



Review Article

Lipomers as Hybrid Nanocarrier: Innovation in Targeted and Controlled Drug Delivery

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ABSTRACT

Lipomers or lipid-polymer hybrid nanoparticles (LPNs) represent a promising class of nanocarriers aiming to combine the benefits of polymeric and liposome nanoparticles, while avoiding their drawbacks. These composite structures offer excellent drug-loading efficiency, improved biocompatibility and remarkable structural stability stemming from the core-shell lipid encapsulation around a polymeric core. Due to their unique coreshell architecture allowing for targeted, controlled and prolonged release of drugs lipomers can be used as carriers of various types of therapeutic agents such as peptides, vaccines, hydrophilic and hydrophobic pharmaceuticals and nucleic acids. Current formulation strategies, such as solvent evaporation, nanoprecipitation and surface functionalization further improved tissue targeted accumulation, pharmacokinetics performance and encapsulation efficiency. Society Media also facilitate in stimuli-responsive as well as multifunctional design that aid in the space of precision medicine and theranostic applications. Despite great progress, large-scale production, reproducibility and regulation still pose challenges. Further research in the direction of intelligent and personalized lipomer systems, including artificial intelligence and nanorobotics would probably speed up the clinical translation. As a whole, lipomers figure as an unprecedented breakthrough in targeted and controlled drug administration which sets the stage for safer, more efficiently working and patient-customized therapeutics.

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INTRODUCTION

i. Newer Generation of Nano-Carriers for Drug Delivery

Nanotechnology has made a large impact in the pharmaceutical industry. It has resulted in smart, efficient systems that can deliver drugs where they are needed. Of the variety of nanocarriers tested, liposomes and polymeric nanoparticles have received great interest in elevating solubility, stability protection of labile drugs and circulation half-life. But there are down sides to each. Liposome are commonly subjected to drug leakage and low physical stability, meanwhile polymeric nanoparticles may be of inadequate biocompatibility as well as burst release for the loaded drugs. The limitations of these materials prompted the development of a hybrid delivery device that combines the best attributes of both materials as well as neutralizes their deficiencies [1].

ii. The Idea and the Necessity of Hybrid Systems

Lipid polymer hybrid nanoparticles also known as lipomers are a new class of nanocarriers that amalgamate the structural stability of polymers and biocompatibility and flexibility of lipids. Lipomers usually comprise of a hard polymeric core for drug encapsulation and a soft lipid matrix to improve stability, diminish immunogenicity, promote cellular uptake. This combination structure is capable of controllable, sustained-release drug loading and has the potential to be further modified for targeted drug delivery. The lipophilic shell is also similar to biological membranes that enhance the interaction with cells and facilitate endosomal escape, which is particularly useful for gene or protein delivery [2].

iii. Scope and Significance of Lipomer Based Systems

Lipomers are considered a "second generation" nanocarrier platform which combines the

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advantages of both lipid and polymer drug delivery systems. These hybrid NPs demonstrate a synergistic combination of the high drug loading of polymeric NPs and controlled release as well as favorable biocompatibility, membrane permeability of liposomes [3]. Tunable physicochemical and PK properties are introduced through the incorporation of a polymeric core, usually PLGA, PCL or chitosan material shell enclosed by a lipid shell of phospholipids or fatty acids [4]. This bicomposition also contributes to eliminate drug leaks and to maintain the structural stability, in addition the circulation of the system is increased for less uptake by the reticuloendothelial system. In addition lipid layer helps to reach contact with biological membranes, which not only enables effective cellular uptake and targeted delivery of ligands, but also makes lipomers versatile carriers for various therapeutic agents such as small molecules, peptides, proteins and nucleic acids [5, 6].

Besides these properties related to their structure, lipomers also show robust versatility for functionalization and targeting. Its surface modification by ligands such as folic acid, transferrin or antibodies allows receptor-mediated uptake and site-specific accumulation including tumor or inflamed tissues. Recent advances have allowed the design of stimuli-responsive lipomers which only release their load when an environmental change occurs (e.g., as that caused by alterations of pH, temperature or enzyme activity) [7]. This renders the procedure more precise and safer for the organism in general. Because of these characteristics of lipomers, they have been considered for various biomedical applications including anticancer treatment, anti-inflammatory therapeutics, gene and vaccine carriers and for delivery to the nervous system. Their modular nature, scalable production and compatibility with regulatory agencies via their biodegradability render them a potential framework for future clinical translation. Overall, lipomers in general constitute a landmark technological advancement applicable to the targeted and controlled delivery of drugs; which may entirely revolutionize the current forms of treatments by means of superior effectiveness, diminished side effects, and personalized approach to therapy [8].

Design and Structure of Lipomers

Lipomers, or lipid polymer hybrid nanoparticles (LPNs), are a new generation of nanocarriers that unites the mechanical stability of polymers and the biocompatibility and functional variability of lipids. They can be designed for improved drug loading/capturing, release regulation and targeting. The structure of lipomers is one of the most important aspects with regard to their behavior, it affects stability, loading and interaction with biological systems [9].

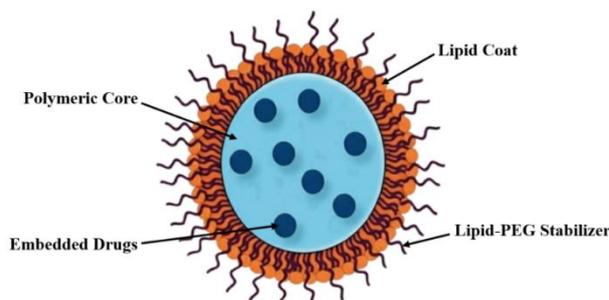


Figure 1: Schematic representation of drug-loaded Lipomer

i. Core-Shell Architecture

Lipomers are commonly characterized by a core-shell structure, in which the core is constituted by a polymeric matrix and covered with a lipid layer. The polymeric core not only imparts mechanical support and regulates the release kinetics of entrapped drug but also protects fragile molecules from degradation. Meanwhile, the lipid envelope is beneficial for biocompatible purposes and cell-membrane interaction as well as incorporating hydrophobic drugs effectively. This can be advantageous as dual drugs loading is feasible by having hydrophilic drugs entrapped in the polymeric core while lipophilic drugs are encapsulated within the lipid shell.

The core-shell structure also decreases the opsonization of plasma protein, to prolong circulation time *in vivo*. It is reported that manipulation of the thickness and composition of lipid shell can be used to modulate the release profiles as well as enhancing cellular uptake, which makes lipomers widely applicable for targeted continuous drug delivery [3].

ii. Lipid-Polymer Interactions

The lipid/polymer interface is the determinant factor for stability and performance of lipomers. Hydrophobic forces, van der Waals interaction hydrogen bonding or electrostatic interaction

depending on the nature of lipids and polymers may be involved in interactions between two components [10].

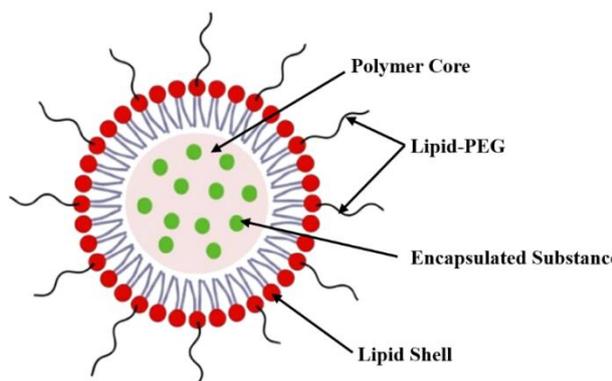


Figure 2: Lipid-Polymer hybrid Nanoparticle

Strong interactions between lipids and polymers can stabilize the structure of the nanoparticle for storage and transport, while weaker interactions might enable payload release. Furthermore, such interactions determine drug EE%, particle size (PS) and surface charge, parameters that are critical for *in vivo* performance. For example, biodegradable polymers PLGA combined with phospholipid drugs produced nanoparticles with better stability, long-term release and reduced cytotoxicity.

iii. Surface Functionalization and Targeting Ligands

Modified ligands can be grafted on the surface of lipomers for active targeting of particular tissues or cells. Common modifications involve conjugation of antibodies, peptides, aptamers or small molecules that recognize receptors which are overexpressed in target cells and polyethylene glycol (PEG) to reduce immune clearance [11]. Surface functionalization has been designed in order to improve cellular uptake, targeted delivery and augmented therapeutic impact while minimizing off-target effects. Furthermore, the ligands can be worked in combinations with stimuli-responsive lipids or polymeric molecules as smart lipomers to release drugs under pH changes, enzymatic action or temperature alteration for achieving an additional drug-release control. This strategic change ultimately results in higher bioavailability, longer circulation half-life, and better therapeutic performances [12].

Fabrication and Formulation Techniques

i. Single Step and Two Steps Approach

These normally require a single step process to assemble the polymer and lipid components sequentially, which can routinely produce monodisperse nanoparticles with well characterized core shell structure. In these methods, the polymer is dissolved in an organic solution containing drug, and lipid is dispersed in an aqueous medium [13]. Simply by mixing the organic and aqueous phases in a controlled manner, self-assembly takes place leading to one step formation of the lipomer. This simple, scalable and highly reproducible approach is advantageous [14]. In the other hand, two sequential step methods include the synthesis of polymeric core and lipid shell separately followed by joining them to construct hybrid nanoparticle. The polymeric nanoparticles are commonly prepared using standard polymer nanoparticle methods and subsequently surrounded by a lipid layer, for example using sonication or extrusion. Slightly more challenging, but better achieving shell-thickness, surface properties and functionalization control are the two-step methods that can further improve targeting and drug-release profiles [15].

ii. Solvent Evaporation, Nanoprecipitation, and Emulsification

Various conventional nanoparticulate preparation methods have been modified for development of lipomers, including:

- Solvent evaporation in this process, both polymer and drug are dissolved in a volatile organic solvent and emulsified with an aqueous lipid phase [16,17]. The solvent is subsequently removed and the polymer solidifies around the drug. The lipid behaves as a coating surrounding the polymeric core, which in coexistence forms safe lipomers with high drug content [18-20].
- Nanoprecipitation (solvent displacement method): The polymer and drug are dissolved in a water-miscible organic solvent, and the solution is added drop by drop to an aqueous lipid containing solution with stirring [21, 22]. Fast evaporation of the solvent results in polymer precipitation and self-assembly on top of the lipid monolayer. Nanoprecipitation is the method of choice to obtain small, homogeneous particles and a low size distribution [23, 24].
- Emulsification Procedures: These are based on single and double emulsion

techniques where the polymerdrug solution is emulsified in the aqueous lipid phase by mechanical or ultrasonic agitation. For example, double emulsion techniques are useful for encapsulation of hydrophilic drugs in the core and use of the lipid shell to stabilize the particle and enhance biocompatibility [25, 26].

iii. Factors Influencing Formulation Efficiency

The performance of the lipomer formulation is influenced by several factors:

- *Type of Polymer and Lipid:* Biodegradable polymers (e.g., PLGA) and lipids (e.g., phosphatidylcholine) determine particle stability, drug encapsulation efficiency and release kinetics [27].
- *Polymer-to-Lipid Ratio:* It affects the thickness of lipid shell and the parent core-shell structure [28].
- *Selection of solvent:* Organic and aqueous solvents used impact particle size, drug solubility/F (%) and encapsulation efficiency (EE%) [29].
- *Process parameters:* Stirring speed, sonication time, temperature and rate of addition of dispersed phase could affect the particle size, poly dispersity as well as drug loading [30].
- *Properties of the drug:* The hydrophilic or hydrophobic character, molecular weight, and solubility of the drug determine its annular location either in polymer core or lipid shell and therefore influence release [31].

Table 1: Summary of Lipomer Compositions and Methods of Preparation

Sr. No.	Lipomer Material Used	Active Ingredient	Method of Preparation	Ref
1.	Lipomers composed of a PLGA polymeric core surrounded by a lipid shell containing lecithin and DSPE-PEG	Model anticancer agents such as paclitaxel, docetaxel, and doxorubicin.	Prepared mainly by single or double emulsion solvent evaporation and nanoprecipitation methods.	[1]
2.	Hybrid systems combining biodegradable polymers (PLGA, PLA, PCL) with lipids such as lecithin, cholesterol, or DSPE-PEG	Wide range of drugs including anticancer, antifungal, and anti-inflammatory molecules.	Prepared mainly by single or double emulsion solvent evaporation and nanoprecipitation methods.	[2]
3.	Polymeric-lipid hybrid nanoparticles using PLGA or PEG with lecithin or phosphatidylcholine	Reviewed examples involving small molecules, peptides, and nucleic acids	Commonly fabricated through emulsification-solvent evaporation, nanoprecipitation, or self-assembly techniques	[3]
4.	General lipid-polymer hybrid configurations featuring a polymeric inner core and lipid outer layer	Broadly applicable for the delivery of drugs, proteins, and imaging agents	Solvent displacement and nanoprecipitation methods discussed as main fabrication techniques	[8]
5.	Lipid-polymer nanoparticles of different geometries, such as spherical and rod-shaped particles	Model systems studied mainly for shape-dependent biological interactions rather than specific drugs	Produced through solvent evaporation followed by extrusion to control shape.	[9]
6.	Lipid-polymer nanocarriers designed with amphiphilic polymers and phospholipids for macrophage targeting	Amphotericin B	Developed via solvent evaporation and modified nanoprecipitation for receptor-mediated macrophage uptake	[11]
7.	Hybrid nanoparticles composed of PLGA polymer core and lipid shell	Fisetin (phytochemical)	Formulated through emulsification-solvent evaporation followed by homogenization and sonication	[13]
8.	Lipid-polymer hybrid nanoparticles combining biodegradable polymer (PLGA) with lipids (lecithin, cholesterol)	Hydrocortisone	Optimized using nanoprecipitation coupled with statistical design (Box-Behnken design)	[14]
9.	Multilayered liposomes stabilized with polyelectrolyte polymers	Paclitaxel	Layer-by-layer electrostatic deposition and self-assembly	[27]
10.	Lipid-polymer hybrid nanoparticles with PLGA polymer and phospholipid components	Melphalan	Formulated and optimized using Central Composite Design (CCD) via solvent evaporation	[16]

These features should be optimized for the design of stable, reproducible and efficient lipomer formulations suitable for targeted controlled drug delivery applications.

Drug Encapsulation and Release Mechanisms

Due to their hybrid lipid-polymer nature, lipomers have a distinct ability to encapsulate diverse therapeutic molecules. This binary nature provides particles with the structural stability of polymeric nanoparticles and biocompatibility or fluidity of lipid systems, leading to enhanced drug loadings, controlled release patterns and improved bioavailability. The encapsulation and subsequent release behavior of the lipomers plays a key role to

optimize its performance in drug targeting as well as controlled delivery.

i. Encapsulation of Hydrophilic and Hydrophobic Drugs

The encapsulation efficiency of lipomers is highly contingent on the physicochemical nature of the drug and formulation technique. Hydrophobic drugs are typically solubilized in the lipid core or polymer matrix with which nonpolar interactions involve to stabilize the drug molecules and consequently preventing premature leakage. e.g., solvent evaporation or nanoprecipitations are commonly used to obtain high encapsulation efficiency and homogeneous dispersion of lipophilic drugs.

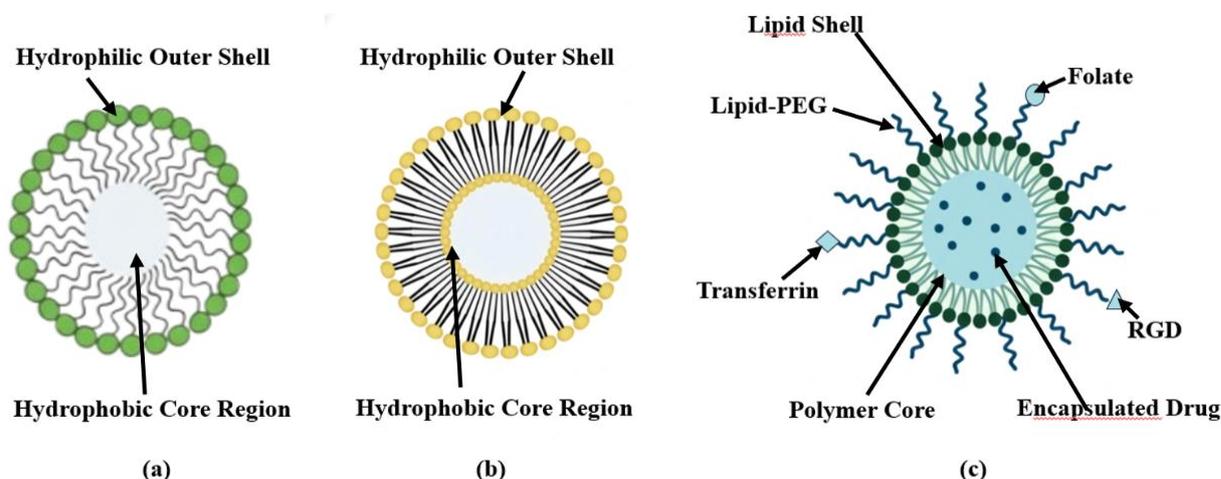


Figure 3: Polymeric micelle(a), liposome(b), polymeric lipid hybrid nanoparticle(c)

In contrast, hydrophilic drugs with low partition to lipid domains are incorporated usually in the aqueous spaces or adsorbed on the polymer surface through ionic or hydrogen bonding. The entrapment of such polar molecules can also be improved by the presence of charged lipids, amphiphilic polymers or surface modifiers. The specific lipid-to-polymer ratio, solvent polarity and surfactant concentration will dictate the location of both hydrophilic and hydrophobic drugs within the lipomeric matrix. This versatile property makes lipomers universal nanocarriers for various types of therapeutic agents, such as small-molecule drugs and macromolecules including peptides and nucleic acids [32].

ii. Controlled and Sustained Release Profiles

A key benefit of lipomer systems relates to the possibility to control drug release. The hybrid structure (polymeric inner shell/lipid core or vice versa) can function as both a barrier that

controls the release and diffusion and degradation-controlled gate. A good barrier for burst release and protection from environmental degradation is given by the lipid layer, whereas a long-term modulated release can be attributed to the polymeric part by erosion or diffusion-controlled mechanism. By optimizing the polymer (PLGA, PCL, or PEGylated polymers), lipid (phospholipids, cholesterol, and fatty acids) as well as fabrication parameters researchers can engineer lipomers exhibiting tunable release kinetics. For example, longer polymer molecular weight and lipid rigidity together can prolong release duration, while more lipidic or hydrophilic polymers would promote faster diffusion. Controlled release patterns not only help ensure drug levels at the site of action, but also reduce dosing frequency and systemic toxicity, and hence improve efficacy of therapies as well as patient compliance [33].

iii. Stimuli-Responsive Lipomers (pH, Temperature, Enzyme)

From recent developments with lipomer technology, current interest has shifted towards the design of stimuli-responsive (stimuliS) or on demand drug delivery systems that can release drugs at a desired site based on local and biological cues. The intelligent lipomers are based on the idea of using functional lipid or polymer components that experience structural and/or physicochemical transitions to have finely tunable spatiotemporal control over drug release.

In pH-sensitive lipomers, typified by weakly acidic or basic polymers like poly(L-histidine) or Eudragit derivatives, they expand or dissolve in the acidic tumor and endosomal regions with consequent selective drug release. Temperature sensitive lipomers are also possible, which contain thermo responsive polymers such as poly(N-isopropylacrylamide) (PNIPAM) that undergo phase transitions at around the body temperature and thereby release the included drug upon heater treatment. Likewise enzyme-responsive lipomers are engineered to selectively degrade in the presence of disease-related enzymes, such as lipase or protease enzymes, also providing site-specific activation [34]. These stimulus-responsive systems fill the void between traditional sustained-release systems and intelligent nanomedicines, adjusting the therapy in all respects to match biological conditions. Thus, stimuli-responsive lipomers constitute promising candidates for enhancing the therapeutic index, minimizing off-targeting effects and personalized drug delivery.

Pharmacokinetics and Biodistribution

Pharmacokinetics and biodistribution are key parameters, which play an important role in the *in vivo* efficacy and therapeutic outcome of lipomer-based delivery systems. Lipomers are hybrids and can be engineered to favor drug circulation, avoid premature clearance, and enhance preferential accumulation into the target tissue. These features are dictated by a number of parameters among which these have included particle size, surface charge, lipid-polymer composition and, the surface functionalization with targeting ligands or hydrophilic polymers such as polyethylene glycol (PEG). Rational design of lipomers can provide a controlled pharmacokinetic profile and altered biodistribution leading to effective drug delivery with lower systemic toxicity [35].

i. Circulation Time and Clearance Mechanisms

For lipomers, the circulation time in the blood stream fundamentally determines whether there will be sufficient exposure of drug at the site of action. The mononuclear phagocyte system (MPS), particularly in the liver and spleen, often rapidly recognizes and clears traditional nanoparticles. This problem is resolved by lipomers that can be surface modified using PEGylation or lipid coating, which allows the steric hindrance against opsonization and protein adsorption [36].

The lipid shell could provide better biocompatibility and lower immunogenicity, whereas the core polymer keeps its structure in systemic circulation. The hydrophilic lipophilic balance and surface charge (usually near neutral or somewhat negative) can be modified to lipomers so that they have a long circulation half-life. Furthermore, slow degradation of biodegradable polymers such as PLGA and PCL are necessary to achieve sustained release in systemic circulation without premature burst elimination. Together, these properties result in the therapeutic payload to be present in the circulatory system long enough to reach its target site, thereby increasing bioavailability and pharmacological effectiveness [12].

ii. Target Tissue Accumulation

The distribution of lipomers depends to a large extent on their retention at the pathological site after passive or active mechanisms. Passive targeting is based on the EPR effect, a phenomenon often observed in tumors and inflamed tissues with leaky vasculature enabling nanoparticles of 100-200 nm to extravasate and be retained at the site. The lipid shell of lipomers gives them an increased affinity for biologic membranes and, as such, contributes also to the accumulation in regions with high lipid or inflammatory content [36]. Active targeting is accomplished by conjugating certain ligands, including antibodies, peptides, folic acid or aptamers to the lipomer surface. These ligands bind to overexpressed receptors in target cells, thus making it possible for receptor-mediated endocytosis and selective intracellular delivery. Reinforcement of EPR effect with ligand-based specificity allows lipomers to release disease modulating drugs specifically at diseased sites without affecting healthy cells. The outcome is a higher therapeutic selectivity, lower systemic exposure and better therapeutic effects in

challenging pathologies such as cancer, infections or autoimmune diseases [37].

iii. Cellular Uptake and Intracellular Trafficking

Upon reaching the target, efficient cellular internalization and well-directed intracellular trafficking of lipomers are necessary for successful treatment. The hybrid nature of lipomers in terms of their advantages for membrane interactions and cell internalization [38]. The polymeric layer contributes mechanical strength during internalization, and the lipid coat supports endocytosis and promotes membrane fusion. Lipomers, as a function of surface characteristics can be taken up by cells by clathrin or caveolae mediated uptake or micropinocytosis [35].

After cell internalization, the lipomers have to evade the endosomal trap to release the drug into cytoplasm. Polymers that include pH-sensitive or proton-sponge properties (e.g., polyethyleneimine and polyhistidine conjugates) have the ability to facilitate endosomal escape by osmotic swelling and membrane breaching [39]. Lipid ingredients also help in fusion of the membrane, promoting rapid penetration of drugs into cytosol. Both lipids and polymers have a role in the function of these lipomers so they not only travel to target tissue but also release their payload directly where it is required within cells [40,41]. The ability of lipomers to retain long circulation, accumulate selectively, and traffic effectively into cells is responsible for their superior pharmacokinetics relative to conventional single-component nanocarriers. Their tunable properties and flexible behavior made them as a promising candidate in future generation drug delivery systems to surpass biological barriers and increase therapeutic efficacy [42].

Lipomers for Drug Delivery Formulations

i. Cancer Therapeutics

In the field of oncology drug delivery, lipomers have drawn enormous attention in consideration of their excellence to combine the positive characters present in lipid and polymeric nanocarriers. The lipid layer provides biocompatibility, good cell targeting performance and transmembrane drug delivery across tumor cells, whereas the polymeric matrix affords structural supporting function as well as controlled release of incorporated antitumor drugs [43]. Such dual-modality features long

systemic circulation and active/passive tumor accumulation, including for example the enhanced permeability as well as retention (EPR) effect of any drug delivery system and receptor mediated targeting [44].

The potential of lipomer platform to combine both hydrophilic and hydrophobic drug for synergistic effect is the advantage they can offer in cancer therapy. For instance, a combination of doxorubicin with paclitaxel has proven to be more effective and less toxic systemically than its conventional counterpart. Surface functionalization of lipomers using folic acid, transferrin, or antibodies as targeting ligands also facilitates specific accumulation in tumor microenvironment to reduce off-target effects. Additionally, recent studies also demonstrate the incorporation of stimuli responsive polymers in lipomers allowing that responds to tumor related triggers such as acidic pH, high temperature and overexpressed enzymes thereby increasing localized therapy efficiency. In addition, lipomer platforms have exhibited promise in overcoming multidrug resistance (MDR), an important obstacle in cancer chemotherapy [45]. Through prolonging the retention of drugs in cells and regulating the efflux transporter activity, these nanocarriers enhance intracellular accumulation of chemotherapeutics. Overall, the combination of lipomers with their hybrid nature provide an accelerated, tunable and promising platform for remotely targeting responsive or controlled cancer therapy and pave in open a door to much more efficient nanomedicine-oncology treatments [16].

ii. Gene and RNA Delivery

Nucleic acids, such as DNA, RNA (siRNA), and mRNA are difficult to be delivered due to their fast systemic clearance, low cellular uptake and susceptibility of enzymatic degradation. An efficient method Lipomers for solving this is the incorporation of these genetic elements into the polymeric core and shielding to protect against degradation. The endosomal escape and cellular uptake are also enhanced by the lipid shell. Further, the surface of lipomers can be modified with targeting ligands, e.g. aptamers or peptides, for tissue-specific delivery to reduce non-site specific side effects. The latter feature makes lipid-based vector as a safe and promising non-viral gene therapy, RNA interference, mRNA therapy. It has been shown that the lipomer mediated gene delivery can efficiently regulate target gene expression and result in the silencing

of detrimental genes and better therapeutic effects with less immunogenicity than those achieved by using a traditional viral vector [46].

iii. Anti-inflammatory and Antimicrobial Agents

Lipomers have several advantages in delivery of anti-inflammatory and antimicrobial drugs that involve sustained release leading to improved efficacy in therapy with minimal systemic toxicity. The release kinetics can be modified based on the polymeric core, and the tissue penetration and bioavailability are enhanced by lipid coating [47,48]. In inflammatory diseases, lipomer formulations may be able to sustain high local drug levels if they promote prolonged exposure while avoiding unnecessary dosing frequency. Like this, lipomers increase the drug stability and delivers them effectively to infection sites in antimicrobial therapy which can contribute anti-microbial resistance [49-51]. Furthermore, their flexible construction allows the co-delivery of multiple agents to provide a promising opportunity for combination therapies against wound healing, chronic inflammatory

diseases and bacterial or fungal infections as well in future [52,53].

iv. Vaccine Delivery and Immunotherapy

Recent studies conclude that as innovative adjuvant/vaccine carriers, lipomers are potent antigen plus immunomodulatory agents delivery systems. Their hybrid composition combines the advantages of lipid-based systems (cell membrane-contact, endocytic uptake predominantly by antigen-presenting cells) and polymer-based ones (prolonged/controlled release of encapsulated antigens). This overlapping property increases the levels and length of immune responses.

Additionally, lipomers can be surface-decorated with targeting ligands or adjuvants to direct immune activation towards certain subtypes of cells (e.g. dendritic or macrophage) populations. Such accuracies can promote the antigen presentation and cytokine generation, which is beneficial for humoral and cell mediate immune with good responses.

Table 2: Summary of Lipomer Compositions and their Therapeutic Applications

Sr. No.	Lipomer Material Used	Active Pharmaceutical Ingredient	Application	Reference
1	PEG-PLA polymeric nanoparticles stabilized with cationic lipids	Small interfering RNA (siRNA)	Systemic gene silencing for cancer therapy	[32]
2	Lipid-polymer hybrid nanoparticles combining cationic lipids and biodegradable polymers	Therapeutic siRNA	Delivery of siRNA for gene regulation and treatment of various diseases	[33]
3	Hybrid nanoparticles composed of biodegradable polymer (PLGA, PEG) and lipid shell	Various oral drugs (model compounds)	Oral delivery to enhance drug stability and intestinal absorption	[34]
4	Stealth lipid-polymer hybrid lipomers with PEGylated lipid coating	Combined antiepileptic and anti-inflammatory drugs	Targeted brain delivery for Parkinson's and neuroinflammatory disorders	[35]
5	Nanocarriers exploiting lipid-polymer hybrid systems	Various chemotherapeutics	Enhanced tumor accumulation through EPR effect and improved intratumoral penetration	[36]
6	Polymeric-lipid nanoparticles and other hybrid carriers	Multiple anticancer drugs	Controlled and targeted drug delivery for cancer therapy	[37]
7	Lipid-polymer hybrid nanocarriers functionalized with targeting ligands	Wide range of small molecules and biologics	Active and passive targeting of specific tissues and organs	[38]
8	Lipid-polymer hybrid nanoparticles optimized for <i>in vivo</i> biodistribution	RNA molecules	Bone marrow-specific RNA delivery identified via directed evolution	[43]
9	Lipomer nanoparticles made of PLGA and lipid excipients	Delafloxacin	Enhanced antimicrobial efficacy, sustained release, and improved oral bioavailability	[47]
10	Lipid-polymer hybrid nanoparticles combining biodegradable polymer (PLGA) with lipids (lecithin, cholesterol)	Hydrocortisone	Controlled topical drug delivery with optimized release	[14]

Lipomer-based vaccine systems are being studied for cancer immunotherapy, viral vaccines and emerging infectious diseases and promises, a safer and efficient alternative to traditional vaccine adjuvants. These nanoparticles are tunable in composition, biodegradable and biocompatible, which make them the next generation candidate to design effective and personalized immunotherapeutic approaches [54].

Advantages and Limitations

Lipomers are a versatile hybrid nanocarrier system constructed by the combination of advantages from lipid-based and polymeric nanoparticles here. They are capable of entrapping different drugs with regulation and site-specific release due to their particular material structure. Nevertheless, burdened by the challenge of mass production and regulation, their clinical application as lipomers is hampered. It is important to know their relative pros and cons in order to judge whether they are effectively integrated into the wide context of nanocarriers.

i. Comparative Analysis Numbers with Liposomes and Polymeric Nanoparticles

Lipomers can bridge the gap in functionality between liposomes and polymeric nanoparticles, combining some of their best features while avoiding some weaknesses. Liposome, the most characteristically drug delivery system which encapsulated hydrophilic drugs and lipophilic drugs, is widely accepted as it is biocompatible; while stability and leakage of drug are important factors it has a weakness issue. Polymeric nanoparticles, however, may lack the biomimetic properties necessary for optimal cell interaction, even though they are structurally more robust and achieve better controlled release [55].

Lipomers mitigate these problems with a core-shell architecture; the polymeric core provides sustained drug release and the lipid shell imparts stability, bioavailability, and cellular uptake. By modifying the surface with ligands or antibodies, this hybrid design serves not only to improve pharmacokinetic profiles but also for active targeting purposes. Through comparative studies, it has been demonstrated that lipomers are a potential GMDS primarily due to better drug retention, extended circulation half-lives and improved therapeutic efficacy compared to traditional delivery systems [12].

ii. Biocompatibility and Safety Profiles

The biocompatibility and safety of lipomers are two important aspects which determine whether they can be further used clinically. Due to the biodegradable polymers and physiological lipid components, this kind of nanosystems (lipomers) are usually known for inducing low cytotoxicity and high tolerability. Lipid shell used in most of the nanoparticles, such as phospholipids or cholesterol derivatives, similar to cell membranes which is advantageous for cellular uptake and reduced immune recognition and inflammation [56]. The polymeric-core material is composed of a degradable, biocompatible polymer (e.g., PLGA, PCL or PEG) allowing for safe breakdown to nontoxic entities [37]. *In vitro* and *in vivo* test have suggested that lipomers exhibit good hemocompatibility, low immunogenicity, as well as slight impact on the target organs after systemic administration. Nevertheless, the toxicity profile can differ by lipid and polymer type and ratio used, surface charge, particle size, and preparation method. Accordingly, among preclinical testing, thorough examination of toxicity is necessary to confirm their long-term biocompatibility and inhibition effects within safe dose ranges. Lipomers are potential nontoxic, biodegradable and nonimmunogenic nanocarriers for selective and extended targeting of a drug with proper optimization [57].

iii. Challenges in Manufacturing and Scale-Up

However, although with great promise, the up-scale production of lipomers is still a big challenge. Solvent evaporation, nanoprecipitation or emulsification-based fabrication methods also generally offer great control over particle size and morphology at a laboratory scale, but they are difficult to “scale-up” for an industrial setting. Obtaining uniform batch-to-batch quality of NPs, keeping encapsulation efficiency constant and controlling the lipid polymer ratio are crucial but challenging operations during scale-up [58]. Another critical issue is the reproducibility of physicochemical characteristics as small modifications on processing parameters (e.g. temperature, mixing speed and solvent evaporation) could have a huge influence on the final formulation. In addition, the use of organic solvents, and necessity of rigorous purification steps complicates, increases cost and regulatory oversight in producing lipomers. To address this, microfluidic and continuous manufacturing are

investigated as alternatives that offer more control over formulation parameters and the possibility of scale-up. However, scale-up of manufacturing processes and protocols remains under development. Stuck together so addressing these is critical to transport LpDD Market.

Regulatory and Translational Considerations

While lipomers have generated a lot of interest in preclinical studies due to their promising results, they still need to meet regulatory demands for successful translation into approved products. As hybrid nanocarriers, lipomers prove to be challenging in terms of characterization, safety profiling and up-scaling of production, which tasks are vital for approval by regulatory agencies. Full understanding of the toxicological properties, stability and quality attributes for these biologically active particles is crucial to ensure durability, efficacy and patient safety. In addition, establishing standardized evaluation methods and concise regulatory guidance will be essential to seamlessly translate them from laboratory research into clinically applicable agents [59].

i. Toxicological Assessments

Toxicological evaluation is a mandatory step in the regulatory approval of lipomer formulations. Due to their hybrid (lipid+polymer) composition, both lipid and polymer constituents should be studied for biocompatibility, immunogenicity and the capacity of tissues retention. In preclinical studies, *in vitro* cytotoxicity test, hemolysis test and *in vivo* biodistribution and organ toxicity study are conducted for the determination of safety margin. Biodegradable and FDA-approved materials, including PLGA, PCL and natural lipids have been employed to eliminate toxicity issues. Nevertheless, particle size, surface charge and the content of residual solvent are important parameters that may affect biological activities and safety profiles. Thus, standard toxicological procedures are required to accurately assess their prolonged effects, in particular for chronic treatment. In addition to regulatory filings, comprehensive safety data help build confidence for the clinical translation of lipomer-based therapies [59].

ii. Quality Control and Stability

One of the regulatory requirements that prevent the clinical translation of lipomer formulations is to ensure their quality and stability. Owing to their hybrid properties, lipomers possess

complex physicochemical properties that require tuning during the manufacturing process. Critical quality attributes like the particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency and drug release profile need to be rigorously characterized and defined limits set around them for achieving reproducible products with consistent therapeutic performance. Stability is another significant concern since both lipid and polymer components are susceptible to degradation induced by temperature, light, and moisture. The instability may result in the formation of particle aggregate, drug leaking out or degradation which affects efficacy and safety. Accordingly, suitable storage conditions, the addition of cryoprotectants and freeze drying methods are frequently used to prolong shelf-life and retain structure [58]. Authorities underline the need for valid analytical methods and ongoing stability tests using procedures established by the ICH (International Council for Harmonisation). Standardized protocols for quality control and long-term stability testing should be developed to guarantee that the lipomer preparations are in compliance with global regulatory agencies expectations, as well as remain constant throughout their shelf life [58].

iii. Clinical Translation and Commercialization Prospects

Transition to the clinical sector or broader commercial application of lipomer-based systems is surely ongoing but slow. Despite compelling preclinical evidence for their efficacy and safety, few LPMer have been evaluated in clinical trials with the absence being contributed to complexity of regulatory clearance, scale-up manufacturing difficulties faced during manufacture. Translation is a multi-disciplinary pursuit that requires the interplay between formulation science, toxicology, process engineering and regulatory knowledge. Lipomers for commercial development can be used in enclosing different medical agents including proteins, nucleic acids and small molecules. Their robust *in vivo* release properties and targeting attributes are well suited for emerging opportunities in precision and personalized medicine. By partnering with academia, industry and regulatory agencies to work together in collaboration in a strategic way, development pipelines are expedited as is clinical assessment. Developing standard procedures, achieving Good Manufacturing Practice (GMP) compliance and gradually advancing through clinical trials are

the necessary steps for industrialization. While regulatory science changes to support a hybrid nanocarrier, lipomers can consolidate their future as clinically viable and marketable drug delivery systems allowing innovative research to meet real-life therapeutics [60].

Future Directions and Emerging Trends

The lipomer technology in drug delivery is evolving and expanding with contributions from Nanotechnology, Material Science, and BioMedical Engineering. Recent investigations have been devoted not only to trying increasing therapeutic efficiency and safety but also to incorporating multifunctional features including diagnosis, targeting, and physiologically responsive response. These technologies represent lipomers being more than standard delivery systems, into extremely high-tech platforms applicable for personalized and precision medicine [33].

i. Smart Lipomer Systems and Theranostics

Smart lipomer systems have been elaborated that can be triggered by biological or external stimuli (i.e., pH, temperature, enzymes, or light) to provide tailored drug release at specific sites. Such a responsive behavior can promote the therapeutic efficiency due to specific drug release at targeting site with minimized systemic side effect and enhanced bioavailability. Furthermore, theranostic lipomers co-presence both therapeutic and diagnostic functionalities in a same nanocarrier. These systems enable on-demand imaging of drug delivery, biodistribution, and treatment efficacy by use of imaging agents, fluorescent/contrast molecules. This seamless marriage of therapy and diagnostics has tremendous potential for cancer, infectious disease, and personalized medicine therapies to provide clinicians with actionable information that can be used to tailor treatments [61].

ii. Personalized Nanomedicine and Targeted Therapies

Personalised nanomedicine seeks to administer therapies according to that individual patient's genetic, molecular and physiological signature. In these amplification of lipomers, which have core-shell structure and can be functionalized on the surface, are particularly attractive. Through the introduction of receptor-specific ligands, antibodies or aptamers, lipomers can be actively directed towards diseased cells or tissues to elevate drug accumulation in the target site and

mitigate side effects. This precise targeting is especially important for oncology, where the heterogeneity of a tumor can often render traditional therapies ineffective. The lipid/lipid-based system can be designed to codeliver combination therapies by encapsulation of Drugs with dual bioactivity in complementary complex disease pathways. In addition, the tunable loading and release profile permits the activation of drug-delivery at specific stages of patient physiology for more efficient personalized therapy [33].

Integration of lipomer scope for personalized medicine foresees better therapeutic response as well as lower side-effect profiles and treatment expenses, depicting progress towards the goal of patient-driven drug delivery.

iii. Integration with AI and Nanorobotics

AI and nanorobotics with lipomer drug delivery are frontier precision oncology. To overcome these obstacles, AI-based algorithms are capable of determining formulation parameters in an optimum way, predicting the kinetics of drug release and also improving the efficiency of targeting through the analysis of complex biological data. Such predictive ability lessens the need for trial-and-error tests to help reduce development time and enhance the design of patient-specific lipomer formulations. In the field of actuation targeting, nanorobotics allows the active navigation of lipomer carriers to particular tissues or cellular environments, even through biological barriers such as blood-brain barrier or dense matrix of tumors. Lipomers possessing sensitive actuators or nanoscale robots could release drugs in a controlled manner upon arrival to the target area, thereby enhancing therapeutic specificity and minimizing systemic exposure [35].

Integrating lipomer technology with AI and nanorobotics has the possibility to change how drugs are administered, by providing completely self-regulating therapeutic systems. These improvements might open the door to next-generation precision medicine, one that is not only targeted and regulated but also responsive to real-time physiological signals. These units may also offer remote monitoring and control of therapy response through AI-assisted feedback loops, allowing clinicians to adjust treatment parameters. These smart nano robotic platforms lipomers might be potentially employed as autonomous therapeutic cargo with the

capability of accurate detection, delivery and regulation of treatment within human body [37].

CONCLUSION

Nanocarriers based on lipomers are a substantial improvement in drug delivery as they combine the physicochemical durability of polymers with the biocompatible and biomimetic aspects of lipids. Their double core-shell design enables a better stability, precise targeting ability and prolonged release that contribute to lower systemic toxicity and a higher therapeutic efficiency. Many studies have shown their broad applications in cancer treatment, gene transfection, antimicrobials administration and vaccines manufacture. Because of their ability to fine-tune composition, surface performance, and release profiles, lipomers can be designed to accommodate a variety of medical needs. Nevertheless, for laboratory discoveries to become industrial production and clinical strategies, standard manufacturing practices must be developed, regulation is critical, and toxicological analysis should be comprehensive. Their precision and readiness will be further optimized through the integration of smart materials, artificial intelligence (AI) and nanorobots in future to develop next-generation personalized nanomedicine. In the end, lipomers have significant potential of directing future in targeted and controlled drug delivery through smart, competent and patient friendly design.

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CONFLICT OF INTEREST

The author declares no competing interests.

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