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Review Article

Hybrid Nanoparticle for Pharmaceutical: An Overview

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ABSTRACT

Nanomedicine holds a great role to improve therapeutic strategies against drug delivery as to develop multi-functionality and advanced targeting tactics. Hybrid nanoparticles (HNs) having small particle size, because of small particles it is used in traditional therapies. HNs improving pharmacokinetics and pharmacodynamics characteristics against disease or treatment. HNs circulating in the circulation for an extended period of time to reach targeted spot. Recent years have seen a rise in interest in polymer-based nano-medicines due to their potential to increase the effectiveness of cancer therapeutics. This field includes the use of polymer DNA complexes (Polyplexes), polymer-drug conjugates, lipid polymer type of nanoparticles as hybrid nano-medicines, and polymer micelles bearing hydrophobic drugs. In this review the HNs of lipid and polymer are taken in focus in accordance with benefits and drawbacks of lipid as well as polymer drug targeted delivery and how the combination of lipid and polymer as hybrid nanoparticle is beneficial to achieve desired therapeutic effect in treatment with their types and preparation with some available formulations and drugs.

INTRODUCTION

An important and long term goal of a pharmaceutical company is to develop a therapeutic agent that can be specifically delivered to specific area in the body to maximise the therapeutic index [1]. Norio Taniguchi discovers the phrase "nanotechnology" in 1974 at the University of Tokyo [2]. It entails molecular-scale engineering of functioning systems [3].

Due to its distinctiveness, nanotechnology focuses on the design, manufacture and characterisation of extremely small particles and has applications in a wide range of fields including engineering, pharmaceuticals, and medicine [4]. The application of nanotechnology has the potential to significantly enhance patient health and well-being. Nanomedicine, which employs the technology to highly specialized medical treatments for the prevention, diagnosis, and treatment of illness, is one of the most significant areas of research in the field.

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Nano-materials with a size range resembling that of the macromolecular structures present inside live cells, such as proteins. With their distinctive properties, nanoparticles that contain medications that are encapsulated, distributed, absorbed and conjugated work better in a range of dosage forms [3].

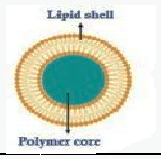
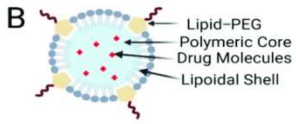
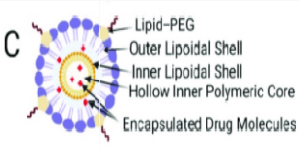
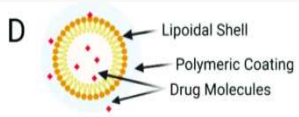
The capacity of NPs is to delivered medications at therapeutic sites with specific times and specific dosages that lead to attraction towards NPs is more. According to their physicochemical and biological qualities, two most common kinds of drug nano-carriers are liposomes and biodegradable polymeric NPs, each of having different advantages and disadvantages. The majority of drug delivery systems like liposomes, solid lipid NPs, nanostructure lipid carriers, and lipid drug conjugates contain lipids [5].

The majority of liposomes are flexible, non-immunogenic, non-toxic, biocompatible, and biodegradable for administration. They are constrained in some way by their sterilization, drug entrapment, physical and chemical stability, batch-to-batch consistency and manufacturing of scale-up batches. With some limitations, such as the use of toxic organic solvents in the production process, poor drug encapsulation for

hydrophilic drugs, drug leakage before reaching target tissues, polymer cytotoxicity and availability of multiple polymers, simultaneously polymeric NPs have a number of advantages, including small particle size, tissue penetration ability, a greater variety of preparation methods, and more stability in biological fluid. According to the constraints of polymer and liposome NPs, both of them have the potential to be employed as potent , which are made up of two or more distinct NPs that have been put together to create a new and more useful nanoscale structure [5, 6]. As their name suggest lipid polymer HNPs are made of lipids and polymer. The polymers used should be biocompatible, biodegradable, and nontoxic and have been used in approved products like PLGA, PCL, dextran and albumin. The lipids used should be zwitterionic, cationic, anionic and natural phospholipids like lecithin, DPPC, DOPE. Inorganic materials like silica, magnetic iron oxide or organic materials like polysaccharides, polystyrene, poly-electrolyte capsules or polymer micro-gels were used to create the core of hybrid micro-particles and NPs, which had a lipid shell around it [5, 6].

These hydrophobic and hydrophobic polymeric lipid HNPs have a high loading capacity and a hydrophobic core that is less or more water soluble in drugs. The lipid layer that surrounds the core serves as a highly biocompatible shell that encourages drug retention within the polymeric core. Van der Waal and hydrophobic interactions are mostly connected to the lipid shell and polemic core.

Table 1: Lipid Polymer Hybrid Nanoparticles of Several Forms

Types	Structure	Description	References
Polymer core lipid shell		It has supramolecular structures that are colloidal and simplest form contains polymer particle core which coated with lipid [PEG and a lipoidal shell.	[7-12]
Polymer caged nanobins		The liposomes are coated with polymers like PEG, Eudragit EPO, poly (L-lysine), etc. to protect from degradation and improve stability of liposome.	[7, 13, 14]
Core shell type hollow lipid-polymer-lipid hybrid nanoparticles		Innermost layer is empty, followed by a polymeric layer, which is encased in one or more layers of lipid-PEG. Aqueous buffer or water fills the gap between the lipid layer and the polymer core.	[7, 15]
Monolithic polymer lipid nanoparticles		Additionally referred to as combined lipid-polymer hybrid nanoparticle. The polymeric core matrix that holds the medication is dispersed with lipid or lipid PEG molecules.	[7, 16]
Erythrocyte membrane coated polymer lipid nanoparticles		Also known as biomimetic nanoparticles, they are sub-100 nm in size and coated with an RBC polymer to create vesicles. They effortlessly pass the membrane barrier and administer medications for a long time.	[7, 17]

Characteristics

The physicochemical properties of NPs aid in promoting increased blood circulation, additionally they aid in the absorption, clearance, and interaction with plasma proteins. The main role of characteristics of NPs in the delivery of drug is help to design NPs with specific geometry, centrifugation, etc. [18].

HNPs are characterised by great structural integrity, storage stability, and controlled release profile with good biocompatibility and bioavailability. The characteristics according to structure, during the creation of the lipid polymer HNPs, the inner lipid layer served as a molecular fence to reduce leaking of the encapsulated substance. Furthermore, reduce the rate of polymer degradation. Below is a discussion of several significant physicochemical properties, including particle size, zeta potential, surface morphology, particle shape, drug release studies, etc.

1) Particle Size

It is a most important factor which plays a crucial part in response of body to drug absorption, distribution, metabolism and its elimination. The efficiency of a NPs and its ability to enter cells are also influenced by particle size. Size has an impact on the movement and dispersion of many kinds of NPs, including gold, silver, and quantum dots. For the large particle size the clearance is also high so, the approximately administered NPs having size ranges from 20-100 nm. Typically, photon correlation spectroscopy, dynamic light scattering, and transmission electron microscopy are used to quantify the particle size [5, 18, 19].

2) Surface Properties

This includes hydrophobicity and surface charge that mainly affects phagocytosis, circulation in blood and bio-distribution of NPs and also affect the stability of NPs. The surface charge is one of the most important because it affects the adsorption of plasma protein. In correlation with phagocytic uptake the negatively charged NPs show low and positively charged NPs show increased phagocytic uptake [18, 19].

3) Particle Shape

It plays an important role in biological processes because it has multiple shapes like disc, cubic, cones, cylindric, etc. and also has complex type of shapes which may affect the targeting ability of the NPs [18].

4) *In Vitro* Cytotoxicity Study

The characteristics of the cytotoxicity research are those that typically aid in determining the compatibility and security of the NPs or medication administration into the human body.

Different Techniques for Making Lipid Polymeric HNPs

Lipid polymeric HNPs are created using two important methods, each of which results in a distinct form, as seen in Fig. 1.

A. Two Step Method-

When formulating monolayer, bilayer, and multilayer shells, the two-step process of creating HNPs is employed as the initial step [7]. The formation of polymeric core and lipid shell separately, followed by hydration, sonication and/or extrusion process [5, 20]. Particle size is obtained by membrane extrusion is about 100 nm as compared to hydration 250 nm and sonication is 500 nm [5]. In this method cationic lipid vesicles and anionic polymeric NPs are combined by electrostatic interactions [5, 7]. At first, the lipid NPs is prepared by micro-emulsification, ultra-sonication, high pressure homogenisation i.e. hot or cold, melt emulsification, solvent injection method, simultaneously the polymeric core is created by combining a water-immiscible organic solvent, such as chloroform, with a biodegradable polymer [5, 7, 20].

Table 2: Instrumental methods used for measurement physicochemical characteristics of lipid polymer HNPs

Physicochemical characteristics	Instrumental methods of measurement	Reference
Particle size distribution, Zeta potential	Photon correlation spectroscopy, Dynamic light scattering, Transmission electron microscopy.	[2, 12]
Surface Morphology	Fluorescence microscopy, Atomic force microscopy (AFM), Confocal laser scanning microscopy (CSLM), scanning electron microscopy (TEM), and transmission electron microscopy (TEM)	[2, 12]
Lipid shell thickness	Small x-ray scattering, Transmission electron microscopy	[2, 12]
Interface chemical composition	X-ray photoelectron spectroscopy, optical emission spectroscopy.	[2, 12]
Lipid shell fluidity	Fluorescence recovery after photobleaching, fluorescent probes	[2, 12]
Lipid shell transition	Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and powder x-ray diffraction	[2, 12]
Drug loading and entrapment / encapsulation efficiency	Dialysis, centrifugation, high-performance liquid chromatography (HPLC), and membrane filtering	[2, 12]
Drug release studies	Dialysis followed by HPLC/UV-visible spectrophotometry, sample and separate method	[2, 12]
In vitro cellular uptake	Fluorescence	[2, 12]
Cell viability and cytotoxicity	Trypan blue staining, the clonogenic assay, the MTT cell viability assay, the MTS cell proliferation assay, and the ATPLite1-step luminescence ATP detection assay.	[2, 12]

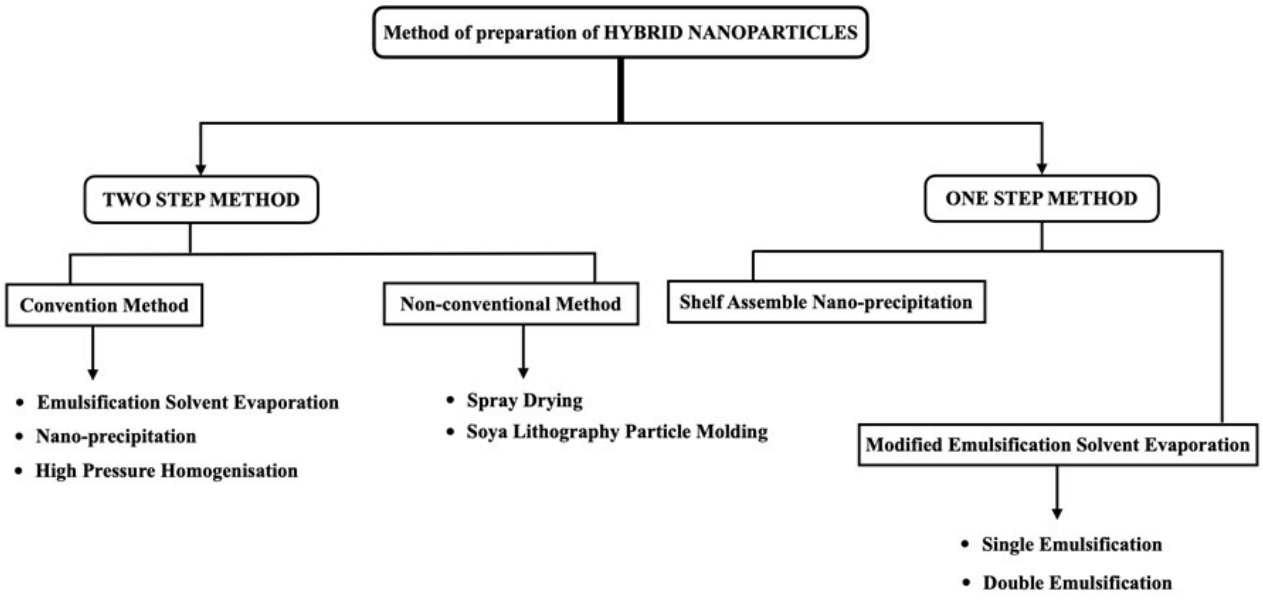


Figure 1: Preparation Method of Lipid Polymeric HNPs.

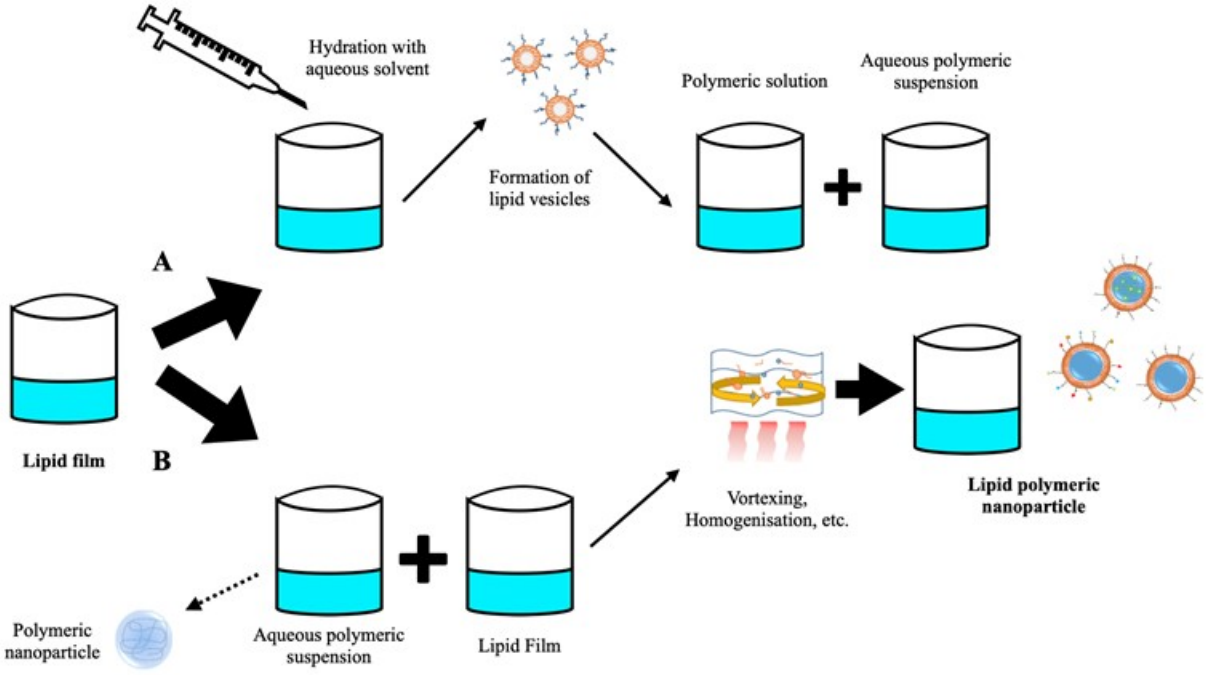


Figure 2: Two-step process of formulation of HNPs

Then the polymeric solution is added in lipid NPs by using low energy mixing process i.e. vortexing or by needle extrusion or ultra-sonication high pressure homogenisation of resulting mixture to form a lipid polymer HNPs [5, 7]. Then, this combination is heated above the temperature at which lipids go from gel to liquid. Then non absorbed polymer, lipid or micelles are being separated by using centrifugation method to obtained final hybrid preparation [5, 21].

By taking an example we may find that about the two step method, according to Sengupta et.al. the preparation of lipomer i.e. lipid polymer HNPs loaded with Combretastatin and Doxorubicin. PLGA polymeric NPs and doxorubicin are joined by the process of solvent evaporation. Compounds such as PC, cholesterol, and PEG-DSPE were used to create the lipid vesicles that contained the combretastatin. Following this, polymeric dispersion was extruded along with the lipid vesicles, and it was found that this

caused the combretastatin to release more quickly than doxorubicin. The drug release was determined to be a factor depending on drug loading and polymer features, therefore the polymeric core and outer lipid shell may be produced differently to preferentially load the drug. This can be accomplished by adjusting the particle size and drug loading [20].

1) Conventional Method

The conventional method of preparation of lipid polymeric HNPs is nothing but a type of two step method which is used mainly for preparation of small scale HNPs [7]. This technique uses high-pressure homogenisation, nanoprecipitation, or solvent evaporation to create polymeric NPs. In the nanoprecipitation process, the drug and polymer are first dissolved in a water-miscible solvent before being added to aqueous lipid dispersion. The mixture is then agitated using sonication, and the size is decreased using a homogenizer [7, 20]. This method relies on the initial hydration of thin lipid films and involves the direct addition of previously created polymeric NPs to dried lipid films as well as the insertion of preformed NPs in preformed lipid vesicles to make HNPs [22]. For instance, Zhao et al. created cationic lipid HNPs utilising PLGA polymer, which constitute the inner core, and cationic lipids comprising FA-OQLCS, PEG-OQLCS, and cholesterol for the outside shell [7] (Table 3).

Table 3: Lipid polymer nanoparticle by conventional two-step method

Polymer	Lipids	Material encapsulated	Ref
Polystyrene	EPC, Chol, Mal-PEG-DSPE	Tumor necrosis factor	[23]
PLGA	PC, Chol, DSPE-PEG	Doxorubicin, combretastatin	[24]
PLGA	RBC membrane derived vesicles	Dye	[25]
PLGA	FA-OQLCS, Chol, PEG-OQLCS	Paclitaxel	[26]
PLGA	FA-OQLCS, Chol, PEG-OQLCS	doxorubicin, pEGFP DNA	[27]

2) Non-conventional Method

This technique includes spray drying and soft lithography particle folding for the manufacture of lipid polymer HNPs, which are typically generated on a large scale [7, 22]. Polyglutamic acid and poly-lysine (400–500 nm in size) are utilized as polymers in spray drying, and they are subsequently disseminated in a dichloromethane solution that contains tripalmitin, tristearin, and acetyl alcohol as lipids. Additionally, the mixture is spray-dried to create polymeric NPs with a lipid coating. Because of spray drying the NPs are have large size range and to obtained small particle range newly Nano-spray dryer method is used.

Soft lithography particle folding technique, also known as PRINT, is another unconventional preparation approach. With genetic material added, PLGA is dissolved in an organic solvent, such as DMSO or DMF, and then placed on a PET sheet. In order to create a NPs, this sheet is heated in contact with a PRINT hold after which polymer is allowed to stream into the cold and solidify there. After that, an aqueous lipid solution is used to remove the NPs from old PET sheets that have been coated with PVA. Furthermore, by employing freeze drying, liquid polymer HNPs with a needle-like form and a 200 nm length were created, each with a (+) 5mV zeta potential.

B. One Step Method

One step is one of the most efficient, economical, highly scalable and traditional ways to make lipid polymer HNPs [7]. One step methods were developed to prepare two step methods without the time-consuming second step [5, 21]. By using the nanoprecipitation and emulsification process, the one-step approach comprises the direct mixing of lipid solution and polymeric NPs. After mixing they are self-assemble to form lipid polymer NPs [21]. Material used is, lipids or PEG used as stabilising agent in hybrid preparation and ionic and non-ionic surfactants i.e. PVA, DMAB, poloxamer are used as stabilising agent in non-hybrid polymeric preparations [28].

1) Self Assemble Nanoprecipitation

In a water-soluble solvent (ethanol or acetone), a drug and a polymer are dissolved. Beyond the respective lipids' gel-to-liquid transition temperature, lipid and lipid-PEG dissolve in water together. Then the lipid dispersion is continuously stirred with addition of drops of a polymer or drug solution. This causes the lipids or lipid-PEGs to aggregate around the NPs core due to their hydrophobic contact (Table 4) [7, 21, 28].

2) Modified Emulsification Solvent Evaporation

Gurny et al. are the ones who initially described this approach. It is merely emulsion modification or solvent evaporation. Drug and polymer are fully dissolved in an organic solvent that is miscible with water (dichloromethane, chloroform or ethyl acetate). Then, a predetermined quantity of fat is dispersed in water using heat, mechanical stirring, or sonication. The aqueous phase is combined with an organic solution, and the resultant dispersion is sonicated using a probe solicitor and a cold bath. Breaking up or converting the organic dispersion phase into small NPs that solidify into nano-spheres covered in a lipid layer. By using the rotary evaporator's evaporating technique while stirring overnight, organic solvent is evaporated. Following regulated washing with clean water, centrifugation is used to clean the particle suspension. After that, a medication powder is created by freeze-drying the cleaned particles (Table 5) [5, 20, 21].

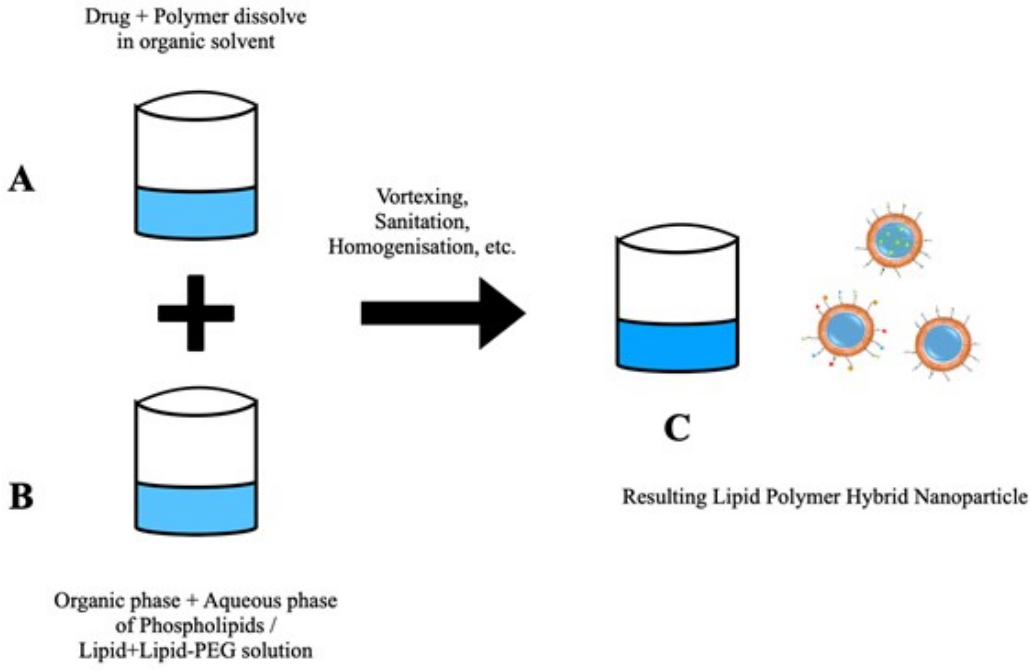


Figure 3: One-step method forming hybrid nanoparticles.

Table 4: Lipid polymer NPs by self-assemble one-step nanoprecipitation method

Polymer	Lipid	Material encapsulated	Reference
PLGA	Lecithin/DSPE–PEG	Docetaxel	[29]
PLGA	Lecithin/DSPE–PEG	Paclitaxel-Cisplatin	[30]
mPEG–PLA	BHEM-Chol	siRNA	[31]
PLGA	Lecithin/DSPE–PEG	Gold nanocrystals, quantum dots	[32]
PBAE	DOPC, DOTAP/DSPE–PEG	mRNA	[33]

Table 5: Creating lipid polymer nanoparticles using a one-step modified emulsification process and solvent evaporation;

Polymer	Lipids	Material encapsulated	Reference
PLGA	DLPC	Paclitaxel	[34]
PLGA	PEG–PE	Doxorubicin	[35]
PEI	PC, triolein, DSPE–PEG	DNA	[36]
PLGA	Lecithin, EPC/DSPE–PEG	siRNA	[37]
PLGA	DOTAP, DC-Chol	DNA	[38]

Table 6: Utilising pharmaceuticals as hybrid lipid-polymer nanoparticles;

Drug	Type of hybrid NPs	Name of Drug	Material used/ Synthesis	Use for the treatment of	Ref
Curcumin	Gold Nanoparticle	HA-CuR@AUNPs Or PEG-FAHACUR@AUNPs	Hyaluronic acid, Folic acid, Polyethylene glycol.	Cancer treatment.	[6]
Observation	In the cellular uptake studies the 56% uptake for HUCUR@AUNPs And PEG-FA-HUCUR@AUNPs 95% for PC this is because of presence of folic acid that to internalisation of nanoparticle via endocytosis due to folate receptor on cell membrane in addition to presence of hyaluronic acid receptor. So, PEG-FA-HUCUR@AUNPs is more effective than HUCUR@AUNPs				
Curcumin	Chitosan	HNT@CUR-AU/CS OR HNT-CUR NPs	HNT CUR ↓ Au^{+} HNT@CUR-Au ↓ CS HNT@CUR-Au/CS	Cancer treatment	[6]
Observation	HTN-CUR NPs are stable under physiological condition i.e. pH 7.4, but presence of glutathione or decrease in pH of cellular microenvironment of hepatic cancer cell causes release of curcumin because of reduction of disulphide bond between CUR and HNT by presence of GSH & pH sensitivity of mine bond conjugating curcumin to hallosite. So, HNT-CUR@AUNPs coated with Chiton via electrostatic interaction to surface cage structure of HNTs. According to FTIR result presence of hydrogen binding between CUR & CS, that increase loading capacity of hybrid NPs.				
Curcumin	Lipid Polymer Hybrid Polymer	Apt-Cur-PLGA-lecithin-PEG NPs	Polyethylene glycol, Poly (lactide-co-glycolide)	In treatment of HT29, Colon cancer cell	[6]
Observation	CuR encapsulated in Apt-CuR-NPs of CUR after 24 hours in comparison to free CUR more cytotoxicity of Apt-CUR-NPs in HT29 colon cancer cell as compared to free CUR				
Itraconazole	Polymeric core-Lipid shell type	Itraconazole [prepared by single evaporation emulsification method.]	Dissolve Soy-lecithin in solvents like tetrahydrofuran [solubilizer] + poly-ε-caprolactone itraconazole solution (drop wise) ↓ Centrifuged and re-dispersion of pellets in double dist. water ↓ PEG layer around lipid-polymer hybrid NPs provide stability	Broad spectrum of Anti-fungi	[20]
Observation	It enhanced oral bioavailability due to its ability to enters in systemic circulation from lymphatic vessels and paracellular pathway that avoid food interaction and first pass metabolism.				
Erlotinib	Polymeric core-Lipid shell type	Erlotinib [prepared by single step sanitation method]	Erlotinib + polycaprolactone solution + Acetone (solubilizer) + DSPE-PEG200 and HSPC + Drug polymer solution (drop wise) in lipid dispersion & then sonicated Evaporation ↓ overnight Nanoparticle dispersion were purified with water	Non-small cell lung cancer	[20]
Observation	Block activity of tyrosine kinase so cell proliferation and angiogenesis is prevented.				
Docetaxel	Core-shell type lipid polymer hybrid	Docetaxel	Folic acid conjugate, 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC)[Emulsifier]	Chemotherapeutic drug, Prostate cancer.	[2, 39]
Observation	Decrease is in mean particle size of core shell type lipid polymer hybrid with increasing concentration of lipid.				

Application

The main application of the HNPs is used in the drug delivery of drug too particular site. This tendency is mainly due to presence of multi drug resistance cells. The HNPs are more convenient for the combinational drug delivery.

There are mainly following classes by which the application of HNPs or lipid polymer HNPs are classified as,

1. Therapeutic delivery
2. Imaging agent delivery.

1. Therapeutic Delivery

Lipid-polymer NPs are combined to form HNPs. The hydrophobic medications are put into the NPs alone or in conjunction with two or more other types of medications in this method. Single drug delivery, combination drug delivery, and active targeted drug delivery are all included in this area. According to Zhang et al. and Chan et al., paclitaxel-conjugated PLA core lecithin/DSPE-PEG shell is produced into a nano-burr system for distribution, which is subsequently modified as a basement membrane targeting peptide to treat damaged vasculature [21, 40, 41]. The combinational drug delivery is also played a potential role in the delivery of drug. According to Wang. et. al., HNPs drug delivery system delivers chemotherapy and radiotherapy agent to treat prostate cancer [21, 42]. Additionally, Sengupta et al. created a drug delivery system that combines chemotherapeutic and anti-angiogenesis medications [43].

2. Imaging Agent Delivery

In this drug delivery iron oxide, fluorescent drugs and quantum dots are encapsulated inside polymer core. The imaging techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), computer tomography (CT), ultrasound (US), and optical imaging and each imaging modality has distinct benefits of its own as well as inherent drawbacks, such as inadequate sensitivity or spatial resolution [43].

CONCLUSION

Nanoparticles are effectively being used for drug delivery. Lipids and polymers are commonly employed as material of nanoparticle construction. Bothmaterial has certain advantages and limitations. Lipid polymer hybrid nanoparticles overcome challenges of lipidic and polymeric nano particulate system. Numerous characterization technique including size distribution, zeta potential, surface morphology, X-ray scattering, optical emission microscopy, DSC, FTIR, NMR, etc. reported. Different technique involving single step, two step process yields hybrid nanoparticles. The hybrid nanoparticles demonstrated its application in therapeutic delivery and targeting agent delivery; could be novel strategy in nanotechnology.

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