Chapter

Lipid Polymer Hybrid Nanoparticles: A Novel Approach for Drug Delivery

Nayab Tahir, Muhammad Tahir Haseeb, Asadullah Madni, Farzana Parveen, Muhammad Muzamil Khan, Safiullah Khan, Nasrullah Jan and Arshad Khan

Abstract

Applications of nanotechnology and material sciences emerge in the development of various novel drug delivery systems that have been proven as promising clinically. Among these, liposomes, noisome, polymeric carriers and lipid-based delivery system were extensively explored and enter into clinical trials and clinical applications. However, each system has its own pros and cons in term of different physicochemical, pharmacokinetics and therapeutics aspects. Lipid-polymer hybrid carriers merge the potential benefit of these structural components and can be prepared by different approaches to improve the therapeutic outcomes. In this chapter, we provide the useful insight about the lipid-polymer hybrid nanoparticles (LPHNPs) that can be prepared by using the different structural components including the synthetic and natural polymers and lipids. Among these, we also explain the various methods to prepare the LPHNPs with various desired characteristics. Finally, the various therapeutic and clinical applications have been presented briefly.

Keywords: lipid-polymer hybrid, nanoparticles, drug delivery, targeted release

1. Introduction

The advances in the field of nanotechnology and the material sciences have been open a new horizon for the development of various drug delivery systems (DDS) for the effective and efficient delivery of therapeutic and diagnostic agents [1]. During last few decades, many new DDS have been explored in term of their structural components and medical applications. These systems enhance the application of novel approaches toward the translational medicines by improving the preparation techniques and combing the natural and synthetic polymers and materials [2]. Formulation of these DDS helps to encapsulate a variety of chemotherapeutic agents, vaccines, proteins, antibodies, nucleic acids and diagnostic agents [3]. These agents might be encapsulated inside the core of NPs or might be adsorbed on the surface individually or in combination. These formulations enhance the pharmacokinetic and pharmacodynamics properties of the NPs by increasing the solubility, dispersion, permeability and overall bioavailability of the formulation. The release of the drug might be controlled passively or actively through various stimuli such as

temperature, and pH [4]. All these factors results in the higher concentration of the entrapped drug that reached the systemic circulation that helps to attain the mean effective concentration without producing any toxic effects [5].

Among these DDS, polymeric nanoparticles (NPs), liposomes, niosomes, dendrimers and porous silicon NPs have been extensively employed in the pharmaceutical delivery. Polymeric NPs have versatility in term of their chemical composition and applications. Large type of chemical material based NPs were formulated such as polymeric NPs, Porous silicon NPs, Carbon nanotubes, Graphene NPs and quantum dot. All these DDS have their own pros and cons in term of drug loading, encapsulation, release and applicability [6]. Furthermore, all these DDS were decorated with different chemical reagents and ligands to impart the desired characteristics through modifying the physicochemical properties of the NPs including (1) enhanced means residence time and improved stability, (2) external stimuli driven drug release, (3) controlled and targeted delivery of various chemotherapeutics agents and (4) administration of various theranostic agents [7].

These nanocarriers have been explored due to their extensive potential applications and excellent in vitro performances, but these NPs still have poor in vivo properties in term of their poor solubility in various body fluids, rapid uptake and excretion by the body defense system, poor penetration among the various biological membranes and body tissues, uncontrolled fluctuations in the plasma levels of the active therapeutic components and dose related toxicity issues [8, 9].

The most important domains of these nanocarriers include the polymeric DDS and the lipid based vesicular systems. The polymeric DDS provide the variety in term of their structural materials and chemical composition [6]. Different polymers include from the synthetic and natural sources have been employed for the medical applications. These DDS include the polymeric NPs, mesoporous silicon NPs, metal coated NPs, inorganic NPs, dendrimers and the carbon nanotubes [10]. Vesicular DDS include the liposome and noisome. These were defined as the single and the multilayer lipid vesicles while the niosomes were made up of nonionic surfactants instead of the phospholipids [11]. These novel systems provide excellent compatibility with other ingredients, higher and simultaneous encapsulation of the hydrophilic and lyophilic therapeutic moieties and due to lipid nature it provide better pharmacokinetic profiles that might lead to improved therapeutic response of the encapsulated drug. But still this system might suffer from some draw back in term of drug leakage, stability problems and difficulty in the scale up of the process [12].

The above-mentioned problems associated with these DDS including liposomes and polymeric nanoparticles can be overcome by merging their structural components by formulating the lipid-polymer hybrid nanoparticles (LPHNPs). These NPs combine the potential benefits and reduce the different drawbacks of all the individual structural components [13]. These hybrid particles might be produced in different morphologies including the core shell and matrix type LPHNPs. The core or the central material may be encapsulated in single and/or multiple layers of the lipid on the polymeric core materials that also provide the site for the surface modification with different targeting moieties and ligands that help to induce the desired characteristics in the DDS [14].

In this chapter, the different structural components such as lipids and polymers were explained along with the different formulation methods to prepare the LPHNPs along with various process parameters and their pros and cons.

2. Structural components and their arrangement mechanism

The core and the shell materials might include different polymeric materials, oils, metal oxides, organic and inorganic compound from the natural and synthetic

sources that successfully employed for the fabrication of the NPs. These systems have been composed of following major layers and components given as fellows

i. The inner most layer consist of different polymers, organic and inorganic materials that act as a core material. These core materials might be coated with other agents or may form a matrix structure that then functionalized by using the different targeting moieties. These cores of the NPs might encapsulate the hydrophilic or hydrophobic drugs [15].

ii. The second layer of these hybrid NPs is fabricated with the natural or derived lipid that impart the desired pharmacokinetic properties to the DDS. This layer encapsulates the central polymeric core and enhances the compatibility with the biological system. While it also act as a permeability control barrier that limit the release of loaded therapeutic agent as a function of water penetration [16].

iii. The third layer is composed of either lipid or polymer-conjugate that help in the functionalization or surface decoration of the NPs to provide the desired therapeutic of pharmacokinetic effects in term of target specific release and improved retention time of the NPs in the biological system [17].

The mechanism of the arrangement in different layers and their compilation with each other might need further investigation. However, different mechanisms

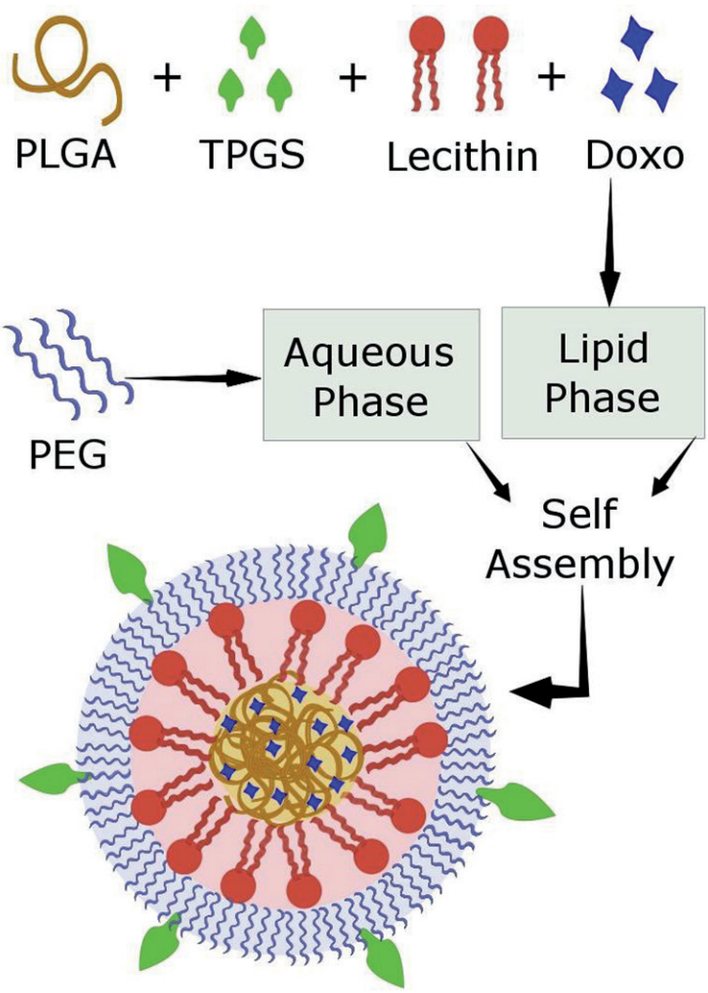

Figure 1.
Schematic diagram of the lipid-polymer hybrid nanoparticles.

explored indicate that the arrangement and fusion process are based on the method of preparation (that were discussed in the next section). In the two-step conventional method, the layer might be due to formation of lipid by layer that get adhere to the core particle that followed by the integration due to hydrophilic and hydrophobic interaction among the lipid and polymer component. However, in the single-step method, the most investigated and revealed mechanism is the precipitation of the lipid component on the polymeric core material. Some newer techniques might also involve the self-assembling of these structural components (**Figure 1**) [18].

3. Method of preparation

Various formulation methods have been designed and employed for the preparation of LPHNPs based on the chemical and physical nature of the structural components and the desired therapeutic purpose or outcome. These hybrid DDS include the lipid-polymer, lipid metal, polymer-inorganic hybrid, metal (Gold, Silver or Iron) along with polymer hybrid NPs have investigated and employed for the clinical use. Conventionally, two different approaches have been investigated including the two-step and single-step processes. First approach employed the mixing of the inner core and the outer layers to prepare the LPHNPs. While the single-step approach the lipid and polymer that are assembled using the different mechanisms to form the LPHNPs that overcome the drawback of individual components.

3.1 Two-step conventional method

Two-step method was the most primitive and frequent method applied for the preparation of different hybrid nanoparticles and other DDS. In the method, the different layers comprise of structurally, different components were separately fabricated and then co incubated to make a complete particle by using the various approaches including the adsorption, self-assembling and encapsulation. The core and shell morphology might be obtained and the various hybrid nanoparticles were obtained by using the sonication [19], solvent emulsification, solvent evaporation [13], nanoprecipitation [20], extrusion, high speed homogenizers and other techniques. However, the selection of the method is based on the physicochemical properties of the loaded drug, size of the core particle and the desired properties that you want to introduce in the NP formulation [18]. For example, the single-step method has been chosen when the encapsulating materials are miscible with the coating substance and soluble in the organic solvent [21].

This method involves multiple preparatory steps to prepare the polymeric core materials and then the lipid vesicles by the different techniques. The polymeric core material might be prepared by dissolving the polymer in a suitable solvent and then precipitated into some nonsolvent phase. Finally, the both components are co-incubated and mixed under gentle stirring for certain time period to allow them to get assembled into lipid-polymer hybrid particles [22, 23]. The mixing may be carried out by vortexing, thin film hydration, probe sonication or extrusion processes so that the final LPHNPs were obtained. These processes actually provide the energy for the mixing, layering or adsorption of the outer coating material on the polymeric core material that might be strengthen by the electrostatic forces among these structural components.

3.2 Modified two-step method

Different modifications have been suggested in the conventional two-step process for the fabrication of the LPHNPs. These modifications might include the use spray drying and lithographic molding along with the freeze drying [24]. The inner central core of the NPs have been prepared with the process that further suspended or dispersed in any suitable organic solvent containing the different structural components of the LPHNPs [2]. Different studies indicate the formulation of LPHNPs loaded with various antibiotics agents including levofloxacin, ciprofloxacin and isoniazid in the form of freeze dried powders for the inhalation therapy that were entrapped in the mono or multiple layers of the lipid shell. The coating of the lipid might provide the core shell morphology to the NPs. This modification in the preparation of the NPs added advantage in term of better inhalation efficiency and greater control on the overall average particle size of the LPHNPs relative to the conventional method [25]. The nanoparticles and hybrid microfiber fabrication are the some other examples that utilized the polyglutamic acid, poly lysine and various grade of PLG and PLA using the freeze-drying method [26, 27].

3.3 Single-step preparation method

The poor entrapment and easy leakage of the drug from the polymeric core of the LPHNPs prepared by the conventional two-step methods urged the development of some newer methods that overcome these shortcomings and enhance the therapeutic efficiency of the prepared formulation [14, 28]. The development of single-step method provides the way to control the particle size, PDI, uniformity of the structural components. It also overcomes the variability in different batches and other properties of the LPHNPs in term of their physicochemical properties and stability. The method involves the single preparatory step that considers the mixing of two different phases containing the lipid and polymer in each of the given phase. The mixing process followed by the self-assembling of the structural components that either make the matrix or core shell morphology [29].

Various techniques in the single-step preparation method might include the single or double emulsification method, sonication technique, nanoprecipitation, solvent evaporation method and solvent diffusion method.

4. Biomedical applications

LPNs have been prepared for efficient encapsulation and delivery of the wide range of therapeutic agents either alone or in combinations. LPNs have wide range of applications in cancer therapy and delivery of protein based therapeutic agents, i.e., small interfering RNA, nucleic acid and genes delivery etc. Additionally, LPNs can be used for oral drug delivery of many drugs [46]. LPN has wide range of applications in gene and DNA delivery, vaccines and diagnostic imaging agents as shown in **Figure 2** [2].

4.1 Cancer therapy

Doxorubicin loaded polymer-lipid hybrid nanoparticles (Dox-PLN) were designed and injected intratumorally in mice. At a dose of 0.1 and 0.2 mg, 70 and 100% tumor growth delay was observed, respectively. Dox-PLN treated mice have not shown any sign of toxicity and only 2 mice out of 15 exhibited transient fur

Type of hybrid nanoparticles	Structural components	Physicochemical properties			Biological properties	Application	Reference
		Size (nm)	Zeta potential	Entrapment efficiency			
Lipid-polymer hybrid	Paclitaxel PLGA Soybean lecithin DSPE-PEG (conjugated with folic acid)	186.9 ± 8.52	−29.5 ± 2.0	81.34 ± 3.41	$T_{1/2}$ 18.08 AUC $_{0-\infty}$ 109.21 MRT 30.06	Brain targeting in glioblastoma multiform	[1]
Lipid-polymer hybrid	Melatonin PLA DDAB CTAB	180–218	+15.4 to −36.1	90.35	N/A	Ophthalmic delivery	[2]
	PLGA DOX in polymeric core and Sorafenib in lipidic core β-cyclodextrin Dipalmitoyl glycerol phophocholine (DPPC) Distearoyl glycerol phosphoethanolamine (DSPE) PEG	85.1 PDI 0.103			Sustained release for 21 days	Colon cancer	[4]
Lipid-polymer hybrid	Gemcitabine, hypoxia-inducible factor 1α, ε-polylysine co-polymer, PLGA, mPEG, Lecithin, double emulsion method and ultrasound assisted self-assembly	141.8	−34	42		Pancreatic cancer	[7]
Lipid-polymer hybrid	Budesonide, PLGA, dioleoyltrimethylammonium propane (DOTAP), double emulsion solvent evaporation method	PDI 0.09–0.14, 136–169 nm	−3 to 54	20–36 and 27–80		Chronic obstructive pulmonary disease (COPD)	[13]

Type of hybrid nanoparticles	Structural components	Physicochemical properties			Biological properties	Application	Reference
		Size (nm)	Zeta potential	Entrapment efficiency			
Lipid-polymer hybrid	Dextran, bovine serum albumin (BSA), astaxanthin, prepared through organic solvent free homogenization and sonication technique, Precirol® ATO 5 (glyceryl palmitostearate)	139–180 nm, PDI 0.199		70%	40% release in SGF and 50% in SIF, Diffusion based released	Antioxidant activity and sustained release	[14]
Lipid-polymer hybrid	Erlotinib, single-step sonication method, polycaprolactone (PCL), hydrogenated soy phosphatidylcholine, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol)-2000 (DSPE-PEG2000)	159.6–173 nm, PDI 0.09–0.14	−1.22 to −47.3	18.1–66.4%	50% in first 3 h, 100% in 24 h	Anticancer, lung cancer	[19]
	PLGA, paclitaxel, PVA	200–300 nm		34.8 ± 1.6 to 62.6 ± 7.9%	Fast release in first 3 days (60%) followed by slow first order release for 21 days (cumulative release 72%)	Anticancer	[22]
Lipid-polymer hybrid	Doxorubicin, stearic acid, tristearin, HPESO (hydrolyzed polymer of epoxidized soybean oil), Pluronic-F68	290 nm		5%		Anticancer	[30]
Lipid vesicles	Carboxymethyl chitosan, paclitaxel, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DPPC)	200–300 nm		85.2 ± 3.3 and 83.8 ± 7.5%	Sustained release formulation	Anticancer	[31]

Type of hybrid nanoparticles	Structural components	Physicochemical properties			Biological properties	Application	Reference
		Size (nm)	Zeta potential	Entrapment efficiency			
Lipid-polymer hybrid	Doxorubicin, epoxidized soyabean oil, Pluronic F68	80–350 nm	−19.7 ± 0.65	60–80%	50% drug released in first few hours and additional 10–20% in 2 weeks	Anticancer (breast cancer)	[32]
Lipid-polymer hybrid	Mitoxantrone hydrochloride, dextran sulfate, Cremophor (polyethoxylated castor oil), emulsification-ultrasonication method	130.3 ± 4.7 to 136.7 ± 8.6	−19.9 ± 1.4 to −31.6 ± 0.8	97.4%	Sustained 86.9% at 72 h, C_{max} (ng/mL) 421.6 ± 24.6, $t_{1/2}$ (h) 8.49 ± 1.23, AUC_{0-t} (ng/mL.h) 690.9 ± 83.5, $AUC_{0-\infty}$ (ng/mL.h) 722.6 ± 94.1	Anticancer	[33]
	Sorafenib, PLGA, Single-step nanoprecipitation, D-α-tocopherol polyethylene glycol 1000 succinate, TPGS, dioleoylphosphatidic acid (DOPA)	150–200 nm (average 175.25 ± 1.82 nm), PDI 0.148 ± 0.004	−19 to −55	85%		Highly vascular hepatocellular carcinoma	[34]
	Mitomycin C, PLA, Soybean phosphatidylcholine (SPC), PEG, folate	215.6 ± 5.1 nm, PDI 0.143	−25.88 ± 2.39	95%		Anticancer	[35]
Lipid-polymer hybrid	Paclitaxel, PLGA, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG-2000), folic acid, soybean lecithin			74.93 ± 3.93 to 81.34 ± 3.41%	87.2 ± 4.28 to 96.9 ± 4.93% in 5 days	Anticancer	[36]
Lipid-polymer hybrid	Nanoprecipitation process, PLGA, PEG, docetaxel	25 nm	−10 to −50	20%	50% in first 12 h and remaining in 72 h	Anticancer	[37]

Type of hybrid nanoparticles	Structural components	Physicochemical properties			Biological properties	Application	Reference
		Size (nm)	Zeta potential	Entrapment efficiency			
	PLGA, Curcumin, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[succinyl(polyethylene glycol)-2000] (DSPE-PEG), emulsion/solvent evaporation technique	150 nm, 171.6 ± 8.2 nm in DI water and 177.3 ± 6.2 nm in PBS, PDI of 0.174 ± 0.023 and 0.159 ± 0.026		12%	30% in first 5 h	Anticancer	[38]
Lipid-polymer hybrid	Poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE), emulsifying-solvent evaporation method, egg yolk phosphatidylcholine, plasmid DNA	128 nm	+35.2			Nonviral gene delivery	[39]
	Poly-(β-amino ester) (PBAE), double emulsion/solvent evaporation, PLGA, Phospholipids	230 ± 40 to 300 ± 50, PDI 0.100 ± 0.05 to 0.182 ± 0.10	32 ± 8 to 42 ± 8			mRNA based vaccine	[40]
Lipid-polymer hybrid	siRNA, PLGA, PEG, modified double-emulsion solvent evaporation technique, lecithin	225 ± 8 nm	−10 to 0 mV	78–82%	50% of siRNA released in 12–20 h		[41]
Lipid-polymer hybrid	PLGA, siRNA, Particle Replication in Nonwetting Templates (PRINT) process	198 ± 3.45 to 207 ± 4.461, PDI 0.045 ± 0.009 to 0.092 ± 0.005	−3.45 ± 1.9 to 5.29 ± 1.5	32–46%		Prostate cancer	[42]
Lipid-polymer hybrid	Norfloxacin, PLA, emulsification solvent evaporation method, PVA, carbopol K-940	178.6 ± 3.7 nm to 220.8 ± 0.66 nm, PDI 0.206 ± 0.36 to 0.383 ± 0.66	+23.4 ± 1.5 mV to +41.5 ± 3.4 mV	53.29 ± 0.30 to 72.34 ± 0.23	89.72% drug released in 24 h	Topical antibiotic	[43]

Type of hybrid nanoparticles	Structural components	Physicochemical properties			Biological properties	Application	Reference
		Size (nm)	Zeta potential	Entrapment efficiency			
Lipid-polymer hybrid	Lidocaine, Chitosan, Cholesterol, cetyltrimethyl ammonium bromide, 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), hyaluronic acid	71.2 ± 2.8 to 145.6 ± 5.9 nm, PDI 0.09 ± 0.02 to 0.19 ± 0.02	−4.6 ± 0.7 to +32.7 ± 4.6	78.6 ± 4.3 to 85.2 ± 3.1	40% in 8 h and remaining in 72 h	Local anesthetic therapy	[44]
Lipid-polymer hybrid	Tenofovir disoproxil fumarate, melt emulsification-probe sonication technique	239 nm	−42.1 ± 2.46 to −55.39 ± 3.12	87.14%, 63.83 ±3.74 to 90.84 ± 5.73%	85.34 ± 5% at the end of 12 h	Antiviral	[45]

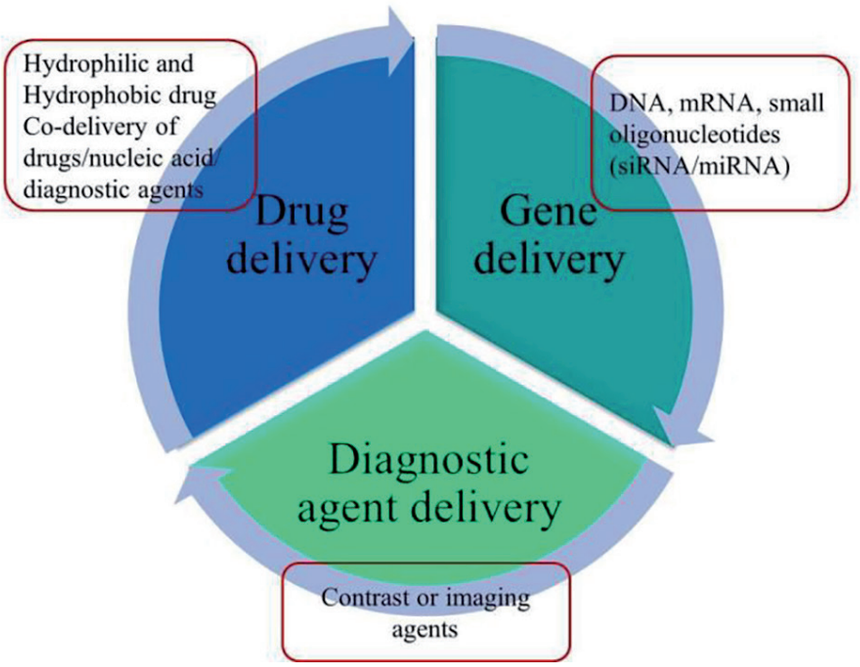

Figure 2.
Applications of lipid-polymer hybrid nanocarriers [46].

roughing. These results indicated that Dox-PLN expressed a good cytotoxic activity against solid tumors and improved the therapeutic efficacy [30].

Paclitaxel loaded LPNs were prepared with a size range of 200–300 nm for oral administration. Theses LPNs were designed to withstand harsh gastrointestinal tract conditions and improve the bioavailability of paclitaxel. On comparison with Taxol, 1.5- and 5.5-fold increase in bioavailability and elimination half-life was observed, respectively. Additionally, reduction in the reticuloendothelial system mediated uptake by liver and spleen was noted due to stealth characteristics of biopolymer blanket of these LPNs [31].

To overcome the multidrug resistance (MDR) of anticancer drugs, a new strategy was adopted in which doxorubicin loaded solid lipid nanoparticles (SLNs) were complexed with anionic polymer. Due to high encapsulation efficiency (60–80%) of doxorubicin, the cytotoxicity in tumor cells was increased to 8-fold. Due to physical interaction between drug and polymer and smaller size of nanoparticles (80–350 nm), drug was difficult to clear from target cells by efflux pump [32]. Another strategy to counter MDR is to synthesize lipid-anionic dextran sulfate hybrid carriers loaded with mitoxantrone hydrochloride. The interaction between cationic drug (mitoxantrone hydrochloride) and anionic dextran not only increased drug accumulation but also enhanced the cytotoxicity in breast cancer cell lines. Sustained release of drug (86.9%) was maintained for 72 h with an encapsulation efficiency of 97.4% [33].

Sorafenib is an antiangiogenic agent used in highly vascular hepatocellular carcinoma (HCC). The development of resistance during HCC therapy is mainly due to activation of CXC receptor type 4 (CXCR4). Gao et al. developed PLGA nanoparticles loaded with sorafenib and evaluated the antitumor activity both in vitro and in vivo. On comparing with control group, sorafenib loaded PLGA nanoparticles have shown an improved survival in HCC model, delay in progression of tumor and enhanced antiangiogenic effect [34].

Mitomycin C is a water soluble drug and major disadvantages associated with this drug are poor water stability, rapid elimination and lacking in target specificity. A sustained (up to 120 h) and effective delivery of mitomycin C from LPH

nanoparticles was observed with improved encapsulation efficiency of 95%. Improved cell uptake and site specific accumulation of drug are the major advantages of LPNs [35]. Paclitaxel and folic acid loaded polymer-lipid hybrid nanoparticles were prepared to bypass the tight junctions of blood-brain barrier (BBB) and target the glioma cells. The survival time of mice was increased to 42 days as compared to free paclitaxel which last only 18 days. These targeted nanoparticles have shown better pharmacokinetics and biodistributions which result in better therapeutic outcomes [36].

Ultra-small lipid-polymer hybrid nanoparticles were fabricated using modified nanoprecipitation method. The prepared nanoparticles loaded with docetaxel have the size of 25 nm which exhibited a better antitumor activity than Taxotere. It was observed that the survival time of Taxotere treated mice were 44 days whereas more than half of the mice treated with ultra-small nanoparticles survived for 64 days. These ultra-small nanoparticles have better biodistribution properties and enhanced permeation ability [37]. Long circulating PLGA nanoparticles loaded with curcumin were fabricated to counter cancer metastasis. The adhesion of cancer cells onto endothelial cells and vascular deposition were reduced by 70 and 50%, respectively. Therefore, these nanoparticles could improve the therapeutic efficacy by preventing metastasis and impairing circulating tumor cells [38].

Core-shell LPN was fabricated to deliver erlotinib using single-step sonication method. In vitro cellular uptake, colony forming assay and luminescent cell viability assay was performed in human lung adenocarcinoma cell line (**Figure 3**). The mean particle size of LPN is 170 nm and entrapment efficiency of 66% with excellent storage stability. The enhanced and efficient uptake of these LPN by cancer cells makes these nanoparticles a potential delivery system for erlotinib [19].

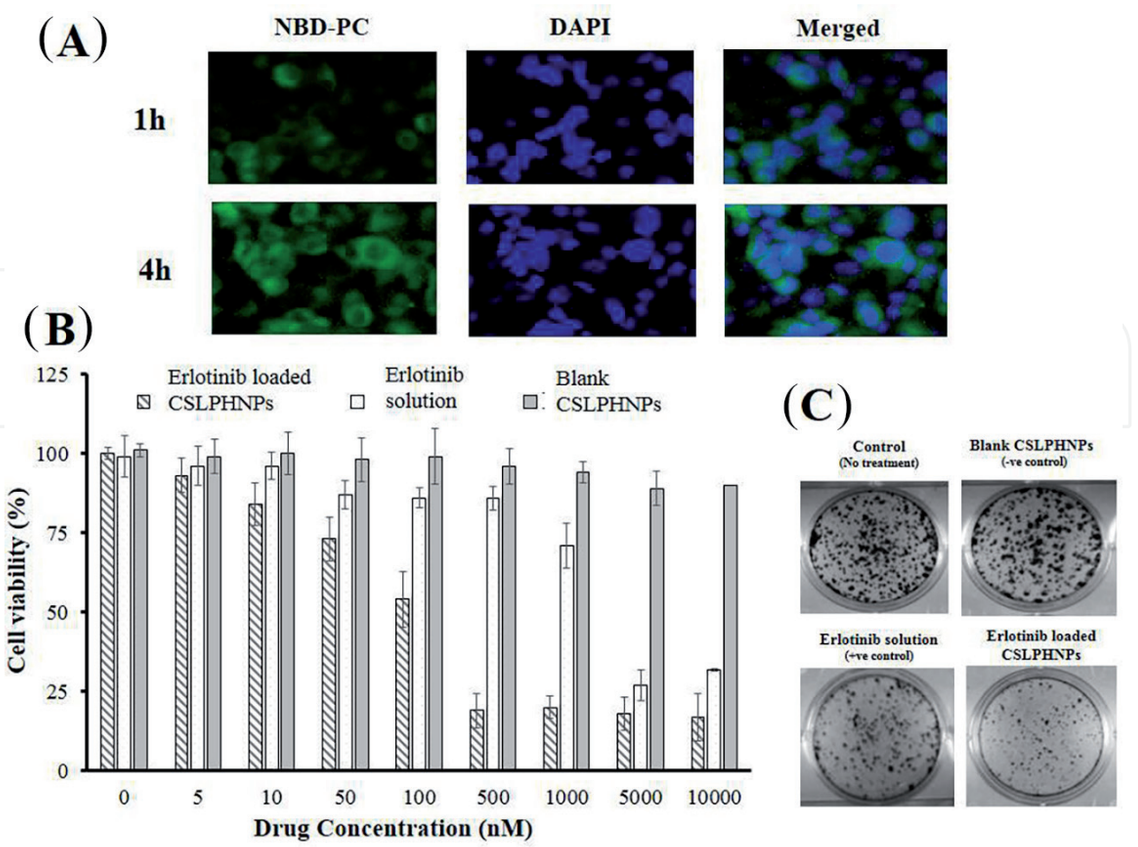

Figure 3.
(A) Confocal microscopy images of erlotinib loaded CSLPHNPs uptake in A549 cells after 1 and 4 h, (B) in vitro cellular viability result in A549 cells after 72 h, and (C) colony formation assay in A549 cells [19].

4.2 Gene delivery

Plasmid DNA, miRNA and siRNA are now gaining much of the interest of researchers for cancer therapy. Both miRNA and siRNA have different origin and mechanism but similar physicochemical properties. miRNA is endogenous in nature and target the mRNA by developing imperfect pairing and hence act by mRNA degradation, mRNA endonucleolytic cleavage or suppression of translation. siRNA is exogenous in nature and primarily act by endonucleolytic cleavage of target mRNA. siRNA has single mRNA target whereas miRNA has multiple targets. Plasmid DNA carries the recombinant gene or gene of interest and can be administered locally of systemically for cancer therapy [47–50].

Lot of challenges is associated with effective gene delivery especially for cancer therapy. Viral vectors are also facing problems such as development of immunity and inflammatory response, limited carrying ability of DNA and short shelf life [51]. Therefore, the research has now been shifted to nonviral vectors due to nonimmunogenicity, nontoxicity, low cost and feasibility in large scale production. Polyethylene glycol (PEG) and its copolymers have widely used for gene delivery because of its low toxicity, increase water solubility and reduced ability to interact with serum proteins [52].

Effective gene delivery through nonviral vectors with reduced toxicity was developed by emulsification solvent evaporation method. The particle size of newly developed positively charged LPN is in the range from 130 to 240 nm. Fluorescent protein was complexed with plasmid DNA by adsorption and transfection efficiencies was recorded as 37.2 and 34% for LPN and commercially available product, respectively [39].

Core shell LPN was fabricated using three different methods for incorporation of DNA and the resulted nanoparticles were in the range from 100 to 400 nm. Surface adsorbed DNA, encapsulated DNA and combination of adsorbed and encapsulated DNA are three important methods for fabrication of these nanoparticles. For sustained release of active ingredient, combination method is employed which is necessary for booster vaccination followed by decline release. For primary vaccination (strong and short effective delivery), surface adsorbed mechanism is followed. By adjusting the concentration of different ingredients, the drug release properties can be adjusted [53].

SiRNA delivery through cationic complexes such as polyplexes and lipoplexes has many disadvantages, e.g., development of inflammatory responses, instability and toxicity etc. Small size (100 nm) with prolong circulation time nanoparticles containing siRNA was developed using PLGA. These hybrid nanoparticles has 80% encapsulation efficiency of siRNA without any significant degradation until 24 h. Immunofluorescence studies revealed the in vitro apoptosis and >90% knockdown of nonsmall cell lung cancer [54].

LPNs are also used for incorporation of mRNA for mRNA vaccines. mRNA was complexed with LPN through electrostatic adsorption to develop 150–300 nm size nanoparticles. These newly developed nanoparticles have shown successful transfection through intranasal route and taken up by dendritic cells with minimum toxicity [40].

A novel approach, modified double emulsion/solvent evaporation method, was used to fabricate hollow core/shell LPNs in which PLGA core was surrounded by lipid shell attached with PEG chains. The size of nanoparticles was 230 nm, 80% encapsulation efficiency and 50% siRNA was sustained release for 12–20 h. Moreover, enhanced gene silencing ability was also observed with profound inhibition of gene expression in xenograft tumor [41]. PLGA/siRNA nanoparticles coated with lipids are prepared using Particle Replication in Non wetting Templates technique and exhibited 32–46% encapsulation efficiency for the treatment of prostate cancer [42]. siRNA was localized in PLGA core at high concentration by varying the

concentration of polymer and lipid. This localized siRNA then modifies the release, physicochemical properties and transfection efficiencies [55].

4.3 Theranostic agents

LPNs not only used for delivering of therapeutic agent but also used for diagnostic purpose. Different type of imaging agents such as quantum dots, fluorescent dyes and iron oxide are incorporated in polymer core. Lipid-polymer and lipid-quantum dot nanoparticles were prepared in a single step with narrow size distribution [56]. Physicochemical properties can be controlled by varying the experimental conditions. Such multicomponent nanoparticles can be used therapy and diagnosis simultaneously.

LPNs are used for theranostic purposes in which phospholipids are attached on one side of polymer chain and fluorophores are linked on the other side. LPNs were designed to incorporate MRI contrast agent, gadolinium, chelated with lipid-PEG in PLGA core. These agents have shown effective uptake of nanoparticles within 3 h by J-774 cells [57]. Instead of conjugation with imaging agent, fluorescence dye was uploaded in LPNs core surrounded by lipid-PEG shell. The final size of such nanoparticles was in the range from 20 to 30 nm and bright fluorescence was observed due to lipid tail and polymeric core [58].

4.4 Stimuli responsive LPNs

Stimuli responsive drug delivery systems have the ability to deliver therapeutic agents at target sites in a controlled manner with minimum side effects. LPNs comprise of magnetic beads. Stimuli responsive drug delivery system has the advantage to deliver the therapeutic agent in a controlled manner at target site. In a core (PLGA) shell (soyabean lecithin) nanoparticle system, magnetic beads were used for stimuli responsive release of camptothecin when exposed to radio frequency magnetic field. The release of drug was increased by 60% using radio frequency which significantly decreased the mouse breast cancer cell growth. Such system can be beneficial in cancer chemotherapy due to easy preparation, bio-stability and site specific drug delivery [59].

4.5 Miscellaneous pharmacological applications

Hepatitis C is a chronic disease which leads to liver cirrhosis and hepatocellular carcinoma. LPNs are used to label HCV viral particles for their detection, possible interaction and entrance pathway into host cells [60].

SLNs are developed for topical administration of norfloxacin using solvent evaporation method. These nanoparticles have shown antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* and could be used for the treatment of burn wound and topical infections. SLNs have shown 89.72% drug release after 24 h and passed the skin irritation and stability tests [43].

LPNs have recently used for improving the local anesthetic action of lidocaine. Two different kinds of nanocarriers, i.e., liposomes and LPNs were prepared and evaluated the skin permeation ability, in vitro and in vivo drug release studies, encapsulation efficiency and particle size. Results indicated that LPNs has better and improved efficacy of lidocaine as compared to liposomal delivery system due to smaller size (88.6 nm). The steady state flux of LPNs was found to be 65.4 μg/h/cm^2 which showed increased skin permeation capacity [44].

LPNs were used for nasal delivery of an antiviral drug, tenofovir using melt emulsification-probe sonication technique. Intranasal flux of 135.36 μg/cm^2/h and enhanced fluidity improved the drug permeation through membrane phospholipids, which increase the bioavailability of the drug [45].

Author details

Nayab Tahir[1*], Muhammad Tahir Haseeb[1], Asadullah Madni[2], Farzana Parveen[2], Muhammad Muzamil Khan[2], Safiullah Khan[2], Nasrullah Jan[2] and Arshad Khan[2]

1 College of Pharmacy, University of Sargodha, Sargodha, Pakistan

2 Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

*Address all correspondence to: nayabtahir132@gmail.com

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