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Polymer Lipid Hybrid Nanoparticles: An Overview on Critical Aspects and Pharmaceutical Applications

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Abstract

In the health care system nanoparticles gain a lot of attention due to its vast advantages over other formulations. Various types of nanosystems are used for drug delivery such as polymeric nano-particles (NP), solid lipid NP, and liposomes. But they have some inherent limitations like drug leakage, low biocompatibility, use of specific drug molecule that is being enumerated in the literature. Drug-loaded lipid Polymer Hybrid Nano-Particles (LPHNP) is intentionally created for resolving all the constraints of conventional nano systems. The pros of both polymer and lipid NP are rendered in LPHNP. The release of water-soluble drugs is restricted by it due to its structure as the polymeric center of the structure is coated by the lipid. This brings about the augmented efficiency of trapping. Thus, oil or water-soluble drugs can be encapsulated ingeniously when creating lipid polymer hybrid nano-Particles (LPHNP). The development of hybrid polymer materials can avoid the synthesis of new molecules, which is an overall expensive process that can take several years to get to the proper elaboration and approval. Thus, the combination of properties in a single hybrid system can have several advantages over non-hybrid platforms, such as improvements in circulation time, structural disintegration, high stability, premature release, low encapsulation rate and unspecific release kinetics. Thus, the aim of the present review is to outline a rapid and well-oriented scenario concerning the knowledge about polymer-hybrid nanoparticles as well as requirements for the choice of drugs, lipids, polymers, disparate production techniques, various applications of lipid polymer HNP in gene delivery, cancer therapy, together with antibacterial therapy, are deemed in the proposed study.

Keywords: Lipid; Polymer; Hybrid Nanoparticles; Cancer Therapy; Gene Therapy; Antibacterial Therapy

Abbreviations: PLNs: Polymer Lipid Hybrid Nanoparticles; NPs: Nanoparticles; DCM: Dichloromethane; LPHNP's: Lipid Polymer Hybrid Nanoparticles; LNP: Lipidic Nanoparticle; MNP: Magnetic Nanoparticle; ICG: Indocyanin Green; CSLPHNs: Core-Shell Lipid-Polymer Hybrid Nanoparticles.

Introduction

Polymeric lipid hybrid nanoparticles (PLNs) are a new generation of drug delivery systems that focus on the unique characteristics of polymeric nanosystems and liposomes that attributed to their early pharmacological potential even as also discussing downsides like structural disintegration, curtailed biodistribution, and material loss. This hybrid system has the ability to be a reliable drug delivery method with efficient pharmacokinetic profile, high entrapment efficacy, and improved bioavailability, as well as molecular targets and suitable tissue [1]. PLNs is a protean platform for drugs which is created to overcome the restriction of polymer [2,3] and lipid nanoparticles (NPs) [2]. The PLN consists of three different lucid components such as lipid, polymer, and bioactive (drug). The combined strength of the polymer and the lipid NPs have been related to accommodate PLN. Lipid polymer hybrid nanoparticles (LPHNPs) are consisting essentially of three subsequent layers:

- An internal aquaphobic core layer where large quantities of lipophilic drugs can be encapsulated;
- An interfacial lipid layer that becomes versatile and biocompatible shell;
- An outer layer of hydrophilic polymer stealth improves circulation time and LPHNPs stability [4].

The lipid is a biodegradable hydrographic core in PLN that includes a drug (water-insoluble), while a hydrophilic coat is of the polymer. This improves stability, transmits control release properties, and helps to avoid the recognition of the immune system. PLN can therefore be an adaptable drug platform with increased drug capacity, configurable, long release characteristics, stability, and differential cell or tissue targeting in an easy manner [5]. LPN also have an application in various drug delivery like cancer, gene delivery, for the activation of retina signaling pathways in CNS by intravenous administration, for encapsulation of polyphenols [6].

Method of Preparation of LPHNP's

LPHNP's are prepared by one step or two step method.

Two Step Process

The two-step technique (Figure 1) is typically used for the preparation of LPHNP's with a lipid bi or multilayer shell. A process of emulsion, a nanoprecipitation method or a high-pressure homogenization method forms the polymer core [7]. Alternative methods of preparing LPHNP's are mentioned in the literature, including as after hydrating, sonicating, or extruding the lipid with the polymeric dispersion or buffer, the polymeric core and lipid shell are combined [8].

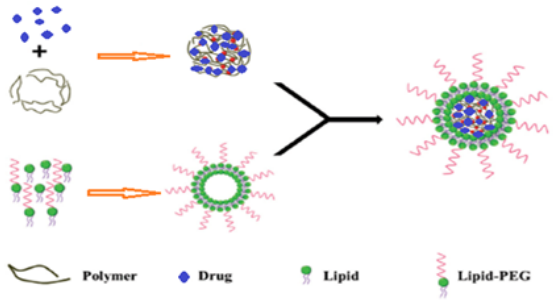

Figure 1: Diagrammatic presentation of bilayer LPHNP's using a two-step approach (Reproduced with permission from Royal Society of Chemistry Krishnamurthy, et al. [7]).

Double Emulsion Solvent Evaporation Method

One of the two step methods for producing of LPHNP's (Figure 2) is also the double emulsion solvent evaporation method [9]. If the bioactive molecule is hydrophilic but won't dissolve in an organic solution, the preparation of the polymer core require a water-in-oil-in-water i.e. w/o/w double emulsion method Cheow WS, et al. [10], Yalcin TE, et al. [11] have described the fabrication of Gemcitabine LPHNs using a double emulsion solvent evaporation technique. In brief, the oil phase (O) was created using Soya phosphatidylcholine (SPC), a PLGA dichloromethane: acetone blend as an organic solvent, and a 1% (w/v) PVA solution containing Gemcitabine. To obtain primary emulsion, the mixture was sonicated with a probe sonicator. The secondary emulsion (water-in-oil-in-water) was made by combining the initial emulsion with an external aqueous PVA solution containing DSPE-PEG2000 and subjected to probe sonication. As a result, it's considered that the present LPHNs design has the potential to increase GEM systemic availability and extend systemic circulation [11].

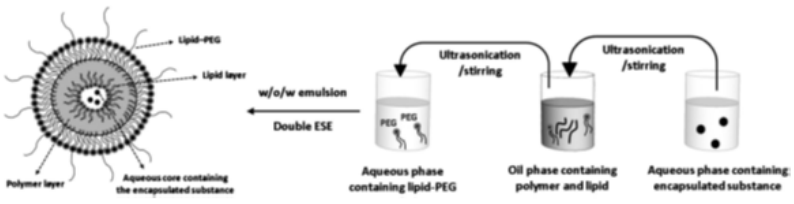

Figure 2: LPHNP's Prepared by Double Emulsion Solvent Evaporation Method (Reproduced with permission from Elsevier [9]).

One Step Process

Emulsion Solvent Evaporation Method: This approach is used when the drugs are soluble in organic (oil phase) solvent. Here organic phase is firstly prepared to contain polymer and drug. This phase is then mixed to an aqueous phase having lipid under ultrasonication/constant agitating to cause the formation of o/w emulsion. Formation of polymer core arises when the oil phase is allowed to evaporate, which subsequently yields lipid self-assemble structure to develop LPHNP's [10,12] as shown in Figure 3.

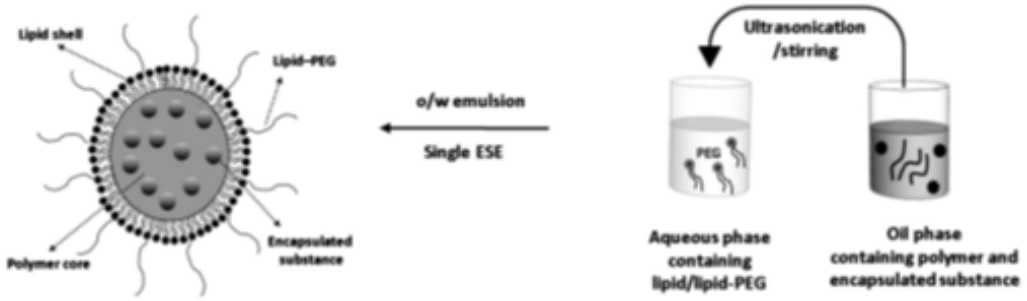

Figure 3: LPHNP's Prepared by Emulsion Solvent Evaporation Method (Reproduced with permission from Elsevier Hadinoto, et al. [9]).

Modified Solvent Extraction/ Evaporation Method

Here, an organic solvent is chosen, in which bioactive and lipid are dissolved (organic/polymer phase). Simultaneously polymer and surfactant are dissolved in water (aqueous phase). Slowly organic phase is mixed with aqueous phase dropwise under constant stirring to form a primary emulsion and homogenize using high speed homogenizer. Then favorable crosslinking agent is added, and rendered dispersion is subjected to the solvent evaporation method by using a magnetic stirrer to form LPHNPs. These LPHNPs will be separate out using centrifugation technique [4].

Ultrasonication Method

Hydrophilic actives are ideal for this technique. Using an ultrasonic probe, the melted lipids, bioactive, and polymer are incorporated and dispersed in a surfactant-containing aqueous media. LPHNPs were formed when the sample was cooled and solidified. Microparticles also have an impact on the dispersion value of the LPHNPs generated by these techniques, resulting in physical instability after processing. Lipid concentrations are minimal (< 1%), whereas surfactant concentrations are comparatively high. Metal corrosion is another important issue with ultrasonics [13,14].

High Pressure Homogenization Method

The drugs (for hydrophilic and lipophilic drugs.) along with polymer heated first cooled and dispersed in aqueous, lipid-present form. This phase results in a primary emulsion being subjected to high pressure and expansion of decompression, after which the droplets of the liquid are slowly broken down to the desired nanoparticles diameter range by strong shear forces. Here both hot and cold methods are possible, and homogenization pressures along with cycles are the most critical optimization parameters. [15].

Thin-Film Hydration and Ultrasonic Dispersion: In this procedure, bioactive is solubilized in an organic solvent (suitable) and allowed to evaporate under vacuum. As a result, a film forms around the vessel wall. Simultaneously, a suitable organic solvent is used to prepare a polymer solution. The polymer is then allowed to dissolve completely in the film. To achieve uniform mixing of bioactive and polymer, the used solvent should be recovered at lower pressure. An aqueous solution containing lipid is added, then the mixture is subjected to ultrasonic dispersion using an ultrasonic probe to create LPHNPs. This method is widely used because of its inherent advantages, such as its ability to produce uniform nanoparticles [16].

Nanoprecipitation Method

Nanoprecipitation is the simple production processes for LPHNP. Aqueous miscible solvent (e.g., ethanol, acetone, and acetonitrile) is chosen to incorporate polymer and drug. This solution then drops into a lipid-containing aqueous dispersion with the continuation of stirring. This causes the polymer to coil into LPHNP's this method of preparation is based on the process of emulsification, using a lipid replacement for surface-active agents. The oil phase dissolves lipids, polymers, and drugs to mix with the water to yield an O/W emulsion. Lipid's hydrophobic region attaches to the polymer core, and lipid's hydrophilic end extends to the aqueous phase to form LPHNP's efficiently recently, the nanoprecipitation process was used to fabricate LPHNs loaded with lidocaine (LDC), which can be act as a local anaesthetic [17-19].

Critical Aspects

GI absorption of LPHNP's

Literature reveals LPHNP's may improve the absorption of bioactives via increased uptake from M-cells of Peyer`s patches. LPHNP shows lymph system absorption [20]. Numerous drugs show low and variable bioavailability because of their low aqueous solubility [21] High-fat foods may be co-administered to boost the bioavailability of such medicines. The introduction of high fat meals ensures that GI tract residence time is increased, bile and lymph secretions enhanced, lymph movement is strengthened, the penurial wall is improved, metabolism and efflux activity are decreased, and blood flow improvements in mesenteric and liver disease significantly improve oral bioavailability of drug products [22] LPHNP's can easily cross the biological membrane with the help of four mechanism as transcellular transport, paracellular transport, carrier-mediated transport and receptor-mediated [23]. Lipids are vulnerable to enzyme degradation (gut wall), which leads in the development of surface-active mono- and di glycerides on the surface of lipid droplets/LPHNPs, improving absorption. Thus, molecules are separated, and micelles form. Such micelles interact and form mixed micelle with surface-active bile Salts. Bioactives absorbed through epithelial cells (small intestine) have two options:

- Can enter the lymph cells or
- Blood capillaries.

Lymphatic capillaries are also slightly more nanoparticle permeable as compared with blood capillaries. Bioactives targeted via intestinal lymphatics are never undergoing for first pass metabolism as the liver is completely bypassed during bioactive transportation. Thus, by transport through the lymphatic system, bioavailability (on oral administration) of bioactives undergoing extensive first-pass hepatic metabolism is drastically improved. Nevertheless, the length of the fatty acid chains depends on lymphatic absorption. According to the literature, co-administration of fatty acids with C-14 to C-18 chains improves lymphatic absorption [24,25].

Selection Criteria of Drug, Lipid and Polymer for LPHNP's

Lipid polymer hybrid nanoparticles (LPHNP's) are composed of three major elements with distinguishable properties, i.e. active pharmaceutical ingredients, lipid, and polymer. Selection of these three constituents is, therefore, a critical step in LPHNP's formulation. On this basis, bioactive should withstand to specific parameters along with few rate limiting factors. Both, i.e., drug selection criteria and rate limiting factors are discussed herewith [26].

While Selecting Drug Should Withstand to Certain Parameters

Bioactives that are available in various forms, for example, many non-ionic and ionic bioactives have successfully encapsulated in LPHNs with effective towards multidrug resistance [4].

Electrostatic interactions may sometimes precede LPHNP formulations Example: Cationic or zwitterionic phospholipids have been used to create lipoparticles shells to facilitate electrostatic interactions with oppositely charged polymers [28].

Drugs have a low solubility in water, to tackle poorly water soluble bioactives, Drug delivery membranes that dissolve rapidly are used to deliver ibuprofen and polymer (PVP) by orally [29].

Drugs that undergo first pass metabolism via oral route are ideal candidates for LPHNP's [4]

A drug having 3-4h elimination half-life [30,31].

Sr. No	Component	Charge
1	PVA	Non-ionic [20]
2	Soy lecithin	Anionic [20]
3	Chitosin	Cationic [32]
4	Poly-L-Lysein	Cationic [32]
5	Alginate	Cationic [32]
6	Geodin	Neutral [33]
7	NADP	Cationic [34]
8	CTAB	Cationic [35]
9	Phospholipid	Anionic [36]
10	Phosphatidylserine	Anionic [37]

11	Pjospatidic acid	Anionic [37]
12	Phosphatidylglycerol and Phosphatidylinositol	Anionic [37]
13	Pluronic F68	Non-ionic [37]
14	Precirol	Anionic [37]
15	Phosphatidylcholine	Anionic [37]
16	Stearic acid	Anionic [38]
17	Oleic acid	Anionic [38]
18	Lecithin	Anionic [38]
19	PLGA	Anionic [39]
20	Labrafil M 1944 CS	Cationic [40]
21	Labrafac and Compritol	Anionic [40]
22	DPPC	Cationic [28]
23	DPTAP	Anionic [28]
24	DOTAP	Neutral [28]
25	Low-molecular-weight heparins LMWHs	Anionic [29]
26	Ciprofloxacin	Cationic [41]
27	PEI	Cationic [42]
28	Hyaluronic acid	Anionic [43]
29	Lysine	Cationic [44]
30	Arginine	Cationic [37]
31	Glutamic	Anionic [44]
32	Aspartic acid	Anionic [44]

Table.1: LPHNs reported in literature along with their Charge.

Rate Limiting or Determining Factors

Two rate limiting/determining factors are physicochemical properties of the drug and gastrointestinal physiological factors [45].

Selection of Lipid and Polymer Followed by Drug: Successfully employed a versatile way of incorporating polymer and lipid into a one system to develop the bioactive oral bioavailability [46]. The adoption of an appropriate lipid-based surface engineering technique is critical, and depending on the chemical composition of the lipid and polymer, it may differ in certain biomedical applications [46,47]. Lipid shell that envelops the heart is biocompatible and displays cell membrane-like behavior [28]. In general, the key chemical forces responsible for the lipid self-assembly process on polymer surfaces are electrostatic attraction and hydrophobic interaction [28,47]. LPHNs have successfully encapsulated several ionic and non-ionic drugs and their efficacy against multidrug repellents [45]. Lipid based surface technology of PNPs provides many advantages in the production of bioactive and gene delivery platforms, counting wide array of versatile approaches and surface engineering amenities, stretched half-life circulation, improved target specificity and enriched nanocarrier transfection performance [47].

Applications of Lphnp's

Gene Therapy

Gene therapy is the well-established treatment method for different diseases like cancer, diabetes, tuberculosis, etc.; there are well-known therapeutic agents for cancer therapies are genetic coding including plasmid DNA, siRNA, and miRNA (targeted expressed gene). Both siRNA and miRNA are short RNAs of 19–25 base pairs with two 3'end overhanging nucleotides. miRNA and SiRNA has an identical physicochemical and target mRNA, but their origins and mechanisms are distinct [48]. In comparison, plasmids are small, two-stranded DNA molecules that carry recombinant genes of interest and which can be systematically or locally delivered into the cancer tissue [49-51]. In addition to optimal oncology conditions, illnesses related to hereditary disorders

as well as long-lasting diseases, the delivery of the above-listed agents presents a significant challenge [52]. It shows short shelf life, anti- vector immunity, inflammatory responses, limited capacity to carry DNA, etc. Thus, the attention has been shifted to non-viral vectors for gene delivery. Because of their benefits, such as significantly reduced toxicity [53] and immunogenicity, viral recombination deprivation, large-scale production capability, and economic viability at low cost [54,55].

The underlying mechanism involved in the transmission of genes is the insertion of a gene encoding a functional protein that alters endogenous gene expression and has the potential to cure or prevent disease progression. Iron oxides, such as NiFe2O4, MnFe2O4 and CoFe2O4 exhibit greater efficiency associated to other magnetic materials but are vastly toxic to the cells. The base of magnetic nanoparticles (MNP) is highly responsive when applied in vivo, avoids oxidation and leakage. In the MNP delivery device, the gene fixes directly to the carrier. To improve/boost gene transmission in the presence of a magnetic field, magnetic fields are used to allocate magnetofection as the association between MNP and gene vectors. The magnetic field is used to transfer MNP-gene vector multiplexes towards target area [56,57]. The temperature also influences the strength of the magnetic nanoparticles due to the transfer of energy from solvent molecules to nanometric particles. Therefore, a biologically compatible polymer can be used for magnetic nanoparticle to enhance its stability [58,59]. The overall applications of LPHNPs' in gene therapy are compiled in Table 2.

Gene	Polymer	Lipid	Type of Cells
DNA	PLGA	DOTAP/DcChol	HEK-293 human, Prostate cancer cells [60]
DNA	Polyethyleneimine	PEGDSPE, Triolein, PC	Healthy HEK293, MDA-MB-231Breast cancer cells [60]
siRNA	PLGA	PEGDSPE	HeLa cervical cancer, HepG2 liver cancer [61]
mRNA	PBAE	PEG-DSPE, DOTAP	Dendritic cells [62]

Table2: Application of LPHNP's in Gene delivery.

Anticancer Therapy

LPHNs are simple to formulate and shows amazing stability when compared to other drug delivery methods, LPHNs are considered as a succinct and reliable drug administration strategy. Natural, semi-synthetic, and synthetic polymers are used to make LPHNs, which are drug nanocarriers. Targeted LPHNP's have shown an active position in areas deep inside tumors and, when packed with chemotherapeutic docetaxel, have been able to exceed the commonly used formulation of the drug. In the end, the introduction of an ultra-small form to the size reserve of hybrid nano-particles tends to improve the platform's value further and can provide a means of improving the therapeutic performance of bioactive freight across a wide range of different claims [63]. Nanoparticles containing chemotherapy drugs may be able to solve some of the problems associated with unrestricted traditional medicines, such as pitiable solubility, low bioavailability, region stability, renal clearance, increased bioactive resistance, and/or a general lack of selectivity, which could lead to non-specific toxicity to normal cells and prevent dose increases [64].Photo thermal treatment, which uses indocyanin green (ICG), gold nanoparticles, or carbon nanotubes to absorb NIR light and convert it to cytotoxic warmth for tumour action, is a non-invasive, safe, and very successful therapeutic approach [56].

Antibacterial Therapy

Research Factors that influence the encapsulation and stability of drugs Polymer-LPHNPs are polymeric nanoparticles encapsulated with lipid layers, combination the biocompatibility of phospholipids with the structural integrity of polymeric nanoparticles. LPHNs are being studied in vitro for their efficacy, drug loading, stability, and release patterns. Ciprofloxacin-encapsulated nanoparticles are more extensive than polymeric nanoparticles and show lower drug charging. Additional, drug loading and releases are intensely inclined by the lipophilicity of drugs and there is a greater amount of lipophilic product (i.e., levofloxacin) and a more prolonged release period due to the association with lipid coat [41].

After 24 hours release study, VCM-CHT exhibited the improved performance in terms of sustained drug release, with a score of 36.15±5.35%. This LPHNP is, therefore, a promising tool for the supply of VCM and other antibiotics [65].

As a novel colloidal nano carrier [66], core-shell lipid-polymer hybrid nanoparticles (CSLPHNs) are collected from an inner cross-connected solid core that is outside formed by phospholipid layer that incorporates mechanical welfares of biodegradable polymer nanoparticles and the biomimetic benefits of liposomes [67].

Theranostics

Theranostics, which combines diagnostics and therapy, it is a new trend in nanomedicine that has been engineered

for personalized medication, mainly for improving antineoplastic therapy, by providing appropriate system to administer the correct drug dosage to the targeted area at the predetermined time by molecular imaging the disease's progression and monitoring therapeutic efficacy in real time. In order to develop the best theranostic system, the nanocarrier matrix must carry both therapeutic and imaging contrast chemicals at the same time, ensuring their optimal distribution. MRI scans are the most commonly utilized techniques among the researched approaches, safeguarding a very high determination, good quality of the contrast agent entrapped into nano-transporter system, and the ability to cover most of the human organs [68].

Method of Preparation	Encapsulated Drug	Imaging Agent	Size (nm)	Charge (mV)	Application	Indication
One Step	Au/QDs	-	50-60	NA	Diagnostic and Optical Imaging [69]	NA
-	doxorubicin	ICG	(Avg) 120	−24.9 ± 1.68	Imaging-Guided Surgery and Multitherapy	Anti-glioma Therapy [70]
single-step nanoprecipitation method	ICG	ICG	39.4 ±2.8	−53.6 ± 0.3	Better Phototherml Damage	INP can easily absorbed from pancreatic carcinoma tumor cells [71]
	Gadolinium	Polymers	66-128	-	Fluorescent organic bimodal that overcomes the toxicity of QDs	Anti-Tumor [72]
single-step sonication method	Doxorubicin and ICG	ICG	86.3 nm	-21.71	Chemo-photothermal Combination Therapy	Breast Cancer [73]
solvent evaporation method	Docetaxel	fluoresceinamine	154 ± 12	-25.8 ± 0.9	dual modal imaging and chemotherapy	Breast Cancer [74]
Emulsification Sonication Method	Paclitaxel, Cisplatin	RGD-peptide	191.3 ± 5.3	−37.2 ± 3.9	Synergistic combination Chemotherapy	Lung Cancer Treatment [75]

Table 3: Various applications of nanocarriers matrix used in development of theranostics are summarized in table.

Conclusion

If proper consideration has been given to the structure of hybrid nanoparticles, a broad range of drugs can be used by various routes and depending on the therapeutic aims. LPHNP's can play a noteworthy role in the extension half-life of nanoparticles in the circulation, maintaining bioactive stability, providing a distribution obstacle that regulates release, and serves as a targeting agent for the delivery of specific bioactive products. Characterization of LPHNPs should be performed at both pharmacodynamic and pharmacokinetic scales. Results of both (in vitro and in vivo) studies should be associated with IVIVC determination. Long-term researchers will pursue studies of stability. The data from these stability studies (drug content) should be used to estimate the expiry date, as well as the industrial scale up efforts that should be made. LPHNP's are predominantly used in cancer therapy due to their ability to deliver bioactive at the target site, increase therapy effectiveness, decrease possible side effects and toxicity; or even used to deliver proteins such as insulin for oral administration due to carrier's capability to protect proteins from enzymatic degradation and increase intestinal absorption. Such nanoparticle technologies can dramatically improve the patient's quality of life. In addition to the positive results achieved so far, more work is needed to deeply understand the interactions between hybrid nanoparticles and cells, identifying possible toxicity problems, and demonstrating their safe application. Such carriers have been suggested as good candidates by the ongoing developments of lipid polymeric hybrid nanoparticles to deliver extensive range of bioactive and be able to capture the market soon.

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