



General justification in terms of effectiveness and toxicities for the use of nanocarriers

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Abstract This review highlights the potential benefits and drawbacks of using nanocarriers as drug delivery systems. Nanocarriers have been widely utilized to enhance drug efficiency, overcome drug resistance, and reduce adverse effects. However, the interaction between nanocarriers and biological systems can lead to toxic responses. Therefore, it is crucial to carefully select optimized nanocarriers to minimize toxicity and maximize efficiency. Every type of nanocarrier has its own advantages and disadvantages. Hybrid nanocarriers have been engineered to address the limitations of existing nanocarriers and are considered more suitable for developing new formulations. The article discusses various aspects of nanocarriers, including their applicability, potential toxicity, and strategies for utilizing appropriate nanocarriers in nanoformulations. To mitigate the toxicity of nanocarriers, several approaches can be employed, such as PEGylation, coating, charge coating, and injections of free PEG; moreover, by modifying the preparation method or utilizing hybrid

nanocarriers, the efficiency of drug delivery systems can be improved. Overall, the article emphasizes the importance of selecting appropriate nanocarriers and employing strategies to reduce toxicity while enhancing drug delivery efficiency.

Keywords Nanocarrier · Toxicity · Drug delivery · Immune system · Hybrid carrier · selection strategy

Abbreviation

PLA	Poly-(lactic acid)
PLGA	Poly-(lactic-co-glycolic acid)
PEG	Polyethylene glycol
NP	Nanoparticle
SLNs	Solid lipid nanoparticle
NLCs	Nanostructured lipid carriers
FDA	Food and drug administration
APCs	Antigen-presenting cells
EPR	Enhanced permeability and retention
RBC	Red blood cells
DOPC	1,2-Dioleoyl-sn-glycero-3-phosphocholine
SM	Sphingomyelin
DOPS	1,2-Dioleoyl-snglycero-3-phospho-L-serine (DOPS)
DOPE	1,2-Dioleoyl-snglycero-3-phosphoethanolamin
TPGS	D- α -Tocopheryl polyethylene glycol 1000 succinate
DLPC	1,2-Dilauroylphosphatidylcholine
EE%	Encapsulation efficiency
HPMC	Hydroxypropyl methylcellulose

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CF	Carboxyfluorescein
PC	Soya phosphatidylcholine
DPPC	Dipalmitoylphosphatidylcholine
5FU	5-Fluorouracil
DOPG	Diioleoylphosphatidylglycerol
ABC	Accelerated blood clearance
PEI	Polyethylene imines
ROS	Reactive oxygen species
TEMPO	,2,6,6-Tetramethylpiperidine-1-oxyl
ACE2	Angiotensin-converting enzyme 2
CMC	Carboxymethyl cellulose

Introduction

Numerous medications have been developed for the treatment of different pathologies; however, they may exhibit severe adverse effects on normal tissues. Therefore, it is very important to direct the drug to the target tissues while bypassing normal cells. In addition to side effect reduction, this approach can also increase the efficiency of the drug. One of the important issues in pharmaceutical technology is the delivery of drugs into the operation site. In this regard, use of pharmaceutical carriers has long been considered. Targeted formulations are designed to improve effectiveness and reduce toxicity of existing drugs. This improvement, although it may be called “old wine in new bottles,” can modify the efficiency of a medication in a way as if a new medication has been introduced. This becomes even more important when we consider that the introduction of new drugs is a very time-consuming and expensive process, generally taking 10 to 15 years [1].

Nanotechnology plays a significant role in improving pharmaceutical formulation [2]. Encapsulation of drugs in nanocarriers may overcome those mentioned concerns. Many structures have been designed as nanocarrier to improve the kinetic of drugs, reduce their side effects, and prevent drug resistance. Nanomaterials are defined as a material in the range of 1 and 100 nm [2] and employed as powerful agents for the treatment of diseases, imaging, and diagnosis [3]. Liposomes, as the first nano-drug delivery systems, were discovered by Alec D Bangham in the 1960s [4] which are composed of lipid bilayers with an aqueous core [5]. Following the introduction of liposomes, improving them and introducing other nanocarriers have widely been studied in the past years. For

some different nanocarriers, their development has occurred simultaneously. For example, poly-(lactic acid) (PLA) together with the copolymer poly-(lactico-glycolic acid) (PLGA) was developed as surgical sutures in the 1960s as well [6]. Dendrimers were produced during 1970–1990 by Buhleier et al. and Tomalia et al. [7]. Subsequently, the first polymer drug conjugate was approved by the Food and Drug Administration (FDA) in 1990 [8]. At the same year, polyethylene glycol (PEG) was discovered to enhance the blood circulation times for liposomes [9], and a few years later, PEGylated PLGA nanocarriers also found to have longer circulation times (1994) [8]. In 1995, the FDA approved Doxil (liposomal doxorubicin) for the treatment of AIDS-related ovarian cancer and Kaposi sarcoma. [10]. Polymersome was described in the 1999 [8]. Abraxane (an albumin-based nanoparticle (NP), protein-bound paclitaxel) and NanoTherm (iron oxide NPs) were also approved in 2005 and 2012, respectively [11]. Some approved nanomedicines since 2015 are listed in Table 1.

In this review, we have discussed about the selection of optimal nanocarriers for application in new nanoformulation preparation based on their comparative toxicity and physico-chemical properties. Approaches to avoiding nanocarrier toxicity and escaping from immune response have been discussed as well.

Nanocarriers as drug delivery systems

Various nanocarriers including carbon nanotubes [15], liposomes [16], dendrimers [17], solid lipid nanoparticles (SLNs) [18], archaeosome [19], ethosomes, transferosomes [20], polymeric NPs [21], nanoemulsions [22], niosomes [23], and nanogels [24] were developed for drug delivery in recent decades.

To improve the efficiency of drugs, choosing the right nanocarrier for drug delivery is very decisive and is mostly based on the physico-chemical characteristics of the drug. However, toxic biological responses may be induced by contact of nanocarriers with natural biological systems. For example, dendrimers can induce hemolytic effects which limit their clinical application [25]. It was observed that SLNs induce inflammatory reaction in animals [26]. More details regarding the toxicity and adverse effects of nanocarriers have been provided in the next sections.

Table 1 Some approved nanomedicines by FDA since 2015

Drug	Formulation	Indication	Company	Year	Ref
Onivyde	Liposomal irinotecan	Pancreatic cancer	Merrimack	2015	[12]
Adynovate	Polymer-protein conjugate (PEGylated factor VIII)	Hemophilia	Baxalta	2015	[12]
Glatopa	Glatiramer acetate (synthetic protein) containing polymer	Multiple sclerosis	Novartis	2015	[13]
CPX-351 (Vyxeos™)	Daunorubicin- and cytarabine-containing liposome	Acute myeloid leukemia	Jazz Pharma	2017	[13]
Zilretta®	Triamcinolone acetonide loaded in PLGA hydrogel	Knee osteoarthritis	Flexion Therapeutics	2017	[14]
Onpattro®	Patisiran (siRNA)-containing liposome	Hereditary transthyretin amyloidosis	Alnylam Pharmaceuticals	2018	[13]

Although a large number of nanocarriers have been designed during the past few decades, there is still a need for further strategies for improving of their efficacy and reduction of side effects.

Polymersomes are synthetic structures similar to liposomes (hydrophilic inner core and hydrophobic double-layer) composed of amphiphilic copolymer units instead of lipids (Fig. 1A) [27]. Polymersomes are more efficient than liposomes due to their higher stability, slower cargo release, longer circulation time, capability to encapsulate of both hydrophilic and hydrophobic drugs, and rapid uptake by cells [27, 28]. Moreover, the chemical, physical, and biological properties of these nanocarriers can be modified by functionalization and adjusting the length of polymers (Table 2) [57].

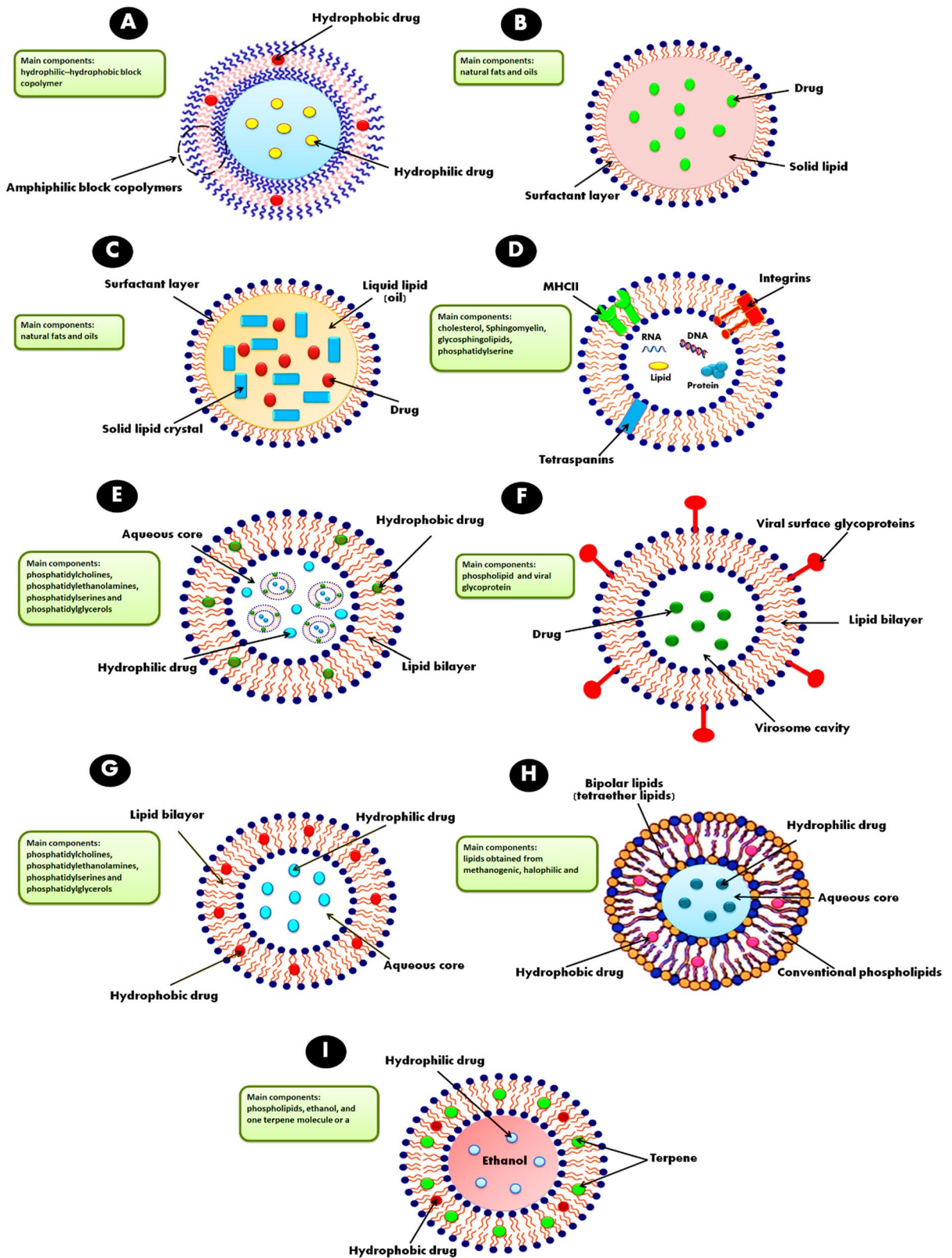
SLNs (Fig. 1B) contain a lipid crystalline core that is enclosed with one or more emulsifiers for stabilization [58]. Nanostructured lipid carriers (NLCs), as the second generation of lipid nanosystems, contain solid lipids in a liquid lipid matrix (Fig. 1C). In comparison to SLNs, NLCs confer higher drug loading due to their liquid oil droplets in a solid matrix [12]. NLC formulations are prepared by incorporating a drug in the mixture of different ratios of solid and liquid lipids. Degree of crystallinity in NLCs is lower than SLNs, and NLCs are more stable than SLNs at room temperature (Table 2) [32].

Exosomes (extracellular vesicles) are membrane-enclosed vesicular structures with a size distribution between 30 and 200 nm which are released by most cell types of the body including macrophages, dendritic cells, B cells, and T cells. These vesicles are usually composed of a lipo- or glycoprotein shell

surrounding a hydrophilic core that comprises proteins and nucleic acids extracted from the parent cell (Fig. 1D) [44–47]. Exosomes can be extracted from several extracellular fluids such as amniotic fluid, urine, saliva, and cerebrospinal and fluid blood. These nanocarriers are considered as drug delivery system for lipid, proteins, and RNA [59] because of their low immunogenicity and efficient cargo delivery [44, 45]. Exosomes act as a kind of “invisible cloak” because they can escape from the endosomal pathway and lysosomal degradation and reduce the clearance of phagocytic cells, which increases drug delivery to target tissues [47]. Nevertheless, therapeutic application of exosomes is restricted due to their structure complexity and non-efficient procedure for isolation and drug loading (Table 2) [44, 45].

Vesosomes (as multicompartiment systems) are liposomes encapsulating smaller liposomes in their aqueous core (Fig. 1E). These nanocarriers provide a dual protection layer for incorporated drugs, since the drug loaded smaller liposomes surrounded by second larger bilayer liposomes [42]. Vesosomes can be employed for delivery of drug cocktail (such as antibiotics) when a synergistic effect is expected to achieve at a fixed ratio of combined medications. This formulations also may prevent pathogen resistance to an individual drug [60]. Furthermore, the release of drugs from vesosomes as multicompartiment systems is more efficient than single-compartment systems, which leads to increase of permeability, specificity, and stability (Table 2) [42].

Virosomes are virus-like particles with altered viral envelopes and without genetic material of the native virus (Fig. 1F). Since virosomes mimic the intact



◀**Fig. 1** Structure of **A** polymersome, **B** SLN, **C** NLC, **D** exosome, **E** vesosome, **F** virosomes, **G** liposome, **H** archaeosome, and **I** invasome

virus and present the viral envelope glycoprotein (the most important viral antigens for inducing immune responses), they are able to combine the antigen and an adjuvant within a single particle which can induce both cellular and humoral immune responses. Therefore, virosomes can provide a platform for vaccine delivery systems. The virosomes enter the antigen-presenting cells (APCs) through the receptor-mediated endocytosis. Acidic pH of endosomes triggers the fusion of virosomes and endosomal membranes that leads to release of encapsulated antigen into cytosol of the APCs, presenting in MHC class I and then interact with T cell receptor on CD8⁺ lymphocytes and as a result inducing cytotoxic T lymphocyte (CTL) responses (Table 2) [38].

Marinosomes are a type of liposomes which are prepared from natural phospholipids extracted from marine organisms that contain high amounts of polyunsaturated fatty acids (PUFAs). These phospholipids possess more bioavailability than triglyceride which result in more efficient absorption into the body. These lipids are not naturally produced in normal human epidermis and upon the absorption; their metabolism in the epidermis results in production of anti-inflammatory and anti-proliferative metabolites. Therefore, marinosomes are potentially applicable in the cosmetic science for treatment of dermal inflammatory diseases (Table 2). Marinosomes reveal good tolerability in skin and eye [40]. Apart from dermal application, curcumin was encapsulated in marinosomes for improving of its anticancer activity. Marinosome-encapsulated curcumin exhibited a potent antioxidant and cytotoxic activity and a sustained release behavior on lung cancer cells. In addition, these nanocarriers showed good physico-chemical stability following 8 weeks of storage at 4 °C [61].

The major limitations of liposomes is instability of phospholipids in acidic pH of stomach owing to aggregation of phospholipids which causes the liposomal membrane to rupture and make them vulnerable to degradation by intestinal lipases [62]. Archaeosomes are a new generation of liposomes that are prepared from diether and/or tetraether lipids extracted from the Archaea (Fig. 1G and H). Compared to liposomes, archaeosomes exhibit distinctive structures which have considerable stability in alkaline or acidic pH, high

temperatures, and oxidative conditions and are resistant to the action of lipases and bile salts (Table 2) [52, 53]. Archaeal lipids in contrast to eukaryotic ester bound lipids are made from saturated isoprenoid chains that attached via ether bonds to *sn*-2, 3 carbons of the glycerol backbone [63]. It has been reported that ether links are more resistant than ester links in harsh condition [64]. Moreover, the crystallization and membrane permeability are decreased with the help of branching methyl groups in archaeosomes [19]. Therefore, these nanocarriers can open up a new avenue for the oral delivery of peptide and protein drugs. Furthermore, archaeosomes are biodegradable [53], and in vitro and in vivo studies indicated that archaeosomes are safe and do not induce toxic effects in mice. Their high thermo-stability made archaeosome formulations appropriate for sterilization by autoclaving [19].

Invasomes are liposomal vesicles composed of soy-phosphatidylcholine, lysophosphatidylcholine, ethanol, and terpenes (Fig. 1I). This soy-phosphatidylcholine invasomal bilayer surrounds the matrix. Lysophosphatidylcholine is an edge activator that confers appropriate flexibility to the phosphatidylcholine bilayers. Ethanol and terpenes are used as penetration enhancers for drugs (by disrupting the tight lipid packing of *stratum corneum*) and grant higher fluidity and flexibility to the phospholipid bilayers as well [35]. These nanocarriers are suitable drug delivery systems for skin penetration of hydrophilic and hydrophobic agents (Table 2) [35, 36].

Vaults are ribonucleoprotein nanocapsules with a thin protein shell enclosing an internal cavity that are present in most eukaryotic species from worms to humans. These particles can be produced in large quantities after the in situ expression of several copies of a structural protein assembled. Biochemical analysis determined that these nanocarriers are composed of three protein species and an RNA component. One of the proteins is the major vault protein (MVP) which its expression alone is necessary and sufficient for recombinant vault particle formation. Two additional proteins are telomerase-associated protein 1 (TEP1) and poly-(ADP-ribose) polymerase (PARP). The RNA component (rRNA) is a small untranslated RNA that associates with the vault through its binding to TEP1. Comparatively large number of materials can be loaded in the internal cavity due to its high capacity. Vaults can be applied as drug and vaccine delivery system. Vault therapeutic delivery systems are safe and relatively nontoxic [65–67].

Table 2 Benefits and limitations of some nanocarriers

Nanocarriers	Benefits	Limitations	Ref
Liposomes	Biocompatible and biodegradable	Unstable, inefficient for intracellular drug delivery, sensitivity to pH, ultrasound, heat and light	[5, 29–31]
SLN	Suitable for encapsulation of hydrophobic drugs	Lower loading of hydrophilic drugs	
NLC	Higher loading than SLN, more stable than SLNs	Poor incorporation of the hydrophilic drug, high rate of coagulation, lipid modification requirement and separation of the lipid phase	[12, 32–34]
Invasomes	Suitable drug delivery for skin penetration of hydrophilic and hydrophobic agents	Temperature instability over normal ranges	[35–37]
Virosomes	Capable to combine antigen and adjuvant for vaccine development for inducing of both cellular and humoral immune response	Adverse immune reactions	[38, 39]
Marinosomes	More bioavailability than triglyceride, applicable in the cosmetic	Efficiency is highly dependent on the lipid concentration and size of nanocarrier	[40, 41]
Vesosomes	Dual protection layer for incorporated drugs, higher permeability and stability	Premature content release in physiological environments	[42, 43]
Exosomes	Low immunogenicity, evade the endosomal pathway and lysosomal degradation, reduce clearance by phagocyte cells, enhance drug transport to the target tissues	Structural complexity, lack of efficient procedure for isolation and drug loading	[44–47]
Polymeric micelles	Prolonging the circulation time of the drug, high drug loading and sustained release	Low stability in biological media	[25, 48]
Alginate nanocarrier	Good biocompatibility, biodegradation and chemical versatility	Drug leakage and unstable at room temperature	[49–51]
Archaeosomes	Higher stability in alkaline or acidic pH, high temperatures, oxidation, resistant against the action of lipases and bile salts	High formulation reproducibility variation	[52–54]
Polymersomes	Higher stability, slower cargo release, long circulation times and rapid uptake into cells	Low permeability to small molecule, lack of biocompatibility and biodegradability	[27, 28, 55, 56]

Alginate is a hydrophilic, anionic polysaccharide and biodegradable polymer that is extracted from marine brown algae. Alginate can form nanocarriers by ionotropic gelation with divalent cations or cationic polymers; however, these nanocarriers are not stable at room temperature and loaded drug can be easily released from the nanocarriers (Table 2) [49, 50].

Micelles and liposomes have been widely considered for oral delivery of drugs due to their protection against degradation of loaded drugs by gastrointestinal enzymes and improvement of bioavailability. However, along with these advantages, there are some problems with liposomes and micelles including lower stability and drug encapsulation, rapid release of loaded drugs and lower cellular uptake [68].

Polymeric micelles are colloidal particles that self-assembled by amphiphilic block copolymers

in aqueous media, with a narrow size distribution and diameter of 10–100 nm. These nanocarriers have a hydrophobic core with hydrophilic shell that facilitates the encapsulation of lipophilic drugs. The hydrophilic shell structure of the micelles prevents the reticuloendothelial system to uptake them and permits a prolong circulation time for the drug. Polymeric micelles exhibit high drug loading and sustained drug release (Table 2) [25, 48].

Lipids and polymeric nanocarriers have been frequently used as nano-drug delivery system. Lipid nanocarriers such as liposomes are biocompatible, are biodegradable, and have capability to encapsulate hydrophilic and hydrophobic drugs [5, 29]. However, limitations of liposomes are their instability during storage, content leakage, and short blood circulation [69]. Polymeric nanocarriers exhibit higher structural

integrity and longer clearance time [70, 71]. These nanocarriers can be administered through different routes including parenteral, nasal, intra-ocular, and oral [71]. Nonetheless, in contrast to liposomes, loading of hydrophilic drugs in polymeric nanocarriers is relatively low owing to the fast leakage of the drug from the nanocarriers during their preparation [72]. To overcome the limitations of lipids and polymeric nanocarriers, a novel combination of drug delivery systems, i.e., hybrid NPs, has been developed. Hybrid nanocarriers present characteristics of both lipid and polymeric nanocarriers for improving their loading and stability. However, the control and prediction of physico-chemical properties and biological interaction of nanocarriers are difficult that alongside with their reproducibility problems limited their applications [73].

An update on nanocarrier modification and targeting

NPs are capable to increase the bioavailability of an encapsulated drug and, in addition to giving longer duration of action, facilitate its cellular uptake and provide a controlled release profile. Improved solubility and stability and decreased side effects are among the other advantages [16, 74, 75].

Since NPs are identified as foreign particles in the body; opsonins bind to their surface which causes their phagocytosis. Several approaches have been used to extend the circulation time of NPs. Functionalization of NPs with polymers, such as PEG, can prevent opsonization by avoiding protein adsorption (protein corona) to their surface [76]. Nanocarriers adsorb various proteins and biomolecules to form a layer known as “protein corona” [77]. Conjugation of PEG to the surface of nanocarriers provides a hydrating layer that prevents the formation of a protein corona [78]. Attachment of CD47 peptides at the surface of nanocarriers leads them to escape from macrophage identification and eradication. CD47 interacts with SIRP α (signal regulatory protein α) which is expressed on dendritic cells and macrophages. This binding leads to the phosphorylation of the cytoplasmic tail of SIRP α , resulting in binding and activation of protein phosphatases that prevent phagocytosis, probably via the decreasing of motor protein myosin-IIA amount necessary for phagocytosis [78, 79]. Coating of nanocarriers

with cell membranes obtained from red blood cells (RBCs) provides a biomimetic surface, making them undetectable by immune system, and as a result, a longer blood circulation time is achieved [80]. Recently, a pH-responsive dimethylaminoethane-carbamoyl-functionalized liposome (DC-liposome) was designed for escaping of endosomal degradation. DC-liposomes, through the electrostatic interaction, increase the membrane fusion with anionic endosomal membrane and consequently provide conditions for endosomal escape [81].

Nanocarriers have been widely employed as delivery system for chemotherapeutic agents due to enhanced permeability and retention (EPR) effect. EPR effect is based on the abnormal leaky vasculature around tumors which facilitates the penetration of NPs in the tumor tissue and reducing the side effects on the normal tissues. However, EPR effect is only presents in limited types of tumors since it is influenced by several factors including pore size of tumor vessels, amount of infiltration by macrophages, and tumor location [82, 83]. For improving their clinical application, numerous approaches have been investigated, of which active targeting is among them. In order to enhance cell-specific and intracellular delivery, nanocarriers can be modified with targeting ligands including antibodies [84], folic acid [85], carbohydrate [86], transferrin [87], aptamers, and vitamins [88]. Epithelial cell adhesion molecule (EpCAM, also known as CD326), is a dominant surface antigen on human colon cancer cells which can be considered as a biomarker [89]. PEGylated EpCAM aptamer-functionalized dendrimers were employed for getting the efficacy of celastrol better for treatment of colon cancer. Aptamers, as chemical antibodies, were used for better tumor tissue penetration beside the PEGylation of dendrimers that was employed to improve the safety. The results showed that this bioconjugate nanocarrier induced higher apoptosis than free celastrol in cancer cells. In addition, *in vivo* findings indicated that targeted NPs reduced tumor volume significantly in comparison with free celastrol [89].

One of the limitations of liposomes is their short duration of blood circulation and ineffective intracellular drug delivery. Exosome-mimicking liposomes can be employed as an approach to assist positive feedback between these two nanocarriers [44, 45]. Lu et al. prepared exosome-mimicking liposomes with 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC)/sphingomyelin (SM)/

cholesterol/1,2-dioleoyl-snglycero-3-phospho-L-serine (DOPS)/1,2-dioleoyl-snglycero-3-phosphoethanolamine (DOPE) for delivery of VEGF siRNA to A549 and HUVEC cells. Compared with conventional cationic liposomes, cellular uptake of exosome-mimicking liposomes was considerably improved. Moreover, exosome-mimicking liposomes showed more safety, higher storage stability, and anti-serum aggregation effect. These findings indicated that the unique lipid composition highly improved the intracellular delivery efficiency of exosome-mimicking liposomes [44].

There are a number of chemical approaches to synthesize dendrimers, for improvement of their physico-chemical properties and biocompatibility. Various monomers can be utilized to produce spherical dendrimers; however, most of them lead to the creation of cytotoxic components, mainly owing to their high charge. Moreover, they display short half-life and quick clearance. Functionalizing and coating of spherical dendrimers can overcome these restrictions and improve their specificity and targeting efficiency. Peptide dendrimers are made of amino acids residues (dendrimers with peptide bonds in their structures) [90]. This structure provides some peripheral functional groups for covalent binding of other molecules such as peptides and proteins. Poly-amidoamine (PAMAM) core is one of the most common polymeric cores for synthesis of peptide dendrimers [90, 91].

For alginate nanocarriers, coating with chitosan (cationic polysaccharide) can effectively enhance their stability at room temperature and prevent the leakage of the nanocarrier. Chitosan-alginate nanocarriers have been extensively explored as nanocarriers for various bioactive compounds [49]. When curcumin diglutamic acid was loaded in chitosan-alginate nanocarriers, the results displayed higher *in vitro* cellular uptake in Caco-2 cells and more cytotoxic activity against Caco-2, HepG2, and MDA-MB-231 cells [49].

PEG and polyoxyethylene are frequently used for preparation of polymeric micelles [25]. One of the major limitations in the clinical application of polymeric micelles is their low stability in biological media upon their systemic administration. This happens because of dilution below the critical micelle concentration (CMC) or pulling out of the drug from micelles by plasma proteins such as lipoproteins and serum albumin. Cross-linking of the polymer core and incorporation of the drug to the micellar

scaffolding are general approaches to overcome these issues. It was reported that using of platinum (II) as a drug to micelle core linker can modulate the drug retention and sustain the release. Platinum linker reacts with aromatic nitrogen atoms and as a result conjugates with drug that otherwise has not enough functionalities to be employed for conjugation reactions [48].

A hybrid nanocarrier consisting of liposome and micelle can reduce the problems associated with each of these components including nanocarrier instability, drug leakage, and its inadequate intracellular concentration. A liposome-micelle-hybrid carrier was designed for oral formulation of lovastatin, as a model of poorly soluble drug. D- α -Tocopheryl polyethylene glycol 1000 succinate (TPGS), as surfactant, was also used for enhancing of absorption. This hybrid nanocarrier consisted of liposomes with TPGS micelles in their aqueous core. In this system, the release of drug is controlled by loaded micelles while the liposomal shell increased the encapsulation efficiency and protected the drug against first pass effect. These hybrid nanocarriers increased the uptake of lovastatin in Caco-2 cells and inhibited the P-gp efflux in comparison with free drug [68].

Main parameters for appropriate nanocarrier selection

Selection of nanocarriers for suitable drug delivery is dependent on the physico-chemical properties of drugs/carriers, pharmacological targets, and therapeutic purposes. Liposomes can encapsulate both lipophilic and hydrophilic drugs. Lipophilic drugs can be loaded into the phospholipid double layers, while hydrophilic drugs can be entrapped into the aqueous core [92]. Micelles (hydrophobic core which is formed by the tails of the surfactant molecules) are suitable for encapsulation of lipophilic drugs considering their phospholipid tails which constitute a drug holding compartment [93]. Polymeric micelles are usually considered for the delivery of hydrophobic drugs due to core/shell nanostructures, stability, and long circulating duration, EPR effect, and active targeting [94, 95].

SLNs are composed of a solid hydrophobic core that is surrounded by surfactants. These nanocarriers are suitable for loading hydrophobic drugs. SLNs are more stable than liposomes and show lower toxicity

than polymeric nanocarriers [93]. As mentioned, SLNs are appropriate drug delivery system for encapsulating of hydrophobic drugs owing to their lipophilic nature of the lipid matrix. Due to the insufficient affinity between drug and lipid, loading of hydrophilic drugs in SLNs is not desirable. Hydrophilic drugs are readily incorporated into the external aqueous phase during the preparation process. However, it has been reported that by employing of some techniques like organic solvent-free double emulsion/melting dispersion, hydrophilic drugs can also be effectively encapsulated [96]. Integrating a hydrophilic polymer with SLNs in the core can lead to improved loading and controlling release of hydrophilic drugs owing to increased hydrophilic interaction with the drug. Poly(*N*-vinylcaprolactam) was incorporated in SLNs for controlling delivery of gemcitabine (a hydrophilic drug). Apparently, the hydrophilic-hydrophilic interactions between the polymer and the drug make these hybrid NPs have advantages compared to SLNs, including reduced immediate drug release, improved encapsulation, and controlled release. Moreover, these nanocarriers significantly increased the cellular uptake of the drug in cancer cells [97].

Liposomes are frequently used as nanocarriers for drug delivery because of their similarity with human cell barriers, capability to encapsulate hydrophilic and hydrophobic, biocompatibility, biodegradability, and their contribution to reduce the administered dose and drug toxicity [16, 98–100]. However, the efficiency of liposomes is limited due to their sensitivity to pH, ultrasound, heat, light, low circulation time in the blood, and low stability (hydrolysis of the ester bond, oxidation, and peroxidation of the acyl chains) along with the possibility of drug leakage during storage [70, 88, 92, 101]. Compared with liposomes, polymeric nanocarriers display higher structural integrity that provide increased stability, longer clearance time, more protection for drugs, facilitated controlling of size distribution, and prolonged drug release [70, 71].

Polymeric nanocarriers are solid colloidal particles that prepared from natural (e.g., alginate, chitosan), synthetic (e.g., PLGA, PCL) or semi-synthetic (e.g., carboxymethyl cellulose; CMC) polymers [71, 102, 103]. Nevertheless, unlike liposomes, encapsulation of hydrophilic drugs in polymeric nanocarriers is low owing to the rapid leakage of the drug during high-energy emulsification step used in their preparation. An approach

to overcome this limitation is developing of hybrid nanocarriers in which a lipid layer coats a polymeric core. Nanocarriers with this superficial lipid coat are kept away from the quick leakage of hydrophilic drugs which increases drug loading [72]. These liposomes containing polymeric nanocarriers are mainly useful for anti-biofilm designing since the liposomes fuse with bacterial cell membrane and permit controlled release of antibiotics from loaded polymeric nanocarriers [72]. The covering lipid and polymeric core are connected via hydrophobic interactions, electrostatic interactions, Van der Waals forces, and noncovalent forces [104]. Numerous studies indicated appropriate effectiveness for this delivery system. Liu et al. reported that 1,2-dilauroylphosphatidylcholine (DLPC)-coated paclitaxel containing PLGA NPs were more effective than Taxol® on cancer cells [105].

Lipid chitosan hybrid nanocarriers that are formed by the interaction of positively charged chitosan and negatively charged lipid in ionic gelation method showed the advantages of both polymeric and liposomal nanocarriers. Using this approach, cisplatin-loaded polymer-lipid hybrid nanocarrier exhibited superior cellular uptake and cytotoxicity [106]. Furthermore, chitosan and glyceryl monostearate-based matrix lipid polymer hybrid NPs were designed for oral delivery of itraconazole. According to the obtained results, these hybrid NPs can be employed as a promising approach to increase the dissolution of itraconazole which ultimately improves its bioavailability [107].

Lipid-PLGA hybrid NPs have been extensively considered as drug delivery systems for chemotherapeutic agents. It has been reported that dual lipid (stearyl amine and soya lecithin)-coated PLGA NPs with human serum albumin as surfactant exhibited controlled release of paclitaxel with blood compatibility improvement [99].

A hybrid PLGA-cationic lipid nanoparticles was designed for oral delivery of siRNA to the colon. These NPs targeted TNF- α in mice with ulcerative colitis and reduced the level of TNF- α without inducing significant toxicity in mice [108].

Hydrophilic drugs are widely used for the treatment of different conditions including inflammation, infectious diseases, and cancer. However, their clinical applications can be limited due to short biological half-lives, rapid clearance, low bioavailability, and low permeability across membrane barriers [109,

110]. Gemcitabine hydrochloride, a hydrophilic drug is widely used for the treatment of pancreatic cancer, ovarian cancer, bladder cancer, and non-small cell lung cancer [111, 112]. Yalcin et al. prepared PEGylated liposomes and PLGA NPs containing gemcitabine to attain enhanced encapsulation efficiency (EE%) and improved controlled drug release. In their study, prepared liposomes exhibited higher EE% than PLGA NPs, while PLGA NPs were more stable than liposomes. They concluded that using lipid polymer hybrid nanocarriers displayed a combined beneficial characteristics of both liposome and polymeric nanocarriers, and this approach may offer new insight for increasing of EE% and stability of gemcitabine [113].

Conversely, coating the liposomes with polymeric layer increases the stability of liposomes and decreases the leakage of loaded drug [114]. However, coated liposomes exhibited lower encapsulation efficiency in comparison to uncoated liposomes, because the drug escapes the liposomes during the coating process [114]. This issue depends on the type of the polymer. Refai et al. reported that higher loading was obtained for hydroxypropyl methylcellulose (HPMC)-coated liposomes containing sildenafil citrate which may be related to the higher thickness of the polymeric coat. While chitosan-coated liposomes displayed lower encapsulation efficiency for sildenafil citrate that may be due to electrostatic repulsion between the drug with positive charge and the cationic chitosan [114].

Molecular property of the drug can exhibit variable release profiles from nanocarriers. Huang et al. reported that carboxyfluorescein (CF) as a small molecule, encapsulated into the aqueous core of liposomes, was released around T_m (transition temperature). However, albumin as a larger molecule

with slower diffusion has hydrophobic units for interaction with lipid bilayer, and its release was different from CF [115].

Selecting a suitable nanocarrier for anti-cancer drugs poses a significant challenge, as the efficacy and cell death mechanism of the drugs can be influenced by the chosen nanocarriers. In our previous study, we developed two types of liposomes encapsulating 5-fluorouracil (5FU), one composed of soya phosphatidylcholine (PC) and the other using dipalmitoylphosphatidylcholine (DPPC), both targeted with folic acid. Analysis in Table 3 reveals notable variations in the IC_{50} values for liposomal 5FU and folate-liposomal 5FU across different cell types for each type of liposome. Additionally, we observed differing mechanisms of cell death between PC liposomes and DPPC liposomes on HT-29 and HeLa cells, likely due to the distinct properties of the respective liposome types (Table 3) [85, 116].

Decreasing in tumor volume by targeted PC liposome and DPPC liposome was also different (88.75 vs. 169.00 mm³) [85, 116].

Physico-chemical properties of liposomes are influenced by their composition. In our previous work, EE% of 5FU for DPPC liposomes with particle size of 174 nm was 39.71%. However, EE% and particle size of liposomes prepared by PC were 60.79% and 104.8 nm, respectively [85, 116]. As it can be seen, smaller liposome size and higher EE% of the drug were observed for PC liposomes compared to DPPC liposomes. The lower EE% of DPPC liposomes is probably due to higher rigidity of liposomal membrane associated with saturated lipid contents [113]. These findings were confirmed by a recent study which indicated that EE% of PC liposomes (23.8%) was more than DPPC liposomes (16.2%) containing gemcitabine, owing to lower rigidity of PC than

Table 3 IC_{50} values (μ M) and mechanism of cell death determined by applying of targeted formulations on different cell lines [85, 116]

Cells	PC liposome		DPPC liposome	
	Liposomal 5FU	Folate- liposomal 5FU (cell death)	Liposomal 5FU	Folate- liposomal 5FU (cell death)
HT-29	53.70	19.95 (apoptosis)	74.13	39.81 (necrosis)
Caco-2	-	79.43282	64.56	39.81
HeLa	97.72	15.49 (necrosis)	190.54	93.32 (apoptosis)
MCF-7	933.25	323.593	-	588.84
Fibroblast	575.44	147.91	794.32	-

DPPC lipid [113]. It has been reported that EE% of liposomes depends on the rigidity of the bilayer membrane and liposomes composed of saturated (e.g., DPPC) or unsaturated phospholipids (e.g., PC) reveal different membranes fluidity [117, 118]. These results indicated that the choice of lipid type for the preparation of liposomes profoundly affects their physico-chemical properties.

Therapeutic purpose and route of administration are also important in the selection of nanocarriers. Liposomes can be employed as vaccine delivery systems against pathogens and tumors [119]. Furthermore, it was reported that surface-linked liposomal peptides were able to provide tumor eradication and protection against viral infections in mice. Ohno et al. observed that liposomes can be used as excellent adjuvant vehicle for a synthetic peptide vaccine against severe acute respiratory syndrome when peptides are chemically coupled to the surface of liposomes [120]. Transdermal absorption of drugs can be increased by employing liposomal formulations. It was observed that *ex vivo* transport of diclofenac from liposome gel was enhanced compared to emulsion gel. It was suggested that the components of the liposome act as a permeability enhancer which increase the penetration of diclofenac [121].

PAMAM dendrimers have been widely studied as absorption enhancers for oral delivery and as carriers for transepithelial transfer of small drugs. PAMAM dendrimers modulate tight junctions, intestinal epithelial endocytosis, and potentiate paracellular transferring of small drug molecules [122]. PAMAM dendrimers (G4.5) encapsulated with curcumin can interfere with α -synuclein aggregation. α -Synuclein is a presynaptic neuronal protein associated with Parkinson's disease. This dendrimer could increase the solubility of curcumin in aqueous media, enhance its cellular uptake, and thus modify its pharmacokinetic properties and biodistribution [123]. Moreover, it was reported that utilizing the functionalized G4 PAMAM dendrimers can increase the poor physico-chemical properties and anticancer activity of hydrophobic drugs. Phenylboronic acid-conjugated PAMAM G4 dendrimers loaded with usnic acid were prepared as drug delivery system to gastric cancer cells. These nanocarriers could increase anticancer activity and cellular internalization of usnic acid loaded compared to free usnic acid nanocarriers over time in cancer cells [124].

NLCs improve gastrointestinal uptake of the incorporated drugs via the lymphatic transportation or Peyer's patches [125]. Diindolylmethane, a lipophilic anti-cancer metabolite of indole-3-carbinol derived from cruciferous vegetables, has limited bioavailability. Oral bioavailability of DIM-loaded NLC formulations was increased due to enhancing drug solubility and absorption [126]. TPGS decorated gefitinib loaded NLCs were TPGS decorated NLCs gefitinib loaded were developed as lymphatic drug delivery for prevention and treatment of cancer metastasis. Results showed that TPGS-NLC was able to increase gefitinib bioavailability via lymphatic system, enhance lung drug deposition more than free drug, and improve its cytotoxic activity against cancer cell line [127].

Approaches to reduce the toxicity of nanocarriers

Nanocarriers enter the blood, tissue fluid, and lymph through the skin and digestive and respiratory tracts where they attach to biological macromolecules due to their high surface area and nanoscale size [128].

Cationic liposomes (e.g., N-[1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethylammonium chloride; DOTMA) [129] interact with the negatively charged surface of the cell membrane via electrostatic interaction and absorption to the cell surface which may trigger toxic reactions. Cationic liposomes displayed genotoxic effects in *in vitro* studies [130]. It was observed that cationic liposomes caused lung inflammation through the production reactive oxygen species (ROS) [131]. Addition of targeting moieties to the cationic liposomes can address these concerns. By targeting of nanocarriers, less concentration of drug/nanocarriers is required and fewer side effects are seen. Selection of an appropriate ligand for nanocarrier targeting is also important. It has been reported that conjugation of whole antibodies to the surface of liposomes induced complement activation and reduced their blood circulation since the Fc fraction of antibodies is recognized by macrophages. It has been reported that Fab' fragments of antibody exhibited less cytotoxicity than whole antibody; therefore, conjugation of Fab' fragments instead of the whole antibody is suggested [132, 133].

Nanocarriers with anionic charge exhibited fewer toxicity than nanocarriers with cationic properties due to their restricted interaction with the negatively charged surface of cell membranes [134] (Fig. 2). However, it has been reported that anionic liposomes

(e.g., dioleoylphosphatidylglycerol; DOPG) [129] can trigger complement activation and immune reactions. C1q (complement component 1q) binds to liposomes with anionic charge on surface. The top of the C1q head is basic and allows interfering with liposomes. Hydrogen bonding and hydrophobic interactions have also been suggested to further play a role in C1q binding to anionic liposomes [135]. Contrary to some previous findings which suggested that PEGylated liposomes prevent complement activation, it has been shown that PEGylated liposomes can induce PEG-specific antibodies and trigger the complement system in human serum [135, 136]. It is probably due to accelerated blood clearance (ABC) phenomenon. In this phenomenon, antibodies against nanocarrier components, such as PEG, are produced that decrease its efficacy and safety [137]. Anti-PEG IgM binds to the PEG on the liposomes, provokes the complement system, and consequently complements mediated phagocytosis [137] which promotes the secretion of cytokines by the immune cells [138]. Another immune response is complement activation-related pseudoallergy (CARPA). In CARPA, complement

activation leads to the release of anaphylatoxins (C5a and C3a), stimulation of basophils, macrophages, and mast cells and consequently release of secondary mediators such as histamine, leukotrienes, tryptase, and platelet-activating factor (PAF) [137]. These reactions may raise concerns about the use of PEGylated liposomes for clinical purposes. McSweeney et al. reported that infusion with high-molecular-weight free PEG is a promising solution for overcoming this problem. They believe that infusion of free PEG molecules can bind and saturate circulating anti-PEG antibodies which reduce the formation of immune complexes. They observed that infusion of 40 kDa free PEG effectively provided the prolonged circulation of PEGylated liposomes in the presence of high titers of pre-existing anti-PEG antibodies for at least 48 h in mice [139] (Fig. 2).

Induction of inflammatory reactions is one of the mechanisms by which NPs exert their toxic effects [140]. Silva et al. reported an inflammatory response in adipose tissue and also deposition of visceral and subcutaneous fat in mouse treated with SLNs. Lipid matrix and the surfactants used in preparation of

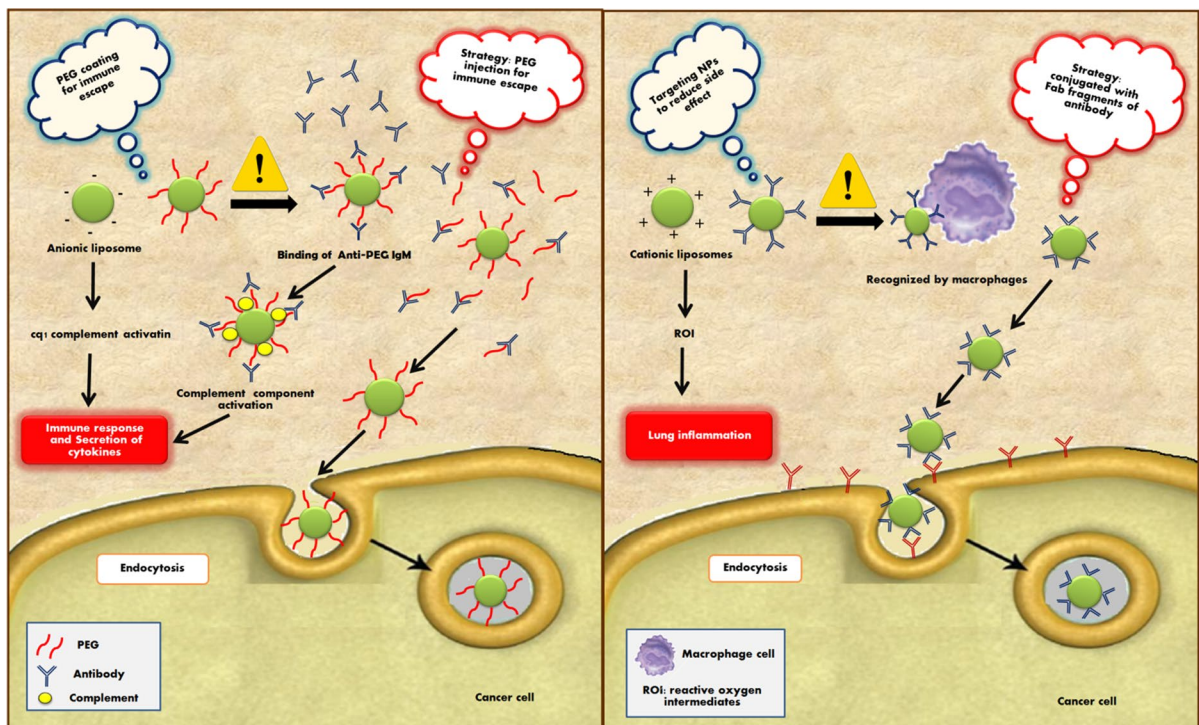


Fig. 2 Cytotoxicity of anionic and cationic liposome and approaches for improving their safety

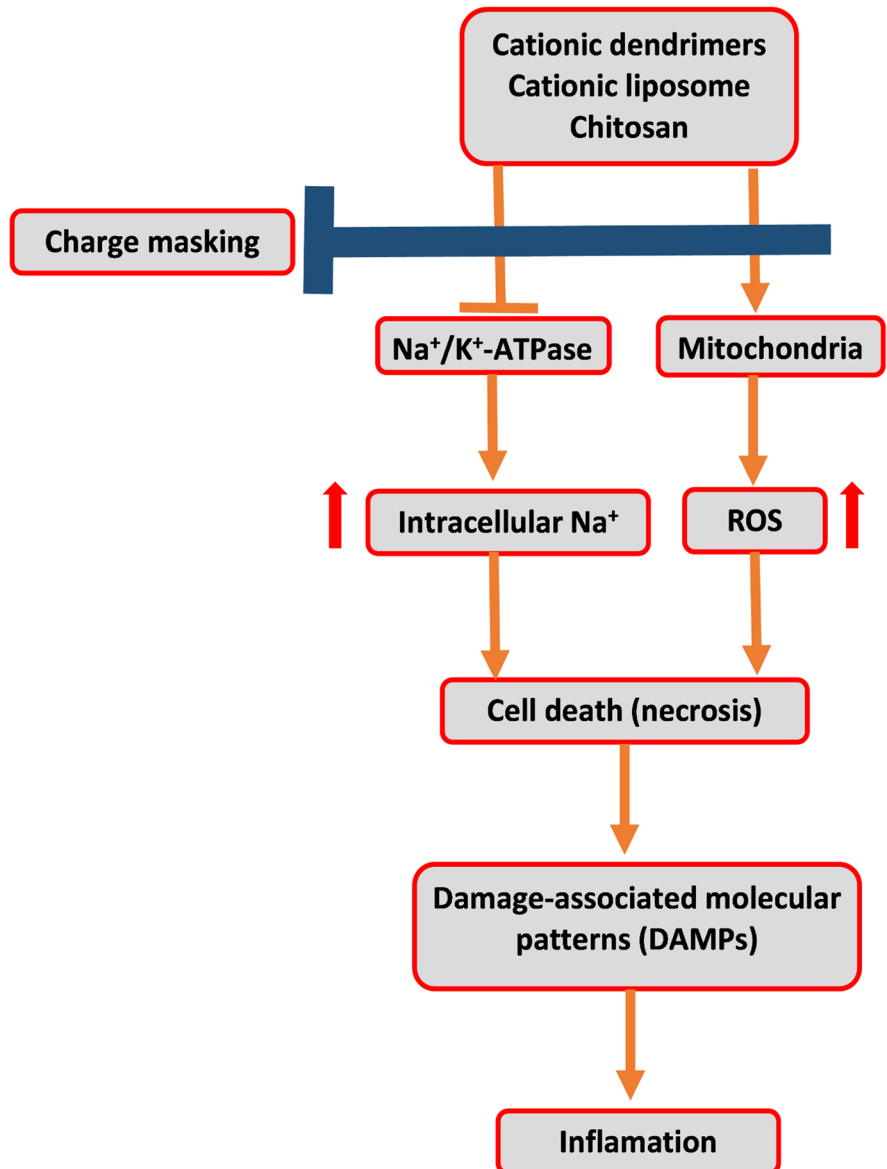
SLNs can induce inflammatory reaction in animals. Moreover, the accumulation of visceral and subcutaneous fat may be related to the slow degradation of the lipid matrix used in SLNs preparation and the intraperitoneal route of administration which may trigger local inflammation and more accumulation of visceral and subcutaneous fat [26].

Along with the composition of NPs, the surface charge may also affect the cell death mechanism. It was found that cationic NPs including polyethylene imines (PEI), cationic liposomes, and chitosan impaired the activity of Na^+/K^+ -ATPase in cell membrane which

may contribute to the consequent intracellular Na^+ overload and finally necrosis (Fig. 3) [141].

NPs can produce reactive oxygen species (ROS) and cause cell damage [140]. It has been shown that dendrimers overproduced ROS from mitochondria which caused oxidative stress, apoptosis, and DNA damage. Higher generations of dendrimers showed higher toxicity [142]. However, this issue can be solved by altering the surface functional groups. 2,2,6,6-Tetramethylpiperidiny-1-oxy was used to functionalize of dendrimers. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) as a stable nitroxide free

Fig. 3 Cytotoxicity of cationic nanocarriers and approaches for improving their safety



radical exhibited antioxidant activity by ROS scavenging. It was observed that TEMPO-functionalized dendrimers exhibited significant cytotoxicity on A549 tumor cells, while it protected normal cells (L132 cells) against oxidative cell damage [143].

Compared to virosomes and liposomes, dendrimers have higher transfer efficiency and stability, which can increase the circulation time of drugs in the body. However, the hemolytic activity and cytotoxicity of dendrimers have hindered their clinical application [25]. Cationic dendrimers (G2, G3, and G4) have been reported to be more cytotoxic than anionic dendrimers (G2.5, G3.5) [144]. As mentioned for liposomes, modification of surface is an appropriate approach for escaping of immune responses and adverse effects (Fig. 2). For dendrimers and to overcome this problem, it was found that conjugation of lauroyl chain can reduce the cytotoxicity of dendrimers [25] by charge masking of the primary amine groups (Fig. 3) [145]. Furthermore, it was observed that modification of the dendrimers with lauroyl moieties reduced the lysosomal accumulation and resulted in lower concentration of modified dendrimers in lysosomal acidic compartment and hydrolytic enzymes as well. This modification increased the uptake of the modified dendrimers into human intestinal epithelial cells and improved their delivery [146].

Furthermore, cationic PAMAM nanocarriers caused acute lung injury in mice. In the lung, these nanocarriers reduced the activity of angiotensin-converting enzyme 2 (ACE2) by directly binding to it and reducing its expression, thereby disrupting the renin-angiotensin system. Interestingly, losartan administration was found to ameliorate nanocarrier-induced lung injury, including inflammatory cell infiltration. Losartan decreased IL-6 concentration in bronchoalveolar lavage fluid after dendrimer injection [147].

Conclusion

Each of the nanocarriers discussed in this review has a number of advantages and disadvantages. However, the selection criteria of a suitable nanocarrier with maximum compatibility and minimum toxicity have not been widely considered. In this review, some modifiable changes in nanocarriers were discussed to improve their efficiency and reduce their toxicity.

Modification of nanocarriers can reduce their toxicity on normal cells and increase their efficiency on target cells. Studies indicated that hybrid nanocarriers are potentially able to overcome the common problems of using conventional nanocarriers. Hybrid nanocarriers have several advantages over non-hybrid platforms, including improved circulation time, increased stability, controlled release, and increased drug loading. Therefore, these nanocarriers can be considered as a promising platform with the least toxic side effects and the most efficiency for drug delivery.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

References

- Dunne S et al (2013) A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. *BMC Pharmacol Toxicol* 14(1):1
- Patra JK et al (2018) Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol* 16(1):71
- Oroojalian F et al (2020) Recent advances in nanotechnology-based drug delivery systems for the kidney. *J Control Release* 321:442–462
- Farokhzad OC, Langer R (2009) Impact of nanotechnology on drug delivery. *ACS Nano* 3(1):16–20
- Bozzuto G, Molinari A (2015) Liposomes as nanomedical devices. *Int J Nanomedicine* 10:975–999
- Hines DJ, Kaplan DL (2013) Poly (lactic-co-glycolic) acid– controlled-release systems: experimental and modeling insights. *Crit Rev Ther Drug Carrier Syst* 30(3):257–76
- Kesharwani P et al (2014) Dendrimer as nanocarrier for drug delivery. *Prog Polym Sci* 39(2):268–307
- Dang Y, Guan J (2020) Nanoparticle-based drug delivery systems for cancer therapy. *Smart Materials in Medicine* 1:10–19
- Klibanov AL et al (1990) Amphipathic polyethyleneglycols effectively prolong the circulation time of liposomes. *FEBS Lett* 268(1):235–237
- Bulbake U et al (2017) Liposomal formulations in clinical use: an updated review. *Pharmaceutics* 9(2):12
- Li Z et al (2017) Cancer drug delivery in the nano era: An overview and perspectives. *Oncol Rep* 38(2):611–624
- Prasad M et al (2018) Nanotherapeutics: an insight into healthcare and multi-dimensional applications in medical sector of the modern world. *Biomed Pharmacother* 97:1521–1537

13. Bhardwaj V et al (2019) Recalcitrant Issues and New Frontiers in Nano-Pharmacology. *Front Pharmacol* 10:1369
14. Farjadian F et al (2019) Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. *Nanomedicine* 14(1):93–126
15. Badea N et al (2020) Systems based on carbon nanotubes with potential in cancer therapy. *Mater Chem Phys* 241:122435
16. Vakhshiteh F et al (2020) Peptide-conjugated liposomes for targeted miR-34a delivery to suppress breast cancer and cancer stem-like population. *J Drug Delivery Sci Technol* 57
17. Keshtiar P et al (2020) New dendrimers containing ruthenium nanoparticles as catalysts for hydrogenation of citral to 3, 7-dimethyloctanol. *Mater Chem Phys* 249
18. Moghimipour E et al (2013) Solid lipid nanoparticles as a delivery system for *Zataria multiflora* essential oil: formulation and characterization. *Curr Drug Deliv* 10(2):151–157
19. Kaur G et al (2016) Archaeosomes: an excellent carrier for drug and cell delivery. *Drug Deliv* 23(7):2497–2512
20. Zylberberg C, Matosevic S (2016) Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape. *Drug Deliv* 23(9):3319–3329
21. Handali S et al (2019) Co-delivery of 5-fluorouracil and oxaliplatin in novel poly (3-hydroxybutyrate-co-3-hydroxyvalerate acid)/poly (lactic-co-glycolic acid) nanoparticles for colon cancer therapy. *Int J Biol Macromol* 124:1299–1311
22. Jiang T et al (2020) Recent advances in encapsulation of curcumin in nanoemulsions: A review of encapsulation technologies, bioaccessibility and applications. *Food Res Int* 132
23. Sett R et al (2020) Effect of temperature and salts on niosome-bound anti-cancer drug along with disruptive influence of cyclodextrins. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 234
24. Shah S et al (2020) Nanogels as drug Carriers-Introduction, chemical Aspects, release mechanisms and potential Applications. *Int J Pharm* 15. <https://doi.org/10.1016/j.ijpharm.2020.119268>
25. Peng Y et al (2020) Research and development of drug delivery systems based on drug transporter and nano-formulation. *Asian J Pharm Sci* 15(2):220–236. <https://doi.org/10.1016/j.ajps.2020.02.004>
26. Silva AH et al (2014) Solid lipid nanoparticles induced hematological changes and inflammatory response in mice. *Nanotoxicology* 8(2):212–219
27. Lee JS et al (2010) Thermosensitive hydrogel-containing polymersomes for controlled drug delivery. *J Control Release* 146(3):400–408
28. Aibani N et al (2020) Liposome mimicking polymersomes; A comparative study of the merits of polymersomes in terms of formulation and stability. *Int J Pharm : X* 2:100040
29. Toh M-R, Chiu GN (2013) Liposomes as sterile preparations and limitations of sterilisation techniques in liposomal manufacturing. *Asian J Pharm Sci* 8(2):88–95
30. Zavec AB et al (2014) Archaeosomes can efficiently deliver different types of cargo into epithelial cells grown in vitro. *J Biotechnol* 192:130–135
31. Atallah C et al (2020) Development of cysteamine loaded liposomes in liquid and dried forms for improvement of cysteamine stability. *Int J Pharm* 15(589). <https://doi.org/10.1016/j.ijpharm.2020.119721>
32. Salvi VR, Pawar P (2019) Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. *J Drug Deliv Sci Technol* 7(1):41–55
33. Karmakar G et al (2018) Role of PEG 2000 in the surface modification and physicochemical characteristics of pyrazinamide loaded nanostructured lipid carriers. *J Chem Sci* 130(4):42
34. Müller RH (2007) Lipid nanoparticles: recent advances. *Adv Drug Deliv Rev* 59(6):522–30. <https://doi.org/10.1016/j.addr.2007.04.012>
35. Zhou X et al (2018) Nano-formulations for transdermal drug delivery: a review. *Chin Chem Lett* 29(12):1713–1724
36. Shah SM et al (2015) LeciPlex, invasomes, and liposomes: A skin penetration study. *Int J Pharm* 490(1-2):391–403
37. Amnuakit T et al (2018) Vesicular carriers containing phenylethyl resorcinol for topical delivery system; liposomes, transfersomes and invasomes. *Asian J Pharm Sci* 13(5):472–484
38. Zheng C, Lü FL (2013) The Virosome as a Novel Concept for High Pathogenic Porcine Reproductive and Respiratory Syndrome Virus (HP-PRRSV) Vaccines. *J Integr Agric* 12(7):1215–1224
39. Pörtl-Frank F et al (1999) Use of reconstituted influenza virus virosomes as an immunopotentiating delivery system for a peptide-based vaccine. *Clin Exp Immunol* 117(3):496
40. Moussaoui N et al (2002) Marinosomes®, marine lipid-based liposomes: physical characterization and potential application in cosmetics. *Int J Pharm* 242(1-2):361–365
41. Cansell MS et al (2007) Prostaglandin E2 and interleukin-8 production in human epidermal keratinocytes exposed to marine lipid-based liposomes. *Int J Pharm* 343(1-2):277–280
42. Paleo CM et al (2013) Formation of artificial multi-compartment vesosome and dendrosome as prospected drug and gene delivery carriers. *J Control Release* 170(1):141–152
43. Mishra DK et al (2018) Lipid based nanocarriers: a translational perspective. *Nanomedicine* 14(7):2023–2050
44. Lu M et al (2018) Comparison of exosome-mimicking liposomes with conventional liposomes for intracellular delivery of siRNA. *Int J Pharm* 550(1-2):100–113
45. Stremersch S et al (2016) Comparing exosome-like vesicles with liposomes for the functional cellular delivery of small RNAs. *J Control Release* 232:51–61
46. Donoso-Quezada J et al (2019) Exosomes as nanocarriers for the delivery of bioactive compounds from black bean extract with antiproliferative activity in cancer cell lines. *Mater Today: Proc* 13:362–369
47. Niu X et al (2019) Nanocarriers as a powerful vehicle to overcome blood-brain barrier in treating neurodegenerative diseases: Focus on recent advances. *Asian J Pharm Sci* 14(5):480–496
48. Shi H et al (2020) Folate decorated polymeric micelles for targeted delivery of the kinase inhibitor dactolisib to cancer cells. *Int J Pharm* 30(582)
49. Sorasitthyanukarn FN et al (2018) Chitosan/alginate nanoparticles as a promising approach for oral delivery

- of curcumin diglutaric acid for cancer treatment. *Mater Sci Eng C* 93:178–190
50. Saralkar P, Dash AK (2017) Alginate nanoparticles containing curcumin and resveratrol: preparation, characterization, and in vitro evaluation against DU145 prostate cancer cell line. *AAAPS PharmSciTech* 18(7):2814–2823
 51. Sosnik A (2014) Alginate particles as platform for drug delivery by the oral route: state-of-the-art. *Int Scholarly Res Notices* 20142014(2014)
 52. Moghimipour E et al (2014) Archaeosomes as means of nano-drug delivery. *Rev Med Microbiol* 25(2):40–45
 53. Li Z et al (2010) Investigation of archaeosomes as carriers for oral delivery of peptides. *Biochem Biophys Res Commun* 394(2):412–417
 54. Agbayani G et al (2020) Mechanistic insight into the induction of cellular immune responses by encapsulated and admixed archaeosome-based vaccine formulations. *Hum Vaccin Immunother* 16(9):2183–2195. <https://doi.org/10.1080/21645515.2020.1788300>
 55. Le Meins J-F et al (2011) Recent trends in the tuning of polymersomes' membrane properties. *Euro Phys J E* 34(2):1–17
 56. Poma A et al (2018) Polymersomes: Synthesis and Applications. In: *Encyclopedia of Polymer Science and Technology*, pp 1–43
 57. Pan XQ et al (2019) Folate-conjugated pluronic/polylactic acid polymersomes for oral delivery of paclitaxel. *Int J Biol Macromol* 139:377–386
 58. Pink DL et al (2019) On the structure of solid lipid nanoparticles. *Small* 15(45):1903156
 59. Johnsen KB et al (2014) A comprehensive overview of exosomes as drug delivery vehicles—endogenous nanocarriers for targeted cancer therapy. *Biochimica et Biophysica Acta (BBA)-Rev Cancer* 1846(1):75–87
 60. Kisak E et al (2004) The vesosome-A multicompartiment drug delivery vehicle. *Curr Med Chem* 11(2):199–219
 61. Ibrahim S et al (2018) Curcumin marinosomes as promising nano-drug delivery system for lung cancer. *Int J Pharm* 540(1–2):40–49
 62. Dey M et al (2019) Breaking the barricade of oral chemotherapy through polysaccharide nanocarrier. *Int J Biol Macromol* 1(130):34–49. <https://doi.org/10.1016/j.ijbiomac.2019.02.094>
 63. McCluskie MJ et al (2017) Sulfated archaeal glycolipid archaeosomes as a safe and effective vaccine adjuvant for induction of cell-mediated immunity. *Hum Vaccin Immunother* 13(12):2772–2779
 64. Moghimipour E et al (2013) The potent in vitro skin permeation of archaeosome made from lipids extracted of *Sulfolobus acidocaldarius*. *Archaea* 2013
 65. Muñoz-Juan A et al (2019) Latest Advances in the Development of Eukaryotic Vaults as Targeted Drug Delivery Systems. *Pharmaceutics* 11(7):300
 66. Yang J et al (2013) Vault nanoparticles engineered with the protein transduction domain, TAT48, enhances cellular uptake. *Integr Biol* 5(1):151–158
 67. Casañas A et al (2012) Vault particles: a new generation of delivery nanodevices. *Curr Opin Biotechnol* 23(6):972–977
 68. Romana B et al (2020) A liposome-micelle-hybrid (LMH) oral delivery system for poorly water-soluble drugs: Enhancing solubilisation and intestinal transport. *Eur J Pharm Biopharm* 154:338–347
 69. Hadinoto K et al (2013) Lipid–polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review. *Eur J Pharm Biopharm* 85(3):427–443
 70. Emami F et al (2019) Poly (lactic acid)/poly (lactic-co-glycolic acid) particulate carriers for pulmonary drug delivery. *J Pharm Investig* 1–1630(3):257–76
 71. Sur S et al (2019) Recent developments in functionalized polymer nanoparticles for efficient drug delivery system. *Nano-Structures Nano-Objects* 20:100397
 72. Cheow WS, Hadinoto K (2011) Factors affecting drug encapsulation and stability of lipid–polymer hybrid nanoparticles. *Colloids Surf B: Biointerfaces* 85(2):214–220
 73. Ghitman J et al (2020) Review of hybrid PLGA nanoparticles: Future of smart drug delivery and theranostics medicine. *Mater Des* 193(1)
 74. Macedo AS et al (2020) Novel and revisited approaches in nanoparticle systems for buccal drug delivery. *J Control Release* 10(320):125–141. <https://doi.org/10.1016/j.jconrel.2020.01.006>
 75. ud Din, F. et al (2017) Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int J Nanomedicine* 12:7291
 76. Behzadi S et al (2017) Cellular uptake of nanoparticles: journey inside the cell. *Chem Soc Rev* 46(14):4218–4244
 77. Wang H et al (2018) The protein corona on nanoparticles as viewed from a nanoparticle-sizing perspective. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 10(4):e1500
 78. Blanco E et al (2015) Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol* 33(9):941
 79. Qie Y et al (2016) Surface modification of nanoparticles enables selective evasion of phagocytic clearance by distinct macrophage phenotypes. *Sci Rep* 6(1):1–11
 80. Li H et al (2019) Size Dependency of Circulation and Biodistribution of Biomimetic Nanoparticles: Red Blood Cell Membrane-Coated Nanoparticles. *Cells* 8(8):881
 81. Rayamajhi S et al (2020) pH-responsive cationic liposome for endosomal escape mediated drug delivery. *Colloids Surf B: Biointerfaces* 188:110804
 82. Nogueira E et al (2015) Design of liposomal formulations for cell targeting. *Colloids Surf B Biointerfaces* 136:514–526
 83. Nair KL et al (2011) Biological evaluation of 5-fluorouracil nanoparticles for cancer chemotherapy and its dependence on the carrier, PLGA. *Int J Nanomedicine* 6:1685–1697
 84. Yang W et al (2018) Antibody fragment-conjugated gemcitabine and paclitaxel-based liposome for effective therapeutic efficacy in pancreatic cancer. *Mater Sci Eng C* 89:328–335
 85. Handali S et al (2019) New folate receptor targeted nano liposomes for delivery of 5-fluorouracil to cancer cells: Strong implication for enhanced potency and safety. *Life Sci* 227:39–50
 86. Chen J et al (2016) Nanostructured glycopolymer augmented liposomes to elucidate carbohydrate-mediated targeting. *Nanomedicine* 12(7):2031–2041
 87. Moghimipour E et al (2018) A mechanistic study of the effect of transferrin conjugation on cytotoxicity of targeted liposomes. *J Microencapsul* 35(6):548–558

88. Calori IR et al (2020) Determination of critical micelle temperature of Pluronic® in Pluronic/gel phase liposome mixtures using steady-state anisotropy. *J Mol Liq* 304
89. Ge P et al (2020) Enhanced cancer therapy of celestrol in vitro and in vivo by smart dendrimers delivery with specificity and biosafety. *Chem Eng J* 383:123228
90. Mirakabad FST et al (2019) Peptide dendrimers as valuable biomaterials in medical sciences. *Life Sci* 15(233)
91. Sreelekshmi, P. et al. (2020) Peptide dendrimer stabilized gold nanoparticles as sensors. *Materials Today: Proceedings*. <https://doi.org/10.1016/j.matpr.2019.12.060>
92. Forier K et al (2014) Lipid and polymer nanoparticles for drug delivery to bacterial biofilms. *J Control Release* 190:607–623
93. Watkins R et al (2015) Natural product-based nanomedicine: recent advances and issues. *Int J Nanomedicine* 10:6055
94. Wang Y et al (2020) Biotin-decorated all-HPMA polymeric micelles for paclitaxel delivery. *J Control Release* 10(328):970–984. <https://doi.org/10.1016/j.jconrel.2020.09.013>
95. Tao J et al (2020) Toward understanding the prolonged circulation and elimination mechanism of crosslinked polymeric micelles in zebrafish model. *Biomaterials* 256:120180
96. Peres LB et al (2016) Solid lipid nanoparticles for encapsulation of hydrophilic drugs by an organic solvent free double emulsion technique. *Colloids Surf B: Biointerfaces* 140:317–323
97. Surapaneni SG, Ambade AV (2022) Poly (N-vinylcaprolactam) containing solid lipid polymer hybrid nanoparticles for controlled delivery of a hydrophilic drug gemcitabine hydrochloride. *RSC Adv* 12(27):17621–17628
98. Gallez A et al (2020) Liposomes and drug-in-cyclodextrin-liposomes formulations encapsulating 17beta-estradiol: An innovative drug delivery system that prevents the activation of the membrane-initiated steroid signaling (MISS) of estrogen receptor alpha. *Int J Pharm* 573:118861
99. Godara S et al (2020) Lipid-PLGA hybrid nanoparticles of paclitaxel: Preparation, characterization, in vitro and in vivo evaluation. *Mater Sci Eng C* 109:110576
100. Trucillo P et al (2020) Production of liposomes loaded alginate aerogels using two supercritical CO₂ assisted techniques. *Journal of CO₂ Utilization* 39:101161
101. Hu Y et al (2014) In vitro performance of lipid-PLGA hybrid nanoparticles as an antigen delivery system: lipid composition matters. *Nanoscale Res Lett* 9(1):434
102. Fathi M, Barar J (2017) Perspective highlights on biodegradable polymeric nanosystems for targeted therapy of solid tumors. *Bioimpacts* 7(1):49
103. Shende P, Gupta H (2020) Formulation and comparative characterization of nanoparticles of curcumin using natural, synthetic and semi-synthetic polymers for wound healing. *Life Sci* 15(253)
104. Dave V et al (2019) Lipid-polymer hybrid nanoparticles: Synthesis strategies and biomedical applications. *J Microbiol Methods* 160:130–142. <https://doi.org/10.1016/j.mimet.2019.03.017>
105. Liu Y et al (2010) Nanoparticles of lipid monolayer shell and biodegradable polymer core for controlled release of paclitaxel: effects of surfactants on particles size, characteristics and in vitro performance. *Int J Pharm* 395(1-2):243–250
106. Khan MM et al (2019) Lipid-chitosan hybrid nanoparticles for controlled delivery of cisplatin. *Drug Deliv* 26(1):765–772
107. Yousaf R et al (2023) Development and in-vitro evaluation of chitosan and glyceryl monostearate based matrix lipid polymer hybrid nanoparticles (LPHNPs) for oral delivery of itraconazole. *Heliyon* 9(3)
108. Arruda DC et al (2022) Spheroplexes: Hybrid PLGA-cationic lipid nanoparticles, for in vitro and oral delivery of siRNA. *J Control Release* 350:228–243
109. Ramazani F et al Strategies for encapsulation of small hydrophilic and amphiphilic drugs in PLGA microparticles: state-of-the-art and challenges. *Polym Particles Sustained Local Drug Delivery* 499(1-2):358–367. <https://doi.org/10.1016/j.ijpharm.2016.01.020>
110. Vrignaud S et al (2011) Strategies for the nanoencapsulation of hydrophilic molecules in polymer-based nanoparticles. *Biomaterials* 32(33):8593–8604
111. Ding N et al (2020) Improving plasma stability and anti-tumor effect of gemcitabine via PEGylated liposome prepared by active drug loading. *J Drug Deliv Sci Technol* 57(2):101538. <https://doi.org/10.1016/j.jddst.2020.101538>
112. Yin L et al (2020) Comparative pharmacokinetic study of PEGylated gemcitabine and gemcitabine in rats by LC-MS/MS coupled with pre-column derivatization and MSALL technique. *Talanta* 206:120184
113. Yalcin TE et al (2018) Gemcitabine hydrochloride-loaded liposomes and nanoparticles: comparison of encapsulation efficiency, drug release, particle size, and cytotoxicity. *Pharm Dev Technol* 23(1):76–86
114. Refai H et al (2017) Development and characterization of polymer-coated liposomes for vaginal delivery of sildenafil citrate. *Drug Deliv* 24(1):278–288
115. Huang X et al (2017) The effect of thermosensitive liposomal formulations on loading and release of high molecular weight biomolecules. *Int J Pharm* 524(1-2):279–289
116. Handali S et al (2018) A novel 5-Fluorouracil targeted delivery to colon cancer using folic acid conjugated liposomes. *Biomed Pharmacother* 108:1259–1273
117. Jacquot A et al (2014) Morphological and physical analysis of natural phospholipids-based biomembranes. *PLoS One* 9(9)
118. Monteiro N et al (2014) Liposomes in tissue engineering and regenerative medicine. *J R Soc Interface* 11(101):20140459
119. Jin Z et al (2019) Adjuvants and delivery systems based on polymeric nanoparticles for mucosal vaccines. *Int J Pharm* 15(572)
120. Ohno S et al (2009) Synthetic peptides coupled to the surface of liposomes effectively induce SARS coronavirus-specific cytotoxic T lymphocytes and viral clearance in HLA-A* 0201 transgenic mice. *Vaccine* 27(29):3912–3920
121. Sacha M et al (2019) Ex vivo transdermal absorption of a liposome formulation of diclofenac. *Biomed Pharmacother* 111:785–790
122. Sadekar S et al (2013) Poly (amido amine) dendrimers as absorption enhancers for oral delivery of camptothecin. *Int J Pharm* 456(1):175–185

123. Igartúa DE et al (2023) PAMAM dendrimers of generation 4.5 loaded with curcumin interfere with α -synuclein aggregation. *OpenNano* 11:100140
124. Jangid AK et al (2023) Phenylboronic acid conjugated PAMAM G4 dendrimers augmented usnic acid delivery to gastric cancer cells. *Eur Polym J* 192:112073
125. Shrivastava P et al (2020) 20 - Nanotechnology for oral drug delivery and targeting. In: Mozafari M (ed) *Nano-engineered Biomaterials for Advanced Drug Delivery*. Elsevier, pp 473–498
126. Godugu C et al (2016) Novel diindolylmethane derivatives based NLC formulations to improve the oral bioavailability and anticancer effects in triple negative breast cancer. *Eur J Pharm Biopharm* 108:168–179
127. Harisa GI et al (2023) TPGS decorated NLC shift gefitinib from portal absorption into lymphatic delivery: Intracellular trafficking, biodistribution and bioavailability studies. *Colloids Surf B: Biointerfaces* 223:113148
128. Liu N et al (2019) The interaction between nanoparticles-protein corona complex and cells and its toxic effect on cells. *Chemosphere* 245
129. Balazs DA (2011) Godbey W (2011) Liposomes for use in gene delivery. *J Drug Delivery* 2011
130. Knudsen KB et al (2015) In vivo toxicity of cationic micelles and liposomes. *Nanomedicine* 11(2):467–477
131. Dokka S et al (2000) Oxygen radical-mediated pulmonary toxicity induced by some cationic liposomes. *Pharm Res* 17(5):521–525
132. Perche F (2013) Torchilin VP (2013) Recent trends in multifunctional liposomal nanocarriers for enhanced tumor targeting. *J Drug Deliv* 2013
133. Cheng W, Allen T (2010) The use of single chain Fv as targeting agents for immunoliposomes: an update on immunoliposomal drugs for cancer treatment. *Expert Opin Drug Deliv* 7(4):461–478
134. Knudsen KB et al (2014) Differential toxicological response to positively and negatively charged nanoparticles in the rat brain. *Nanotoxicology* 8(7):764–774
135. Moghimi SM, Hamad I (2008) Liposome-mediated triggering of complement cascade. *J Liposome Res* 18(3):195–209
136. Hayat SMG et al (2019) (2019) Stealth functionalization of biomaterials and nanoparticles by cd47 mimicry. *Int J Pharm* 569
137. Mohamed M et al (2019) PEGylated liposomes: immunological responses. *Sci Technol Adv Mater* 20(1):710–724
138. Inglut CT et al (2020) Immunological and Toxicological Considerations for the Design of Liposomes. *Nanomaterials* 10(2):190
139. McSweeney MD et al (2019) Overcoming anti-PEG antibody mediated accelerated blood clearance of PEGylated liposomes by pre-infusion with high molecular weight free PEG. *J Control Release* 311:138–146
140. Ajdary M et al (2018) Health concerns of various nanoparticles: A review of their in vitro and in vivo toxicity. *Nanomaterials* 8(9):634
141. Wei X et al (2015) Cationic nanocarriers induce cell necrosis through impairment of Na⁺/K⁺-ATPase and cause subsequent inflammatory response. *Cell Res* 25(2):237–253
142. Mukherjee SP et al (2010) Mechanistic studies of in vitro cytotoxicity of poly (amidoamine) dendrimers in mammalian cells. *Toxicol Appl Pharmacol* 248(3):259–268
143. Ali BM et al (2020) Radical dendrimers: Synthesis, anti-tumor activity and enhanced cytoprotective performance of TEMPO free radical functionalized polyurethane dendrimers. *Eur Polym J* 122:109354
144. Jevprasesphant R et al (2003) Engineering of dendrimer surfaces to enhance transepithelial transport and reduce cytotoxicity. *Pharm Res* 20(10):1543–1550
145. Sadekar S, Ghandehari H (2012) Transepithelial transport and toxicity of PAMAM dendrimers: implications for oral drug delivery. *Adv Drug Deliv Rev* 64(6):571–588
146. Saovapakhiran A et al (2009) Surface modification of PAMAM dendrimers modulates the mechanism of cellular internalization. *Bioconjug Chem* 20(4):693–701
147. Sun Y et al (2015) Cationic nanoparticles directly bind angiotensin-converting enzyme 2 and induce acute lung injury in mice. *Part Fibre Toxicol* 12(1):4

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