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Review Article

LIPID-POLYMER HYBRID NANOCARRIERS AS A NOVEL DRUG DELIVERY PLATFORM

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ABSTRACT

The main aim of my review to discuss the most prominent nanocarrier, "Lipid-Polymer Hybrid Nanoparticle" (LPHNPs) that overcomes the limitation of lipid and polymeric nanoparticles. That consists of polymeric core and lipid outer layer. The polymeric core encapsulates both hydrophilic and hydrophobic drugs and lipid shell provides a coat that gives a barrier to prevent drug leakage and easily penetrate into the skin. The LPHNPs has significant application in drug delivery, drug targeting, cancer treatment, brain drug delivery, multiple drug delivery, delivery of diagnostic imaging agent and Small interfering Ribonucleic acid (siRNA).

This session is based on literature information in which LPHNPs were prepared by Two-step and Single-step method. Most of the researcher use the Single-step method by emulsification solvent evaporation and Nanoprecipitation method that are easy to prepare LPHNPs. The Polylactic Glycolic acid (PLGA), Poly € caprolactone, Chitosan, Alginate, Dextron, Sodium Alginate, etc used as polymeric core and Stearic Acid, Palmitic Acid, Cetyl Alcohol, Behenol Alcohol, etc used as lipid core. All results were analyzed by us according to the literature and authors' expertise. The drug release depends on diffusion processes, followed by erosion, then swelling of the matrix. The lipid shell provides a biocompatible shield that acts as the phospholipid bilayer of skin and easily penetrates into the skin. That also capable to deliver the multidrug and diagnostic imaging agent for the treatment of cancer.

The Lipid-Polymer Hybrid Nanoparticles are the most prominent nanocarrier for drug delivery. That is capable to deliver both Hydrophilic and Lipophilic drugs and show high bioavailability.

Keywords: Diagnostic, Hydrophobic, Lipophilic, Biomimetic, Biocompatibility, Biodegradable

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INTRODUCTION

Now a day, in the pharmaceutical field, Nanotechnology is highly used for the drug delivery system as a transporter. Nanoparticles (NPs) attract high devotion because of their capability to deliver the appropriate amount of drug to the specific site at relevant times. The general nanoparticulate systems, include lipid-based Nanoparticle and biodegradable polymeric-based Nanoparticles are two most promising class of Nanocarriers, as demonstrated by increasing numbers of clinical trials, research reports, and standard drug products [1-5]. Both classes of nanocarrier have some advantages and some drawbacks in terms of their physicochemical and biological properties. For a long time the Lipids are broadly been used in various drug delivery systems like liposome, nanostructured lipid carriers [6], and lipid–drug conjugates, solid lipid Nanoparticles [7]. The most lipids are biocompatible, biodegradable, harmless or mildly toxic, stretchy, and non-immunogenic in nature for the systemic and non-systemic administration because it is obtained from natural sources [8]. However, the lipid-based Nanoparticle having some drawbacks like insufficient drug loading, fast drug release and physical and chemical instability during storage [9]. Polymeric Nanoparticles are made from natural and synthetic polymer and have various advantages like lesser particle size, tissue permeability, better stability in biological fluids, high drug loading capability, and ability to encapsulate hydrophobic or hydrophilic agents offers controlled drug release rates and stability aspect [10]. But the polymeric Nanoparticle also has some limitations like containing toxic organic solvents in the production process [11], poor drug encapsulation for water-soluble drugs, drug leakage prior to reaching target tissues, polymer cytotoxicity, polymer degradation, and scale-up issues. Thus, to overcome these limitations of Nanocarriers, develop a new carrier known as a lipid-polymer hybrid Nanoparticle.

Lipid-polymer hybrid nanocarriers

Lipid-Polymer hybrid Nanoparticle (LPHNPs) as shown in (fig. 1) is a rising Nanoparticle drug delivery system consisting of two major components: polymer cores and single or multiple lipid layers that make an outer shell. Physically LPHNPs are solid at the body temperature, same as solid lipid nanoparticles, but it differs from the conventionally used lipid-based Nanoparticle–like liposomes, these are consist of a hydrophilic core surrounded by a lipid bilayer. In the LPHNPs the polymer core (the inner part) is capable for encapsulating both hydrophilic and hydrophobic drugs and the lipid shell (the outer part) is coating the external surface of the polymer core, which forms barrier to prevent the fast leakage of drug, allowing the prolonged and controlled release of the drug. Therapeutic agents can be entrapped, adsorbed, or covalently attached to the lipid and polymer both. LPHNPs show a number of exclusive advantages, including-(1) highly selected biocompatible polymer and lipid and numerous polymer-lipid combination, (2) easy preparation methods like single-step method, and (3) greater ability to co-encapsulating therapeutic and imaging agents (4) used as multiple drug delivery system. LPHNP system increases the drug loading efficiency, allow controlled drug release, improve drug uptake and intracellular drug transport, and help in easily cross the membrane efflux transporter-mediated multidrug resistance (MDR) in cancer cells. Like other than nanocarriers, LPHNPs can also be conjugated with targeting moieties for targeted drug delivery to tumor vasculature and tumor cells [12-14].

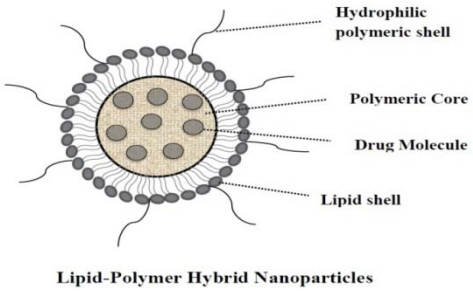

Fig. 1: Schematic diagram of the lipid-polymer hybrid nanoparticle. That shows the drug integrate into the polymeric core, and lipid outer layer provides a coat on the core

Advantages of lipid-polymer hybrid nanoparticle

- The solid polymeric core act as a cytoskeleton that provides mechanical stability, controlled morphology, and high available specific surface area.
- The lipid shell enveloping the core is biocompatible and exhibits behavior similar to that of cell membrane.
- Improved encapsulation of hydrophobic drug, high drug entrapment efficiency and drug loading capacity for a number of the drug compared to liposomes or Polymeric Nanoparticles.
- The LPHNPs entrap and deliver multiple hydrophilic and hydrophobic therapeutic agents simultaneously.
- Particles smaller than 100 nm are promising for intracellular drug targeting.

An ingredient used in the preparation of Lipid-polymer hybrid Nanoparticle [LPHNPs]-There are many more ingredients used that are shown in table 1

Table 1: Different type of polymer, lipid, surfactants are used for the preparation of LPHNPs

Polymer	Polylactic Glycolic acid (PLGA), Poly € caprolactone (PCL), Dextron Sulphate, Polyethylenimine (PEI), Soyabean oil, 2-Hydroxyethyl methacrylate (HEMA), Chitosan, Chitin, Pectin, Starch, Alginate, Dextron, Galactan, Sodium Alginate.	[5, 15-22]
Lipid	Disteroyl-Sn Glycero-3Phaspho ethanolamine-N-Carboxy Polyethylene Glycol 2000 (DSPE-PEG-2000), 1,2 Dilouroyl Sn-Glycerol-3 Phospho Choline (DLPC), Stearic Acid, Glycerotripalmitate, Palmitic Acid, Cetyl Alcohol, Coconut oil, Glyceryl Behenate, Witepsol w35, Behenol Alcohol, Glyceryl Palmitostearate, Dynason 118, Hydrogenated Coco-glycerides, tricaprin.	
Surfactant	Lecithin, Pluronic F-127, Poly Sorbate 80, Lipid Polyethylene Glycol (PEG) 2000, Polyvinyl Alcohol (PVA), Soy lecithin (Lipoid S75), Egg Lecithin (Lipoid 80), Phosphatidyl Choline, Poloxamer, Tyloxapol, Sodium Cholate	

Mechanism of drug release from lipid-polymer hybrid nanoparticle

The anatomy of a hybrid Nanoparticle consists of a polymer core, a lipid monolayer that surrounding the core. The polymeric core affects drug encapsulation and release. Drug release from the Nanoparticle begins with diffusion processes, followed by erosion, then swelling of the matrix [23]. The polymer degrades due to hydrolysis and the degradation rate depends on the polymer composition and molecular weight. The lipid shell serves the purpose as a biocompatible shield, a template for surface modification, and a barrier for preventing the water-soluble drug from leaking out of the core [24, 25], in the topical application of hybrid Nanoparticle that is shown in fig. 2, the lipid layer act as the phospholipid bilayer of skin and easily penetrates into the skin. The polymer gets swell or erosion due to the moisture of the skin and resulting drug release from polymer due to diffusion.

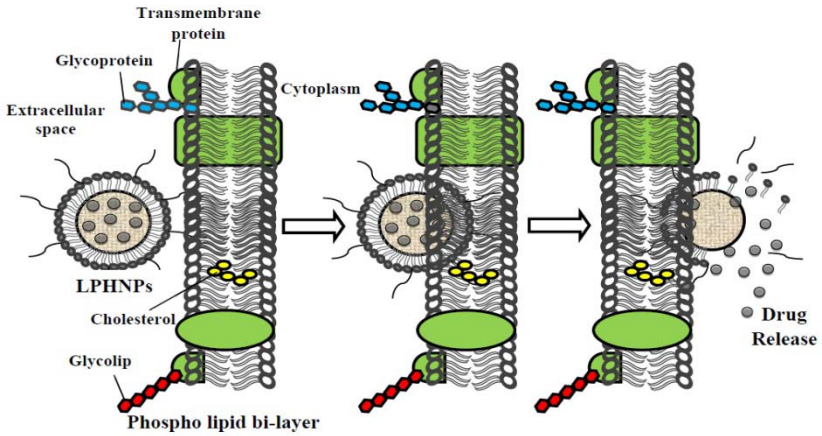

Fig. 2: Schematic diagram of drug release from the LPHNPs

Method of preparation of lipid-polymer hybrid nanoparticle

Method used to prepare Lipid-polymer hybrid Nanoparticle broadly fall into two categories: Two-step method and Single-step method.

Two-step method

The two-step method is the most common method used for the preparation of LPHNPs. In this method, take the previously prepared polymeric Nanoparticle and a thin lipid film prepared by dissolving the lipid in an organic solvent (Chloroform) by evaporation in a rotary evaporator. And add the polymeric Nanoparticle to the prepared lipid vesicle. The polymer/lipid suspension mixed properly by overtaxing or ultra-sonication process and Provide a temperature higher than the gel to liquid transition temperature to adsorb the lipid on polymeric Nanoparticle and the Non-adsorbed lipid separated by centrifugation method and collect a fine LPHNPs. The suspension is homogenized or extrusion to obtain a monodisperse LPHNPs. In Extrusion, the LPHNPs suspension is passed through a porous membrane to find a homogenous size particle as membrane pore size [5, 12, 17, 26-33].

Non-conventional method

In addition, the Non-Conventional method is spray drying and soft lithography particle molding [29, 34-37].

Spray drying method

In this method the polymeric Nanoparticle is prepared by spray drying technique and then this preparation is dispersed into the lipid solution. Finally, the Lipid-polymer suspension later spray-dried and produces LPHNPs.

Soft lithography particle molding technique

In this method, the LPHNPs is prepared for Gene delivery. The polymer (Polylactic Glycolic acid [PLGA]) dissolves in an organic solvent with a gene material Small interfering Ribonucleic acid

(siRNA). This polymer solution is a cost on to a polyethylene tetra phthalate (PET) sheet and heat the PET sheet for conformal contact with mold (containing 80*320 nm patterns) so that Polymer completely fill into the mold and get Solidify by returning on ambient temperature and produce a Polylactic Glycolic acid (PLGA) Polymeric Nanoparticle. The Nanoparticle harvested/remove from the mold by adhering the Nanoparticle to the polyvinyl alcohol coated polyethylene terephthalate (PET) sheet and then Nanoparticle release from the Polyvinyl Alcohol (PVA) coated polyethylene terephthalate (PET) sheet using an aqueous solution of lipid; these lipid solutions dissolve the Polyvinyl Alcohol (PVA) layer and obtained the free LPHNPs.

Governing parameter in the two-step method

- Size homogeneity of the performed lipid vesicle.
- Lipid formulation charge.
- The ionic strength of the continuous phase.
- Lipid vesicle to polymeric Nanoparticle ratio.

Single-step method

The main drawback of the 2 step method that the polymeric Nanoparticle and lipid vesicle are prepared separately, and that takes more time and more energy expense. The encapsulation efficiency of the water-soluble drug may decrease and the drug may leak from the polymer core before the phospholipid shell is formed. The one-step method is a very instead method. In this method mix the polymer with a lipid solution after which they self-assemble to form LPHNPs by either nanoprecipitation or emulsification-solvent-evaporation [5, 12, 17, 38-41].

The single-step method by nanoprecipitation

In this method, the polymer, and encapsulated substance dissolve in an organic solvent and the lipid or lipid Polyethylene Glycol (PEG) are dispersed in water. Heat the lipid or lipid Polyethylene Glycol solution (65-70 °C) to form a homogeneous dispersion. The polymer solution adds dropwise into the aqueous lipid dispersion under continuous stirring and the lipid get self-assemble around the polymeric Nanoparticle shown in fig. 3. The hydrophobic tail attache to the polymer core and hydrophilic head sticks out to the external surface. Stirrer continues to evaporate the solvent and centrifuge it to recover LPHNPs [1, 5, 42].

Governing formulation parameter in nano-precipitation

- Lipid to polymer mass ratio (Lipid/Polymer Ratio)–It is influence the encapsulation efficiency, loading and release kinetic of encapsulating substance [23, 29, 38].
- Lipid/Polymer ratio (10-15% w/w) is optimum to sufficiently cover the surface of the polymer and produce a stable mono-disperse LPHNPs.
- Lipid/Polymer ratio (≈25% w/w) led to a concentration higher than CMC resulting in the formation of the liposome.
- Lipid/Polymer ratio lower than≈(10% w/w) causes LPHNPs aggregate due to insufficient lipid coating.

Recent advancements in nanoprecipitation

In this advancement developing a rapid nanoprecipitation process by supplying a high and uniform level of energy by both sonications. Which causes fast and quick assembling of LPHNPs resulting in a twenty-fold increase in productivity. This advanced method eliminates the length of solvent evaporation step by using a small amount of organic solvent [29, 43].

The single-step method by emulsification solvent evaporation

The ESE method is divided into 2 types of single and double emulsification methods [5, 25, 29, 41, 44-49].

Single emulsification solvent evaporation

In the ESE method, dissolve the polymer, lipid and encapsulated substance in the oil phase or organic solvent and this oil phase is added into an aqueous phase containing liquid Polyethylene Glycol or any surfactant under constant stirring or ultrasonication as shown in fig. 4. Resulting oil-in-water (o/w) emulsion formed. When the oil phase is evaporated, then the lipid is self-assembled around the polymer and form LPHNPs.

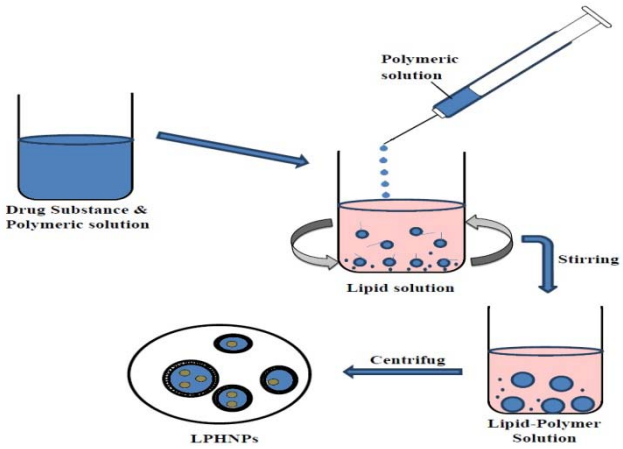

Fig. 3: Schematic diagram of the preparation of LPHNPs by single-step nanoprecipitation method

Double emulsification solvent evaporation

This method is employed when the encapsulated substance does not dissolve in the oil phase or an organic solvent. In this method, Firstly, encapsulated substance dissolve in the aqueous phase and this aqueous phase adds into the oil phase containing polymer and lipid under continue stirring or ultrasonication resulting from a primary emulsion (w/o) [25, 29]. Then this emulsion is added into the again aqueous phase containing the lipid-Polyethylene Glycol to form w/o/w emulsion and evaporate the oil phase and obtained finely LPHNPs as shown in fig. 5.

Here the inner lipid layer surrounding the aqueous hollow core and a middle layer polymer and third outer layer is lipid-Polyethylene Glycol (PEG).

Governing formulation parameter in ESE

The most prominent parameter is lipid to polymer mass ratio. If the polymer ratio is high, then lipid forms an outer layer.

Novel colloidal carrier system and its limitations

There are many more carriers and its limitations shown in table 2.

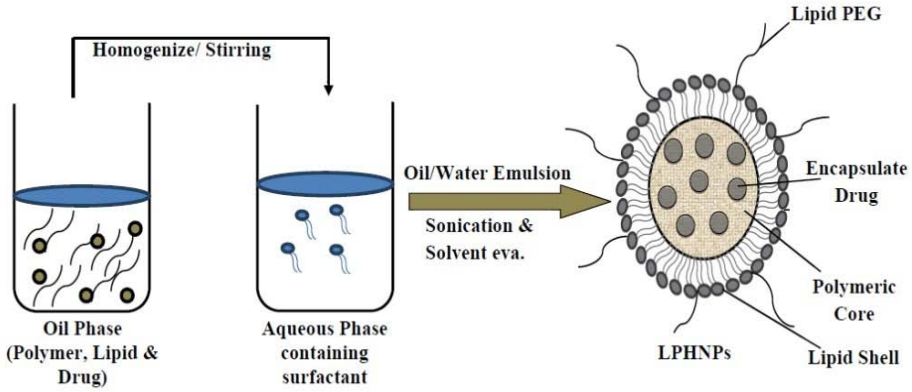

Fig. 4: Schematic diagram of the preparation of LPHNPs by a single emulsification solvent evaporation method

Table 2: Different types of novel carrier systems and its drawback

S. No.	Novel carrier system	Limitations
1	Lipid vesicular carrier [51-53]	• Brust effect means immediate drug release. • Physically and chemical instability during storage. • Rapid oxidized or hydrolyzed during storage. • Rapid drug leakage.
2	Liposome [54-56]	• Rapid drug leakage. • Poor encapsulation efficiency for the hydrophilic drug. • A liposome is expensive. • Liposome has a short half-life. • Low stability during storage.
3	Niosome [57-59]	• Less skin penetration, Do not reach up to the deeper skin layer. • Weak loading of the drug. • Physically and chemically less stable during storage. • Niosome is also expensive.
4	Transferosome [60, 61]	• They are chemically unstable. • They are expensive.
5	Aquasomes [50, 51]	• Chance of drug leakage. • The drug gets degrade due to the acidic environment of the stomach. • Weak drug loading capacity. • Very expensive.
6	Colloidosomes [62]	• They have poor production yields. • When it transferred from organic to the aqueous solvent, production yield reduce. • Leakage problem.
7	Ethosome [63-65]	• Low drug loading capability. • The adhesive may not adhere well to all types of skin. • Poor production yield.
8	Microspheres [66-70, 79]	• Burst effect i.e. premature drug release, • Rapidly taken by the reticuloendothelial system (RES). • Poor drug entrapment efficiency.
9	Solid lipid Nanoparticle [71, 72]	• They have poor stability. • Poor batch to batch reproducibility. • They have low drug loading capacity.
10	Polymeric Micelles [73-75]	• Not good for hydrophilic drugs. • Poor batch to batch reproducibility.
11	Dendrimers [76]	• Polymer dependent biocompatibility. • Drug leaking problem • Physically unstable due to enzymatic degradation and environment factors. • Poor batch to batch reproducibility.
12	Polymeric Nanoparticle [77, 78]	• Difficulty of the large-scale production. • Unstable in the acidic $_{P}$H. • Cause tissue toxicity due to reach a high concentration at the site. • Cause allergic reaction. • The production cost is high.
13	Hydrogel [80-82]	• These are expensive. • Cause irritation to the eye. • Low loading capacity. • Leakage problem.
14	Phytosomes [50, 51]	• Low stability

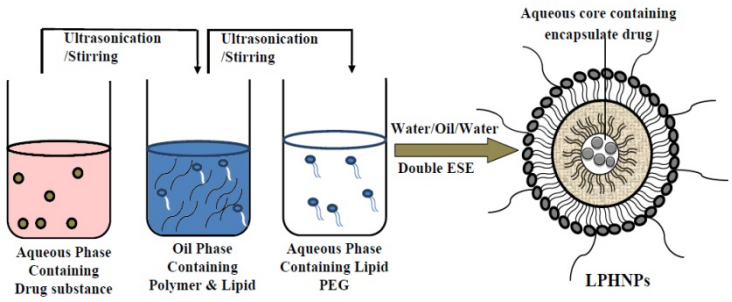

Fig. 5: Schematic diagram of the preparation of LPHNPs by a double emulsification solvent evaporation method

Application of lipid-polymer hybrid nanoparticle system

LPHNPs has various versatile drug delivery applications in the pharmaceutical field-

Drug delivery

Today drug delivery is the most challenging phenomenon for the researcher as well as Pharma companies. In recent the most carriers are discovering for drug delivery but they have some little bit limitation. Here LPHNPs develop as a carrier that overcomes these limitations and shows high bioavailability. The drug delivery through the hybrid Nanoparticle has been dominated by the delivery of various drugs, here we are focus on the delivery of the anticancer drug. The multidrug-resistant are present in the cancer cells, that are challenging to the delivery of the chemotherapeutic agent to the cells [17, 29, 40].

The drug delivery from LPHNPs are classified into 3 subsections-

Single-drug delivery

In the single drug delivery, various types of chemotherapeutic agents or drugs are used for the different types of cancer cells like Breast cancer, Prostate cancer, Lung cancer, Liver cancer, Cervical cancer [29, 38] as shown in table 3. In previous research, very less *in vivo* data were available for delivery of single drugs from LPHNPs. These are mostly designed for combinational and active targeted drug delivery. The single drug delivery from the LPHNPs has low *in vitro* cytotoxicity, biocompatible with drug, good cellular uptake and high drug release kinetic. According to Chin-Hang *et al.*, and Zhang *et al.* the LPHNPs exhibit high uptake in prostate and cervical cancer cells than in another delivery system [38, 83]. Liv *et al.* reported that LPHNPs exhibit sustains release kinetic like 33% in 12 hr and 100% in 7 d [45]. The LPHNPs formulation is widely used for the delivery of fluoroquinolone antibiotics for lung infection therapy because particle easily penetrates the thick mucus layer nearby the bacteria and prevent lung infection [84, 85]. The antibiotic-loaded LPHNPs as inhaler product has been establishing for lung infection disease [86].

Combinational drug delivery

The combination of a chemotherapeutic agent or drug is highly effective for cancer therapy. In combinational drug therapy, chemotherapeutic or drug is used with another therapeutic agent like Gene, Magnetic Nanoparticle [29, 88], etc as shown in table 4. Develop an LPHNPs carrier that carries multiple drugs at a precise ratio that helps in drug release in a controlled manner and overcomes the limitation of a single drug delivery system. The multiple drug delivery through LPHNPs generally employs two-drug-incorporate into one system. The multidrug loading in the LPHNPs system follows the one-step method in which drug is covalently conjugated with polymer and another drug is conjugate within lipid and mix properly by sonication technique to form multiple drugs loaded LPHNPs. In the two-step method, the drug is entrapped or encapsulated into the polymeric core and another drug conjugate with lipid. The lipid is adsorbed on the polymeric core and form multiple drug-loaded LPHNPs. In contrast the second method, the drugs are conjugate to the LPHNP system with the help of hydrolyzable linker and this drug-conjugate linker gets hydrolyzed upon reaching the cancer cell resulting in the drug are released separately. According to Sengupta *et al.*, the LPHNPs for multi-drug delivery containing an anti-angiogenesis and another chemotherapeutic drug, resulting one inhibit the growth of tumor cells by cutting the blood supply to the cell and another kill the existing tumor cell [26, 89]. But sometimes, the anti-angiogenesis drug blocks the blood supply then the chemotherapeutic agent not reach the cell, In this case, it is important that the drug is simultaneously rich in the tumor cell. Wang at al using the same method (two-step) for the preparation of LPHNPs for delivery of Doxorubicin and Deoxyribonucleic acid. In which the Deoxyribonucleic acid enhances the tumor inhibition by increase the chemotherapeutic-sensitivity to a tumor cell and Doxorubicin directly inhibits the tumor cell [32]. Doxorubicin is incorporated into the polymer and Deoxyribonucleic acid is electrostatically incorporate into the cationic lipid to form LPHNPs. They found that LPHNPs show 43% drug release over 7 d and show a high degree of transfection efficiency as compared to the non-hybrid Nanoparticle. According to Wang *et al.*, they also prepare LPHNPs by using nanoprecipitation methods for delivery of chemotherapeutic agents like Doublecortex (DCX), and radiotherapy agents like Indium-111 or Yttrium-90 [90]. The Doublecortex incorporate into the polymer and a radioisotope incorporate into the lipid chelator layer of lipid for prostate cancer. According to Kong *et al.*, they develop magnetic LPHNPs by using the nanoprecipitation technique for the delivery of chemotherapeutic agents as required [91]. That LPHNPs contain magnetic particle-like Fe_3O_4 that are responsible for drug release when a remote radio frequency magnetic field will be applied. In which Camptothecin (CMT) and Fe_3O_4 incorporate into the Polylactic Glycolic acid (PLGA) core. The rate of drug release depends on the applied magnetic field. They also reported that the drug-loaded magnetic Nanoparticle shows better growth inhibition on Melatonin Receptor (MT2) breast cancer cells and high cellular uptake by the cell. One another example of Aryal *et al.* here they covalently linked Doxorubicin and Camptothecin in the polymer by nanoprecipitation technique and form a lipid-polymer hybrid Nanoparticle (less than 100 nm) [92]. These LPHNPs exhibit higher *in vitro* cytotoxicity against the breast cancer cell because that are easily cross the cell efflux transporter present on the cell resulting the high amount of drug conjugate with LPHNPs rich to the inside of the cell. When the drug is delivered by another delivery system then less drug entered into a cell by passive diffusion due to rapid clearance by the cell's efflux transporter mechanism [93]. According to Aryal *et al.*, they are prepared PCX-gemcitabine HCL loaded LPHNPs that show the higher *in vitro* cytotoxicity for XPA3 pancreatic cancer as compare to another drug delivery system [94].

Table 3: Application of LPHNPs as a smart carrier for delivery of single drug

S. No.	Drug	Drug release	Cancer type	Ref.
1	Levofloxacin	90% (in 24 h)	P. aeruginosa biofilm cells	[84]
2	Paclitaxel	33% (12 h), 100%(7 h)	MCF7 breast cancer	[87]
3	Fluorouracil	70-90% (24 h)	N/A	[34]
4	Doxorubicin	14% (6 h), 50% (44 h)	HeLa cervical cancer	[83]
5	Docetaxel	50% (20 h)	PC3 prostate cancer	[38]

Table 4: Application of LPHNPs as a novel carrier for combinational drug delivery

S. No.	Drug	Drug release	Cancer type	Ref.
1	Doxorubicin, Combretastatin	Slow over 20 h	B16/F10 melanoma, Lewis lung carcinoma	[26]
2	Doxorubicin, Camptothecin	N/A	MDA-MB-435 Breast cancer	[92]
3	Cisplatin, Paclitaxel	Cisplatin (55-75%), Paclitaxel (48-67%, 24 h)	A2780 Ovarian cancer	[95]
4	Camptothecin, Fe_3O_4 Nanoparticles	90% 45 h	Melatonin Receptor (MT2) breast cancer	[91]
5	Doxorubicin, Deoxyribonucleic acid	Doxorubicin-24%, 43% 7 d	MDA-MB-231 breast cancer	[32]
6.	Gemcitabine HCL, Paclitaxel	N/A	XPA3 Pancreatic cancer	[94]

Actively targeted drug delivery

In the anticancer therapy, the delivery of chemotherapeutic agents should be targeted because the chemotherapeutic agents kill the cancerous cell as well as healthy cells. In the targeted drug delivery system, the maximum amount of drug reaches the cancer cell, not to other cells. In which the targeting moiety is attached to the LPHNP system that easily recognizes the cancerous cell and kills them. The targeted vs untargeted drug delivery system shows in fig. 6. For example, folic acid is the one such targeting moiety has high affinity to bind the cancer cells because folate receptor is present on most of the cancer cells. Hence the target moiety (folic acid) is attached to the LPHNP system before the preparation [29, 96] as shown in table 5. According to Liu *et al.*, they prepare FA conjugate LPHNPs. In which the Doublecortex is encapsulated into the polymeric core and Folic acid conjugate with the lipid or lipid Polyethylene Glycol by using the single-step method or two-step method [45]. Resulting FA-loaded-DCX-LPHNPs highly uptake of the MCF7 breast cancer cell through the FA receptor and the high amount of Doublecortex entered into the cancer cell and kill them without affecting the other cells. The DCX-FA-loaded LPHNPs show the 51% higher *in vitro* cytotoxicity as compare to other Doublecortex loaded drug delivery systems. According to Zhao *et al.*, they prepare Folic acid conjugate PCX-loaded LPHNPs by using a single-step or two-step method for HeLa cervical cancer cell [27]. The Folic acid conjugate PCX-loaded LPHNPs show the higher cellular uptake and higher *in vitro* and *in vivo* cytotoxicity to the HeLa cell as compare to the Doublecortex loaded nonhybrid Nanoparticle. The other active targeting moiety used for anticancer cells is such as aptamers, single-chain variable fragments, antibody, transferrin and peptides [29]. According to Zhang *et al.* they use A10 RNA aptamer as a targeting moiety for the treatment of prostate cancer. According to Messerschmidt *et al.*, they take a chemotherapeutic drug that is single-chain tumor necrosis factor (scTNF) and targeted moiety like single-chain variable fragments (scFv) incorporate into the LPHNPs [33]. The Single-Chain Variable Fragments (scFv) targeted moiety target to the fibroblast activation protein that is present in the cancer cell. The Single-Chain Variable Fragments (scFv) conjugated hybrid Nanoparticle shows the higher *in vitro* cytotoxicity compare to the other hybrid Nanoparticle. According to Hu *et al.*, they use Anti-carcinoembryonic (Anti-CEA) half antibody as a targeting moiety [97]. The Anti-carcinoembryonic conjugate with PCX-Loaded LPHNPs for target pancreatic cancer cell. In which the Anti-carcinoembryonic is fussed into the lipid or lipid Polyethylene Glycol and PCX is encapsulated into the polymer core and prepares LPHNPs by single or two-step techniques. The half antibody increases the LPHNPs size from 80 to 100 nm. The Anti-carcinoembryonic targeted moiety is easily recognized the CEA positive Beta XPC3 receptor present in the pancreatic cancer cells. Resulting in higher cellular uptake of PCX-loaded LPHNPs into the cell and cause higher *in vitro* cytotoxicity.

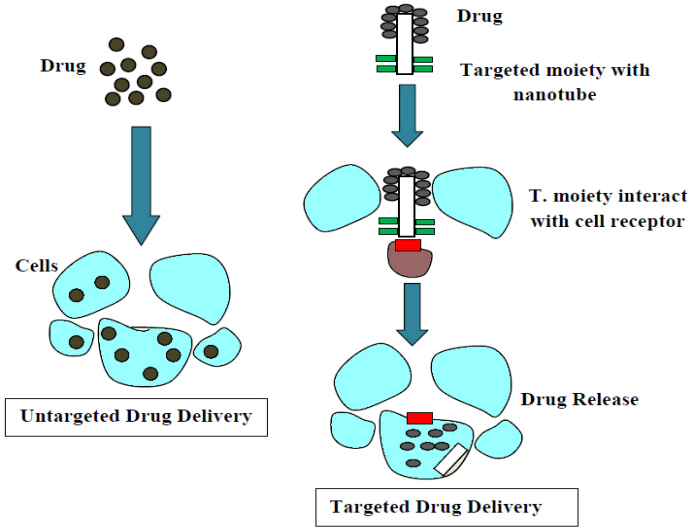

Fig. 6: Schematic diagram of targeted vs untargeted drug delivery system

Table 5: Application of LPHNPs as a novel carrier for delivery of both drug along with the target moiety

S. No.	Drug	Targeted moiety	Drug release	Cancer type	Ref.
1	Docetaxel	Folic Acid	90% in 7days	MCF7 Breast cancer	[45]
2	Paclitaxel	Peptides	50% in 18 h	N/A	[98]
3	Paclitaxel	Folic Acid	19% in 24 h	HeLa cervical cancer, Lung cancer	[27]
4	Paclitaxel	Peptides	94% in 12 d	Human aortic smooth muscle cells	[99]
5	Docetaxel	Aptamer	50% in 20 h	LNCaP and PC3 protate cancer	[38]
6	Paclitaxel	Anti-carcinoembryonic	N/A	Pancreatic cancer	[97]
7	Aromatase inhibitor	Transferrin	N/A	SKBR-3 Breast Cancer	[100]

Gene delivery

Today the delivery of nucleic acid is a very challenging process for the pharmaceutical company. The delivery of nucleic acid is very useful in the treatment of chronic disease, genetic disorder, cancers and another diagnostic purpose [40, 101] as shown in table 6. The cationic lipid and cationic biodegradable polymer-based Nanoparticle are widely used in the gene delivery system [102]. The lipid and polymer-based non-viral carrier systems have various advantages like low immunogenicity, low toxicity absence of viral recombination low production cost [103], but have some limitations like cytotoxicity, stability into the serum, high duration of gene expression and large particle size. The lipid-polymer hybrid Nanoparticle is a more reliable carrier for gene delivery than other carriers because these are biodegradable, stable and long-lived Nanoparticle vector delivery systems. The plasmid Deoxyribonucleic acid encoding luciferase receptor gene encapsulated into the polymer core and lipid is adsorbed on the core [104]. The LPHNPs (100-400 nm) is able to transfer the luciferase gene in the prostate cancer cell. According to Li *et al.*, they are reported that the LPHNPs are efficient non-viral gene delivery with high transfer efficiency and low toxicity as compare to marketed Lipofectamine 2000 [105]. Lipoplexes and polyplexes are widely applied as non-viral gene delivery carrier [29, 106]. The cationic nano-scale complex such as lipoplexes and polyplexes are successfully delivered the small interfering Ribonucleic acid (siRNA) or Deoxyribonucleic acid (DNA) plasmid [40, 107]. The lipoplexes and polyplexes have the capability to deliver the Deoxyribonucleic acid into cells and protect the Deoxyribonucleic acid from unwanted degradation during the transfection process. The plasmid Deoxyribonucleic acid can be enclosed with lipid into an arranged structure like liposome. When the prepared structure encapsulates with Deoxyribonucleic acid then known as Lipoplex. The anionic and neutral lipid is used for construction lipoplex for synthetic vectors and show the little toxicity with the body. The cationic lipid has a positive charge and that makes tightly complex with negative charged Deoxyribonucleic acid (DNA) resulting they interact with the cell membrane and enter into the cell by endocytosis process and release the Deoxyribonucleic acid (DNA) into the cytoplasm. The cationic lipid also protects the degradation of Deoxyribonucleic acid (DNA) by the cell. The Deoxyribonucleic acid (DNA) plasmid or gene complex with the polymer called Polyplex. Most of the polyplexes are made up of cationic polymer. According to Shi and Coworkers, they prepare a neutral surface charged hybrid Nanoparticle that is capable to protect the small interfering Ribonucleic acid (siRNA) and lipoplexes from the physiological environment [40, 108]. These systems composed of a positively charged inner core made up of a cationic lipid, a hydrophobic Polylactic Glycolic acid (PLGA) layer and a neutral lipid layer having outer Polyethylene Glycol (PEG) chain. The LPHNPs system has the capability to release the Small interfering Ribonucleic acid (siRNA) in a sustained manner and enhance the *in vivo* gene silencing. The LPHNPs based gene delivery provides high stability and high biocompatibility from the physiological environment.

Table 6: Application of LPHNPs as a novel carrier for gene delivery

S. No.	Gene	Cancer type	Ref.
1	DNA (PEGFP-N2)	Healthy Human embryonic kidney cells 293, MDA-MB-231 breast cancer	[109]
2	mRNA	Dendritic	[110]
3	DNA (pLuc)	HEK 293	[104]
4	siRNA (siPlk-1)	BT474 breast cancer	[111]
5	siRNA (anti-GFP, anti-Luc, GAPDH	HeLa cervical cancer, HepG2 liver cancer	[108]

Deoxyribonucleic acid (DNA) delivery

According to Zhong *et al.*, here they are reporting that 3 Deoxyribonucleic acid (DNA) incorporation methods for the transfection efficiency in the preparation of LPHNPs-loaded Deoxyribonucleic acid (DNA) luciferase gene. The LPHNPs consist of a polymer and lipid and prepared by a double emulsification solvent evaporation method by using Polylactic Glycolic acid (PLGA) as a polymer and N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate or 3ß-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Chol) as a lipid [104]. There are 3 methods are used for evaluation–

1. Deoxyribonucleic acid adsorbs on the cationic lipid shell of LPHNPs by electrostatic adsorption technique before the preparation of LPHNPs. This method is called out method.

2. Deoxyribonucleic acid is encapsulated into the aqueous hollow core of the LPHNPs this system is called in method.

3. In the last method combine the both in and out method.

Total 6 Deoxyribonucleic acid and lipid-polymer hybrid nanoparticle (DNA-LPHNPs) complex formulation (3 Deoxyribonucleic acid (DNA) incorporate into N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate and another 3 Deoxyribonucleic acid (DNA) incorporate into 3ß-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol are evaluated. The Deoxyribonucleic acid to LPHNPs mass ratio optimizes the Deoxyribonucleic acid (DNA) binding efficiency resulting in the optimal binding efficiency greater than 95% at 1:50 Deoxyribonucleic acid and lipid-polymer hybrid nanoparticle (DNA-LPHNPs) ratio. The Deoxyribonucleic acid and lipid-polymer hybrid nanoparticle (LPHNP-DNA) complex formulation prepared by the out method that exhibits a large initial uptake in human embryonic kidney 293 cells during 4-week incubation followed by a steep decline of the PLuc DNA. A similar result is obtained by using Lipofectamine (a marketed lipid-based carrier). The Deoxyribonucleic acid and lipid-polymer hybrid nanoparticle (DNA-LPHNPs) complex prepared by both methods exhibits a large initial uptake and show the more sustain decline of PLuc DNA. Zhong *et al.* reported that the 'out' method is important for initial strong gene delivery in a very short period of time e. g., priming vaccination [104]. Both methods are used when the sustained response required e. g., booster vaccination. The sustain pLuc activity of N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate (DOTAP) and 3ß-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Chol) are higher in N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate (DOTAP) by using "In" and "out" both methods. The specific application of Deoxyribonucleic acid (DNA) delivery using Lipid-polymer hybrid nanoparticle (LPHNPs) is varied with lipid used in the formulation. According to Li *et al.*, they prepared Deoxyribonucleic acid (DNA) loaded Lipid-polymer hybrid nanoparticle (LPHNPs) by using 'out' method [109]. In which the preformed positively charged Lipid-polymer hybrid nanoparticle (LPHNPs) mix with plasmid Deoxyribonucleic acid encoding the green fluorescent protein. The Lipid-polymer hybrid nanoparticle (LPHNPs) consist of a PEI core and lipid shell of PC/DSPE-PEG. The Deoxyribonucleic acid (DNA) loaded Lipid-polymer hybrid nanoparticle (LPHNP) is successfully transfected into the HEK 293 cell as well as MDA-MP-231 breast cancer cell. The transfection efficiency is higher than the marketed Lipofectamine. These complexes are highly stable and have minimal cytotoxicity toward the HEK 293 cell. They also report that the PEGylated Lipid-polymer hybrid nanoparticle (LPHNPs) have higher transfection efficiency than non-PEGylated Lipid-polymer hybrid nanoparticle (LPHNP) system.

Si-RNA delivery

Small interfering Ribonucleic acid (SiRNA) is an important tool for gene therapy and help in suppressing the expression of the specific gene by the RNA interference process. Ex. The delivery of Small

interfering Ribonucleic acid to the cancer cells that initiate the RNA interference pathway to block the protein expression into the tumor initiation and progression [89]. The formulation method for developing a Small interfering Ribonucleic acid delivery system is some as a Deoxyribonucleic acid (DNA) delivery system (Polyplexes and Lipoplexes) [29, 112] but Deoxyribonucleic acid (DNA) delivery has some limitations like poor stability during oral or systemic administration thus to overcome this problem develop a new system called Small interfering Ribonucleic acid (SiRNA) development. According to Yang *et al.*, they prepared siRNA loaded LPHNPs by out method, in which the LPHNP and SiRNA held together by the electrostatic interaction [111]**.** Here two different polymeric core like Methoxy poly(ethylene glycol)-poly(lactide) copolymer (Methoxy poly(ethylene glycol)-poly(lactide) copolymer) are enveloped by BHEM-Chol lipid and evaluated. The polymeric core of mPEG-PLA/PLA is highly uptake by BT474 human breast cancer cells as compared to the mPEG-PLA core. The LPHNP/siRNA complex of Methoxy poly(ethylene glycol)-poly(lactide) copolymer (mPEG-PLA)/PLA core inhibits the cancer cell growth that showed in BT474 xenograft murine model. According to Shi *et al.*, they using the Double emulsification solvent evaporation method to incorporate the siRNA into the LPHNPs. The LPHNPs of Polylactic Glycolic acid (PLGA) and eggs PC/lecithin/DSPE-PEG exhibit 10 times higher encapsulation efficiency and siRNA loading capacity [108]. The LPHNP system releases the siRNA in a sustainable manner where 50% siRNA is released slowly within 12-20 h. According to Hasan *et al.*, they are prepared siRNA-loaded Polylactic Glycolic acid (PLGA) Nanoparticle by using the two-step PRINT method [36]. That also shows the 35-46% encapsulation efficiency. According to Su *et al.*, they also prepare the Messenger RNA (mRNA) loaded LPHNPs by electrostatic adsorption [110]. This LPHNP system made up of PBAE polymeric core and DOPC/DOTAP/DSPE-PEG-lipid. Here PBAE polymeric core is used because of there inherent pH-responsive character that promotes endolysosomal disruption. The Messenger RNA (mRNA) loaded LPHNPs successfully delivered the mRNA to the cytosol of dendritic cells with minimal toxicity.

Diagnostic imaging agent delivery

The LPHNPs are also used for the delivery of diagnostic imaging agents for the medical diagnostic approach. The common diagnostic agents like quantum dots (QD), inorganic nanocrystals, Barium sulfate, Gastrograffin, etc are used in computed tomography (CT), magnetic resonance imaging (MRI), X-Ray/Mammography, Ultrasound, Fluoroscopy, Nuclear Medicine/Molecular Imaging, and Angiography/Interventional, etc. According to Mieszawska *et al.*, they prepare gold particle and quantum dots loaded two LPHNP systems by nanoprecipitation technique [30]. In which the gold particle and quantum dots are incorporated separately into the Polylactic Glycolic acid (PLGA) polymer by esterification reaction, and the lipid adsorbs on the polymer core. The *in vitro* bioimaging application of gold particle-loaded LPHNPs and quantum dots loaded LPHNPs are done on the macrophage cells of the mouse. According to Kandel *et al.*, they prepare the high fluorescence imaging agent poly[(9,9-dioctylfluorene-2,7-diyl)-co-(1,4-benzo-(2,1,3) thiadiazole)] (PFBT) loaded LPHNP system by using nano-precipitation technique [113]. In which the PFBT-polymer core encapsulates into the lipid-PEG layer. As compared to the non-hybrid nano-particle, the LPHNPs exhibit the higher quantum yield (greater than 50%) hence they have brighter fluorescence. The PFBT loaded LPHNPs have a significant technology for the labeling and imaging in the living biological system.

CONCLUSION

The LPHNP system are the most promising class of nanocarrier, they have various versatile drug delivery applications in the pharmaceutical field. The main goal of the researcher to develop an LPHNPs based drug delivery system for effective and safe therapy of clinic use and increases the efficacy and reduce the toxic side effects. In recent the most of carriers are discover for the drug delivery but they have some little bit limitations, LPHNPs carrier overcome these limitation and various problems associated with lipid-based Nanoparticle and polymeric nanoparticle like drug leakage, polymer toxicity, unstable during storage, less permeable, etc, because the polymer core is coated with lipid monolayer that prevents the drug leakage, and the lipid layer easily permeate into the phospholipid bilayer of human skin resulting maximum drug rich to the targeted site and show the high bioavailability. In the previous study, the LPHNPs is used for various type of disease like Cancer, Tumor, Immunotherapy and it also use in delivery of Antimicrobial agents, Nucleic acids, delivery of hydrophilic as well as Lipophilic drug and single as well as multiple drug delivery, etc. Here we are only focused on the delivery of the anticancer drug. The multidrug-resistant are present in the cancer cells, which is challenging to the delivery of the chemotherapeutic agent to the cells. The multifunctional LPHNP system delivers the imaging and chemotherapeutic agent for the diagnosis and treatment of cancerous cells. These LPHNP systems also help in the delivery of non-viral gene vectors to the cancerous cells. The targeting ability is the recent advancement of the LPHNP system, by applying the target moiety to the outer surface of LPHNPs the drug is directly delivered to the targeted cell. Finally, we expect that the LPHNP system will replace the normal lipid and polymeric Nanoparticle drug delivery system. With more clinical studies and more *in vitro*, *in vivo* reports and more reliable data shows the versatile application of LPHNPs in the field of drug delivery systems.

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CONFLICT OF INTERESTS

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