biodegradable lipids, are extensively [27,28] as mentioned by Nasiri F. et al., 2020. In room temperature environment, these SLN creates a solid lipophilic matrix into hydrophilic or lipophilic drug molecules. Based on their structure, they are formed in a spherical shape with range of 50-1000 nm with a narrow particle size distribution [27]. Previous reported techniques in producing the SLN are via hot and cold homogenization, solvent emulsification, evaporation, microemulsion, water-in-oil-in-water (W/O/W) double emulsification method and microfluidics [29–32]. Depending on the formulation or preparation method, the size of the resulting nanoparticles can be tuned to approximately 100–220 nm or 80–210 nm, respectively [28]. This is particularly important for enhancing drug accumulation and establishing a localized drug depot, which can support controlled drug release over an extended period. Additionally, SLNs exhibit a distinctive occlusive property that may promote drug penetration through the skin of stratum corneum (SC) by minimizing transepidermal water loss. As a result, SLNs are being widely investigated for their therapeutic potential in transdermal drug delivery applications [19]. In most instances, incorporating SLN dispersions into an ointment or gel is required to produce a formulation suitable for topical application. Additionally, repeated ultrasonication cycles may influence the particle size and stability of the dispersion [19].

3.1.2 Nanostructured Lipid Carriers (NLC)

Nanostructured lipid carriers (NLCs), representing a next-generation advancement of lipid-based nanoparticles, are currently the focus of extensive research [28]. NLCs are formulated by blending at least one liquid lipid (oil) with one or more solid lipids to create nanocapsules, in which the liquid lipid phase may be embedded within the solid lipid matrix or situated on the surface of the solid particles [33,34]. In the production of NLC, most reported studies provided several methods in fabrication of NLC which includes high pressure homogenization [35], melt emulsification [36], emulsification-solvent evaporation [37,38], ultrasonication [39], solvent diffusion [39] and spray drying techniques [40]. It was also stated that the ratio of solid to liquid lipid that are suitable in producing NLCs ranges from 70:30 to 90:10 which later will be characterized via dynamic light scattering (DLS), transmission electron microscopy (TEM), intensity and volume of the formed nanosystem [41]. Due to their smaller particle size, NLCs exhibit enhanced surface contact with upper layer of skin, thereby increasing the penetration of active ingredients through the skin. Additionally, their nanoscale dimensions enable close adherence to the skin surface, allowing for more controlled drug release. Moreover, NLCs have successfully offer higher drug-loading capacity compared to SLNs, which contributes to higher concentration of active ingredients on the skin surface which further promotes drug permeation better [42,43]. In addition, NLC have reported in improving drug permeability, skin hydration, controlled drug release

studies and its stability therefore making NLC to be widely studied recently. The drawbacks of NLC due to the unpredictable gelation tendency and low drug incorporation efficiency associated with the crystalline structure of solid lipids [19]. This challenge highlights the need for continued research and development to facilitate more advancements for NLC to be a medium for therapeutic delivery of treatment.

3.2 Vesicular Nanoparticles

3.2.1 Liposomes

Revised by the review obtained by [44], liposomes are displayed as among the promising vesicular nanocarriers that are able to pass the epidermal barrier of the skin. Liposomes are spherical vesicles with the size range of 25 to 5000 nm that are composed of one or more phospholipid bilayers that surrounds an aqueous core [45]. With this unique structural, hydrophilic drugs can be loaded into the aqueous core while hydrophobic drugs can be loaded into the lipid bilayer making liposome are also among the versatile nanocarriers for a wide range of compounds in drug delivery mechanism [46,47]. In the production of liposomes are made via thin-film hydration [48], reversed phase evaporation [49], microfluidic method [47,50,51] and solvent injection techniques [52] which are the most commonly reported formation for liposome preparation. Nevertheless, its good facilitation of delivery, liposomes also have their limitations which are able to induce toxic effects such as inflammation, myelosuppression, proliferation and carcinogenesis [19]. Thus, to demonstrate its potential of liposome delivery mechanism, an in-depth analysis and evaluation on liposome toxicities are necessary for its future potential.

3.2.2 Ethosomes

Ethosomes are lipid-based vesicular systems characterized by the incorporation of high concentrations of ethanol, which enhances their permeability through biological membranes [53]. In general, ethosomes are composed of phospholipids, ethanol and water [52] whereby it can be seen that the structure of them consists of phospholipid bilayer and aqueous inner core that encapsulates the drug inside [54]. Ethosomes can be prepared via conventional methods such as hot and cold method of combining the ingredients that are phospholipids, ethanol and water [52,55,56]. With the presence of ethanol as the ingredient, the range of size for ethosome appears to be smaller than liposome despite being prepared in the same techniques. The decrease in size for ethosome have shown to be exhibiting high encapsulation efficiency for variety of compounds that are lipophilic drugs which are better solubility for many drugs to be loaded [57,58]. Ethanol as the solvent ingredient in ethosome are able to increase the fluidity between ethosomal and skin lipid bilayers for drug penetration [28]. Thus, with the deeper penetration of the drug into the skin bilayer, ethosomes evaluation of safety are taken into account where it can also penetrate into the systemic circulation [59]. Ethosomes' safety for topical assessment on the skin should be investigated by *in vitro* and *in vivo* experiments where the contents of ethosomes are also prone for hydrolysis and stimulate oxidation process that leads to instability for ethosomal nanosystems [19,59].

3.2.3 Niosomes

Niosomes are a vesicular nanosystems made by nonionic surfactants with the range of nanosize between 100 to 2000 nm [60]. The surfactants used in making niosomes are commonly biodegradable, biocompatible and non-immunogenic, which provides these nanosystems to have higher encapsulation efficiency, improved stability, better drug penetration and lower production cost compared with liposomes [60]. Another notable advantage is the relatively simple and scalable production process of niosomes. As versatile carrier systems, niosomes can be administered via multiple routes, including transdermal delivery [61,62]. Previous studies have reported that niosomes are utilized as the nanosystem in carrying minoxidil and ellagic acid for treatment of hair growth and whereby niosomes are able to simultaneously reducing systemic absorption and improving the penetration of the encapsulated substances across the skin barrier [63]. Despite their numerous advantages, niosomes face a significant limitation in terms of stability. Drugs encapsulated within niosomes are susceptible to hydrolysis in the aqueous core, which can result in drug leakage from the entrapment site and subsequent degradation of the vesicular structure. These challenges must be carefully considered when developing niosomal nanosystems as drug carriers for therapeutic applications.

3.2.4 Transfersomes

Transfersomes are firstly designed and established [64] whereby the vesicular nanosystem contain at least one inner aqueous that surrounded by a lipid bilayer [64]. This vesicular nanocarrier are prepared by two basic stages of preparing a thin film hydration and sonication of the ingredients that includes solvent that is vapourised where it will later proceed with homogenization of the vesicles obtained by extrusion through a membrane of multilamellar vesicles [63,65]. Morphologically, transfersomes have the same structural properties that resemble liposomes but exhibits a different functionality [66]. This is because transfersomes are metastable that indicates they exist in a relatively stable, non-equilibrium state that can enhance functional performance where in therapeutic delivery offering the advantage of high deformability, which enables them to penetrate skin pores significantly smaller than their own diameter [67]. The advantage of transfersomes is the size did not change significantly when crossing the barriers for skin interactions making transfersomes as among the

distinguished nanocarriers when compared to conventional lipid vesicles for drug permeation [68,69]. In 2011, it was reported by Duangjit and colleagues that, they successfully produced meloxicam transfersomes which are able to penetrate the disrupting and fluidizing the skin layer which act as penetration enhancers [70]. However, the application of transfersomes is limited by their susceptibility to oxidative degradation. Additionally, the formulation process for transfersomes is costly and not readily accessible, which further restricts their widespread use.

3.3 Fabrication Methods and Characterization of Nanocarriers

Given the previously discussed characteristics, functional nanosystems demonstrate significant potential to enhance transdermal drug delivery while simultaneously minimizing undesirable side effects. In this following section, the lipid nanoparticles (Solid Lipid Nanoparticles – SLN, Nanostructured Lipid Carrier – NLC) and vesicular nanoparticles (liposomes, ethosomes, niosomes and transfersomes) are discussed and we have summarized their fabrication methods and composition of each nanocarriers in Table 1. To support the findings on nanocarriers, the characterization of them is evaluated based on varieties of microscopic, spectroscopic and structural techniques. Among the reported most common characterization techniques are Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) to evaluate its shape and morphology of the nanocarriers formed with ultrastructural spatial resolution down to 0.1 nm [71,72]. Furthermore, Dynamic Light Scattering (DLS) also known as photon correlation spectroscopy (PCS) and zeta potential is among the well-known tools and techniques to study the hydrodynamic size and surface change of the nanocarriers within the colloidal systems [73–75]. Size distribution by number and volume reflects the number of particles within a specific size range and the corresponding volume they occupy. The Z-average diameter in DLS represents an intensity-weighted mean size derived from cumulant analysis, incorporating contributions from intensity, volume, and number distributions. The polydispersity index (PDI) indicates the breadth of the particle size distribution, serving as a measure of the degree of uniformity (monodispersity) or variability (polydispersity) within a colloidal system. For a Gaussian distribution, the PDI is mathematically expressed as the square of the ratio between the distribution width and the mean size, i.e., $(\text{width}/\text{mean})^2$ [75].

Table 1: Summary of fabrication methods and its composition of nanocarriers

Nanocarriers	Compositions	Fabrication Methods
Solid Lipid Nanocarriers (SLN) [27,28]; Spherical Size: 50-1000 nm	Solid lipid, surfactants, co-surfactants	Thin film hydration; reverse phase evaporation; sonication; solvent-injection homogenization; microfluidics
Nanostructured Lipid Carrier (NLC) [28,41]; Spherical Size: 100-200 nm	Solid lipid, liquid lipid, surfactants	High pressure homogenization; ultrasonication; solvent evaporation; solvent emulsification method; microemulsion; hot-melt extrusion (HME) methods
Liposomes [44–46]; Spherical Size:25-5000 nm	Phospholipids	Thin film hydration; membrane extrusion; sonication (probe/bath); ethanol injection; reverse-phase evaporation
Ethosomes [60,63,76]; Spherical Size:10-1000 nm	Ethanol, phospholipids, water	Hot/cold methods; sonication; thin film hydration
Niosomes [52–55,63]; Spherical Size: 100-2000 nm	Nonionic surfactants	Hot and cold methods
Transfersomes [64,66,68–70,77]; Spherical Size: 90-140 nm	Phospholipids, Surfactants, Alcohol, Buffering Agent	Thin film hydration; sonication; homogenization; membrane extrusion

4 MECHANISMS OF DRUG ENCAPSULATION AND RELEASE

Drug encapsulation and release mechanisms in nanocarrier systems play a crucial role in enhancing therapeutic efficacy. Encapsulation protects hydrophilic or lipophilic drugs from enzymatic degradation, improves bioavailability—as seen with poorly soluble drugs like curcumin and paclitaxel—and reduces irritation or unpleasant taste [24,78]. Controlled release enables sustained drug delivery at a specific rate and site, maintaining therapeutic levels and improving compliance, particularly for drugs with short half-lives [79,80]. Advances in stimuli-responsive systems allow drug release in response to pH, temperature, or redox

conditions [81,82]. Targeted delivery involves modifying nanocarriers with ligands like hyaluronic acid to facilitate receptor-mediated uptake, improving selectivity and minimizing toxicity—demonstrated in studies targeting melanoma, pulmonary adenocarcinoma, and breast cancer cells using ligand-coated SLNs and NLCs [83].

5. CHALLENGES AND LIMITATIONS

Nanocarriers, especially those formulated from synthetic materials, have the potential to interact with components of the immune system, which may lead to immunotoxic effects. Such interactions can elicit unintended immune responses, thereby underscoring the critical importance of comprehensive biocompatibility evaluations throughout the nanocarrier development process [84]. The nanoscale dimensions of nanocarriers can potentially induce toxicity through their interactions with biological tissues and fluids [85,86]. In terms of stability nanocarriers may face stability issues such as aggregation, drug leakage, and oxidation during storage, which can compromise their efficacy. Understanding the degradation pathways and developing strategies to enhance stability are crucial for the successful application of nanocarriers. In transitioning scaling up nanocarriers production from the laboratory to industrial levels poses significant challenges, particularly in ensuring reproducibility and adherence to regulatory standards. The application of Quality by Design (QbD] principles offers a systematic approach to overcome these obstacles by promoting consistent product quality and streamlining regulatory compliance [87]. Despite their remarkable advantages, nanocarriers are susceptible to stability challenges during storage, including aggregation, drug leakage, and oxidative degradation, all of which can adversely affect their therapeutic efficacy. A comprehensive understanding of their degradation pathways, along with the development of effective stabilization strategies, is essential to ensure their successful clinical application [88].

6. CONCLUSION AND FUTURE PROSPECTS

Future advancements in nanocarrier systems are increasingly focused on the development of smart, efficient, and specific drug delivery platforms. Stimuli-responsive nanocarriers, which release drugs in response to physiological cues such as pH changes, enzymatic activity, or light exposure, are being actively investigated for their potential to enhance therapeutic precision and control. Concurrently, hybrid systems that combine lipids, polymers, and inorganic components are emerging as multifunctional platforms capable of integrating therapeutic and diagnostic functionalities, thus advancing the field of personalized medicine with the combination of material sciences. Among the most promising novel nanocarriers are lipid-based nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC) offer advantages such as biocompatibility, enhanced skin penetration, and controlled release. Similarly, vesicular nanocarriers such as liposomes, niosomes, transfersomes, and ethosomes provide versatile delivery routes and improved bioavailability due to their structural adaptability and ability to encapsulate a wide range of active compounds. These systems are particularly relevant for transdermal and targeted therapies. Additionally, the incorporation of green nanotechnology helps in utilizing sustainable methods and natural materials for nanocarrier synthesis that can offer a promising route to reduce environmental impact and enhance biocompatibility.

With the recent emergence of Artificial Intelligence (AI) technologies, it helps to play a role in rational design and optimization for potential successful nanoparticles. Additionally, AI plays an emerging role in optimizing nanocarrier design, reducing development time, and ensuring product quality. This review highlights and compares lipid-based and vesicular nanocarriers, emphasizing their structural features, mechanisms, and potential in modern drug delivery.

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