TOPICAL REVIEW

Lipid-polymer hybrid nanoparticles in cancer therapy: current overview and future directions

Francesca Persano$^{1,2}$, Giuseppe Gigli$^{1,2}$$^\ddagger$ and Stefano Leporatti$^2$$^\ddagger$

1 University of Salento, Department of Mathematics and Physics, Via Per Arnesano 73100, Lecce, Italy
2 CNR Nanotec-Istituto di Nanotecnologia, Via Monteroni 73100, Lecce, Italy
E-mail: stefano.leporatti@nanotec.cnr.it

Keywords: hybrid nanosystem, lipid-polymer hybrid nanoparticle, lipid shell, polymeric core, nanomedicine, cancer, drug delivery

Abstract

Cancer remains one of the leading cause of death worldwide. Current therapies are still ineffective in completely eradicating the disease. In the last two decades, the use of nanodelivery systems has emerged as an effective way to potentiate the therapeutic properties of anti-cancer drugs by improving their solubility and stability, prolong drug half-lives in plasma, minimize drug’s toxicity by reducing its off-target distribution, and promote drugs’ accumulation at the desired target site. Liposomes and polymer nanoparticles are the most studied and have demonstrated to be the most effective delivery systems for anti-cancer drugs. However, both liposomes and polymeric nanoparticles suffer from limitations, including high instability, rapid drug release, limited drug loading capacity, low biocompatibility and lack of suitability for large-scale production. To overcome these limitations, lipid-polymer hybrid nanoparticles (LPHNPs) have been developed to merge the advantages of both lipid- and polymer-based nanocarriers, such as high biocompatibility and stability, improved drug loading and controlled release, as well as increased drug half-lives and therapeutic efficacy. This review provides an overview on the synthesis, properties and application of LPHNPs for cancer therapy.

Abbreviations

FA Folic Acid
FR Folate receptor
NPs Nanoparticles
DOX Doxorubicin
GRAS Generally regarded as safe
FDA Food and Drug Administration
LPHNPs Lipid-polymer hybrid nanoparticles
PEG Polyethylene glycol
PGA Poly-γ-glutamic acid
PLA Poly (D, L lactide), poly (lactic acid)
PLG Poly (D,L glycolide)
PLGA Poly (lactic-co-glycolic acid)
PCL Polycaprolactone
DCM Dichloromethane
DPPC 1,2-dipalmitoyl-sn-glycerol-3-phosphocholine
DOTAP 1,2-dioleoyl-3-trimethylammonium-propane
DOPE 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine
DSPE-PEG-COOH 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)—2000] DPTAP 1,2-dipalmitoyl-3-trimethylammonium-propane

1. LPHNPs: structural classification, properties, synthesis methods

In the design of nanocarriers for the delivery of anticancer agents, the most commonly used matrices are polymers and lipids, each of them with specific advantages associated with their use [1]. Among the polymeric nanosystems, we distinguish mainly polymeric NPs, polymeric micelles and polymer-drug conjugates, while among the lipid-based nanosystems we distinguish liposomes, solid lipid NPs and nanostructured lipid vectors [2]. Lipid-based nanocarriers offer several advantages such as a low production cost, greater trapping efficiency of the therapeutic agent, however they tend to display a reduced stability, a fast load release and high polydispersity [3]. In addition, there is a limited possibility for the chemical modification/functionalization of these nanostructures, thus reducing their application for active targeting approaches [4]. Polymeric nanosystems, on the other hand, are characterized by a high possibility of chemical modifications, an essential feature in the development of personalized therapies [5]. In addition, polymeric NPs offer other advantages such as the possibility of obtaining NPs of small dimensions and with reduced polydispersity, as well as diversity in the synthesis procedures, simple and reproducible synthesis process, and better stability [6]. However, polymeric nanosystems also display limitations, such as the use of organic solvents in the synthesis process, the toxicity linked to the degradation products of the polymer and the limited trapping capacity of drugs [7]. A new generation of nanosystems has been created to exploit the advantages of both polymeric systems and lipid-based systems, thanks to the production of a hybrid system composed of a polymeric core coated by a lipid shell, named lipid-polymer hybrid nanoparticles (LPHNPs) [8]. Such systems combine the advantages of lipid-based nanocarriers, such as increased drug carrying capacity, biomimetic nature and biocompatibility, with the advantages of polymeric nanocarriers such as desirable drug release profile and variety of surface chemical functionalization/modification. In the simplest design, LPHNPs consist of a hydrophilic or hydrophobic polymer core encapsulating the therapeutic agent of interest, surrounded by a lipid layer, which improves nanoparticles’ biocompatibility and stability upon systemic administration [9–11]. Several polymers have been proposed for the development of LPHNPs, among the most widely employed are polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), Poly(lactic acid) (PLA), poly β-amino ester (PbAE), Chitosan [12, 13], which are highly biocompatible and biodegradable polymers, in some cases approved by the Food and Drug Administration (FDA). Regarding the lipid shell, its composition can be tailored based on the type of therapeutic agent that is intended to be release, and the desired surface properties needed to achieve efficient uptake, controlled drug release, and biodistribution [14]. The outer layer properties can be easily modulated by changing the lipid composition and exploited to facilitate non-covalent or covalent attachment of antibodies, ligands, aptamers, and bioactive molecules such as DNA, RNA or proteins [15]. Additionally, charged or zwitterionic lipids are often preferred to promote electrostatic interactions between the lipid layers and the opposite charge of the polymeric core, thus promoting self-assembling of the nanostructure. Similarly, the preparation of a lipophilic core can favor its interaction with the hydrophobic tail domain of the lipids constituting the lipid layer [16]. Finally, pegylated lipids (PEG-lipids) can be included into the outer shell, to improve the circulation time of nanoparticles in the bloodstream since it can prevent the interaction with serum proteins [17].

1.1. Structural classification of LPHNPs

Based on their structure, LPHNPs can be classified as follows: (1) Monolithic hybrid nanosystems, (2) core–shell nanosystems, (3) Hallow core–shell nanoparticles, (4) Biomimetic lipid-polymer hybrid nanosystems and (5) Polymer–caged liposomes [11]. The monolithic hybrid nanosystems (figure 1(A)) are characterized by a polymeric matrix in which the lipid molecules are dispersed randomly [18]. core–shell nanoparticles (figure 1(B)) are formed by a polymeric core that acts as a support for the deposition of a highly biocompatible lipid shell. A variant of this kind of nanovehicles is represented by the hollow core–shell nanosystems (figure 1(C)), which possess a lipid layer composed of PEG-lipids and neutral lipids surrounding an inner polymer layer, which may interact with a cationic lipid layer, delimiting a hallow inner aqueous core [19]. The biomimetic lipid-polymer hybrid (figure 1(D)) nanosystems are composed of a polymeric core coated with cell-derived membranes [20]. The last class of LPHNPs are the polymer–caged liposomes constituted by an external polymer layer anchored on the surface of liposomes (figure 1(E)) [21].

1.2. Properties of LPHNPs

LPHNPs offer the possibility to integrate in the same nanocarrier the advantages of both polymeric and lipid delivery vectors, leading to the realization of a new generation of nanoformulation with improved physical,
chemical and functional properties [22]. Due to their composition, LPHNPs display good biocompatibility, and the entire nanovector can be potentially metabolized by the body. They also possess a large surface area available for conjugation with drugs or ligands, and their morphology along with surface properties can be tuned by varying the composition of the core and lipid shell [23], enabling a greater entrapment efficiency and a controlled release of the therapeutic agents. Furthermore, LPHNPs tend to display a high mechanical stability both during storage and in serum, thanks to the polymeric core which acts as a cytoskeleton and to the PEG-coated lipid layer, which improves their circulation time in vivo by eluding the immune system [24–28]. LPHNPs of core–shell type with dimensions equal to or less than 100 nm allow the intracellular release of the drug causing reduced cytotoxicity [29]. Finally, thanks to the amphiphilic character of the lipids, hydrophilic molecules can be adsorbed on the lipid bilayer, while hydrophobic molecules can be trapped at the level of the hydrophobic lamellar region. Thus, LPHNPs can trap and co-administer multiple hydrophilic and hydrophobic therapeutic agents, acting as a universal cancer therapy platform [30, 31]. Figure 2 summarizes the main advantages of LPHNPs.

1.3. Synthesis methods for LPHNPs
Various methods have been developed for the synthesis of LPHNPs, but they can be broadly grouped in two main strategies: (1) Two-step methods and (2) One-step methods [32], see figure 3.
1.3.1. Two-step methods

The approaches proposed for the synthesis of LPHNPs in the initial studies, were based on a two-step method, wherein polymeric nanoparticles are mixed with the prepared liposomes, and the incorporation of the lipid shell onto the surface of the polymer core is promoted by electrostatic forces \[33\]. Otherwise, the prepared polymeric nanoparticles can be added to dried lipid film. In either case, the assembling of the two components is promoted through the introduction of energy via vortexing and/or ultrasonication and heating at a temperature above the phase transition temperature of the lipid layer \[34\]. The polymeric core can be prepared by nanoprecipitation, emulsification–solvent evaporation or high-pressure homogenization \[35\]. A purification step can be introduced to ensure the removal of lipidic or polymeric nanoparticles and obtain the isolation of LPHNPs \[36\].

1.3.2. One-step methods

Two-step methods have shown to be time-consuming and poorly suitable for their scaling-up \[37\]. Therefore, large efforts have been dedicated to the development of more efficient synthesis methods that can allow obtaining LPHNPs in a single step \[38\]. Usually, most of the previously reported one-step methods are based on

---

**Figure 2.** Main advantages associated with the individual components (polymeric core, lipid shell, external pegylated lipid layer) and the overall structure of the LPHNPs.

**Figure 3.** Schematic representation of the one-step (A) and two-step (B) methods used for the preparation of LPHNPs.
the nanoprecipitation technique or emulsification-solvent evaporation techniques [39]. However, nanoprecipitation has shown important advantages over emulsification-solvent evaporation procedure, such as simplicity, and the possibility of obtaining nanoparticles with a narrow size distribution [40]. Furthermore, nanoprecipitation only requires the use of non-toxic solvents (e.g. ethanol), and it involves a procedure that can be automated using a microfluidic platform and, in some cases, allows a superior loading efficiency, especially with macromolecules (i.e. mRNA, pDNA and protein) [41]. In the conventional nanoprecipitation technique, an organic phase, containing the lipophilic drug and polymer dissolved in a water-miscible organic solvent (Acetone, ethanol, methanol, etc), is mixed with the lipid/PEG-lipid dissolved in water. The aqueous phase is heated above its gel-to-liquid transition temperature in a pre-mixing step, in order to prepare a homogeneously dispersed lipid solution [42]. The mixing of the organic phase with the aqueous phase triggers the reorganization of the polymer into nanoparticles and the simultaneous self-assemble of the lipids surrounding the polymer core, where the hydrophobic tails of the lipids are directed toward the inner side and the hydrophilic head groups face out toward the external aqueous solution [43]. The removal of the organic phase can be ensure by evaporation, dialysis or ultrafiltration. Other one-step approaches have been previously reported. For instance, Fang et al showed ultrafast synthesis (~5 min) of small and well monodisperse LPHNPs. About a decade ago, Valencia et al demonstrated that LPHNPs with relatively narrow size distribution can be prepared in microfluidic reactors, where the organic and aqueous phases are rapidly mixed together [44]. In the second decade of the 21st century, Kim et al reported a pattern-tunable microvortex platform for large production (~3 g hour\(^{-1}\)) of LPHNPs with a controllable size (~30–170 nm) and low PDI (~0.1) [45].

2. Application of LPHNPs in cancer therapy

In the last two decades, the use of nanodelivery systems has emerged as an effective way to potentiate the therapeutic properties of anti-cancer drugs by improving their solubility and stability, minimize drugs’ toxicity by reducing its off-target accumulation [46, 47]. Many efforts are currently concentrated on the design of formulations capable of a highly specific interaction with cancer cells to improve the therapeutic efficacy of conventional cancer therapies [48]. Recently, several research groups have focused on the development of nanoplates capable of delivering the different anticancer therapies in a targeted way while sparing healthy cells. These nanostructures must be able to maintain their integrity while on circulation and release their cargo in a controlled manner once the desired site is reached [49]. LPHNPs compared to other nanosystems, such as lipid-based systems and polymeric NPs, have numerous advantages, resulting in valid alternatives in the treatment of cancer [50]. The main advantage of the use of LPHNPs in the administration of anticancer agents is represented by the possibility of incorporating therapeutic agents with different physicochemical properties, thanks to their hybrid structure characterized by a polymer and lipid components that can possess distinct properties [51]. In addition, hydrophobic drugs can be co-administered with emerging therapeutic agents such as nucleic acids, proteins and peptides. In this regard, a possible approach is to encapsulate the hydrophobic drugs into the lipophylic polymeric core, while charged biomolecules are conjugated or adsorbed to the lipid shell [52, 53]. Several studies have confirmed a greater drug encapsulation efficiency of LPHNPs compared to polymer nanomatrixes, as well as greater stability with non-significant drug losses and controlled load release kinetics [54]. In this regard, the group of Wong et al reported that LPHNPs characterized by SLN (solid lipid NPs) that coat a negatively charged polymer for the administration of salidroside (Sal), a positively charged hydrophilic drug [55]. Sal is a water-soluble anticancer drug, and in this study the authors attain its encapsulation exploiting its affinity with the hydrophobic portion of the outer lipid membrane of the hybrid vector. With this strategy, the authors generated small nanoparticles with high loading capacity, able to efficiently target the tumor site upon administration [55]. There are several limitations related to the use of anticancer drugs, such as unwanted biodistribution, rapid drug clearance and non-targeted action, leading to a series of adverse effects on non-diseased tissues [56, 57]. A controlled and selective administration of therapeutic agents will lead to a significant reduction of adverse systemic effects. Due to their structure, LPHNPs are particularly suitable for the conjugation of ligands directed towards the over-expressed receptors on tumor cells, thus improving the tumor targeting and maximizing the therapeutic action of the administered agents towards tumor cells [58, 59]. Different types of ligands, such as small molecules, peptides, antibodies and aptamers have been employed for the functionalization of the outer surface of hybrid nanoparticles in active targeting strategies [60]. Such targeting ligands are directly bound on the outermost surface of LPHNPs through electrostatic interactions or through strong covalent attachment [61]. The internalization by tumor cells of hybrid nanoformulations decorated with targeting ligands occurs through a mechanism of receptor-mediated endocytosis, with significantly higher affinity for the target tissue and lower affinity for non-diseased tissues [62]. For example, hybrid nanosystems with a core–shell structure have been produced using a natural polymeric composite of chondroitin sulfate and chitosan coated with a PEGylated lipid layer in order to increase stability
In addition, the lipid layer was functionalized with Folic acid (FA) for targeted delivery to cancer cells. The results obtained from the uptake studies performed using fluorescently labeled nanoparticles revealed that functionalization with FA enhanced nanoparticles’ internalization by cancer cells. In addition, active targeting also resulted in a prolonged release of the therapeutic agent (sorafenib) with a consequent enhancement of the anti-tumor effect [64]. Similarly, another study reported a folate-decorated LPHNP, synthesized using the lipid DSPE-PEG2000 and a PCL-PEG-PCL poly(ε-caprolactone) -poly(ethylene glycol) -poly(ε-caprolactone) copolymer) to constitute the core of the NPs, for the prolonged, controlled and targeted release of paclitaxel (PTX) [65]. In this study, the folate receptor positive mouse carcinoma cells (EMT6 cells) displayed a greater uptake of the folate–functionalized LPHNPs compared to the folate receptor negative cells (L929 fibroblasts); thus confirming that the internalization of nanoformulations in EMT6 tumor cells is achieved through receptor-mediated endocytosis. Furthermore, in vitro cytotoxicity tests confirmed that folate–functionalized and PTX-loaded LPHNPs have a two times greater cytotoxic effect over non-targeted LHPNPs. This higher cytotoxic effect was also confirmed in vivo, as tumor-bearing mice treated with folate–functionalized LHPNPs showed a superior tumor growth inhibition compared to mice treated with non–functionalized LHPNPs [65, 66].

In another study conducted by the group of Gu et al a hybrid nanoformulation was developed to overcome the drawbacks associated to the use of cisplatin and Indocyanine green (ICG), a photosensitizer used for clinical imaging and photothermal. The authors proposed a single-step sonication method for the manufacturing of folate-modified, cisplatin/ICG-loaded LHPNPs. The LHPNPs exhibited optimal monodispersity and stability, as well as excellent near infrared (NIR) penetration ability. The folate–functionalized LPHNPs showed an improved targeting efficacy in MCF-7 tumor cells over-expressing folate receptors (FR), compared to FR-negative A549 tumor cells. In addition, the functionalized formulation was more effective than free PTX or ICG treatment alone at mediating apoptosis and necrosis of MCF-7 cells, thus proving LPHNPs may be a suitable kind vector for multimodal tumor-targeted therapy [67, 68].

In line with the above, in a recent study Yugui et al applied core–shell LPHNPs functionalized with FA and loaded with an gefitinib, an EGFR inhibitor, and a radioisotope (yttrium 90) for the development of an effective combination treatment for nasopharyngeal cancer [69]. These FR targeted nanosystems demonstrated a synergistic chemoradiotherapy effect, with improved antitumor efficacy in vivo and 90% drug accumulation at the desired site [69]. In a similar study Guo et al through the use of hybrid nanoparticles consisting of a PLGA polymeric core and a lipid shell functionalized with transferrin (Tf), demonstrated the antiproliferative action of DOX. Tf ligands were conjugated to the lipid shell via a post-insertion process. The hybrid nanoformulations were internalized by A549 cells through TIR-mediated endocytosis, with an efficiency 2.8–4.1 times greater than PLGA polymeric nanoparticles. In addition, the release rate of the hybrid nanoparticles was lower than that of the non–hybrid ones, pointing out that hybrid nanovectors can promote a prolonged and sustained drug release [70]. A similar approach was applied in the design of a hybrid nanoform system formed by PLGA coated with a lipid shell, produced through the solvent injection technique, for the delivery of an aromatase inhibitor. [71]. This hybrid nanoform system demonstrated a 3.6–fold greater trapping efficiency of the aromatase inhibitor (7α- (4′ amino) phenylthiol-1,4-androstadiene-3,17-dione (7α–APTADD) and an improved therapeutic action thanks to the functionalization with the Tf ligand, thus achieving a targeted delivery. Indeed, the nanovector showed a high uptake in SKBR-3 cells human breast cancer cells through TIR-mediated endocytosis [71]. The prolonged release of 7α–APTADD demonstrated a dose-dependent inhibition of aromatase with superior accumulation in tumor mass, which confirmed effective inhibition of targeted aromatase inhibitors versus that of a non-targeted hybrid system [71].

Current advances in cancer research have revealed that biomolecules such as nucleic acids (DNA and RNA), proteins and peptides have shown an important therapeutic potential in the treatment of cancer, when administered together with other drugs for a synergistic therapeutic effect, constituting a promising strategy against chemo-resistance [72]. However, the co-encapsulation and release of hydrophobic drugs, such as conventional chemotherapy drugs, together with these biomolecules presents a major challenge, which may be overcome with hybrid nanoparticles [73]. Sengupta et al, in this regard, developed a hybrid nanoparticle with a diameter of 180 and 200 nm, consisting of a central block polymer core coated with a pegylated phospholipid [74]. DOX, cytotoxic drug, was conjugated to the polymer core, and an anti-angiogenic agent, combretastatin–A4, was then, entrapped in the lipid layer. The lipid shell was disrupted within the tumor leading to the rapid release of combretastatin–A4 and a consequent vascular collapse [74]. All this led to the retention of intra-tumoral retention of the nanoparticles with subsequent release of DOX from the PLGA-DOX oligomer for the killing of tumor cells [74]. This study highlighted the versatility offered by hybrid core–shell nanosystems in the application of combinatorial therapies. The group of Aryan et al followed a similar strategy by encapsulated Paclitaxel–cisplatin conjugate, chemically conjugated through the glutaric acid linker, into hybrid LPHNPs. Non-encapsulated drug conjugate versus drug conjugates trapped in LPHNPs demonstrated reduced cytotoxicity towards a human ovarian cancer cell line [75]. The nanoparticles facilitated the internalization of drug conjugates through endocytosis, overcoming the limitation of their transport ability across the lipid bilayer. LPHNPs have been employed for the co-administration of chemotherapeutic agents in combination with
radioisotopes, nucleotide sequences, proteins and diagnostic agents [76]. In a recent study, the selective co-administration of DOX with pDNA encoding GFP was realized through a hybrid nanosystem consisting of a hydrophobic polymer core of PLGA and a self-assembled PEGylated lipid coating coated with hydrophilic folate. In this system, DOX was trapped in the polymer core while the cationic lipid shell was employed to bind the DNA via electrostatic interactions [77]. LPHNPs have been recently applied for cancer immunotherapy, and they may be particularly suitable for the development of combinatorial immunotherapies targeting different immune escape mechanisms. A hybrid nanoformulation was proposed by Park et al, consisting of liposomal polymeric gels of drug-complexed cyclodextrins and cytokine-encapsulating biodegradable polymers for the delivery of a small hydrophobic molecular inhibitor of transforming growth factor β (TGF-β) and water-soluble protein cytokine, interleukin-2 (IL-2), to the tumor microenvironment for the treatment of metastatic melanoma [78]. The results obtained showed a significant delay in tumor growth with an increase in survival time of tumor-bearing mice, providing evidence of the efficacy of hybrid nanovectors for multi-drug delivery [78]. Overall, in the various studies reported the co-administration strategies resulted in significant benefits for an improved tumor inhibition potential compared to single drug administration, and a reduction in drug chemoresistance. Table 1 shows several lipid-polymer hybrid nanosystems used for the delivery of anticancer agents.

3. Future directions and conclusions

The relative high loading capacity for different therapeutic agents, excellent stability in the bloodstream and drug cargo-transporting capability in vivo, renders LPNNPs a highly appealing delivery vehicle for cancer therapeutics. In addition to numerous other advantages such as improved biocompatibility, long circulation time in the body, targeted targeting, adjustable drug release kinetics and reduced drug degradation thanks to the external PEGylated lipid layer, both compared to liposomes and polymer NPs, believed to date the nanostructures of choice for the administration of anticancer therapies. All these features reveal the extraordinary potential of LPHNPs as versatile delivery platforms with unique therapeutic potential in the treatment of cancer. The LPHNPs as a whole represent structures with adjustable characteristics in terms of release kinetics, which allow the administration of an optimal quantity of therapeutic agent in the desired site with limited adverse effects off target. Numerous ligands that target proteins over-expressed by tumor cells have been explored for the functionalization of hybrid NPs, frequently reporting an improved accumulation of the therapeutic agent in the tumor. Therefore we believe that future efforts should focus on programming in vivo experiments that lead to the optimization of the ligand density, with the aim of improving the pharmacokinetics of NPs. Furthermore, LPHNPs are capable of encapsulating a large variety of therapeutic agents due to their unique structure. These nanocarriers can trap multiple drugs (co-encapsulation) by exploiting their synergistic effect. Consequently, another interesting prospect would be the optimization of loading protocols in order to improve the co-entrapment efficiency of drugs with different properties (hydrophilic and hydrophobic), considering that the co-administration strategy is proving to be more and more a promising approach in the treatment of incurable diseases, such as cancer. Several studies have highlighted the unique therapeutic potential of LPHNPs loaded with two drugs. In this regard, the control of the molar ratio of the two drugs and their loading efficiency is fundamental. Many lipid-based medications have been and are currently tested in clinical trials, and a good number is already commercially available. However, the clinical implementation of polymeric NPs remains limited, as there are still concerns regarding their safety profile. Preclinical studies have provided evidences that the use of LPNNPs can offer the potential to integrate the advantages of both lipid- and polymeric- based systems in the same platform and overcome the major limitations of polymeric NPs related mostly with toxicity concerns. Indeed, the introduction of an outer layer lipid shell could consent to modulate properties like hydrophobicity, stimuli-triggered drug release, targeting efficiency and polymer charge-associated toxicity. However, the implementation of large-scale production procedures and the selection of materials with a good biocompatibility represent the major obstacles for their introduction into the clinic. For instance, there is a need for a proper selection of solvent to be utilized during synthesis, as this can significantly affect the stability of the NPs and its inefficient removal may induce undesired toxicity issues.

Once challenges related with the scale-up of the manufacturing procedures are addressed, more exhaustive studies both in preclinical and clinical settings are needed to allow the full exploitation of LPNNPs in cancer treatment. Guo et al have recently showed that nanoparticles’ rigidity is a tunable feature in LPNNPs, which can be opportunely modulated to enhance tumor delivery efficiency by improving their tumor accumulation and uptake by target cells. However, still little is known about the influence of this parameter in defining the interaction of LPNNPs with immune cells and how this aspect can be eventually harnessed to potentiate the effectiveness of cancer immunotherapies [103]. We conclude our review by stating that LPNNPs constitute an intelligent and attractive platform for anticancer therapy since multiple pharmacological action and targeted
### Table 1. Applications LPHNPs in anticancer therapy delivery.

| Type of LPHNPs                                      | Polymer                  | Lipids             | Cancer model                                      | Therapeutic agent                  | Encapsulation Efficiency (EE) and activity | Reference |
|-----------------------------------------------------|--------------------------|--------------------|--------------------------------------------------|------------------------------------|------------------------------------------|----------|
| Lipid-coated PLGA/PLGA NPs                         | PLGA                     | DOTAP/DOPE         | LNCaP, PC3, and DU145 cells line (prostate cancer) | siRNA                              | EE = 32%–46%                             | [79]     |
| Polymer-Lipid Hybrid Nanoparticles (PLN)            | HPESO (hydrolyzed polymer of epoxidized soybean oil) | Stearic acid       | human MDR breast cancer cell line (MDA435/ LCC6/MDR1) | Doxorubicin (DOX) and GG918         | EE = 89.3 ± 4.7%                          | [80]     |
| Folic acid modified lipid-shell and polymer-core nanoparticles (FLPNPs) | PLGA                     | OQLCS or FA-OQLCS, PEG-OQLCS and cholesterol | Hela human cervix carcinoma cells over-expressing folate receptor, human lung adenocarcinoma A549 cell line and SCID mice | Paclitaxel (PTX)                  | IC₅₀ = 0.34 mg mL⁻¹ EE = 87 ± 2% within 55 days of injection 78% of the mice were alive | [81]     |
| TLNP's (conjugated folic acid)                      | PLGA                     | DLPC, DSPE-PEG₂₅, and DSPE-PEG₅₀-FOL | MCF7 breast cancer cells, which are of folate overexpression | Docetaxel                         | EE = 66.88 ± 0.67%                        | [82]     |
| Transferrin (Tf)-conjugated lipid-coated poly(l,l,lactide-co-glycolide) (PLGA) nanoparticles | PLGA                     | DOPE, TF-DOPE, MB-DOPE | SKBR-3 (breast cancer cell line) | 7α-(4'-aminophenylthio-1,4-androstadiene-3,17-dione (7α-APTADD)) | IC₅₀ = 0.00323 mg ml⁻¹ EE = 36.3 ± 3.4% | [71]     |
| cyclic RGD- modified lipid–polymer hybrid nanoparticles | PLGA                     | DSPE, DSPE-PEG-COOH | MDA-MB-435s and MCF-7 cell lines | 10-hydroxycamptothecin            | IC₅₀ = 0.77–1.21 nM EE = 65.93 ± 0.52% | [83]     |
| Curcumin loaded poly-hydroxyethylmethacrylate/stearic acid nanoparticles (C-PSA-NPs) | HEMA (2-hydroxyethyl methacrylate) | Stearic acid       | MCF-7 cell line | Curcumin                          | EE = 53.2%                               | [84]     |

IC₅₀ = 7 µg ml⁻¹
| Type of LPHNPs | Polymer | Lipids | Cancer model | Therapeutic agent | Encapsulation Efficiency (EE) and activity | Reference |
|---------------|---------|--------|--------------|------------------|------------------------------------------|-----------|
| lipid–polymer nanoparticles encapsulating curcumin (NANOCurc) | PLGA | DPPC and DSPE-PEG | MDA-MB-231 and HUVEC cell lines | Curcumin | Higher anticancer activities. Better apoptotic activity than free curcumin EE = 12% decrease by ~70% the number of adhering tumor cells | [85] |
| DLPC shell PLGA core NP formulation | PLGA | DLPC | MCF-7 cells | PTX | EE = 56.1 ± 0.07% | [86, 87] |
| lipid–polymer hybrid NPs | PLGA | Soybean lecithin and DSPE-PEG-COOH | MDA-MB231 (MB231) and HONE1 cell lines | DOX and 2′-deoxy-5-azacytidine | EE = n.d. improved sensitivity of tumor cells to DOX by inhibiting cell growth rate and inducing cell apoptosis | [88] |
| polymer–lipid hybrid nanoparticle (PLN) | HPESO (hydrolyzed poly-mer of epoxidized soybean oil) | stearic acid and tristearin | murine solid tumor model (by injecting EMT6 tumor cells into BALB/c mice) | DOX | EE = n.d. delay in tumor growth time up to 1.13 g compared to untreated control | [89] |
| Fucose anchored lipid polymer hybrid nanoparticles (Fu-LPHNPs) | PCL | DSPE-PEG-NH₂ | MDA-MB-231 and MCF-7 cell lines | Methotrexate (MTX) and aceclofenac (ACL) | EE = 83.1% (MTX) and 86.5% (ACL) only 12%–15% of cells remain viable after 72 h of treatment | [90] |
| fructose- tethered lipid-polymeric hybrid nanoparticles (F-BC-MTX-LPHNPs) | PLA | DSPE-PEG, SA (stearyl amine) | MCF-7 breast cancer cells | MTX and beta-carotene (BC) | EE = 71.3 ± 2.2% (MTX) and 62.7 ± 1.9% (BC) | [91] |
| PCLHNPs | Chitosan | Chondroitin sulphate, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N[amino(polyethylene glycol 2000)- Folic acid (DSPE-PEG-FA) | hepto-cellular carcinoma cell line SMMC-7721 | Sorafenib | IC₅₀ = 2.75 ± 0.25 μg ml⁻¹ EE = 100% | [64] |
| Type of LPHNPs | Polymer | Lipids | Cancer model | Therapeutic agent | Encapsulation Efficiency (EE) and activity | Reference |
|----------------|---------|--------|--------------|-------------------|------------------------------------------|-----------|
| CSPLHNPs       | PLGA    | DSPE-PEG-Tf, Lecithin | A549 cells | DOX               | IC\(_{50}\) = 0.78 \mu g ml\(^{-1}\) | [70]      |
|                |         |        |              |                   | EE = 92.48 ± 2.57% Effective inhibition of tumor spheroids |          |
| MLPHNPs        | PCL     | DSPE-PEG, Lecithin, HA | AML bearing mice | Gallic acid (GA) and DOX | EE = 88.9 ± 3.7% (DOX) and 85.6 ± 3.5% (GA) | [92]      |
|                |         |        |              |                   | 77.7% tumor inhibition                        |          |
| PCLNPs         | PLGA    | DOPA, D-\(\alpha\)-tocopherol polyethylene glycol 1000 suc-cinate (TPGS), AMD3100 | HCCs and HUVECs | Sorafenib | EE = 85% Reduced tumor infiltrated macrophages | [93]      |
| RGD-ss-PTX/   | PLGA    | Soybean lecithin, PEG-RGD | C3H mice with orthotopic HCA-1 tumors | PTX, Cisplatin (CDDP) | EE = 85.3 ± 3.3% (PTX) 82.7 ± 4.1% (CDDP) | [94]      |
| CDDP LPNs      |         |        |              |                   | IC\(_{50}\) = 26.7 \mu g ml\(^{-1}\) Significant tumor reduction from 1486 to 263 mm\(^{2}\) |          |
| RGD-L-P        | PLGA    | Lecithin/DSPE-PEG-OMe/DSPE-PEG-RGD | C6 cells orthotropic GBM model | Docetaxel | EE = 77.65 ± 0.57% | [95]      |
|                |         |        |              |                   | 2.69-4.13-fold increased anti-proliferative activity of DOPX |          |
| folate (FA) modified lipid-shell and polymer-core nanoparticles (FLPNPs) | PCL-PEG-PCL | Soybean, DSPE-PEG-FA | EMT6 cancer cells | PTX | EE = 91.16 ± 1.12% | [65]      |
|                |         |        |              |                   | 65.78% growth inhibition compared to nontargeted PTX-loaded LPNPs |          |
| adriamycin-loaded polymer–lipid hybrid nanoparticles conjugated with anti-EGF receptor antibody (PLNP-Mal-EGFR) | PLGA | lecithin, DSPE-PEG-mal-anti-EGFR Fab | EMT6 tumor-bearing BALB/c mice | ADR (adriamycin) | EE = n.d. | [96]      |
| Type of LPHNPs | Polymer | Lipids | Cancer model | Therapeutic agent | Encapsulation Efficiency (EE) and activity | Reference |
|---------------|---------|--------|--------------|------------------|------------------------------------------|-----------|
| PTX- and TL-coloaded LPNs (P/T-LPNs) | PLGA | Soybean, lecithin, DSPE-PEG-5000 | Balb/c nude mice bearing SMMC-7721 HCC xenograft | A549 and A549/PTX (PTX resistant) cells lung tumor xenografts | PTX, Triptolid (TL) | IC<sub>50</sub> = 0.587 μg m<sup>-1</sup> Reduced side population of HCC cells in vivo |
| paclitaxel and etoposide-loaded lipid-polymer hybrid nanoparticles (PE-LPN) | PLGA | Lipoid GmbH, DSPE-PEG | MG63 cancer cells | PTX, Etoposide (ETP) | EE = 88.7 ± 4.1% (PTX) 85.4 ± 4.8% (TL) | [97] |
| Folate-targeted lipid–polymer hybrid nanoparticles (FLPNPs) | PLGA | Lecithin, mPEG-s-s-C<sub>16</sub>, DSPE-PEG-FA | KB cells | DOX | EE = 82 ± 2% | [99] |
| Sal-LPNPs | PLGA-PEG-PLGA | Cholesterol, lecithin | 4T1 and PANC-1 cells | Salidroside (Sal) | EE = 65% Significantly higher anti-tumor activity than free Sal | [55] |
| Nanocells | PLGA | DSPE-PEG | B16F10 and Lewis lung carcinoma cells | DOX, combretastatin A4 | EE = n.d. Better therapeutic index with reduced toxicity | [74] |
| Hybrid nanocomplex formulations | Hyaluronic acid ceramide (HACE) | Egg PC, DSPE-PEG | A549 cells | Ginsenoside Rg3 (S)-Rg3 | EE = from 87% to 92% | [100] |
| | | | | | Showed decreased in vivo clearance of (S)-Rg3 and prolonged circulation in the blood stream | |
### Table 1. (Continued.)

| Type of LPHNPs            | Polymer       | Lipids                                  | Cancer model                        | Therapeutic agent      | Encapsulation Efficiency (EE) and activity | Reference |
|--------------------------|---------------|-----------------------------------------|-------------------------------------|------------------------|-------------------------------------------|-----------|
| ISL-iRGD NPs             | PLGA-COOH     | Lecithin/DSPe–PcG_{2000}–Mal            | MDA-MB-231; 81 MCF-7; 4T1 xenograft mice | Isoliquiritigenin      | EE = 90.8% ± 1.5%                          | [101]     |
| Lipid/rPAA-Chol polymer hybrid nanoparticles | Polyamidoamine grafted cholesterol DOTAP, DOPE, Cholesterol, DSPE-PEG | MCF-7 cell line                     | Anti-EGFR siRNA         | EE = n.d. Anticancer activity against breast cancer (MCF-7 cells) | [102]     |

n.d. = not defined

Greater cytotoxicity and apoptosis against different types of breast cancer cells and even greater efficiency of tumor growth inhibition in mouse models of breast cancer with 4T1.
administration of the therapeutic agent are required in cancer, hence the ability and versatility to be designed as nanosystems of co-delivery opens a new path to the development of personalized and non-invasive nanotherapies with the potential to significantly improve patients’ quality of life. Further explorations in the near future will lead to more exciting developments in the application of LPHNPs as nano-platforms for the targeted and safe transport of anticancer therapies.

Acknowledgments

FP, GG and SL are grateful to the Tecnopolo per la medicina di precisione (TecnoMed Puglia)—Regione Puglia: DGR no. 2117 del 21/11/2018, CUP: B84118000540002 and Tecnopolo di Nanotecnostalia and Fotonica per la medicina di precisione (TECNOMED)—FISR/MIUR-CNR: delibera CIPE no. 3449 del 7-08-2017, CUP: B83B1700010001.

Data availability statement

No new data were created or analysed in this study.

ORCID iDs

Giuseppe Gigli https://orcid.org/0000-0002-2583-5747
Stefano Leporatti https://orcid.org/0000-0001-5912-7565

References

[1] Martinelli C, Pucci C and Ciofani G 2019 Nanostructured carriers as innovative tools for cancer diagnosis and therapy APL Bioeng. 3 011502
[2] Wang Y et al 2020 Current status of in vivo bioanalysis of nano drug delivery systems Journal of Pharmaceutical Analysis. (https://doi.org/10.1016/j.jpha.2020.05.002)
[3] Ghitman J et al 2020 Review of hybrid PLGA nanoparticles: future of smart drug delivery and theranostics medicine Mater. Des. 108805
[4] Kumar R et al 2020 Core–shell nanosstructures: perspectives towards drug delivery application J. Mater. Chem. B 8 8992–9027
[5] Mitchell M J, Billingsley M M, Haley R M, Wechsler M E, Peppas N A and Langer R 2020 Engineering precision nanoparticles for drug delivery Nat. Rev. Drug Discovery 20 101–24
[6] Rivas C J et al 2017 Nanoprecipitation process: From encapsulation to drug delivery Int. J. Pharm. 532 66–81
[7] Ulbrich K et al 2016 Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies Chem. Rev. 116 5338–433
[8] Rao S and Prestidge C A 2016 Polymer–lipid hybrid systems: merging the benefits of polymeric and lipid-based nanocarriers to improve oral drug delivery Expert Opinion on Drug Delivery. 13 691–707
[9] Tahir N et al 2019 Lipid polymer hybrid nanoparticles: a novel approach for drug delivery In Role of Novel Drug Delivery Vehicles in Nanobiomedicine (IntechOpen) (https://www.intechopen.com/books/role-of-novel-drug-delivery-vehicles-in-nanobiomedicine/lipid-polymer-hybrid-nanoparticles-a-novel-approach-for-drug-delivery)
[10] Shi J et al 2014 Hybrid lipid–polymer nanoparticles for sustained siRNA delivery and gene silencing Nanomed. Nanotechnol. Biol. Med. 10 697–900
[11] Mandal B et al 2013 Core–shell type lipid–polymer hybrid nanoparticles as a drug delivery platform Nanomed. Nanotechnol. Biol. Med. 9 474–91
[12] Pandian A, Jeyasubramanian K and Sureshkumar M 2019 Chitosan nanocarrier system for tumour targeting International Journal of Advance Research, Ideas and Innovations in Technology
[13] Scopel R et al 2020 Lipid-polymer hybrid nanoparticles as a targeted drug delivery system for melanoma treatment International Journal of Polymeric Materials and Polymeric Biomaterials. 1–12
[14] Thenvont J et al 2008 Effect of the polymer nature on the structural organization of lipid/polymer particle assemblies J. Phys. Chem. B 112 13812–22
[15] Chowdhury A et al 2017 Nanotechnology and nanocarrier–based approaches on treatment of degenerative diseases International nano letters. 7 91–122
[16] Hadinoto K et al 2013 Lipid–polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review Eur. J. Pharm. Biopharm. 85 427–43
[17] Le Meins J F, Schatz C, Lecommandoux S and Sandre O 2013 Hybrid polymer/lipid vesicles: state of the art and future perspectives Mater. Today 16 397–402
[18] Rozenberg B A and Tenne R 2008 Polymer–assisted fabrication of nanoparticles and nanocomposites Prog. Polym. Sci. 33 40–112
[19] Ghosh Chaudhuri R and Parija S 2012 Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications Chem. Rev. 112 2373–433
[20] Bose R et al 2016 Lipid-based surface engineering of PLGA nanoparticles for drug and gene delivery applications Biomater. Res. 20 34
[21] Lee S M and Nguyen S T 2013 Smart nanoscale drug delivery platforms from stimuli-responsive polymers and liposomes Macromolecules 46 9169–80
[22] Wu X Y 2016 Strategies for optimizing polymer–lipid hybrid nanoparticle–mediated drug delivery Expert Opin Drug Deliv 13 609–12
[23] Beja M et al 2012 Colloidal systems for drug delivery: from design to therapy Trends Biotechnol. 30 485–96
[24] Chang W K et al 2011 The comparison of protein-entrapped liposomes and lipoparticles: preparation, characterization, and efficacy of cellular uptake Int. J. Nanomed. 6 2403
[25] Wang A Z et al 2010 ChemoRad nanoparticles: a novel multifunctional nanoparticle platform for targeted delivery of concurrent chemoradiation Nanomedicine 5 361–8
[26] Hatziantoniou S and Demetzos C 2008 Lipids of membranes: chemistry, biological role and applications as drug carriers Stud. Nat. Prod. Chem. 34 173–202
[27] Li Y et al 2008 Molecular interactions, internal structure and drug release kinetics of rationally developed polymer–lipid hybrid nanoparticles J. Controlled Release 128 60–70
[28] Oliveira M F et al 2013 Strategies to target tumors using nanodevices systems based on biodegradable polymers, aspects of intellectual property, and market Journal of chemical biology. 67–23
[29] Tahir N et al 2017 Development and optimization of metothrexate-loaded lipid–polymer hybrid nanoparticles for controlled drug delivery applications Int. J. Pharm. 533 156–68
[30] Zacheo A et al 2020 Lipid–based nanoveicles for simultaneous intracellular delivery of hydrophilic, hydrophobic, and amphiphilic species Front. Bioeng. Biotechnol. 8 690
[31] Zhang L et al 2008 Self-assembled lipid—polymer hybrid nanoparticles: a robust drug delivery platform ACS nano. 2 1696–702
[32] Soares D C F et al 2020 Polymer–hybrid nanoparticles: current advances in biomedical applications Biom. Pharmacoother. 131 110695
[33] Casalini T et al 2019 A perspective on polyacetic acid-based polymers use for nanoparticles synthesis and applications Front. Bioeng. Biotechnol. 7 259
[34] Jose C et al 2018 Polymeric lipid hybrid nanoparticles: properties and therapeutic applications Crit. Rev. Ther. Drug Carrier Syst. 35
[35] Mukherjee A et al 2019 Lipid–polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives Int. J. Nanomed. 14 1957
[36] Bou S et al 2020 Lipid-core/polymer-shell hybrid nanoparticles: synthesis and characterization by fluorescence labeling and electrophoresis Soft Matter. 16 4173–81
[37] Brodskij E et al 2020 Polymer–lipid hybrid vesicles and their interaction with HepG2 Cells Small. 1906493
[38] Thevent J et al 2007 Steric stabilization of lipid/polymer particle assemblies by poly(ethylene glycol)-lipids Biomacromolecules. 8 3651–60
[39] Jing H et al 2020 Formation and properties of self-assembled nanoparticle-supported lipid bilayer probe through molecular dynamics simulations Langmuir 36 5524–33
[40] Alessandrimi A and Facci P 2014 Phase transitions in supported lipid bilayers studied by AFM Soft matter. 10 7145–64
[41] Fang R H T et al 2010 Quick synthesis of lipid—polymer hybrid nanoparticles with low polydispersity using a single-step sonication method Langmuir 26 16938–62
[42] Ghorbani-amini F et al 2020 Nanohybrid carriers: the yin–yang equilibrium between natural and synthetic in biomedicine Biomater. Sci. 8 3237–47
[43] Qian S, Sharma V K and Clifton L A 2020 Understanding the Structure and Dynamics of Complex Biomembrane Interactions by Neutron Scattering Techniques Langmuir 36 15189–211
[44] Valino A D et al 2019 Advances in 3D printing of thermoplastic polymer composites and nanocomposites Prog. Polym. Sci. 98 101162
[45] Mandal B 2015 Design, development and evaluation of erlotinib–loaded hybrid nanoparticles for targeted delivery to nonsmall cell lung cancer. Theses and Dissertations (ETD) 166
[46] Thun M J et al 2010 The global burden of cancer: priorities for prevention Carcinogenesis. 31 10–10
[47] ud Din F et al 2017 Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors Int. J. Nanomed. 12 7291
[48] Revia R A and Zhang M 2016 Magneti nanoparticles for cancer diagnosis, treatment, and treatment monitoring: recent advances Mater. Today 19 157–68
[49] Chiiverse V T et al 2020 Nanotechnology-based biopolymeric oral delivery platforms for advanced cancer treatment Cancers. 12 522
[50] Palange A L et al 2014 Lipid–polymer nanoparticles encapsulating curcumin for modulating the vascular deposition of breast cancer cells Nanomed. Nanotechnol. Biol. Med. 10 e991–1002
[51] Chakravarty M and Vora A 2020 Nanotechnology-based antiviral therapeutics Drug Deliv. Transl. Res. 1–40
[52] Zhang M, Liu E, Cui Y and Huang Y 2017 Nanotechnology-based combination therapy for overcoming multidrug-resistant cancer Cancer Biol. Med. 14 212
[53] Das S et al 2020 Stimuli-responsive polymeric nanocarriers for drug delivery, imaging, and theragnosis Polymers. 12 1397
[54] Tahir N et al 2020 Lipid-polymer hybrid nanoparticles for controlled delivery of hydrophilic and lipophilic doxorubicin for breast cancer therapy [Erratum] Int. J. Nanomed. 15 839–40
[55] Fang D L et al 2014 Development of lipid-shell and polymer core nanoparticles with water-soluble salidroside for anti-cancer therapy Int. J. Mol. Sci. 15 5373–88
[56] Yingchoncharoen P et al 2016 Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come Pharmacological reviews. 68 701–87
[57] Navya P N et al 2019 Current trends and challenges in cancer management and therapy using designer nanomaterials Nano Convergence. 6 23
[58] Yang Z et al 2015 Dual-ligand modified polymer–lipid hybrid nanoparticles for docetaxel targeting delivery to Her2/neu overexpressed human breast cancer cells J. Biomed. Nanotechnol. 11 1401–17
[59] Singh V K, Saini A and Chandra R 2017 The implications and future perspectives of nanomedicine for cancer stem cell targeted therapies Front Mol. Hoscti. 2017 4 52
[60] Chaudhary Z et al 2018 Lipid polymer hybrid carrier systems for cancer targeting: A review International journal of polymeric materials and polymeric biomaterials. 67 86–100
[61] Lee R J and Low P S 1994 Delivery of liposomes into cultured KB cells via folate receptor-mediated endocytosis J. Biol. Chem. 269 3198–204
[62] Mohanty A et al 2020 Utilization of polymer–lipid hybrid nanoparticles for targeted anti-cancer therapy Molecules. 25 4377
[63] Mohanty A, Uthaman S and Park I K 2020 Utilization of polymer–lipid hybrid nanoparticles for targeted anti-cancer therapy Molecules. 25 4377
[64] Tang S and Li Y 2019 Sorafenib–loaded ligand-functionalized polymer–lipid hybrid nanoparticles for enhanced therapeutic effect against liver cancer J. Nanosci. Nanotechnol. 19 6866–71
[65] Zhang L et al 2015 Folate-modified lipid–polymer hybrid nanoparticles for targeted paclitaxel delivery Int. J. Nanomed. 10 2101
Zheng Y et al 2010 Transferin-conjugated liposomal PLGA nanoparticles for targeted delivery of aromatase inhibitor 7a-APTADD to breast cancer cells Int. J. Pharm. 390 234–41
Aslan B, Ozpolat B, Sood A K and Lopez-Berestein G 2013 Nanotechnology in cancer therapy J. Drug Targeting 21 904–13
Pourjavadi A, Asgari S, Hosseini S H and Akhlaghi M 2018 Codelivery of hydrophobic and hydrophilic drugs by graphene-decorated magnetic dendrimers Langmuir 34 15304–18
Sengupta S et al 2005 Temporal targeting of tumour cells and neovascularisation with a nanoscale delivery system Nature 436 568–72
Dong F et al 2016 Doxorubicin-loaded biodegradable self-assemble zein nanoparticle and its anti-cancer effect: Preparation, in vitro evaluation, and cellular uptake Colloids Surf., B 140 324–31
Jiang T, Mo R, Bellotti A, Zhou J and Gu Z 2014 Gel–liposome-mediated co-delivery of anticancer membrane-associated proteins and small-molecule drugs for enhanced therapeutic efficacy Adv. Funct. Mater. 24 2295–304
Yin Y et al 2020 Nanogel: a versatile nano-delivery system for biomedical applications Pharmaceutics. 12 290
Gidwani B and Vyas A 2015 A comprehensive review on cycloextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs BioMed Res. Int. 2015 198268
Hasan W et al 2012 Delivery of multiple siRNAs using lipid-coated PLGA nanoparticles for treatment of prostate cancer Nano Lett. 12 287–92
Wong H L et al 2006 Simultaneous delivery of doxorubicin and GG918 (Elacridar) by new polymer–lipid hybrid nanoparticles (PLN) for enhanced treatment of multidrug-resistant breast cancer J. Controlled Release 116 275–84
Zhao P et al 2012 Paclitaxel loaded folic acid targeted nanoparticles of mixed lipid-shell and polymer-core: in vitro and in vivo evaluation Eur. J. Pharm. Biopharm. 81 248–56
Liu Y et al 2010 Folic acid conjugated nanoparticles of mixed lipid monolayer shell and biodegradable polymer core for targeted delivery of Docetaxel Biomaterials 31 330–8
Yang Z et al 2013 Targeted delivery of 10-hydroxycamptothecin to human breast cancers by cyclic RGD-modified lipid–polymer hybrid nanoparticles Biomater. 80 253012
Kumar S S D et al 2014 Synthesis and characterization of curcumin loaded polymer/lipid based nanoparticles and evaluation of their antitumor effects on MCF-7 Cells Biochimica et Biophysica Acta (BBA)-General Subjects. 1840 1913–22
Palange A L et al 2014 Lipid–polymer nanoparticles encapsulating curcumin for modulating the vascular deposition of breast cancer cells Nanomed. Nanotechnol. Biol. Med. 10 1691–1002
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. 395 243–50
Dave Y, Tak K, Sohgaura A, Gupta A, Sadhu V and Reddy K R 2019 Lipid-polymer hybrid nanoparticles: Synthesis strategies and biomedical applications J. Microchim. Methods 160 130–42
Su X et al 2013 Lipid–polymer nanoparticles encapsulating doxorubicin and 2′-deoxy-5–azacytidine enhance the sensitivity of cancer cells to chemical therapeutics Mol. Pharmaceutics 10 1901–9
Wong H L et al 2007 In vivo evaluation of a new nanolipid-polymer hybrid nanoparticle (PLN) formulation of doxorubicin in a murine solid tumor model Eur. J. Pharm. Biopharm. 65 300–8
Garg N K et al 2017 Functionalized lipid–polymer hybrid nanoparticles mediated codelivery of methotrexate and a cetuximab: a synergistic effect in breast cancer with improved pharmacokinetics attributes Mol. Pharmaceutica 14 1883–97
Jain A et al 2017 Methotrexate and beta-carotene loaded lipid-polymer hybrid nanoparticles: a preclinical study for breast cancer Nanomedicine 12 1851–7
Shao Y et al 2019 In vitro and in vivo effect of hyaluronic acid modified, doxorubicin and gallic acid co-delivered lipid-polymeric hybrid nano-system for leukemia therapy Drug design, development and therapy, 13 2043
Gao D Y et al 2015 CXCR4-targeted lipid-coated PLGA nanoparticles deliver sorafenib and overcome acquired drug resistance in liver cancer Biomaterials 67 194–203
Wang G et al 2018 RGD peptide-modified, paclitaxel prodruk-based, dual-drugs loaded, and redox-sensitive lipid-polymer nanoparticles for the enhanced lung cancer therapy Biomater. 106 275–84
Shi K et al 2015 Arginine-glycine-aspartic acid-modified lipid-polymer hybrid nanoparticles for docetaxel delivery in glioblastoma multiforme J. Biomed. Nanotechnol. 11 382–91
Gao J et al 2014 Polymer–lipid hybrid nanoparticles conjugated with anti-EGF receptor antibody for targeted drug delivery to hepatocellular carcinoma Nanomedicine 9 279–93
Liu J et al 2018 Synergistic combination therapy of lung cancer using paclitaxel-and triptolide-coloaded lipid–polymer hybrid nanoparticles Drug design, development and therapy. 12 3199
Duan R et al 2017 Polymer–lipid hybrid nanoparticles–based paclitaxel and etoposide combinations for the synergistic anticancer efficacy in osteosarcoma Colloids Surf., B 159 880–7
Wu B et al 2015 Folate–containing reduction-sensitive lipid–polymer hybrid nanoparticles for targeted delivery of doxorubicin Biomater. Sci. 3 655–64
Lee J Y et al 2014 Nanocomplexes based on amphiphilic hyaluronic acid derivative and polyethylene glycol–lipid for ginsenoside Rg3 delivery J. Pharm. Sci. 103 3254–62
Gao F et al 2017 iRGD-modified lipid–polymer hybrid nanoparticles loaded with isoquiritigenin to enhance anti-breast cancer effect and tumor-targeting ability Int. J. Nanomed. 12 4147
Gao L Y et al 2014 core–shell type lipid/iPAA-Chol polymer hybrid nanoparticles for in vivo siRNA delivery Biomaterials 35 2066–78
Guo P et al 2018 Nanoparticle elasticity directs tumor uptake Nat. Commun. 9 1–9