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Review Article

# Recent Advancements in the Lipid Polymer Hybrid Nanoparticles for Drug Delivery: An Overview

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## Abstract

Recent advances in the field of nanomedicine have promoted the development of several novel nanoformulations. Among them, the lipid polymer hybrid nanoparticles (LPHNPs) have gained an increasing attention by the researchers in this field owing to the attractive properties such as high stability and biocompatibility, prolonged circulation time, high drug loading capacity, stealth characteristics, controlled drug release properties, and superior *in vivo* efficacy. They possess the advantages of both the liposomes and polymeric nanoparticles which makes them a chosen one in the field of drug and gene delivery. The application of LPHNPs has not only been restricted to single drug delivery, but has been expanded to combinatorial and targeted therapeutics, and also for the effective delivery of genes, vaccines and diagnostic agents. This review highlights the recent advancements of LPHNPs in the field of drug delivery, including the types of hybrid nanoparticles, fabrication techniques, and their applications for single and combinatorial drug delivery, and gene therapeutics.

**Keywords:** Lipid Polymer Hybrid Nanoparticles; Drug and Gene Delivery; Combinatorial Therapy; Targeted Delivery

## Introduction

The development of nanotechnology in the field of drug delivery has improved the pharmacokinetics of a number of poorly soluble and poorly permeable drugs. During the past few decades, numerous nanoparticulate drug delivery systems have been approved for clinical use [1,2]. The various nanocarriers for drug delivery include polymeric nanoparticles [3], liposomes [4], micelles [5], solid lipid nanoparticles [6], nanostructured lipid carriers [7], dendrimers [8], carbon nanotubes [9], etc. Among them, polymeric nanoparticles and liposomes are the most dominant nanocarriers for drug delivery. Polymeric nanoparticles are the colloidal systems ranging in the nanometric size. They can be composed of either biodegradable or non-biodegradable polymers. The implementation of amphiphilic polymers led to the formation of nanoparticles with hydrophobic core and hydrophilic shell [10,11]. The polymeric nanoparticles permit higher drug loading and also provides controlled drug release kinetics. They could also be tailored to furnish a variety of surface decorated nanoparticles for enhancing their physicochemical properties [12,13]. Polymeric nanoparticles can be synthesized by a number of techniques on the basis of the types of drugs to be encapsulated and their application. Several polymeric nanoparticles have been approved for clinical use such as Genexol-PM, a nanoparticulate formulation comprising of paclitaxel and poly (d,l-lactide)-b-polyethylene glycol-methoxy, approved for metastatic breast cancer therapy [14]. On the other hand, liposomes are spherical vesicles composed of lipid bilayer made up of either natural or synthetic amphiphilic lipid molecules. They are extensively employed for drug delivery owing to their ease of fabrication methods, favorable safety profile, amenable to surface modification, and long systemic circulation half-life [15,16]. Numerous drug loaded liposomal formulations have been approved for clinical use including AmBisome (amphotericin B liposomes), DepoCyt (cytarabine liposomes), DepoDur (morphine liposomes), and DaunoXome (daunorubicin liposomes) [17].

Despite the successful clinical application of both polymeric nanoparticles and liposomes, there are still some issues related to both the formulation which need to be resolved. For example, liposomes face several hurdles such as intricate fabrication techniques, burst drug release and storage instability. Whilst the major concern with polymeric nanoparticles is their circulation half-life. Considering these drawbacks of both the formulations, LPHNPs have been developed, which possess the attributes of both of them [18,19]. They have been reported to exhibit very promising results in the field of nanomedicine. They are composed of core–shell structures comprising of three components: a biodegradable polymeric core for efficient drug loading; a monolayer of lipid surrounding the core for improving the stability and to minimize the drug diffusion to the external environment; and a lipid-polyethylene glycol (PEG) outer corona for enhancing the systemic circulation of LPHNPs and also to protect it against immune recognition. In comparison to other nanoformations for drug delivery, LPHNPs possess several distinct advantages; such as it could be made up of a range of lipids and biodegradable polymers, and the combinations of lipid-polymers improves their physicochemical characteristics to a greater extent, and also their superior ability to encapsulate different types of therapeutic molecules [20].

## Types of lipid polymer hybrid nanoparticles

### Polymer core-lipid shell nanoparticles

Polymer core-lipid shell nanoparticles comprises of an inner polymeric core surrounded by one or more outer layer of lipid membranes. The role of polymer in this type of formulation is to provide stability to the lipid layer [18]. The hydrophobic drugs are quite suited to be incorporated within this formulation, but hydrophilic drugs are not a suitable candidate to be loaded in this system. In order to solve this problem, a complex mixture of lipid and polymer can be used. The amphiphilicity of both the lipids and polymers helps in the development of Nano systems for the simultaneous delivery of multiple hydrophobic/hydrophilic drugs. For instance, a multilayered polymer lipid hybrid nanoparticle was developed for the delivery of three distinct chemotherapeutic drugs in a single delivery vehicle [21]. The nanoparticles were prepared by a modified w/o emulsion technique and allows for the entrapment of 5-fluorouracil (5-FU), oxaliplatin and camptothecin. The inner core of the nanoparticles was composed of diblock copolymer of methoxy polyethylene glycol (mPEG) and polylactide (PLA), surrounded by the mixture of three lipids, DSPE-PEG (1,2-distearoyl-snglycero- 3-phosphoethanolamine-N-poly (ethylene glycol)), lecithin, and cholesterol. The nanosystems were designed in such a way that 5-FU was encapsulated within the PEG hydrophilic core, while hydrophobic camptothecin was entrapped in the PLA shell; and oxaliplatin was incorporated during the lipid coating phase into the lipid/polymer interface.

The various factors governing the drug loading and entrapment efficiency in case of lipid polymer core-shell nanoparticles are methods of preparation, aqueous solubility of the drug, miscibility of drug in lipid and polymeric phases, lipid-polymer ratio, and charge interactions between drug and lipid [18].

### Hollow core/shell lipid-polymer-lipid hybrid nanoparticles

The hollow core/shell lipid-polymer-lipid nanoparticles consist of polymeric nanoparticles (NPs) and PEGylated lipoplexes. These hybrid NPs comprises of the following layers: an inner hollow core made up of lipid layer bearing positive charge, a middle hydrophobic PLGA (poly(lactic-co-glycolic acid)) layer, and an interface between PLGA and an outer PEG layer made up of a neutral lipid layer. They could be prepared by the double emulsification solvent evaporation method [22]. They are unique from other LPHNPs since they exhibit the features of both PLGA NPs and PEGylated lipoplexes. The significance of positively charged hollow core is that they could encapsulate the anionic drugs more readily than the polymers [23]. The middle layer composed of polymer could retard the rate of drug release from the nanosystem [22]. The outer PEG lipid layer in the system signifies that the nanoparticles escapes from the recognition by the macrophages and enhances their stability in the systemic circulation, and also retards the polymer degradation and drug release [22,24].

For stabilizing the formulation, sometimes a combination of lipids might be used to form the outermost layer. One of the lipids might self-assemble with their hydrophilic head facing towards the aqueous phase, while their tail towards the polymeric phase and the remaining portion forming a complex with PEG [25]. In case of such type of complex formation, the concentrations of the lipids should be below their respective critical micelle concentration (CMC) to prevent the risk of formation of liposomes and micelles. The crucial factors governing the formation of hollow core lipid-polymer-lipid nanoparticles are choice of inner cationic lipids, the length of outer PEG chain, and the molecular weight of middle polymeric layer [26]. Shi., *et al.* [25] developed a hollow core/shell lipid-polymer-lipid hybrid nanostructure prepared by a modified double-emulsion solvent evaporation method and self-assembly technique for siRNA delivery. These nanostructures were composed of four components– an inner core made up of positively charged lipid layer, a middle layer of hydrophobic PLGA, and an outer layer

of neutral charged lipid layer forming an interface between the PLGA and the outer PEG layer. As compared to PLGA alone, the inner positively charged core of cationic lipids could encapsulate siRNA much more efficiently.

## Lipid bilayer-coated polymeric nanoparticles

Several researches are available focusing on the development of long-circulating nanoformulations for drug delivery and targeting via both active and passive mechanisms [27,28]. Various strategies such as modifications in particle size, shape, surface charge and targeting ligands attached to the surface have been investigated to increase the residence time of NPs *in vivo* [29]. The adsorption of PEG on the surface of the NPs has solved the issue to some extent, however recently anti-PEG immunological response has been observed in several cases. Recently, advancement in the molecular and cellular biology has encouraged the researchers to develop nanocarriers enclosed within the red blood cells (RBCs), since they are natural long circulating delivery carriers and could easily escape from macrophage uptake [30]. In these types of delivery vehicles, RBCs were extruded to form RBC-membrane derived vesicles and then conjugated with polymeric NPs to form RBC-membrane-camouflaged polymeric NPs [31]. Due to their denser lipid barrier, RBCs provide greater sustained release of drugs than both liposomes and polymeric nanocarriers. Despite of several promising advantages of RBC membrane-camouflaged polymeric NPs, it also encounters some drawbacks that people with different blood groups have different types of surface antigens on RBCs and that have to be cross matched at the time of blood transfusion which is quite a tough challenge [31].

## Polymer caged nanoparticles

Polymer caged nanoparticles are actually liposomes with their surface modified by polymers for better functionality [32]. These nanosytems are quite stable and exhibits stimuli-responsive behavior. For instance, liposomes were formulated and their surface was decorated with a cholesterol-functionalized poly(acrylic acid) whose carboxylate groups form cross-linking bond with telechelic 2,2-(ethylenedioxy) bis(ethylamine) linkers (as shown in Figure 1) [33]. In these types of formulations, the polymeric cage not only protects the drug from outer environment but also allows pH-triggered release of drug in the acidic environment, such as in case of tumor cells [34]. By varying the degree of cross-linking in the polymer cage, the surface properties of the nanocarriers could be altered for prolonged circulation *in vivo*.

**Figure 1:** Schematic representation of polymer cased liposomes [33].

In an investigation by Basel., *et al.* [32], they developed an improved liposome system that could result into more specific targeting, with faster drug release and also prevents drug leaking, by stabilizing the liposomes via cross-linked polymer shell comprised of a consensus sequences for cancer-associated proteases (protease-triggered, caged liposomes). A cholesterol-anchored, graft copolymer, consisting of a short peptide sequence for urokinase plasminogen activator (uPA) and poly (acrylic acid), was synthesized and incorporated into liposomes. The protease-triggered, caged liposomes showed high resistance to osmotic swelling and also prevented leakage of its contents. In another study by Hong., *et al.* [35], they synthesized an acid-degradable polymer-caged lipoplex (PCL) composed of a cationic lipoplex core and a biocompatible, pH-sensitive polymer shell, for effective delivery of siRNA. The system facilitated facile drug loading, acid-triggered release, improved cellular internalization, and significant

## Lipid-enveloped nanogels

The lipid-enveloped nanogels synthesized by a modified two-step technique based on photo crosslinking method showed better physicochemical properties [36]. In this method, a solution containing the macromolecular and/or small molecular monomer, model drugs, and other functional materials is mixed with lipids though a thin lipid film hydration method or co-extruding method. Then polymerization was induced by UV to get the final lipid-enveloped nanogel. Murphy., *et al.* [37] synthesized integrin αvβ3-targeted lipid-coated nanogels with crosslinked human serum

albumin in the core for delivering various anticancer therapeutic agents like paclitaxel, docetaxel, bortezomib, 17-AAG, sorafenib, sunitinib, bosutinib, and dasatinib. This nanogel exhibited a 15-fold enhancement in antitumor activity than Abraxane in orthotopic breast and pancreas tumors in mice. Park., *et al.* [38] also prepared lipid-enveloped nanogel from β-cyclodextrin (β-CD) and PLA–PEG–PLA for the effective delivery of hydrophobic drugs (transforming growth factor-β inhibitor, SB05124) and hydrophilic cytokines (interleukin-2, IL-2, a cytokine for metastatic melanoma). SB05124 was complexed with β-CDs and IL-2 was encapsulated in the outer polymer-hydrogel matrix. This hybrid nanogel formulation allows for the sustained release of both SB05124 and IL-2 simultaneously and inhibited tumor growth, prolonged the survival of tumor-bearing mice, improved the action of natural killer cells and intratumoral-activated CD8+ T-cell infiltration.

## Techniques for the fabrication of lipid polymer hybrid nanoparticles

The techniques for the preparation of LPHNPs are different from the preparation methods for polymeric nanoparticles and liposomes. Previously, an intricate two step synthesis method was employed for the synthesis of LPHNPs. In this technique, the first step involved the formation of polymeric nanoparticles followed by incorporating it within the liposomes. This complicated process also deteriorates the physicochemical properties of the hybrid nanoparticles. For simplifying the technique, a more facile single step synthesis comprising of a combination of nanoprecipitation and self-assembly method has been reported [22]. The outline of the techniques for the preparation of LPHNPs is depicted in figure 2.

## Recent advancements in the LPHNPs for drug delivery

With an increased advancement in the field of nanomedicine, the lipid polymer hybrid nanoparticles for drug delivery has also emerged rapidly. Since these nanocarriers possess the attractive properties of both the liposomes and polymeric nanoparticles, they are more widely investigated by the researchers to be scaled up to the industrial level [39,40]. The appropriate selection of lipids and polymers for the fabrication of LPHNPs is the prime concern for improving their stability and enhancing their blood circulation time. Moreover, drug loaded LPHNPs could be modified accordingly for improving its physicochemical features and site-specific drug delivery [19].

**Figure 2:** Schematic representation for the preparation of LPHNPs.

In this section, we would highlight the recent advancements made in the LPHNPS for drug and gene delivery.

## Anticancer drug delivery

Recently, LPHNPs have proved to be a promising novel approach for the delivery of anticancer therapeutics. These formulations help in the improved biocompatibility and stability, increased circulation time in the bloodstream, and target specific drug delivery [41]. They also possess the capability to deliver a combination of drugs simultaneously in a controlled manner for better efficacy. For example, doxorubicin (DOX) and indocyanine green (ICG) loaded PLGA-lecithin-PEG nanoparticles (DINPs) were prepared by implementing a single-step sonication technique. As compared to the chemo or photothermal treatment alone, the DINPs containing the combination of drugs with laser irradiation synergistically induced the apoptosis and death of DOX-sensitive MCF-7 and DOX-resistant MCF-7/ADR cells, and suppressed MCF-7 and MCF- 7/ADR tumor growth *in vivo* [42]. On the other hand, Wang., *et al*. [43] synthesized core shell lipid-polymer hybrid nanoparticles (CSLPHNPs) with PLGA core and lipid layer loaded with docetaxel and clinically used inhibitor of sphingosine kinase 1 (SK1) FTY720 (fingolimod). CSLPHNPs could significantly target tumor cells and exhibited reduced side effects in comparison to free drugs, mainly, reversing lymphopenia induced by FTY720.

The surface functionalization of LPHNPs with targeting agents such as folic acid (FA), antibodies, and aptamers could result into their active targeting to the desired organs and tissues. For instance, a novel lipid–polymer hybrid drug carrier composed of folate-modified lipid-shell and polymer-core nanoparticles was developed for controlled and targeted delivery of paclitaxel (PTX). The core-shell NPs comprised of a poly (ε-caprolactone) hydrophobic core formed by self-assembly of poly (ε-caprolactone) – poly (ethylene glycol) – poly (ε-caprolactone) (PCL-PEG-PCL) amphiphilic copolymers, a lipid monolayer formed with 1,2-distearoyl-sn-glycero - 3- phosphoethanolamine - N- [methoxy (polyethylene glycol)-2000] (DSPE-PEG2000), and FA as a targeting ligand on the surface of nanoparticles. The hybrid NPs were prepared by a thin-film hydration and ultrasonic dispersion technique [44]. In another study, adriamycin-loaded polymer–lipid hybrid nanoparticles conjugated with anti-EGF receptor antibody was formulated for targeting hepatocellular carcinoma (HCC) [45].

Various stimuli-responsive LPHNPs for drug delivery have been reported by the researchers in this field. Kong., *et al.* [46] developed a lipid–polymer hybrid nanoparticle system containing magnetic beads for stimuli-responsive drug delivery by utilizing a remote radio frequency (RF) magnetic field. These hybrid nanoparticles exhibited long-term stability in terms of particle size and polydispersity index in phosphate-buffered saline (PBS). The effective loading of camptothecin (CPT) and $Fe_3O_4$ in the hybrid nanoparticles was demonstrated. The cellular uptake of the stimuli responsive nanoparticles was observed into MT2 mouse breast cancer cells. The drug loaded nanoparticles showed reduction in MT2 mouse breast cancer cell growth *in vitro* in the presence of a remote RF field.

## Antimicrobial drug delivery

Bacterial biofilms is a community of bacterial cells enclosed by a self-secreted matrix of extracellular polymeric substances (EPS). These bacterial populations can evade the immune system and are highly resistant to the conventional antibiotics [47]. The antibiotic delivery by means of LPHNPs is widely investigated to counter such bacterial biofilms due to their unique physicochemical properties, superb biofilm affinity, and ability to penetrate sputum. These hybrid nanoparticles could significantly deliver the antibiotics to bacterial biofilm, and hence enhances their antibacterial activity [48].

Seedat., *et al*. [49] prepared LPHNPs by employing vancomycin (VCM), glyceryl triplamitate and Eudragit RS100 as the drug, lipid and polymer respectively. Oleic acid (OA), Chitosan (CHT) and Sodium alginate (ALG) were used as co-excipients. The obtained data showed that in vitro antibacterial activity of all nanoformulations showed better results against both *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA), with VCM–OA and VCM–CHT exhibiting better efficacy against MRSA. In another research work, Dave., *et al.* [50] synthesized LPHNPs by using PLA and soya lecithin for topical and targeted delivery of Norfloxacin by emulsification solvent evaporation technique. The lipid polymer hybrid nanoparticles showed an improved antimicrobial activity against both *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

## Gene delivery

In the recent years, the potential of LPHNPs for gene delivery has been widely investigated by the researchers. Due to the same features of LPHNPs for drug delivery (high stability, extended circulation time, high biocompatibility and ability to get escaped from immune recognition), it has also been employed for gene delivery [51,52].

Yang., *et al*. [53] prepared cationic lipid-polymer hybrid nanoparticles by a single-step nanoprecipitation method and comprised of a cationic lipid (N, N-bis (2-hydroxyethyl)-N-methyl-N-(2-cholesteryloxycarbonyl aminoethyl) ammonium bromide, BHEM-Chol) and amphiphilic polymers for systemic delivery of siRNA. The prepared hybrid nanoparticles were highly stable in serum and exhibited excellent biocompatibility in comparison to that of pure BHEM-Chol particles. The hybrid nanoparticles successfully delivered siRNA into BT474 cells and also prevented the loaded siRNA from the endosome into the cytoplasm. The hybrid nanoparticles loaded with polo-like kinase 1 (Plk1)-specific siRNA (siPlk1) downregulated the expression of oncogene Plk1 and induced the apoptosis of cancer cells both *in vitro* and *in vivo* and also suppressed the growth of tumor cells subsequent to systemic administration. On the other hand, Bose., *et al.* [54] also synthesized cationic hybrid nanoparticles comprising of nanospheres with a PLGA core and cationic lipid shell, and the influence of the concentration of cationic lipid on the properties of lipid polymer hybrid nanocarriers was explored. Lipid–polymer hybrid nanospheres (LPHNSs) exhibited significant plasmid DNA-binding capacity. In comparison to the conventional transfection agents, such as Lipofectamine and polyethyleneimine–PLGA, the LPHNSs exhibited less cytotoxicity with HEK293T, HeLa, HaCaT, and HepG2 cells. With an increase in the concentration of cationic lipid, the particle size of LPHNSs decreased while their ζ-potential increased. Moreover, the *in vitro* transfection efficiency of LPHNSs also increased with the increasing concentration of cationic lipid.

In another investigation, lipid-polymer hybrid nanoparticles containing both pemetrexed and miR-21 antisense oligonucleotide (anti-miR-21), have been prepared for the treatment of glioblastoma. The size of the hybrid nanoparticles was below 100 nm and exhibited sustained release of pemetrexed for up to 10 hours. The results showed that the co-delivery of anti-miR-21 significantly improved accumulation of hybrid nanoparticles in the nucleus of U87MG cells [55]. Yet in another research work, novel hybrid lipid-polymer nanoparticles (hNPs) were synthesized that comprised of PLGA and dipalmitoyl phosphatidylcholine (DPPC) as siRNA inhalation system. siRNA loaded hNPs exhibited optimal *in vitro* aerosol performance after delivery with a vibrating mesh nebulizer. Moreover, small-angle X-ray scattering analyses showed high stability upon incubation with artificial mucus, thereby confirming the capability of hNPs for direct aerosolization on mucus-lined airways. Furthermore, upon treatment with siRNA-loaded hNPs, a prolonged inhibition of ENaC protein expression in A549 cells was observed [52].

## Future Directions and Conclusion

The lipid polymer hybrid nanoparticles have revolutionized the field of nanomedicine through its advantageous features of both the polymeric nanoparticles and liposomes. They exhibit high stability, biocompatibility, selective targeting, prolonged circulation time, greater drug encapsulation efficiency, and significant biological response. These unique properties enable them to be potentially applied in the field of drug and gene delivery. However, most of the current researches on LPHNPs have been restricted to its *in vitro* efficacy. Their translation into effective therapeutics is still in its infancy and several challenges in this field are yet to be resolved. The key areas which need to be focused include their stability, safety, toxicity, pharmacokinetic profiles, optimization of the targeting ligands, and *in vivo* fate. The future warrants the implementation of drug delivery vehicles which mimic the lipid-enveloped biological structures to promote the development of combinational therapy. RBC membrane-enveloped structures also showed greater promise as drug delivery vehicle. But several issues such as retaining their properties, prolonging the circulation time, and minimizing drug leakage need to be overcome. The scenario of the development of LPHNPs is likely to change in the near future. In the coming years, we expect interesting advancements in this field with an exponential increase in the researches performed with these hybrid nanosystems for the delivery of encapsulated cargoes. It is foreseen that over the next few years, several clinical studies on these versatile hybrid nanocarriers as a therapeutics delivery system will be reported.

## Competing Interest

No competing interest to declare.

## Bibliography

1. ud Din F., *et al.* "Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors". *International Journal of Nanomedicine* 12 (2017): 7291-7309.

2. Badwaik HR., *et al.* "Oral delivery of proteins and polypeptides through polysaccharide nanocarriers". *Polysaccharide based Nano-Biocarrier in Drug Delivery* (2018): 1-24.

3. Masood F. "Polymeric nanoparticles for targeted drug delivery system for cancer therapy". *Materials Science and Engineering C* 60 (2016): 569-578.

4. Daraee H., *et al.* "Application of liposomes in medicine and drug delivery". *Artificial Cells, Nanomedicine, and Biotechnology* 44.1 (2016): 381-391.

5. Mao J., *et al.* "A simple dual-pH responsive prodrug-based polymeric micelle for drug delivery". *ACS Applied Materials and Interfaces* 8.27 (2016): 17109-17117.

6. Nassimi M., *et al.* "A toxicological evaluation of inhaled solid lipid nanoparticles used as a potential drug delivery system for the lung". *European Journal of Pharmaceutics and Biopharmaceutics* 75.2 (2010): 107-116.

7. Chakraborty S., *et al.* "Inhibitory effect of a new orally active cedrol-loaded nanostructured lipid carrier on compound 48/80-induced mast cell degranulation and anaphylactic shock in mice". *International Journal of Nanomedicine* 12 (2017): 4849-4868.

8. Caminade AM and Turrin CO. "Dendrimers for drug delivery". *Journal of Materials Chemistry B* 2.26 (2014): 4055-4066.

9. Zhang W., *et al.* "The application of carbon nanotubes in target drug delivery systems for cancer therapies". *Nanoscale Research Letters* 6.1 (2011): 555.

10. Chan JM., *et al.* "PLGA–lecithin–PEG core–shell nanoparticles for controlled drug delivery". *Biomaterials* 30.8 (2009): 1627-1634.

11. Colson YL and Grinstaff MW. "Biologically responsive polymeric nanoparticles for drug delivery". *Advanced Materials* 24.28 (2012): 3878-3886.

12. Zhang Z., *et al.* "Folate-decorated poly (lactide-co-glycolide)-vitamin E TPGS nanoparticles for targeted drug delivery". *Biomaterials* 28.10 (2007): 1889-1899.

13. Ruge CA., *et al.* "Pulmonary surfactant protein A-mediated enrichment of surface-decorated polymeric nanoparticles in alveolar macrophages". *Molecular Pharmaceutics* 13.12 (2016): 4168-4178.

14. Werner ME., *et al.* "Preclinical evaluation of Genexol-PM, a nanoparticle formulation of paclitaxel, as a novel radiosensitizer for the treatment of non-small cell lung cancer". *International Journal of Radiation Oncology* Biology* Physics* 86.3 (2013): 463-468.

15. Akbarzadeh A., *et al.* "Liposome: classification, preparation, and applications". *Nanoscale Research Letters* 8.1 (2013): 102.

16. Bozzuto G and Molinari A. "Liposomes as nanomedical devices". *International Journal of Nanomedicine* 10 (2015): 975-999.

17. Chang HI and Yeh MK. "Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy". *International Journal of Nanomedicine* 7 (2012): 49-60.

18. Mandal B., *et al.* "Core–shell-type lipid–polymer hybrid nanoparticles as a drug delivery platform". *Nanomedicine: Nanotechnology, Biology and Medicine* 9.4 (2013): 474-491.

19. Bose RJC., *et al.* "Lipid–polymer hybrid nanoparticle-mediated therapeutics delivery: advances and challenges". *Drug Discovery Today* 22.8 (2017): 1258-1265.

20. Hadinoto K., *et al.* "Lipid–polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review". *European Journal of Pharmaceutics and Biopharmaceutics* 85.3 (2013): 427-443.

21. Li F., *et al.* "Multiple layer-by-layer lipid-polymer hybrid nanoparticles for improved FOLFIRINOX chemotherapy in pancreatic tumor models". *Advanced Functional Materials* 25.5 (2015): 788-798.

22. Zhang L., *et al.* "Self-assembled lipid–polymer hybrid nanoparticles: a robust drug delivery platform". *ACS Nano* 2.8 (2008): 1696-1702.

23. Pautot S., *et al.* "Engineering asymmetric vesicles". *Proceedings of the National Academy of Sciences* 100.19 (2003): 10718-10721.

24. Davis ME. "The first targeted delivery of siRNA in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: from concept to clinic". *Molecular Pharmaceutics* 6.3 (2009): 659-668.

25. Shi J., *et al.* "Differentially charged hollow core/shell lipid–polymer–lipid hybrid nanoparticles for small interfering RNA delivery". *Angewandte Chemie International Edition* 50.31 (2011): 7027-7031.

26. Saad M., *et al.* "Co-delivery of siRNA and an anticancer drug for treatment of multidrug-resistant cancer". *Nanomedicine (Lond.)* 3.6 (2008): 761-776.

27. Moghimi SM., *et al.* "Long-circulating and target-specific nanoparticles: theory to practice". *Pharmacological Reviews* 53.2 (2001): 283-318.

28. Zale SE., *et al.* "Long circulating nanoparticles for sustained release of therapeutic agents". *U.S. Patent No.* 9,198,874. (2015).

29. Jahan ST., *et al.* "Targeted therapeutic nanoparticles: An immense promise to fight against cancer". *Journal of Drug Delivery* 2017 (2017).

30. Tanaka M and Sackmann E. "Polymer-supported membranes as models of the cell surface". *Nature* 437.7059 (2005): 656.

31. Hu CMJ., *et al.* "Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform". *Proceedings of the National Academy of Sciences* 108.27 (2011): 10980-10985.

32. Basel MT., *et al.* "Protease-sensitive, polymer-caged liposomes: a method for making highly targeted liposomes using triggered release". *ACS Nano* 5.3 (2011): 2162-2175.

33. Lee SM., *et al.* "Polymer-caged lipsomes: a pH-responsive delivery system with high stability". *Journal of the American Chemical Society* 129.49 (2007): 15096-15097.

34. Casey JR., *et al.* "Sensors and regulators of intracellular pH". *Nature Reviews Molecular Cell Biology* 11.1 (2010): 50-61.

35. Hong BJ., *et al.* "Acid-degradable polymer-caged lipoplex (PCL) platform for siRNA delivery: facile cellular triggered release of siRNA". *Journal of the American Chemical Society* 135.47 (2013): 17655-17658.

36. Schillemans JP., *et al.* "Synthesis of bilayer-coated nanogels by selective cross-linking of monomers inside liposomes". *Macromolecules* 39.17 (2006): 5885-5890.

37. Murphy EA., *et al.* "Targeted nanogels: a versatile platform for drug delivery to tumors". *Molecular Cancer Therapeutics* 10 (2011): 972-982.

38. Park J., *et al.* "Combination delivery of TGF-β inhibitor and IL-2 by nanoscale liposomal polymeric gels enhances tumour

immunotherapy". *Nature Materials* 11.10 (2012): 895-905.

39. Hallan SS., *et al.* "Lipid polymer hybrid as emerging tool in nanocarriers for oral drug delivery". *Artificial Cells, Nanomedicine, and Biotechnology* 44.1 (2016): 334-349.

40. Shegokar R., *et al*. "Production *and* stability of stavudine solid lipid nanoparticles-From lab to industrial scale". *International Journal of Pharmaceutics* 416 (2011) : 461-470.

41. Ramasamy T., *et al.* "Layer-by-layer coated lipid–polymer hybrid nanoparticles designed for use in anticancer drug delivery". *Carbohydrate Polymers* 102 (2014): 653-661.

42. Zheng M., *et al.* "Single-step assembly of DOX/ICG loaded lipid–polymer nanoparticles for highly effective chemo-photothermal combination therapy". *ACS Nano* 7.3 (2013): 2056-2067.

43. Wang Qi., *et al.* "Core shell lipid-polymer hybrid nanoparticles with combined docetaxel and molecular targeted therapy for the treatment of metastatic prostate cancer". *Scientific Reports* 7.1 (2017): 5901.

44. Zhang L., *et al.* "Folate-modified lipid–polymer hybrid nanoparticles for targeted paclitaxel delivery". *International Journal of Nanomedicine* 10 (2015): 2101-2114.

45. Gao J., *et al.* "Polymer–lipid hybrid nanoparticles conjugated with anti-EGF receptor antibody for targeted drug delivery to hepatocellular carcinoma". *Nanomedicine* 9.2 (2014): 279-293.

46. Kong SD., *et al.* "Magnetic field activated lipid–polymer hybrid nanoparticles for stimuli-responsive drug release". *Acta Biomaterialia* 9.3 (2013): 5447-5452.

47. Kostakioti M., *et al.* "Bacterial biofilms: development, dispersal, and therapeutic strategies in the dawn of the postantibiotic era". *Cold Spring Harbor Perspectives in Medicine* 3.4 (2013): a010306.

48. Cheow WS., *et al.* "The roles of lipid in anti-biofilm efficacy of lipid–polymer hybrid nanoparticles encapsulating antibiotics". *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 389.1-3 (2011): 158-165.

49. Seedat N., *et al.* "Co-encapsulation of multi-lipids and polymers enhances the performance of vancomycin in lipid–polymer hybrid nanoparticles: In vitro and in silico studies". *Materials Science and Engineering: C* 61 (2016): 616-630.

50. Dave V., *et al.* "Lipid-polymer hybrid nanoparticles: development *and* statistical optimization of norfloxacin for topical drug delivery system". *Bioactive Materials* 2.4 (2017): 269-280.

51. Colombo S., *et al.* "Mechanistic profiling of the siRNA delivery dynamics of lipid–polymer hybrid nanoparticles". *Journal of Controlled Release* 201 (2015): 22-31.

52. d'Angelo I., *et al.* "Hybrid lipid/polymer nanoparticles for pulmonary delivery of siRNA: Development and fate upon in vitro deposition on the human epithelial airway barrier". *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 31.3 (2018): 170-181.

53. Yang XZ., *et al.* "Single-step assembly of cationic lipid–polymer hybrid nanoparticles for systemic delivery of siRNA". *ACS Nano* 6.6 (2012): 4955-4965.

54. Bose RJC., *et al.* "Influence of cationic lipid concentration on properties of lipid–polymer hybrid nanospheres for gene delivery". *International Journal of Nanomedicine* 10 (2015): 5367-5382.

55. Küçüktürkmen B., *et al.* "Co-delivery of pemetrexed and miR-21 antisense oligonucleotide by lipid-polymer hybrid nanoparticles and effects on glioblastoma cells". *Drug Development and Industrial Pharmacy* 43.1 (2017): 12-21.

**Volume 3 Issue 2 February 2019**