Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Advances in Liposomal Nanocarriers for Cancer Drug Delivery: Mechanisms, Targeting Strategies, and Clinical Perspectives

Chandraprakash Gond

chandraprakashgond472@gmail.com

Babasaheb Bhimrao Ambedkar University

Akanksha Verma

Babasaheb Bhimrao Ambedkar University

Priya Singh

Babasaheb Bhimrao Ambedkar University

Deepika Singh

Babasaheb Bhimrao Ambedkar University

Anjani Kumar Tiwari

Babasaheb Bhimrao Ambedkar University

Systematic Review

Keywords:

Posted Date: October 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10852478/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

The process of delivering bioactive medication ingredients into a patient's body is known as drug delivery. To create drug delivery systems (DDs), a range of natural resources and synthetic materials derived from natural resources can be used as building blocks. These DDs include liposomal systems, which are composed of a phospholipid membrane with a hydrophilic head and a hydrophobic tail. Lipid-rich spherical or multilayered spherical structures, liposomes vary in size (from 2 to > 5000 nm), manufacturing methods, processing, and medication loading. Modern drug delivery formulations have found numerous benefits of liposomal drug delivery systems over free medication treatment for cancer or conventional liposomes. Recent studies have demonstrated that liposome nanocarriers offer exceptional drug loading capacity, drug protection, increased bioavailability, improved intracellular delivery, and greater therapeutic impact due to their exceptional performance in targeted delivery.

By delivering the medicine that fights metastases over an extended period of time and minimizing systemic adverse effects on healthy tissues and organs, the multifunctional and stimulus-responsive nanocarriers for cancer treatment delivery increase treatment effectiveness. This article provides an overview of the mechanisms underlying the release of pharmaceuticals from liposomes, the interaction between liposomal anticancer treatments and cancer cells, and the encapsulation of various anticancer agents in liposomes. Liposomes have demonstrated exceptional promise in the creation of vaccines, gene delivery, cancer treatment, and diagnostic imaging. Theragnostic applications and targeted drug delivery have become possible because to the combination of liposomes with nanotechnology. Additionally, emerging tendencies

emphasize how they contribute to individualized medicine. Liposomal drug delivery methods are still developing despite obstacles, offering substantial improvements in therapeutic interventions and opening the door for more individualized and efficient treatment plans in contemporary medicine.

Introduction

Drug delivery is the process of administering pharmacological substances to observe a therapeutic effect in living organisms. Drug delivery through the pulmonary and nasal routes is becoming increasingly crucial for the treatment of human illnesses. These techniques offer a promising alternative to parenteral drug administration, especially for peptide and protein therapeutics.[1] However, because of the uncontrolled dosage, certain drugs show a variety of adverse health effects when used under controlled conditions. Because of this, the medication builds up in the body quickly. The pharmaceutical industry synthesizes several physical, chemical, and biological characteristics, including bioavailability, in vivo pharmacokinetics, and stabilities.[2] Due to their general physiological interconnections, many pharmacological drugs also exhibit negative side effects. Furthermore, because of their non-specific physiological interactions, many pharmacological substances have adverse side effects. The drug concentration in the blood plasma increases with repeated dosages, leading to unintended adverse effects in the patient's body.[3] Therefore, it is strongly recommended to use a prolonged release strategy

and deliver little doses. Limitations in specificity are present in most cancer treatments. Patients may experience negative side effects because of the toxicity of those chemotherapy medications, which can damage normal, healthy cells.[4] In addition to these challenges, drug molecules frequently experience pH fluctuations, chemical degradation, and photodegradation during extended periods of storage, all of which are harmful for delivery. To maximize effectiveness and prolong shelf life, it is essential to shield the drug molecules from these environmental impacts. However, a drug's pharmacokinetics are directly impacted by its half-life ($t_{1/2}$), which is the amount of time it takes for a drug to reach half of its initial plasma concentration. Researchers have investigated methods to potentially lengthen the $t_{1/2}$ of pharmacological molecules because the short $t_{1/2}$ of many medications has significant drawbacks. Numerous techniques have already been used to lengthen the $t_{1/2}$ of drugs.[5] It appears that dose frequency can be reduced by lengthening the drug's $t_{1/2}$ (less than 8 hours) to allow for continuous release. Therefore, we must create drug delivery (DD) materials with the following qualities in order to have the biggest impact on the treatment of various diseases: Drug delivery systems (DDs) that are (1) persistent in physiological conditions; (2) site-specificity towards damaged tissues or cells by incorporating stimuli-responsiveness; (3) use of DDs with high drug loading capacity that can increase doses when necessary; (4) more affordable than traditional drug compounds, preventing drug delivery-related multidrug resistance; (5) improvement in cellular uptake potential; and (6) targeted delivery can be used to treat a variety of diseases, lowering side effects and increasing the medication's effectiveness in the cells, tissues, and organs. The drugs used to treat cancer are quite dangerous since they can damage healthy cells and cause serious adverse effects in patients.[6] The use of suitable drug delivery systems can satisfy the needs of focused drug delivery. These methods make use of either passive or active targeting procedures. The duration of circulation and the ability to overcome certain unfavourable physiological conditions are the only factors that determine a drug's effectiveness in active targeting.[7-9] CPX-351 is a liposome that is used to treat leukaemia by combining the anticancer drugs cytarabine (CYT) and daunorubicin (DUN). CYT-loaded liposomes (CLP) are created by first hydrating CYT and then extruding it with the lipid components. These liposomes are then treated with DUN to accomplish dual-drug encapsulation, resulting in CPX-351.[10] LPs are spherical and composed of cholesterol (CHOL) molecules as well as synthetic or naturally occurring phospholipids. Van der Waals forces keep the hydrocarbon tails of LPs together, whereas lipid bilayers are formed by hydrophobic contacts between the lipid heads. Because liposome components resemble cell membranes, they are both biocompatible and biodegradable.[11] Hydrophilic molecules can be encapsulated in LPs' cores, and hydrophobic compounds can be encapsulated in their bilayers. Scientists are now much more interested in using LPs as drug delivery vehicles because of their low toxicity components and ability to carry both hydrophilic and hydrophobic payloads. Furthermore, different sizes of liposomal structures are feasible.[12] Natural phospholipids including lecithin, 1, 3 dipalmitoyl-sn-glycero-3-phosphocholine, and 1, 2 dipalmitoyl-sn-glycero-3-phosphocholine were utilized as the building blocks of dipalmitoyl phosphatidylcholine (DPPC) in the first generation of LPs. Polyethylene glycol (PEG) has been shown in recent studies to enhance the $t_{1/2}$ of liposome circulation in the blood. The nature of LPs, particularly their size and charge, has a significant impact on their effectiveness.[13]

Synthetic lipids such as 1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS) can be used to create negatively charged LPs in order to increase activity, while charge-induced lipids such as dioctadecyl dimethylammonium bromide (DODAB) and 1,2-dioleoyl-3-(trimethylammonium) propane (DOTAP) are commonly used to decrease the release kinetics because their layered xanthan structure with polyelectrolyte properties obstruct fast release pathways.[14] Charge inducer chemicals like stearylamine (octadecylamine, SA) and dicetyl phosphate (dihexadecyl phosphate, DCP) can be used to produce both cationic and anionic LPs. DCP creates anionic or negative vesicles, whilst SA supplies the cationic/positive vessels. The zeta potential value rises when these charge inducers are added to the liposomal phospholipid bilayer. The particles' propensity to aggregate decreases as a result of their tendency to repel one another.[15] As a result, liposomal systems are more stable due to the electrostatic contact. According to Ralf et al., different anticancer medications have been encapsulated in LPs using a variety of technologies. They also gave an overview of the preclinical and clinical data of approved and excellent recently created liposomal anticancer treatments. Liposomal compositions aim to reduce the harmful side effects of conventional cytostatic medications without significantly compromising their effectiveness. It can theoretically be achieved in one of two ways: either by delivering the medications predominantly to neoplastic tissues (drug targeting) or by preventing encapsulated drugs from reaching healthy tissues.[16] However, the mechanisms of drug loading encapsulation, various release mechanisms for drug delivery, and the mechanism of liposomal drug interaction with cancer cells described below are all covered in this paper.[17-22] The specific mechanism of drug encapsulation, distribution to the cancer cells, the effect of co-encapsulating different medications, and a critical examination of the method's strengths and weaknesses are all significantly lacking from the various reviews on the same subject that have been published in the last ten years.[23-25] Sometimes, their primary focus is on clinical therapy rather than the system's development through chemistry.[26] Furthermore, technical concerns regarding chemical formulas and bio-physical correlations have not been addressed in many articles.[27]

1.3.6 Nanotechnology in Drug Discovery: Nano chemistry, which is on the cutting edge of many fields, uses a variety of techniques to design and build materials at the nanoscale, giving them new, distinct properties that distinguish them from their bulk material counterparts in terms of digital, magnetic, spectroscopic, chemical, and electrical properties. Nano chemistry is a multidisciplinary field that draws on information from natural and material sciences, engineering, drug, and pharmacology. Nano chemistry integrates scientific and technical knowledge from various fields, including drugs, pharmacy, natural and material sciences. This challenging task aims to discover new biomaterials, understand their connections, and create innovative products with incredible potential. These perspectives are inspiring and reassuring, with the potential to revolutionize our understanding of the world at the nanoscale.[28]

Polymeric nanoparticles (NPs) have piqued scientists' interest in recent years due to their unique micro dimensional properties. Polymeric nanoparticles (NPs) are effective medication delivery agents due to their sustained release, ability to protect pharmaceuticals, increased accessibility, and improved treatment efficacy. The term "nanoparticle" refers to both nano capsules and nanospheres, which have

various morphological shapes (Fig. 1.1). A polymeric coating that surrounds an oily core, where the drug is frequently soluble, controls the pattern of drug release from the core in nano capsules.[29-33]

Nanospheres are composed of a polymeric network that can contain or bind drugs to its surface. These two types of polymeric NPs are referred to as reservoir (nano capsule) and matrix (nanosphere). Recent research has focused on encapsulating medications into polymeric nanostructures (PNs), both artificial and ambient. The resulting nano systems are biocompatible, biodegradable, reproducible, and mass-produced. PNs are designed to be long-lasting, drug-encapsulating, and capable of delivering several treatments in a single suspension. These features make them ideal for medication administration through several channels and therapeutic approaches. The properties of PNs, such as particle size, zeta potential, and morphology, can be tailored to create nanovesicles such as micelles, dendrimers, vesicles, and capsules with sizes ranging from 100 nm to hundreds of nm, depending on the active component or drug, polymer form and size, and method of preparation as shown in Fig. 1.2. Polymers can be chemically changed to contain, distribute, adsorb, or bind drugs. [34-39]

Research has focused on lipid-based nanostructures such as solid lipid nanoparticles (SLN), liposomes, and nanostructured lipid carriers (NLC), furthermore to polymeric nanoparticles (Fig. 1.2). Nanovesicles have minimal toxicity and can carry both hydrophilic and hydrophobic compounds. They can also lengthen the half-life and control medication release, enhancing therapeutic potential. Chemically altering lipid nanovesicles can enhance medication solubility or avoid immune system recognition.[40-42] They can be made in pH-sensitive formulations to release drugs in acidic conditions and coupled with antibodies targeting tumor cells or related proteins (e.g. folic acid). Nanoparticles can enhance patient response when paired with other therapies.

The latest nano vehicles offer advantages such as biomimetic behaviour of lipid molecules and mechanical benefits from polymeric materials. The latter are distinguished by the incorporation of various environmental/man-made lipids and polymers with unique characteristics (e.g. size, architecture, response to outer stimuli) and suitability for encapsulating a wide range of bioactive compounds that cannot be transferred effectively via conventional techniques or entrapped in a carrier vehicle entirely composed of polymeric or lipid materials. Lipid-polymeric nanomaterials, such as polymer-modified liposomes, polymeric micelles, surface-modified solid lipid NPs, lipid-polymer hybrid NPs (Fig. 1.3), and other combinations of polymer and lipid building blocks, offer numerous benefits in fields such as pharmaceuticals and biomedicine.[43-51]

1.3.7 Polymeric and Lipid-Based Nanostructures

Polymeric nanoparticles serve as versatile and sustainable delivery systems, exhibiting distinctive characteristics depending on their composition. These polymers can be categorized into three main types: natural polymers, which include substances like chitosan, hyaluronic acid, starch, dextran, alginate, albumin, and heparin; semi-synthetic polymers, such as poly(methacrylic acid) and polysorbate 80-grafted starch; and synthetic polymers, including materials like PLGA, PLA, PCL, PEG, PHEMA,

PHPMA, PVA, polystyrene, and amphiphilic polymers (Fig. 1.33). Each type of polymer imparts unique properties to the nanoparticles, influencing their application in various delivery systems with various morphologies such as polymeric micelles, polyplexes, solid nanoparticles, and core-shell systems. Polymer nanoparticles are divided into two types: nanospheres and nano capsules. Nanospheres are of the "matrix type," with pharmaceuticals dispersed throughout the matrix, whereas nano capsules are of the "repository type," with drugs in a core surrounded by a polymeric network.[52]

Biodegradable nanoparticles are highly biocompatible and have showed potential as therapeutic carriers in recent years. However, polymer nanoparticles have a low entrapment rate and, due to their high molecular weight, can easily elicit an immune response. LPNs, or lipid-polymer hybrid nanoparticles, are a new carrier system that addresses these issues. Clearly, the polymer controls drug release, but the lipid increases loading efficacy and penetration. LPNs can increase storage stability and biocompatibility.[53]

Lipid-based nanostructures (LNs) are typically non-spherical because to electrostatic interactions with polar/ionogenic phospholipid heads or the presence of non-polar lipid alkyl moieties in the solvent. These LNs, made of homogenous lipid bilayers or solid cores, can encapsulate a wide range of cytotoxic chemicals. Hydrophilic molecules will be captured in the watery region, while lipophilic molecules will be caught in lipid leaflets. Using lipids and polymers in nano-delivery vehicles is crucial for their biological applications.

Biocompatibility refers to a biomaterial's ability to perform its intended function without causing negative consequences. Fig. 1.3 depicts various groupings of polymeric and lipid nanoparticles.

1.3.8 Lipid-polymer hybrid nanostructures:

Lipid-polymer hybrid nanoparticles integrate the characteristics of both polymeric nanoparticles and liposomes, combining the benefits of each to enhance their functionality (see Fig. 1.31). In these nanoparticles, a lipid coating surrounds the polymer centre. Polymeric nanoparticles have downsides, including hazardous decay and monomer building, as well as a toxic decomposition process that limits their use, despite previously mentioned advancements. Lipid nanoparticles have poor drug encapsulation, barrier retention, and cell barrier fluidity, leading to instability during storage and distribution. To address the shortcomings of lipid and polymeric nanoparticles, lipid-polymeric hybrid nanoparticles (LPNs) were introduced. The term "hybrid" refers to the nanoparticles' polymeric and lipid characteristics.[54-56]

The polymer regulates medication release, whereas the lipid promotes drug penetration and loading across the membrane. Lipid-polymeric hybrid nanoparticles (PLNs) can increase drug biocompatibility and physical consistency, paving the way for their prospective application in successful drug delivery.

1.3.9 Synthesis of polymeric nanostructures: Surfactants may be used during the synthesis of polymeric NPs. Surfactants are synthetic organic molecules that are amphiphilic and may assemble themselves in solution. Surfactants typically consist of a hydrophobic hydrocarbon chain coupled to an

ionic functional group, resulting in cationic or anionic surfactants (e.g., tetramethylammonium hydroxide or sodium laurate).[57]

Non-ionic surfactants with an amphiphilic character result from the fusion of hydrophobic and hydrophilic molecules (e.g., alkyl and non-alkyl phenol ethoxylates, ethoxylated amines).

Light molecular weight polymers, especially block copolymers like Pluronic F127 and F68, can behave as surfactants. These compounds are commonly utilized as stabilizers in nanoparticle formulations and can help achieve a well-structured nano system by stabilizing dispersion during nano emulsion.

Stabilizers can reduce the surface tension of nanoparticles and increase interaction with lipid structures. Surfactants have been found to reduce the diameter of NPs and act as cryoprotectants.[58] Using surfactant-modified nanoparticle systems leads to improved drug retention and deposition in target tissues, longer blood circulation time, reduced nephrotoxicity and hepatotoxicity, decreased cardiovascular activity, and lower macrophage utilisation.

In aqueous/oily core-systems, pharmaceutical drugs' dissolving rate determines the preparation technique. Controlled drug delivery methods include polymerization, physio-chemical processes like solvent evaporation and emulsification, nanoprecipitation, self-healing encapsulation, and mechanical processes like membrane emulsification, spray drying, supercritical fluids, and nanofluidic (Fig. 1.4).

1.3.10 Solvent Evaporation Method:

Solvent evaporation is the primary method for producing polymeric nanoparticles. At the industrial level, it offers benefits such as simplification, reproducibility, faster processing, and less important process parameters (CPP). Polymeric drug solutions are made using the oil-in-water (o/w) single emulsion process, which involves mixing the medication with polymeric media. Then, when an emulsion exists, it is emulsified in a large amount of water. The w/o/w double emulsion method involves injecting a drug mixture into a polyamide organic solution to create a basic emulsion. This is then combined with an aqua medium containing PVA to create a secondary emulsion.[59]

In emulsion processes, organic solvents are evaporated or separated to harden droplets under appropriate conditions. The powdered API (active pharmaceutical ingredients) is disseminated in a polyamide organic solvent using the s/o/w process. This approach requires mechanical processing to ensure consistent crystallization and reduced size.

This approach faces significant challenges, including high manufacturing costs, limited and uniform crystallite size ranges, and the need for large amounts of organic liquid. Using solvents during a process can cause denatured medications or proteins, leading to unpredictable unfavourable side effects such as sensitization and severe toxicity.

1.3.11. Spray Drying:

Spray drying effectively encapsulates medications, peptides, and proteins with low API loss.

It is suitable for industrial processes due to its quick and efficient production method with low CPPs. This method involves atomizing and drying a nanoparticle mixture spread in air. Spray drying or spray congealing refers to the process of drying something by eliminating the solvent or cooling it.[60] This technique involves selecting solvents and equipment settings, such as feeding quantity and jet orientations, to achieve homogeneous, double-walled particles with regulated shell thicknesses (CPPs). This procedure is advantageous for its ability to be done in an aseptic environment. The biggest disadvantage is that particles adhere to the spray-inner dryer's wall.

1.3.12. Reverse Salting-Out:

The salting-out method involves separating a solvent from the aqueous phase, which can produce nanospheres. The o/w emulsion's composition includes a gel, salting-out agents, and a colloidal stabilizing agent in an aqueous medium containing hydro-miscible polymer solvents such as acetone/ethanol. Acceptable salting-out agents include electrolytes ($MgCl_2$), $CaCl_2$, or [$Mg(CH_3COO)_2$], as well as non-electrolytes (sucrose). Saturating an aqueous solution reduces the solubility of acetone and water, leading to the formation of an oil-in-water emulsion by miscible phases.[61] The oil in water emulsion is created at room temperature through vigorous churning. The emulsion is then diluted with aqueous phase to allow the solvent to diffuse to the outer phase, crystallize the polymer, and form microspheres.

Crossflow filtering eliminates residual solvent and salting-out agent. The process is shown in Fig. 1.2. This technique produces nanospheres that range in size from 150 to 900 nm.

1.3.13 Nanoprecipitation:

The solvent displacement method is a popular methodology that requires the use of two soluble fluids. In the internal phase, a polymer is disseminated in a soluble organic solvent, often acetone or acetonitrile. Because of their low adherence to water, they can be easily eliminated through evaporation. This method relies on multilayer polymer deposition after shifting the organic phase from a bioavailable solution to an aqueous media.[62]

The polymer is diluted in a moderately polarized water-soluble solvent and dropped sequentially or at a regulated rate into an aqueous media. Nanoparticles develop quickly to prevent water molecules caused by spontaneous diffusion of a polymeric solution into the aqueous phase. As the solvent diffuses from the nanodroplets, the polymer crystallizes to form nano capsules and nanospheres. Surfactants are utilized to preserve the dependability of colloidal systems but are not required for nanoparticle production. The organic component is typically put into an aqueous solution; however, it can be reversed without affecting nanoparticle synthesis. This process creates polymeric nanoparticles with diameters around 170 nm but can also be used to create nanospheres and nano capsules. When an active substance is dissolved in a polymeric matrix, nanospheres develop. Nano capsules are created by

dispersing medication in oil and homogenizing it using organic polymer solutions before spreading the internal phase into the emulsion's exterior.

1.3.14 Synthesis of Lipid Nanostructures:

Lipid-based nanovesicles can be synthesized using many methods, including high pressure homogenization, microemulsion, membrane contact, inversion temperature, double emulsion, emulsification solvent evaporation, and solvent injection (as shown in Fig. 1.5).[63-65]

1.3.14.1 Homogenization at high pressure (HPH):

HPH is a reliable, established, and efficient mass manufacturing technology (Fig. 1.5). For years, HPH has been used to make nano emulsions for parenteral administration.

This method is the major strategy for producing SLN and NLC nanomaterials. When a liquid is subjected to high pressure, it can reach speeds of over 1000 km/h. This causes shear stress and ultrasonic forces to disintegrate the particles into submicron size. High intensity homogenizers use acceleration to transport liquids across micron size differences. Hot homogenization is one option, although it can also be done at moderate temperatures (cool homogenization). When heated to 5-10^{o}C over the lipid's melting point, the medication spreads or disperses.

This technique offers two key benefits: rapid product manufacturing and easy scaling from small to large-scale production. High-pressure homogenization has numerous benefits, but it consumes a lot of energy and raises heating rates, which can be harmful for compounds sensitive to high temperatures.

1.3.14.2 Micro Emulsion Method:

Microemulsion creation has been used as a step in the production of lipid nanoparticles.

The high surfactant/lipid ratio results in a free form nano emulsion in this method. Pseudo-ternary charts are commonly used to analyse nano emulsion production zones. The ratios of active substances are important. This approach is straightforward and consists of several typical phases. The lipids are melted and mixed with a hot surfactant solution. The nano emulsion is formed after gentle stirring. In the second stage, the hot nano emulsion is mixed with ice water (1-2°C) and gently agitated. As a result, liquid droplets solidify. This method results in spherical SLN or NLC with limited size distribution. However, the technique has considerable drawbacks, including a somewhat diluted final dispersion. This may require further concentration through ultra-filtration, lyophilization, or other methods. Another major disadvantage of this process is the high concentration of surfactants/co-surfactants used.

1.3.14.3 The Membrane-Contact or Method:

This technique uses a cylindrical membrane module containing a liquid phase with surfactant. Molten lipid is forced through the membrane's small pores into a flowing water phase, forming tiny droplets that are displaced by the liquid phase. The water temperature is maintained at the lipid's softening point. To produce lipid nanoparticles, the formulation is then cooled to room temperature. This method is versatile, enabling control over particle size by utilizing membranes with different pore diameters.

1.3.14.4 The Protocol for Phase Inversion Temperature (PIT) Method:

Modifying the temperature can cause phase inversion, which converts an o/w emulsion to a w/o emulsion. The PIT shows the temperature at which the conversion occurs. This method comprises magnetically swirling together lipids, pharmaceuticals, water, and surfactants, followed by three rounds of temperature changes (85-60-85-60-85°C). To create lipid nanoparticles, the mixture is diluted with cold distilled water, resulting in a significant temperature differential. This method has the benefit of requiring no organic solvents and very brief heating.

1.3.14.5 Double Emulsion Method:

The dual emulsion technique utilized to create lipid nanostructures is suitable for hydrophilic medicinal components and peptides. In this technique, the medication's water phase is emulsified in a melting lipid blend to produce a primary w/o emulsion stabilized with appropriate excipients. To make a double w/o/w emulsion, the original w/o emulsion is dispersed in an aqueous solution with a hydrophilic emulsifier. The dual emulsion is then spun and filtered to separate it. This technique creates rather large particles, but it also allows for surface modification, such as the use of PEGs, as well as the insertion of hydrophilic molecules.

1.3.14.6 Microemulsion Cooling Approach:

To generate an o/w micro emulsion, melt an emulsifying wax at 38-56°C and add water warmed to a similar temperature. Stir rarely to obtain a homogenous milky slurry. Using a pharmacologically active polymeric surfactant in the recommended proportions creates a clean and long-lasting o/w micro emulsion like a liquid matrix. To extract nanoparticles from the o/w nano emulsion, it is chilled to normal temperatures. This method is repeatable, simple, and easy to scale. Furthermore, no organic solvents were used during the preparation procedure, and all the components were environmentally safe.

1.3.14.7 The Emulsification-Solvent Evaporation Approach:

This approach requires three steps of preparation. For example, during organic phase preparation, a lipophilic compound is dissolved in an appropriate volume of organic solvent through vigorous stirring. (ii) Pre-emulsification step: Using a high-speed homogenizer, a lipid-containing organic phase is dispersed in an appropriate volume of an aqueous solution to create a coarse pre-emulsion. (iii) Nano-emulsification step: To produce nano dispersion, the coarse pre-emulsion is run through a high-pressure homogenizer at a specific operating pressure. The nano dispersion is vigorously stirred overnight, occasionally under a fume hood, to remove the organic solvent. Nano dispersion occurs when lipids

precipitate in aqueous solutions after the solvent is removed. To remove fat and drug agglomerates, the solidified micro dispersion passes through a sintered glass filter. This method creates nanoparticles that are small, monodisperse, and highly entrapment efficient.

1.3.14.8 The Emulsification Solvent Diffusion Approach- To dissolve solid lipids, water-miscible solvents are used. Lipid nanoparticles were synthesized using solvents that are slightly water soluble, including butyl lactate, benzyl alcohol, isovaleric acid, iso-butyric acid, and tetrahydrofuran. When the temporary o/w suspension is immersed in water and agitated continuously, the dispersion phase solidifies, and lipid nanoparticles develop due to solvent diffusion.

1.3.14.9 Solvent Injection Approach: The solvent injection and diffusion methods share a common underlying principle. The solvent injection method involves rapidly injecting lipids into the water phase of surfactants using an injection syringe after dissolving them in a water-miscible solvent (e.g., isopropanol, acetone, or methanol). To make lipid nanoparticles, two concurrent actions work together: Solvent transport from lipid droplets into the aqueous phase reduces particle diameter and increases lipid content. The dispersion of pure solvent from lipid-solvent droplets causes oscillations in interfacial tension at the particle surface, resulting in droplet size minimization. The size of nanoparticles can be influenced by various process variables, including the solvent used, lipid percentage, volume injected, organic phase lipid percentage, and water phase stiffness.

1.3.14.10 The Supercritical Fluid (SCF) Approach:

The "supercritical fluid extraction of emulsions" technique produces lipid nanostructures from emulsions using the SCF approach. To make the organic combination, pharmaceutical and lipid components are dissolved in an organic solvent, such as chloroform, and a surfactant is added. To make an o/w dispersion, a high-pressure homogenizer blends the organic component with a water phase (which may also include a co-surfactant). The supercritical liquid (kept at constant heat and pressure) is fed counter-currently, while the o/w emulsion is fed via one terminal of the extraction unit (usually the top) at a continuous flow rate. Lipid nanoparticles are created by continually removing solvent from oil-in-water emulsions. Methods for creating lipid-polymer hybrid nanoparticles researchers have described various methods for synthesizing lipid polymer hybrid NPs (LPHN) depending on their application needs. Here are a handful of them.

Single-Step Approach: The single-step process (Fig. 1.5) is a popular way for creating hybrid nanoparticles. Polymers and drugs are spread in water-immiscible organic solvents. Lipids are disseminated in the aqueous phase using heat or sonication. Agitation is also utilized to mix the organic layer with the aqueous layer. This creates lipid-coated, caged polymeric nanospheres. The organic solvent is eliminated by evaporation under reduced pressure. This procedure is fast and inexpensive.

Two-Step Method: Double or multilayer lipid coatings are often applied in a two-step process to maximize loading, restrict drug degradation, and preserve release rate by allowing the drug to diffuse out

of the lipidic and polymeric matrix first. Moreover, this reduces medication leakage and improves formulation storage efficiency.[66-68]

1.3.14.11 Emulsification and solvent evaporation.

Emulsification: Solvent evaporation falls into two categories: single and double emulsion methods.

The single emulsion approach is used to capture components that dissolve in water-immiscible liquids. Continuous agitation or ultrasonication introduces the oil layer containing the polymer and therapeutic component (drug moiety) into the water phase, which also contains lipid.

As a result, an oil/water emulsion is formed. The polymer base is created by vaporizing a water-immiscible solvent under low pressure. The lipid then organizes around the polymer core. Furthermore, the polymer can dissolve the lipid in the oil phase. For hydrophilic components, a double-emulsion approach is used. This component is found in the aqueous phase, which is emulsified with an oil phase consisting of the polymer and lipid. To create a w/o/w emulsion, the resulting w/o emulsion is further emulsified with an aqueous layer as the continuous phase.

Non-conventional two-step approach: Drying, smooth lithographic particle shape, and merging prepared nano vehicles (polymeric and lipid) are examples of non-traditional double-phase approaches.
Dave and colleagues utilized spray drying to produce polymeric tiny particles formed from poly-glutamic acid and poly-lysine. After drying, the nanoparticles were mixed with lipids in dichloromethane to create hybrid nanoparticles.

1.3.14.12 Major Challenges in Nano-Based Drugs:

Nanotechnology is becoming more popular due to its wide range of applications. Nanomedicines are the most important and widely used use of nanotechnology. Nanotechnology, which focuses on the design and production of nanostructures, is one approach to overcoming the limits of existing medication delivery methods.

Nano-treatments offer significant advantages over traditional medications, including improved efficacy, pharmacokinetics, distribution across biotic barriers, and reduced toxicity and sensitivity.

In an article published in "Nature Nanotechnology" in 2008, Behra and Krug outlined three key concerns to address in the future years. Nanoparticle selection for biomedical research and testing. To identify nanoparticles before, during, and after research, measure their physicochemical properties, accumulation and sediment capacities, and other features. It is important to study how live organisms collect man-made nanoparticles in different settings. The organisms and measurement points that could be used in research. However, regulators' opinion is critical in deciding the details required for a new drug application (NDA). The complexity and difficulty of numerous nanomedical processes hampered awareness of general management requirement. The FDA handles industry-specific materials such as

"Liposome drug products" by offering knowledge on chemistry, production, and control, as well as human pharmacology and pharmaceuticals, including nanomaterial-containing biologicals.

According to a recent paper, "variation in published articles regarding the characteristics accomplished and the innovative information" is the main reason for challenges in the advancement of nanomedicine applications. The lack of industry-standard documentation hinders the spread of nanomedicine services and delays desktop-to-bedside translation.

Cancer therapy is a crucial application of nanomedicine, requiring targeted medication delivery to specific cancer cells. However, safely and successfully delivering pharmaceuticals to cancer cells remains a significant barrier. Nanoparticles have not fully met the promise of targeting sick tissue for drug delivery, despite being widely explored. Furthermore, to increasing the fraction of nano-drug injections that accumulate in tumors, it's crucial to explore and support drug duration in tumours. Nanomedicines may also help in this area. The goal of selective drug delivery is vital, but the development of drug-antibody fusion has faced numerous challenges before becoming a viable therapy option.

EPR (Enhanced permeability and retention) has fuelled the creation of nano drugs and their delivery techniques for many years. Several factors, such as nanomedicine circulating plasma concentration, strength, and plasma half-life, as well as tumor type, area, inflammatory status, and biological process, have been linked to positive EPR outcomes. The variability of patients' clinical status is a key factor to consider when analysing EPR impacts.

1.3.15 Application of Nanostructures:

Nanotechnology is a rapidly growing field with significant potential uses in drug. Medication carriers can help monitor and treat many illnesses. Nanoparticles can carry proteins, antibodies, peptides, and contrast agents. Nanocarriers offer advantages such as reduced production costs and high productivity.[69-71]

1.3.15.1 Cancer Treatment:

Graphene is a substance that can be used to detect cancer cells in the early stages. The tumour spheres test can be used to evaluate the function and genetic development of an anchorage-independent primary cancer stem cell.

Graphene oxide effectively suppresses the production of cancer spheres in several cell lines, including ovarian, pancreatic, breast, lung, and glioblastoma.[72]

Graphene oxide is less damaging to cancer cells compared to fibroblastic cells. NRF2 has a role in the antioxidant response, and graphene oxide therapy alters Notch and STAT1/3 signalling pathways.

Graphene oxide can trigger autophagy in cancer cells by activating toll-like receptors. CT26 colon cancer cells absorb graphene oxide, activating the TLR-4 and TLR-9 signalling pathways, as well as autophagy.

Injecting graphene oxide into rats with CT26 colon cancer cells reduces tumor formation while simultaneously activating autophagy. Nano graphene oxide, manufactured using six-arm polyethylene glycol, is highly successful in delivering hydrophobic medications to malignant cell types with high cell absorption. Conjugate polyethylene glycol showed malignancy in xenografts, showing its therapeutic potential as shown in Fig 1.6.

Nano graphene oxide subordinates are considered to have phototherapeutic effects by inducing oxidative stress, depolarizing mitochondria, activating caspases, and causing cell death.

Polyethylene glycol GO was utilized as a transporter for photothermal, Doxorubicin, and chemical therapies, enhancing therapeutic efficacy. Furthermore, graphene/TiO2 nano-hybrid composites supported great therapeutic potential, which is reliant on photocatalytic and photothermal treatment.[73-74]

PEGylated graphene oxide enhances tumor cell uptake in mouse xenograft tumor models, leading to effective anticancer therapy through enhanced penetration and retention (EPR).[75]

The nanosheet, composed of graphene oxide and gold nanoparticles (AuNPs), adheres to cell surfaces and improves cancer therapy through photo-thermal effects.

Lipid-based nanoparticles are also extremely significant in BreC therapy. Liposomes are frequently used due to their biocompatibility and ability to carry diverse cargos. Several therapeutic trials are using lipid nanoparticles, including Doxil and Abraxane, which have already been licensed for BreC therapy.[76]

1.3.15.2 Polymeric nanoparticles serve as drug carriers in neurodegenerative disorders:

Neurodegenerative disorders cause random and progressive loss of neurons, resulting in severe disability and considerable socioeconomic implications. Neurological disorders are rapidly becoming the costliest and deadliest medical conditions (Fig. 1.7). Nanomedicine, specifically focused injection of nanoparticles, is emerging as a promising method for delivering medications to the central nervous system.[77]

PLA nanoparticles preloaded with breviscapine exhibited size-dependent BBB permeation. A study confirmed that adding a trans-activating transcriptor (TAT) peptide to the surface of PLA NPs improved their transport across the brain.[78]

PLGA NPs coated with glycoheptapeptides can easily pass across the blood-brain barrier. The coatings imitate the behaviour of opioid peptides during absorption-mediated endocytosis, allowing them to enter the brain.[79]

Nanotechnology has been used to create drug delivery systems for Alzheimer's disease treatment. PLA NPs have two distinct targeting peptides: one for BBB contact and another with strong affinity for Abeta 1-42 peptide.

Researchers created a medication delivery method using PLGA NPs loaded with ropinirole. This method successfully reversed Parkinson's disease-like effects in mice and monkeys. Another technique involves delivering functionalized PLGA NPs to lysosomes and restoring their functionality.[80]

Curcumin, an antioxidant and anti-amyloidogenic compound, was loaded into functionalized PLGA nanoparticles. It can pass the blood-brain barrier and dissolve amyloid aggregates. This means it shown the potential to both diagnose Alzheimer's disease early and help it retreat.

Fig. 1.36 shows a few examples of nano-based medication delivery systems.

1.3.15.3 Nanoparticles in the Treatment of Eye Diseases and Disorders:

Nanoparticles combined with drug have been shown to effectively treat many eye disorders. The Nanspider TM technology uses poly (L-lactic acid) (PLA) as a polymer for nanoparticle production. The authors conducted macroscopic, histological, and biochemical tests to assess inflammatory response and corneal healing. Nanofibers of drug Cyclosporine-A was found to be quite effective in reducing the inflammatory process and neovascularization. Less contact time with an injured eye was proposed as a reason for eye drops containing the same drug being less effective.[81] On day 12, untreated corneas saw severe vascularization and loss of clarity, while eyes treated with eye drop/blank nanoparticles recovered partially. Drug-loaded nanoparticles can successfully cure many eye ailments and disorders by overcoming a critical barrier in standard ocular drug administration. Pre-clinical trials in rabbit eyes explained improved drug delivery and recovery compared to normal eye drops. However, the application of the dose form remains a concern. Nanoparticles containing timolol maleate and dorzolamide hydrochloride to treat glaucoma, another eye ailment.[82-84] Poly-caprolactone (PCL) and PVA-based nanofibers were considered for their therapeutic potential by injecting them into a rabbit's culdesac. The formulation is beneficial for treating glaucoma, as it significantly lowers intraocular pressures compared to standard eye drops.

1.3.15.4 Nanoparticles in the Treatment of Ear Diseases and Disorders:

The most challenging component of treating periprosthetic infections is dealing with a formed biofilm. Biofilms can form on implanted medical equipment, including ossiculoplasty prosthesis and implantable hearing implants. They are difficult to remove and can cause endo-cochlear irritation, undetected infections, and discomfort for patients. Previously, natural biodegradable PCL nanoparticles were developed to effectively deliver vancomycin to prevent MRSA infection on ossicular prosthesis and otitis media.[85-91] In vitro studies confirmed the absence of biofilm on implantable medical devices. Nanomaterial therapy results in reduced MSRA levels in the otitis media.

1.3.15.5 Gene Therapy using Nanomaterials:

Gene therapy treats inherited problems, including infections, cancer, and degenerative ailments. It affects the expression of one or more functional genes within a cell, tissue, or organ. As a result, it either alters gene expression or corrects a defective gene that may have caused infection or illness. The ability of DNA to enter the nucleus of the target tissue is important for the effectiveness of gene therapy. Carbon nanotubes to target specific gene expression in liver cells for gene therapy.[92-94] Tailored liposomal preparations have been found to be more successful than non-targeted liposomes. Nanotubes boosted the expression of a b-galactosidase marker gene compared to naked DNA transfer, showing that they are less immunogenic than viral vectors used for gene transfer. Liposomes using polyethylene glycol and galactose can treat liver illnesses like Wilson's disease and familial hemochromatosis. Nanobubbles containing the human insulin gene could lead to a potential type 1 diabetes therapy. Dendrimers have the potential to replace standard viral vectors in gene therapy due to their customizable structure and adaptive chemistry for drug or gene delivery. Endocytosis permits them to enter cells and transport DNA to nuclei for gene expression. Various ligands, including transferrin, carbohydrates, and antibodies, can be linked to receptors. Pan et colleagues found that magnetic nanoparticle modified PAMAM dendrimers effectively transport antisense surviving oligonucleotides to tumor cell types. DNA-loaded nanoparticles can effectively treat cystic fibrosis. PEG-coated DNA nanoparticles may penetrate human and animal mucus. An externally concentrated magnetic field can direct and localize nanoparticles in diseased tissue.

Conclusion: In the field of nanomedicine, liposomal drug delivery systems have become a potent and adaptable platform with many benefits over traditional drug formulations. The basic features of liposomes, including their structure, classification, sophisticated manufacturing techniques, drug loading strategies, and targeting mechanisms, have all been covered in this thorough analysis. The wide range of uses covered, including gene delivery, cancer treatment, vaccine research, diagnostic imaging, and other therapeutic fields, highlights the liposomal technology's exceptional promise and versatility. The quick developments in this sector are reflected in the development of liposomal formulations from simple liposomes to complex stimuli-responsive and multifunctional systems. Improved manufacturing processes, the incorporation of new materials and technologies, and a better knowledge of liposome-biological interactions have all contributed to these advancements. The bioavailability of lipophilic medications can be considerably increased by LNPs and surface changes, according to a number of recent LNPs studies. The commercialization of LNPs is still hampered by their possible adverse effects, which include allergic reactions to the substance and the difficulties of scaling up the majority of surface alterations. In order to make LNPs the best DDS for lipophilic drugs, collaboration between LNPs and surface modification can be crucial if these issues are resolved by numerous clinical investigations using LNPs and surface modification processes.

Declarations

Ethics Approval: Not required for this review manuscript since it does not involve any biological experiments.

Consent to Participate: All the authors have their consent to participate in the paper.

Consent for Publication: All authors have given consent to publish this work.

Conflicts of Interest: The authors state that they have no financial interests or personal relationships that could have influenced the work presented in this paper.

CRediT authorship contribution statement

Chandraprakash Gond: Formal Analysis, and Writing **Priya Singh,** Conceptualization**, Deepika Singh:** Investigation**, Akanksha Verma:** Writing and Formal analysis**,** Data Curation, **Anjani Kumar Tiwari**: Writing - review & editing, Supervision, Validation

Acknowledgements

Authors are thankful to BBAU, Lucknow, India for providing the instrumentation facility.

Funding

Authors are grateful to UGC-SRF for providing the financial assistance.

Appendix A. Supplementary data

Supplementary material to this paper can be found online at…

References

1. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Drug delivery systems: An updated review. Int J Pharm Invest. 2012;2(1):2–11. https://doi.org/10.4103/2230-973X.96920.
2. He H, Liang Q, Shin MC, Lee K, Gong J, Ye J, Yang V. Significance and strategies in developing delivery systems for bio-macromolecular drugs. Front Chem Sci Eng. 2013;7(4):496–507. https://doi.org/10.1007/s11705-013-1369-5.
3. Palleria C, Di Paolo A, Giofrè C, Caglioti C, Leuzzi G, Siniscalchi A, De Sarro G, Gallelli L. Pharmacokinetic drug-drug interactions and their implications in clinical management. J Res Med Sci. 2013;18(7):601–10. https://doi.org/10.4103/1735-1995.116516.
4. Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. J Controlled Release. 2022;341:132–46. https://doi.org/10.1016/j.jconrel.2021.11.025.
5. Alalaiwe A. The clinical pharmacokinetics impact of medical nanometals on drug delivery systems. Nanomedicine. 2019;17:47–61. https://doi.org/10.1016/j.nano.2019.01.004.

6. Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Design, functionalization strategies, and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Chem Soc Rev. 2013;42(3):1147–235. https://doi.org/10.1039/c2cs35265f.
7. Patel S, Bhirde AA, Rusling JF, Chen X, Gutkind JS, Patel V. Nano delivers big: Designing molecular missiles for cancer therapeutics. Pharmaceutics. 2011;3(1):34–52. https://doi.org/10.3390/pharmaceutics3010034.
8. Chatterjee B, Gorain B, Mohananaidu K, Sengupta P, Mandal UK, Choudhury H. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. Int J Pharm. 2019;565:258–68. https://doi.org/10.1016/j.ijpharm.2019.05.032.
9. Hu CM, Zhang L. Nanoparticle-based combination therapy toward overcoming drug resistance in cancer. Biochem Pharmacol. 2012;83(8):1104–11. 10.1016/j.bcp.2012.01.008.
10. Figueroa-Robles A, Antunes-Ricardo M, Guajardo-Flores D. Encapsulation of phenolic compounds with liposomal improvement in the cosmetic industry. Int J Pharm. 2021;593:120125. https://doi.org/10.1016/j.ijpharm.2020.120125.
11. Gonzalez Gomez A, Hosseinidoust Z. Liposomes for antibiotic encapsulation and delivery. ACS Infect Dis. 2020;6(5):896–908. https://doi.org/10.1021/acsinfecdis.9b00357.
12. Cao Y, Dong X, Chen X. Polymer-modified liposomes for drug delivery: From fundamentals to applications. Pharmaceutics. 2022;14(4):778. https://doi.org/10.3390/pharmaceutics14040778.
13. Hofheinz RD, Gnad-Vogt SU, Beyer U, Hochhaus A. Liposomal encapsulated anti-cancer drugs. Anticancer Drugs. 2005;16(7):691–707. https://doi.org/10.1097/01.cad.0000167902.53039.5a.
14. Olusanya TOB, Ahmad H, Ibegbu RR, Smith DM, J. R., Elkordy AA. Liposomal drug delivery systems and anticancer drugs. Molecules. 2018;23(4):907. https://doi.org/10.3390/molecules23040907.
15. Chonn A, Cullis PR. Recent advances in liposomal drug-delivery systems. Curr Opin Biotechnol. 1995;6(6):698–708. https://doi.org/10.1016/0958-1669(95)80115-4.
16. Singh K, Biharee A, Vyas A, Thareja S, Jain AK. Recent advancement of polymersomes as drug delivery carrier. Curr Pharm Design. 2022;28(20):1621–31. https://doi.org/10.2174/1381612828666220412103552.
17. Pattni BS, Chupin VV, Torchilin VP. New developments in liposomal drug delivery. Chem Rev. 2015;115(19):10938–66. https://doi.org/10.1021/acs.chemrev.5b00046.
18. Rommasi F, Esfandiari N. Liposomal nanomedicine: Applications for drug delivery in cancer therapy. Nanoscale Res Lett. 2021;16(1):95. https://doi.org/10.1186/s11671-021-03553-8.
19. Kim EM, Jeong HJ. Liposomes: Biomedical applications. Chonnam Med J. 2021;57(1):27–35. https://doi.org/10.4068/cmj.2021.57.1.27.
20. Wang X, Guo Z. Targeting and delivery of platinum-based anticancer drugs. Chem Soc Rev. 2013;42(1):202–24. https://doi.org/10.1039/c2cs35259a.
21. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, Samiei M, Kouhi M, Nejati-Koshki K. Liposome: Classification, preparation, and applications. Nanoscale Res Lett.

2013;8(1):102. https://doi.org/10.1186/1556-276X-8-102.

22. Lombardo D, Kiselev MA. Methods of liposomes preparation: Formation and control factors of versatile nanocarriers for biomedical and nanomedicine application. Pharmaceutics. 2022;14(3):543. https://doi.org/10.3390/pharmaceutics14030543.
23. Feitosa RC, Geraldes DC, Beraldo-de-Araújo VL, Costa JSR, Oliveira-Nascimento L. Pharmacokinetic aspects of nanoparticle-in-matrix drug delivery systems for oral/buccal delivery. Front Pharmacol. 2019;10:1057. https://doi.org/10.3389/fphar.2019.01057.
24. Cortesi R, Esposito E, Gambarin S, Telloli P, Menegatti E, Nastruzzi C. Preparation of liposomes by reverse-phase evaporation using alternative organic solvents. J Microencapsul. 1999;16(2):251–6. https://doi.org/10.1080/026520499289220.
25. Kesharwani P, Kumari K, Gururani R, Jain S, Sharma S. Approaches to address PK-PD challenges of conventional liposome formulation with special reference to cancer, Alzheimer's, diabetes, and glaucoma: An update on modified liposomal drug delivery system. Curr Drug Metab. 2022;23(9):678–92. https://doi.org/10.2174/1389200223666220609141459.
26. Hadian Z, Sahari MA, Moghimi HR, Barzegar M. Formulation, characterization and optimization of liposomes containing eicosapentaenoic and docosahexaenoic acids; a methodology approach. Iran J Pharm Res. 2014;13(2):393–404. https://doi.org/10.22037/ijpr.2014.1725.
27. Wang Y, Grainger DW. Lyophilized liposome-based parenteral drug development: Reviewing complex product design strategies and current regulatory environments. Adv Drug Deliv Rev. 2019;151–152:56–71. https://doi.org/10.1016/j.addr.2019.03.003.
28. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;3(1):16–20. https://doi.org/10.1021/nn900002m.
29. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S, Shin HS. Nano based drug delivery systems: Recent developments and future prospects. J Nanobiotechnol. 2018;16(1):71. https://doi.org/10.1186/s12951-018-0392-8.
30. Lankala CR, Yasir M, Ishak A, Mekhail M, Kalyankar P, Gupta K. Application of nanotechnology for diagnosis and drug delivery in atherosclerosis: A new horizon of treatment. Curr Probl Cardiol. 2023;48(6):101671. https://doi.org/10.1016/j.cpcardiol.2023.101671.
31. de Almeida TS, Júlio A, Mota JP, Rijo P, Reis CP. An emerging integration between ionic liquids and nanotechnology: General uses and future prospects in drug delivery. Therapeutic Delivery. 2017;8(6):461–73. https://doi.org/10.4155/tde-2017-0002.
32. Mishra M, Kumar P, Rajawat JS, Malik R, Sharma G, Modgil A. Nanotechnology: Revolutionizing the science of drug delivery. Curr Pharm Design. 2018;24(43):5086–107. https://doi.org/10.2174/1381612825666190206222415.
33. Ahlawat J, Henriquez G, Narayan M. Enhancing the delivery of chemotherapeutics: Role of biodegradable polymeric nanoparticles. Molecules. 2018;23(9):2157. https://doi.org/10.3390/molecules23092157.

34. Zhang WJ, Hong CY, Pan CY. Polymerization-induced self-assembly of functionalized block copolymer nanoparticles and their application in drug delivery. Macromol Rapid Commun. 2019;40(2):e1800279. https://doi.org/10.1002/marc.201800279.
35. Gormley AJ, Chapman R, Stevens MM. Polymerization amplified detection for nanoparticle-based biosensing. Nano Lett. 2014;14(11):6368–73. https://doi.org/10.1021/nl502840h.
36. George R, Hehlgans S, Fleischmann M, Rödel C, Fokas E, Rödel F. Advances in nanotechnology-based platforms for survivin-targeted drug discovery. Expert Opin Drug Discov. 2022;17(7):733–54. https://doi.org/10.1080/17460441.2022.2077329.
37. Yan B. (2011). Impacts of nanotechnology on medicinal chemistry and drug discovery. *Current Medicinal Chemistry, 18*(14), 2044. https://doi.org/10.2174/092986711795656207
38. Raza K. Nanotechnology-based drug delivery products: Need, design, pharmacokinetics and regulations. Curr Pharm Design. 2018;24(43):5085. https://doi.org/10.2174/1381612824431903280859l7.
39. Bustos Cruz RH, Sanchez MM, Dominguez-Sanchez MA, Barreto GE, Lancheros D, Reynolds J. Nanotechnology in neurosciences: An approach. Curr Pharm Design. 2017;23(28):4154–69. https://doi.org/10.2174/1381612823666170816115452.
40. Edgar JYC, Wang H. Introduction for design of nanoparticle-based drug delivery systems. Curr Pharm Design. 2017;23(14):2108–12. https://doi.org/10.2174/1381612822666161025154003.
41. Pinilla CMB, Lopes NA, Brandelli A. Lipid-based nanostructures for the delivery of natural antimicrobials. Molecules. 2021;26(12):3587. https://doi.org/10.3390/molecules26123587.
42. Ge Z, Liu S. Functional block copolymer assemblies responsive to tumor and intracellular microenvironments for site-specific drug delivery and enhanced imaging performance. Chem Soc Rev. 2013;42(17):7289–325. https://doi.org/10.1039/c3cs60048c.
43. Shankar R, Joshi M, Pathak K. Lipid nanoparticles: A novel approach for brain targeting. Pharm Nanatechnol. 2018;6(2):81–93. https://doi.org/10.2174/2211738506666180611100416.
44. Fan Y, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. J Pharm Biomed Anal. 2021;192:113642. https://doi.org/10.1016/j.jpba.2020.113642.
45. Salvati Manni L, Fong WK, Mezzenga R. Lipid-based mesophases as matrices for nanoscale reactions. Nanoscale Horizons. 2020;5(6):914–27. https://doi.org/10.1039/d0nh00079e.
46. Maier MA, Jayaraman M, Matsuda S, Liu J, Barros S, Querbes W, Tam YK, Ansell SM, Kumar V, Qin J, Zhang X, Wang Q, Panesar S, Hutabarat R, Carioto M, Hettinger J, Kandasamy P, Butler D, Rajeev KG, Pang B, Charisse K, Fitzgerald K, Mui BL, Du X, Cullis P, Madden TD, Hope MJ, Manoharan M, Akinc A. Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. Mol Ther. 2013;21(8):1570–8. https://doi.org/10.1038/mt.2013.124.
47. Tenchov R, Sasso JM, Zhou QA. PEGylated lipid nanoparticle formulations: Immunological safety and efficiency perspective. Bioconjug Chem. 2023;34(6):941–60. https://doi.org/10.1021/acs.bioconjchem.3c00174.

48. Mishra DK, Shandilya R, Mishra PK. Lipid-based nanocarriers: A translational perspective. Nanomedicine. 2018;14(7):2023–50. https://doi.org/10.1016/j.nano.2018.05.021.
49. Ferreira Soares DC, Domingues SC, Viana DB, Tebaldi ML. Polymer-hybrid nanoparticles: Current advances in biomedical applications. Biomed Pharmacother. 2020;131:110695. https://doi.org/10.1016/j.biopha.2020.110695.
50. Cheow WS, Hadinoto K. Factors affecting drug encapsulation and stability of lipid-polymer hybrid nanoparticles. Colloids Surf B. 2011;85(2):214–20. https://doi.org/10.1016/j.colsurfb.2011.02.033.
51. Bose RJC, Ravikumar R, Karuppagounder V, Bennet D, Rangasamy S, Thandavarayan RA. Lipid-polymer hybrid nanoparticle-mediated therapeutics delivery: Advances and challenges. Drug Discovery Today. 2017;22(8):1258–65. https://doi.org/10.1016/j.drudis.2017.05.015.
52. Qiao R. Functional Polymeric Nanoparticles for Drug Delivery. Curr Pharm Design. 2022;28(5):339. https://doi.org/10.2174/1381612828052201111429 51.
53. Hickey JW, Santos JL, Williford JM, Mao HQ. Control of polymeric nanoparticle size to improve therapeutic delivery. J Controlled Release. 2015;219:536–47. https://doi.org/10.1016/j.jconrel.2015.10.006.
54. Maghrebi S, Prestidge CA, Joyce P. An update on polymer-lipid hybrid systems for improving oral drug delivery. Expert Opin Drug Deliv. 2019;16(5):507–24. https://doi.org/10.1080/17425247.2019.1605353.
55. Rizwanullah M, Alam M, Harshita, Mir SR, Rizvi MMA, Amin S. Polymer-lipid hybrid nanoparticles: A next-generation nanocarrier for targeted treatment of solid tumors. Curr Pharm Design. 2020;26(11):1206–15. https://doi.org/10.2174/1381612826666200116150426.
56. Hadinoto K, Sundaresan A, Cheow WS. Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: A review. Eur J Pharm Biopharm. 2013;85(3 Pt):427–43. https://doi.org/10.1016/j.ejpb.2013.07.002.
57. Feng L, Zhu C, Yuan H, Liu L, Lv F, Wang S. Conjugated polymer nanoparticles: Preparation, properties, functionalization, and biological applications. Chem Soc Rev. 2013;42(16):6620–33. https://doi.org/10.1039/c3cs60036j.
58. Kou Z, Dou D, Mo H, Ji J, Lan L, Lan X, Zhang J, Lan P. Preparation and application of a polymer with pH/temperature-responsive targeting. Int J Biol Macromol. 2020;165(Pt A):995–1001. https://doi.org/10.1016/j.ijbiomac.2020.09.248.
59. Trasi NS, Bhujbal SV, Zemlyanov DY, Zhou QT, Taylor LS. Physical stability and release properties of lumefantrine amorphous solid dispersion granules prepared by a simple solvent evaporation approach. Int J Pharm X. 2020;2:100052. https://doi.org/10.1016/j.ijpx.2020.100052.
60. Strojewski D, Krupa A. Spray drying and nano spray drying as manufacturing methods of drug-loaded polymeric particles. Polimery w medycynie. 2022;52(2):101–11. https://doi.org/10.17219/pim/152230.
61. Wang Y, Li P, Truong-Dinh Tran T, Zhang J, Kong L. Manufacturing techniques and surface engineering of polymer-based nanoparticles for targeted drug delivery to cancer. Nanomaterials

(Basel). 2016;6(2):26. https://doi.org/10.3390/nano6020026.

62. Bilati U, Allémann E, Doelker E. Development of a nanoprecipitation method intended for the entrapment of hydrophilic drugs into nanoparticles. Eur J Pharm Sci. 2005;24(1):67–75. https://doi.org/10.1016/j.ejps.2004.09.011.
63. Parhi R, Suresh P. Preparation and characterization of solid lipid nanoparticles—A review. Curr Drug Discov Technol. 2012;9(1):2–16. https://doi.org/10.2174/157016312799304552.
64. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: Structure, preparation, and application. Adv Pharm Bull. 2015;5(3):305–13. https://doi.org/10.15171/apb.2015.043.
65. Corrias F, Lai F. New methods for lipid nanoparticles preparation. Recent Pat Drug Deliv Formul. 2011;5(3):201–13. https://doi.org/10.2174/187221111797200597.
66. Clawson C, Ton L, Aryal S, Fu V, Esener S, Zhang L. Synthesis and characterization of lipid-polymer hybrid nanoparticles with pH-triggered poly(ethylene glycol) shedding. Langmuir. 2011;27(17):10556–61. https://doi.org/10.1021/la202123e.
67. Dave V, Tak K, Sohgaura A, Gupta A, Sadhu V, Reddy KR. Lipid-polymer hybrid nanoparticles: Synthesis strategies and biomedical applications. J Microbiol Methods. 2019;160:130–42. https://doi.org/10.1016/j.mimet.2019.03.017.
68. Wang T, Xue J, Hu Q, Zhou M, Chang C, Luo Y. Synthetic surfactant- and cross-linker-free preparation of highly stable lipid-polymer hybrid nanoparticles as potential oral delivery vehicles. Sci Rep. 2017;7(1):2750. https://doi.org/10.1038/s41598-017-02867-x.
69. Murthy SK. Nanoparticles in modern medicine: state of the art and future challenges. Int J Nanomed. 2007;2(2):129–41. https://doi.org/10.2147/ijn.s1263.
70. Sindhwani S, Syed AM, Ngai J, Kingston BR, Maiorino L, Rothschild J, MacMillan P, Zhang Y, Rajesh NU, Hoang T, Wu JLY, Wilhelm S, Zilman A, Gadde S, Sulaiman A, Ouyang B, Lin Z, Wang L, Egeblad M, Chan WCW. The entry of nanoparticles into solid tumours. Nat Mater. 2020;19(5):566–75. https://doi.org/10.1038/s41563-019-0566-2.
71. Handa M, Singh A, Flora SJS, Shukla R. Stimuli-responsive polymeric nanosystems for therapeutic applications. Curr Pharm Design. 2022;28(11):910–21. https://doi.org/10.2174/1381612827666211208150210.
72. Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. Chem Soc Rev. 2012;41(7):2545–61. https://doi.org/10.1039/c2cs15327k.
73. Wang C, Zhang Y, Dong Y. Lipid nanoparticle-mRNA formulations for therapeutic applications. Acc Chem Res. 2021;54(23):4283–93. https://doi.org/10.1021/acs.accounts.1c00550.
74. Cheng X, Lee RJ. The role of helper lipids in lipid nanoparticles (LNPs) designed for oligonucleotide delivery. Adv Drug Delivery Reviews. 2016;99:129–37. https://doi.org/10.1016/j.addr.2016.01.022.
75. Nasrollahzadeh M, Sajjadi M, Soufi GJ, Iravani S, Varma RS. Nanomaterials and nanotechnology-associated innovations against viral infections with a focus on coronaviruses. Nanomaterials (Basel). 2020;10(6):1072. https://doi.org/10.3390/nano10061072.

76. Orecchioni M, Cabizza R, Bianco A, Delogu LG. Graphene as cancer theranostic tool: progress and future challenges. Theranostics. 2015;5(7):710–23. https://doi.org/10.7150/thno.11387.
77. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, Shen S, Kepp O, Scoazec M, Mignot G, Rello-Varona S, Tailler M, Menger L, Vacchelli E, Galluzzi L, Ghiringhelli F, di Virgilio F, Zitvogel L, Kroemer G. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 2011;334(6062):1573–7. https://doi.org/10.1126/science.1208347.
78. Levine B. Eating oneself and uninvited guests: autophagy-related pathways in cellular defense. Cell. 2005;120(2):159–62. https://doi.org/10.1016/j.cell.2005.01.005.
79. Cordaro A, Neri G, Sciortino MT, Scala A, Piperno A. Graphene-based strategies in liquid biopsy and in viral diseases diagnosis. Nanomaterials (Basel). 2020;10(6):1014. https://doi.org/10.3390/nano10061014.
80. Gonçalves G, Vila M, Portolés MT, Vallet-Regi M, Gracio J, Marques PA. Nano-graphene oxide: A potential multifunctional platform for cancer therapy. Adv Healthc Mater. 2013;2(8):1072–90. https://doi.org/10.1002/adhm.201300023.
81. Zhao Y, Alakhova DY, Kim JO, Bronich TK, Kabanov AV. A simple way to enhance Doxil® therapy: drug release from liposomes at the tumor site by amphiphilic block copolymer. J Controlled Release. 2013;168(1):61–9. https://doi.org/10.1016/j.jconrel.2013.02.026.
82. Calzoni E, Cesaretti A, Polchi A, Di Michele A, Tancini B, Emiliani C. Biocompatible polymer nanoparticles for drug delivery applications in cancer and neurodegenerative disorder therapies. J Funct Biomaterials. 2019;10(1):4. https://doi.org/10.3390/jfb10010004.
83. Cano A, Sánchez-López E, Ettcheto M, López-Machado A, Espina M, Souto EB, Galindo R, Camins A, García ML, Turowski P. Current advances in the development of novel polymeric nanoparticles for the treatment of neurodegenerative diseases. Nanomed (Lond). 2020;15(12):1239–61. https://doi.org/10.2217/nnm-2019-0443.
84. La Barbera L, Mauri E, D'Amelio M, Gori M. Functionalization strategies of polymeric nanoparticles for drug delivery in Alzheimer's disease: Current trends and future perspectives. Front NeuroSci. 2022;16:939855. https://doi.org/10.3389/fnins.2022.939855.
85. Souto EB, Souto SB, Campos JR, Severino P, Pashirova TN, Zakharova LY, Silva AM, Durazzo A, Lucarini M, Izzo AA, Santini A. Nanoparticle delivery systems in the treatment of diabetes complications. Molecules. 2019;24(23):4209. https://doi.org/10.3390/molecules24234209.
86. Barbara R, Belletti D, Pederzoli F, Masoni M, Keller J, Ballestrazzi A, Vandelli MA, Tosi G, Grabrucker AM. Novel curcumin-loaded nanoparticles engineered for blood-brain barrier crossing and able to disrupt Abeta aggregates. Int J Pharm. 2017;526(1–2):413–24. https://doi.org/10.1016/j.ijpharm.2017.05.015.
87. Novais MVM, Gomes ER, Miranda MC, Silva JO, Gomes DA, Braga FC, Pádua RM, Oliveira MC. Liposomes co-encapsulating doxorubicin and glucoevatromonoside derivative induce synergic

cytotoxic response against breast cancer cell lines. Biomedicines. 2021;136:111123. https://doi.org/10.1016/j.biopha.2020.111123.

88. Gagandeep, Garg T, Malik B, Rath G, Goyal AK. Development and characterization of nano-fiber patch for the treatment of glaucoma. Eur J Pharm Sci. 2014;53:10–6. https://doi.org/10.1016/j.ejps.2013.11.016.
89. Tsikopoulos K, Meroni G, Kaloudis P, Pavlidou E, Gravalidis C, Tsikopoulos I, Drago L, Romano CL, Papaioannidou P. Is nanomaterial- and vancomycin-loaded polymer coating effective at preventing methicillin-resistant *Staphylococcus aureus* growth on titanium disks? An in vitro study. Int Orthop. 2023;47(6):1415–22. https://doi.org/10.1007/s00264-023-05757-2.
90. azdani S, Mozaffarian M, Pazuki G, Hadidi N, Villate-Beitia I, Zárate J, Puras G, Pedraz JL. Carbon-based nanostructures as emerging materials for gene delivery applications. Pharmaceutics. 2024;16(2):288. https://doi.org/10.3390/pharmaceutics16020288.
91. Merve K, Silinder-Gunay M, Alper Kursunel M, Esendagli G, Dogan A, Yekta Ozer A. Design and in vitro evaluation of folate-targeted, co-drug encapsulated theranostic LPs for non-small cell lung cancer. J Drug Deliv Sci Technol. 2020;57:101707. https://doi.org/10.1016/j.jddst.2020.101707.
92. Fenske DB, Chonn A, Cullis PR. Liposomal nanomedicines: An emerging field. Toxicol Pathol. 2008;36(1):21–9. https://doi.org/10.1177/0192623307310960.
93. Zhong J, Dai LC. Targeting liposomal nanomedicine to cancer therapy. Technol Cancer Res Treat. 2012;11(5):475–81. https://doi.org/10.7785/tcrt.2012.500259.
94. Fenske DB, Cullis PR. Liposomal nanomedicines. Expert Opin Drug Deliv. 2008;5(1):25–44. https://doi.org/10.1517/17425247.5.1.25.

Figures

Figure 1

Nanomedicine's diverse applications in biomedical research

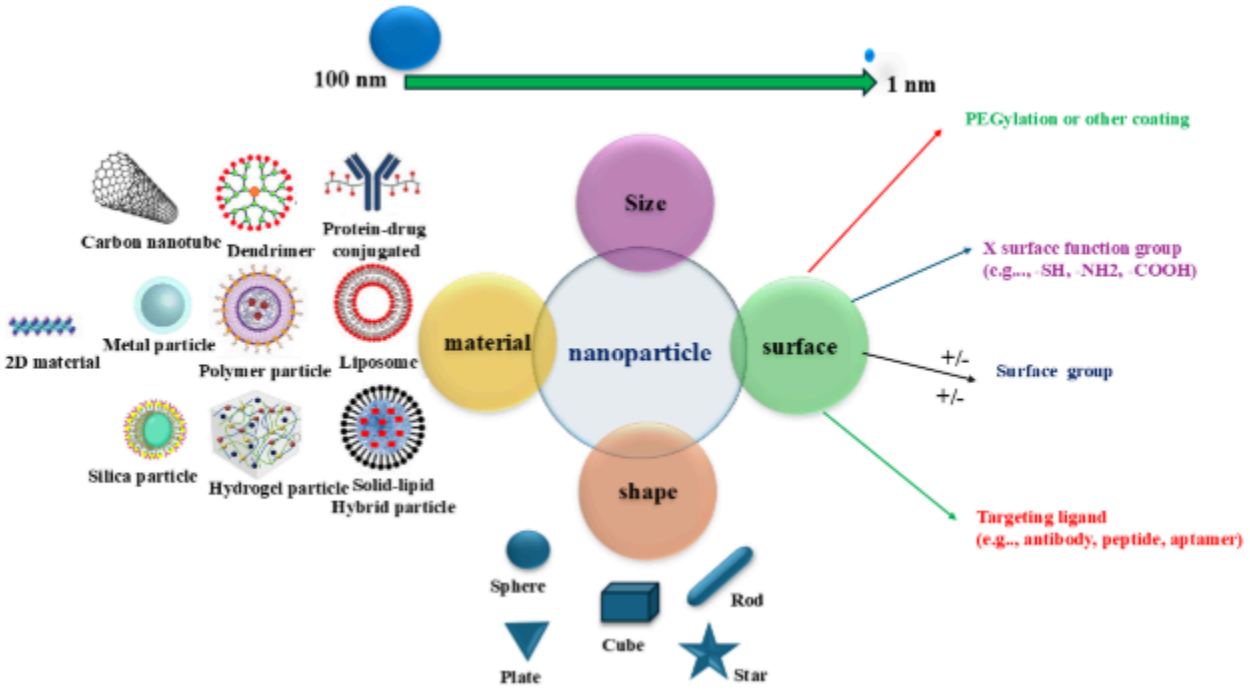

Figure 2

Material, shape, size and surface properties play an important role on the bio-physicochemical properties of nanoparticles

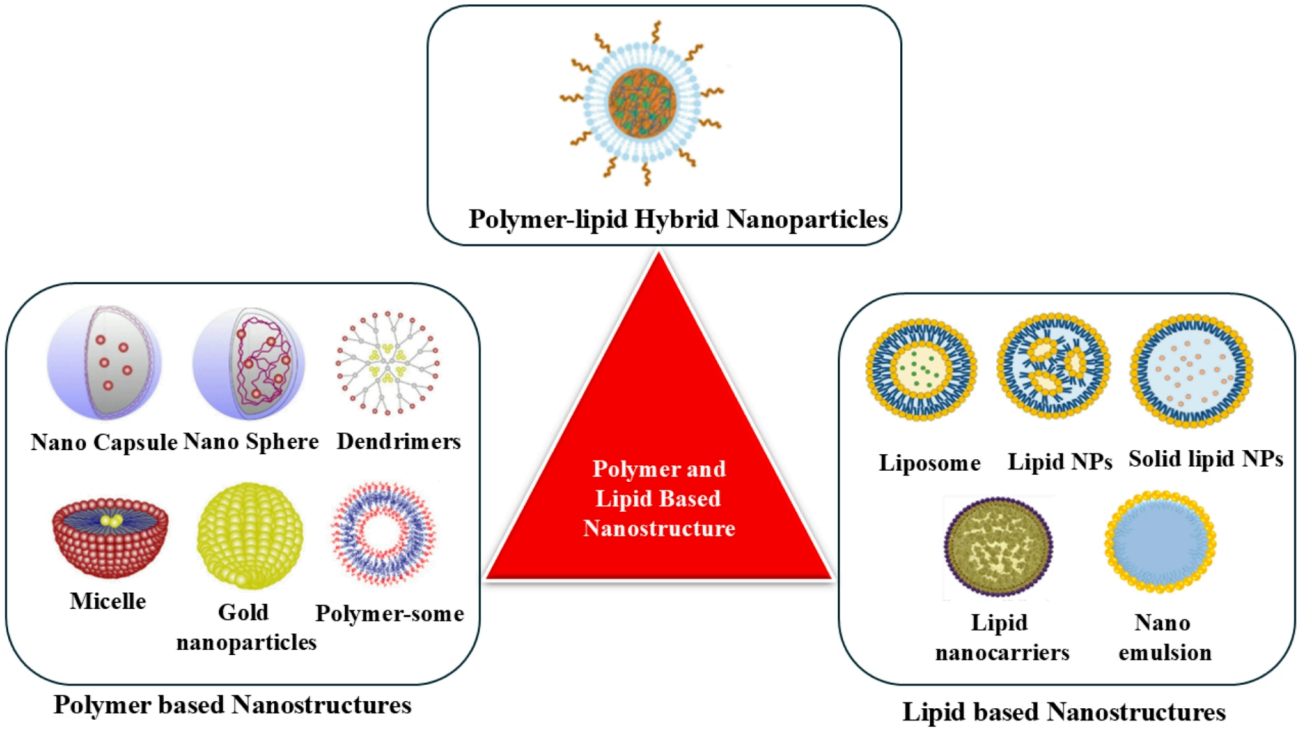

Figure 3

Different classes of lipid and polymeric nanoparticles.

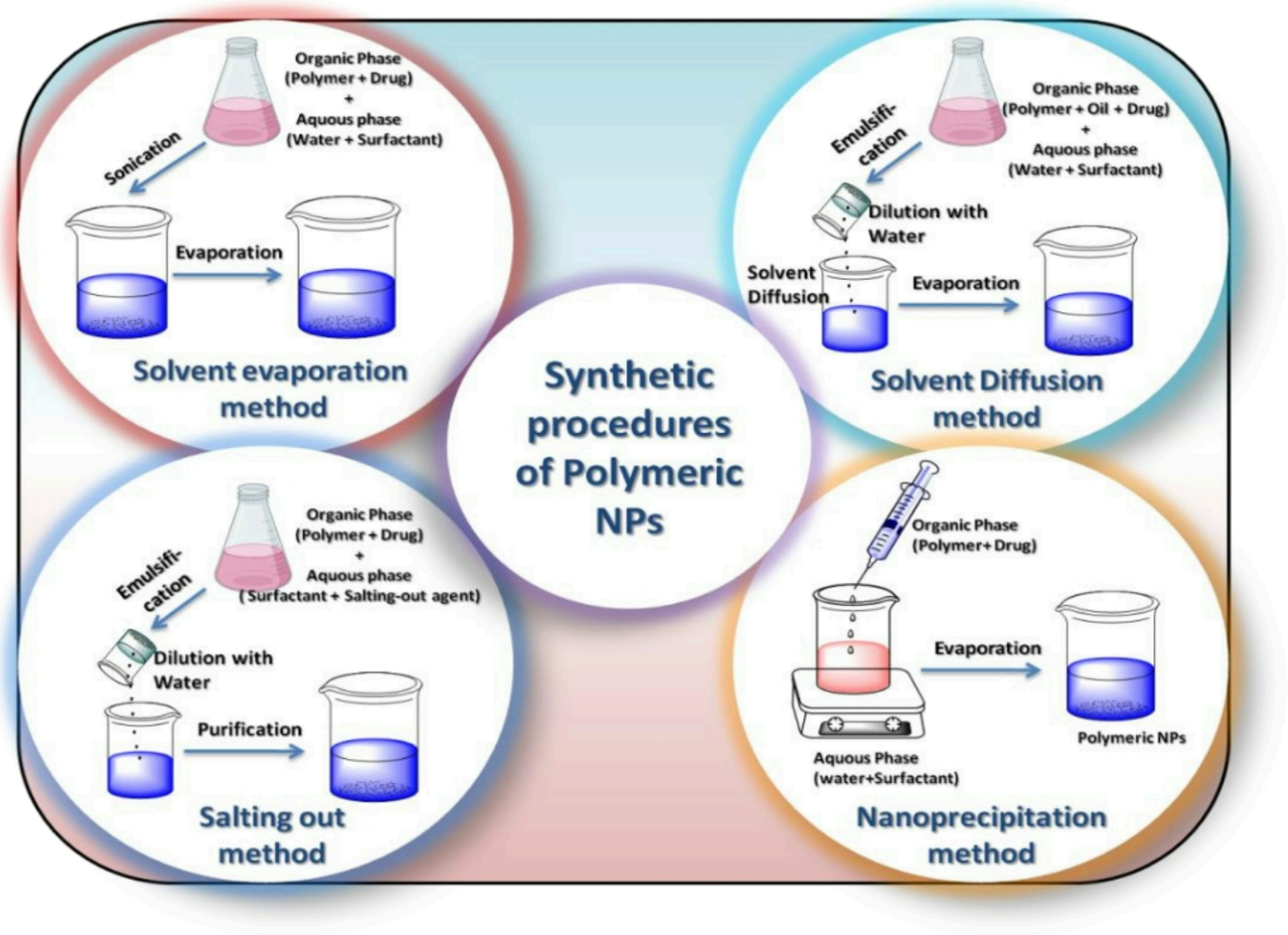

Figure 4

Schematic representation of different methods of polymeric nanoparticles

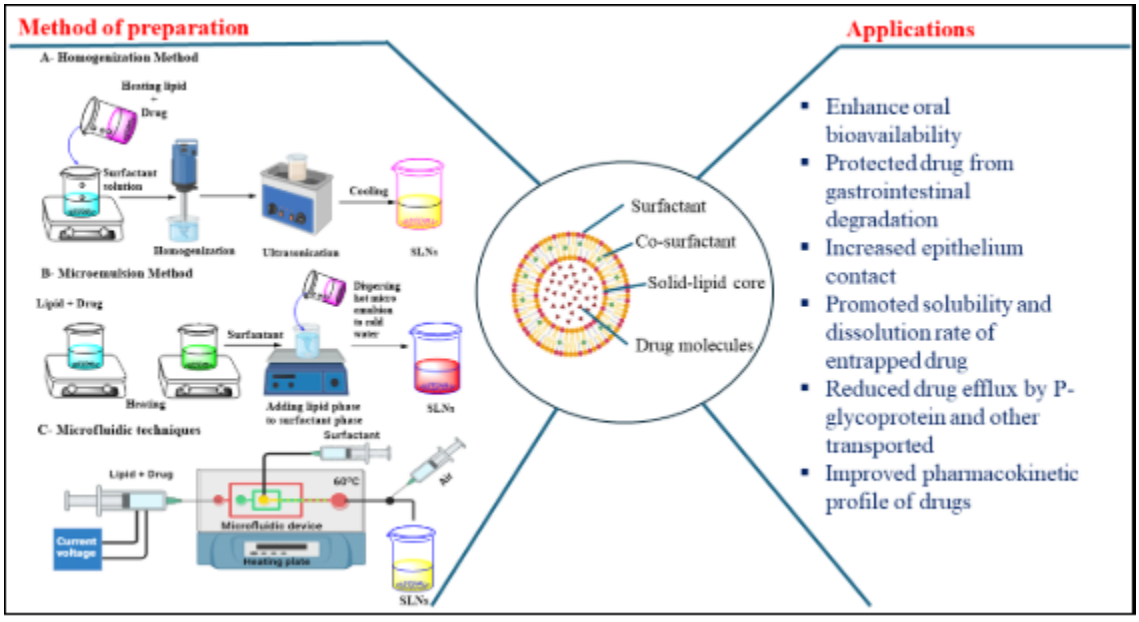

Figure 5

Schematic representation of different methods of polymeric nanoparticles

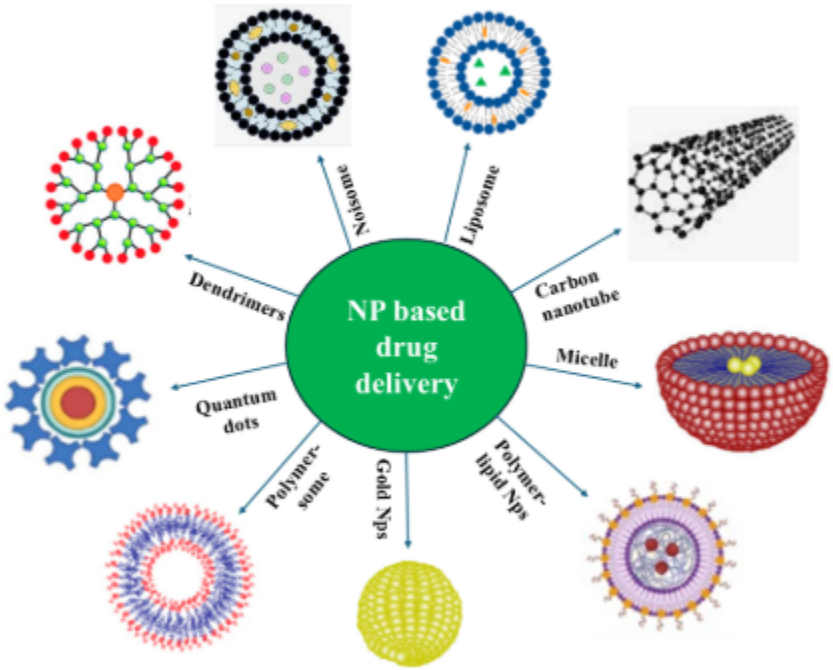

Figure 6

Nanoparticles used drug delivery in cancer

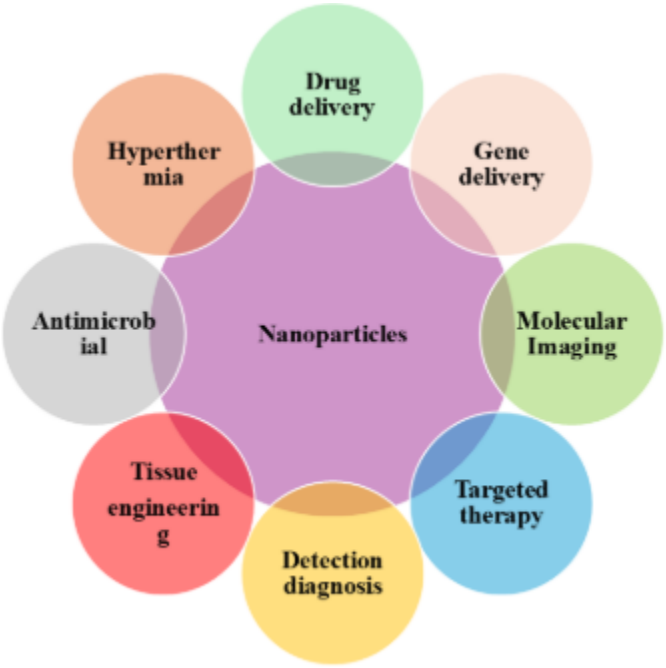

Figure 7

Biomedical applications of Nanoparticles

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementryFile.docx