Chapter 13
Recent Advancements in the Application of Nanomaterial in Modern Drug Delivery and Future Perspective

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Abstract Recently, nanomaterials are widely employed in the medical sector for sensitively detecting biological molecules, imaging of diseased tissues, therapeutics, and drug delivery. Nanomaterials with various biological characteristics and compositions have widely explored for drug delivery uses. It's critical to comprehend the interactions while using drugs for delivery of the nanomaterials with the bio-system, therapeutic agent's stability, surface of target receptors, and release of the drug. Different organic and inorganic based nanomaterials have designed, and their application as nanocarriers was widely investigated. The present chapter focuses on the recent updates of nanomaterial-based drug delivery methods and nanomedicine, along with complete scrutiny of nanomaterial's design, synthesis, and application for improving drug delivery and efficacy. The advantages and challenges of nanomaterials in drug delivery in their clinical applications are also addressed. Additionally, the future opportunities and perspectives of these nanomaterials are discussed.

Keywords Nanomaterials · Nanocarriers · Drug delivery · Nanomedicine · Drug targeting

13.1 Introduction

Human beings have traditionally utilized natural remedies derived from plants/herbsfor the treatment of many different illnesses/disease. Most contemporary medicines are derived from plants/herbs using conventional knowledge. About 25% of the most relevant pharmaceutical active compounds and their metabolites derived

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from nature (Baker 2009). A recent approach in the development of drugs from natural products has synthetically feasible active ingredients which resemble the same structure and properties (Patra et al. 2018). Natural products show remarkable chemical, biological characteristics with macromolecular specificity, and lower toxicity, among other noteworthy traits. Nanomedicine and nano-based delivery systems are newlyemergingtechnologies because of the nanoscale range of size are used as a diagnostic tool or therapeutic agents to specified targeted sites (Fais et al. 2016; Sahu et al. 2021). Nevertheless, Eric Drexler's conception of new molecular altering nanoparticles has transformed the traditional science and broadened the scope of its applications. Due to advancements in modern science, research on nanoparticles is gaining speed and progressing more rapidly among specialists globally. Nanotechnology provides a platform for manipulating and enhancing the essential properties of metals-based nanomedicine in the form of nanoparticles, which have promising applications in diagnostics and treatments (Sowjanya 2015; Mitchell et al. 2021). Nanoparticles' achievement can be attributed to their distinctive biotechnology, which has developed a variety of potent drugs yet many of them have challenges during delivery of biological systems. Due to its contraindications and unique chemical constitution, their therapeutic potential is significantly reduced (Patra et al. 2018; Sahu et al. 2021). Awide range multidisciplinary approach has recently given special focus on nanotechnology to produce nanoparticles. The development of nanoparticles has affected the formulation and medicines delivery (Sahu et al. 2021). Nanomaterials' discovery and application help improve the selectivity of diagnostic tests utilizing disease-related markers to use both new and conventional plant-based drugs (Patra et al. 2018; Sahu et al. 2021).

The application of nanotechnology for drug delivery systems improves performance, effectiveness, safety and reduces health care costs. Additionally, it might improve the performance of medicine that failed to go beyond the clinical trial phases with the use of different approaches, such as targeting trans membranes, transferring chemicals to specific organelles, and reducing delivery, nanotechnology can make these technologies more practical and accessible. As a substitute approach, nanotechnology-based therapeutic agents are being developed to improve therapeutic efficacy and alter the physicochemical characteristics of antiviral treatment (Sahu et al. 2021; Mitchell et al. 2021). Nanotechnology delivers nanomedicine safely and effectively for treating diseases as diabetes, cancer, HIV, asthma, and hypertension etc. Before application, there are many crucial elements, namely immunogenicity, target selectivity, and bio-compatibility (Mitchell et al. 2021). Overview of drug delivery system is given in the Fig. 13.1. In the initial phase small interfering RNA (siRNA) delivery via a target-basednanoparticle approach was conducted in conducted in 2010 on patients with solid tumors (Sahu et al. 2021; Davis et al. 2010). A different clinical investigation revealed a better tumor, effectiveness of a dynamically targeted polymeric nanoparticle as a therapy Contains docetaxel (DTXL), a chemotherapy agent to a DTXL formulation based on solvents (Hrkach et al. 2012). Nanobiotechnology is a part of biomedicine; nanoparticles have been utilized in drug delivery, tissue engineering, and biosensors.

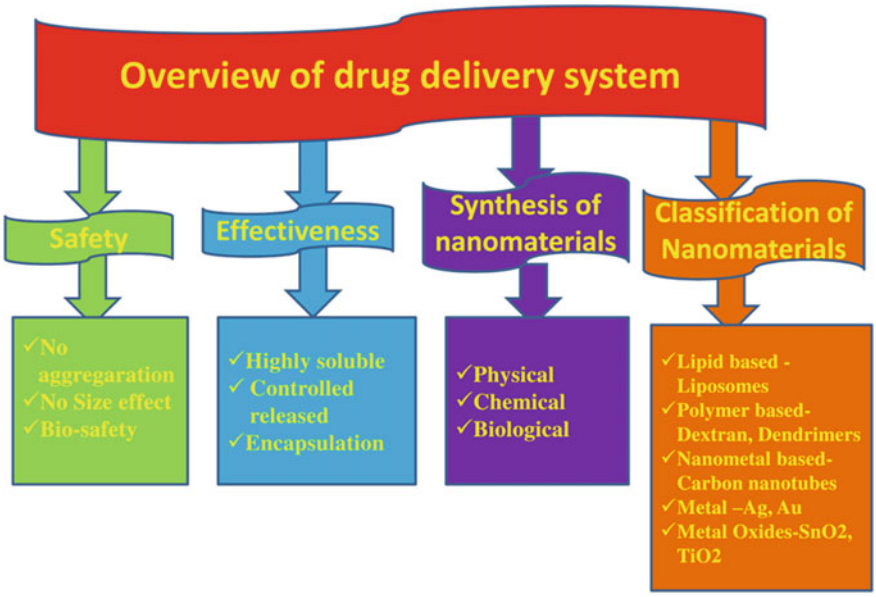

Fig. 13.1 Overview of drug delivery system the major components are safety, effectiveness, classification and synthesis of nanomaterials

Nanoparticles are typically small nanospheres as they are composed of materials manufactured employing atomic or molecular building blocks. As a result, they can move within the human body with greater freedom than more giant molecules. Due to the ability of nanoparticles, the structural, chemical, mechanical, magnetic, electrical, and biological characteristics of nanoscale-sized particles are different to be used in drug delivery by encapsulating therapeutic medicines and transporting allowing them to more accurately target tissues with a controlled release (Patra et al. 2018; Mitchell et al. 2021).

Nanomedicine integrates nanoscience techniques and knowledge to medical biology, disease treatment, and disease prevention. It suggests using nanomaterial-based nanosensors and nanorobots for drug delivery, diagnosis, sensory functions, and actuating materials in living cells (Patra et al. 2018; Mottaghitalab et al. 2019). When it came to material design, execution strategies, and clinical application, experts understood engineering concepts. The primary considerations in drug designing are diffusion, erosion, deterioration, shearing, swelling, binding, surface and the rates of both active and passive cell absorption. Self-emulsifying system and regulated drug delivery are part of the material design. The different controlled drug release systems are osmotic pump, hydrogel, matrix, reservoir, and erodible material. Drugs are released in the matrix system through interconnected pores. Drug permeates through the selectively permeable membrane of the reservoir system. When a substance is degradable, it develops a porous structure that allows a drug to be extruded. The drug is released in an osmotic pump system through hole(s) in an

impermeable membrane whenever the osmotic pressure changes. An erodible the drug is released as substance dissolves. Oil, surfactants, and co-surfactants, which are utilized when combined with water and drugs to create micro- or nanoemulsions, are indeed the components of self-emulsifying drug delivery systems (Holowka and Bhatia 2016; Sultana et al. 2022).Clinical application entails evaluating a drug's efficiency from the medical point of view.

Nanomaterial based nanomedicine also offer platforms for medication cocktail therapy, such as by blocking the action of various medicine resistance pathways, to the cell membrane, for instance (Zhou et al. 2020). Utilizing nanomedicine in the present day has beenpromising to beat Multiple Drug Resistant (MDR) in cancer treatment (Wang et al. 2018; Zhang et al. 2019). New stage strategy for cancer cure management has emerged nonomedicines and has a greater attention thorough multidisciplinary research. There are many conventional methods for delivering the drug to the target tissue, but each of these approaches has some drawbacks. This led to the creation of smart medication delivery systems that can counteract the drawbacks of traditional methods. The fundamental ideas of this chapter are the recent updates in nanomedicine and drug delivery systems based on nanomaterials, synthesis, and application for improving drug delivery and efficacy. Advantages and difficulties of using nanomaterials for medication administration in clinical settings are also discussed. Additionally, the future opportunities and perspectives of these nanomaterials are discussed.

13.2 Nanomaterial Based Drug Delivery System

Numerous treatment methods have invented for nanomedicine development and drug delivery systems. Traditional clinical analytic techniques have been examined to increase medicine selectivity and diagnostic precision. For instance, novel drug delivery systems are being investigated to ensure that they act precisely where they are needed, increasing their availability while reducing their toxicity when ingested (Wang et al. 2018). Polymer based, dendrimers, dextrans, poly (lactic-coglycolic acid) (PLGA) and liposomes and are a few examples of synthetic and natural polymers that have employed to construct a number of nanocarriers for delivering therapeutic and imaging substances. Similar to carbon nanotubes, metal-based nanoparticles (Ag/Au), nanoparticles based on metal oxide (superparamagnetic), and semiconductor-based nanoparticles (quantum dots) are also employed in medical applications (Naresh and Lee 2021; Rabbani et al. 2020; Hirsch et al. 2003). To discuss physicochemical factors contributing to toxicity and approaches for evaluating toxicity related to nanoparticles, initiatives have been attempted to examine the effectiveness and safety of drugs based on nanotechnology for diagnosing and treating cancers. Nanoparticles' physicochemical characteristics are caused by their highly reactive surfaces, chemical composition, solubility, size, shape, etc. Zhou et al. (2020), Wang et al. (2018), Zhang et al. (2019), Naresh and Lee (2021), Rabbani et al. (2020), Nagpal et al. (2010).

Drug delivery systems with the use of in nanomedicine are mostly lipid-based, polymer-based, non-metallic-based, and metal oxide-based nanomaterials are utilized. When it comes to non-biological lipid-based carriers, liposomes are a popular alternative for delivering drugs that enhance the prognosis of kidney, skin, liver, lung, and prostate tumors. Liposomes are preferable to many other nanodelivery systems in a number of ways because of their lower toxicity and significant therapeutic index (Rabbani et al. 2020). Liposomes are classified into neutral, anionic and cationic, nanoparticles based on their net charge. Cationic liposomes generally have included amphipathic cationic lipid, dioleyolphosphatidylethanolamine (DOPE). Once liposome is absorbed into cells, the DOPE concentration ranges (0–50%), and its elastic response DNA by disrupting the endosome. Low transfection efficiencies were explained by liposomes lacking DOPE being discovered entrapped in endosomes and lysosomes. Furthermore, DOPE is a crucial factor that influences a liposomal formulation's capability to transfect cells. Low transmission efficiencies were explained by the finding of Liposomes deficient of DOPE entrapped in lysosomes and endosomes (Wang et al. 2018; Zhang et al. 2019; Naresh and Lee 2021; Rabbani et al. 2020).

Glucose polymers classified as dextrans are utilized in a number of pharmacological activities. High percentage of a-1,6-glucopyranosidic linkages (95%) opposed to 1,3-linkages (5%), which is a characteristic of dextrans. Pharmaceutical agents have been supplied utilizing dextrans of 40–70 kDa molecular weight. Dextrans are synthesized by partial depolymerization utilising acid hydrolysis and separation from native, high-molecular-weight dextrans(10^7–10^8).Hormones, growth factors, enzymes, and imaging compounds can all be conjugated to dextrans by reversible or irreversible processes. Drug and enzyme conjugation to dextrans improves physicochemical qualities including the solubility and stability and assists in drug discovery at the site of action (Mottaghitalab et al. 2019; Holowka and Bhatia 2016; Sultana et al. 2022; Zhou et al. 2020).

To prepare systems for drug loading, poly(amino acids), polyamides, poly orthoesters, polyurethanes, poly(alkyl-a-cyano acrylates), polyacrylamides and polyesters have been used extensively. Since the 1970s, the copolymerpoly (lactic-coglycolic acid) PLGA has been used and is the most well-known biodegradable polymer regarded as a biomaterial that is compatible with humans (Wang et al. 2018; Rabbani et al. 2020).The properties that are biological and biomechanical of indigeneous vascular tissue have been mimicked using PLGA. To extend the period that paclitaxel is delivered, Paclitaxel has been enclosed in PLGA nanomaterial to deliver controlled release drug to the both the luminal surface and interior of extended polytetrafluoroethylene tissue engineering. Dendrimers have multiple branches that resemble large, spherical formations. A dendrimer typically has a spherical three-dimensional structure and is symmetric around a core. Dendrimers have an external surface, an interior shell, and a seat. Each region has a different functionality that can be synthesized to regulate compounds' dispersion, thermal stability, and attachment for a range of diverse applications (Wang et al. 2018; Zhang et al. 2019).

A carbon nanotube is most constituents of graphite. The technique wherein graphite is formed into a tube influences the nanotubes structure. Though carbon

nanotubes are insoluble in all liquids, functionalization and no covalent supramolecular sorption can improve its solubility. Nanotubes are characterize having an aspect ratio >100, sizes between 0.7 and for 1.5 nm single-walled carbon nanotubes; multiwall range in size from 2 to 50 nm and lengths of several millimeters. The technique wherein graphite is formed into a tube influences the nanotubes structure. Though carbon nanotubes are insoluble in all liquids, functionalization and noncovalent supramolecular sorption can improve its solubility. Various biomedical applications are facilitated with use of carbon nanotubes. Applications for both cancer treatment and diagnostic tools can be developed with carbon nanotubes that can be supplied with small-molecule inhibitor and/or imaging agents owing to their enormous surface area conjugated with a variety of compounds (Zhou et al. 2020; Felgner et al. 1987).Metallic nanoparticles typically contain a metal core, which is often surrounded by a shell made of metal oxide or another inorganic substance. The core itself is composed of an inorganic metal or metal oxide. Biocompatible and stable metal oxide nanoparticles can serve as carriers for drugs and diagnostic agents. Additionally, the fluorescence and photo-stability of fluorophores and metals in metal-based nanoparticles may be amplified through interactions with one another (Hrkach et al. 2012; Farokhzad et al. 2006; Nagpal et al. 2010; Felgner et al. 1987; Hirsch et al. 2003; Hainfeld et al. 2004).

The drug design aspects for the purification and characterization of peptides, protein, and biological compounds as well as technological advancements in computer science are necessary for the growth and development of pharmaceutical industry. Finding novel leading medicines based on an understanding of a target tissue has been a promising feature of such a scenario. There are numerous studies emphasize the design of various types of molecules and significanceof looking into diverse medicines release mechanisms. Additionally, natural products development can give practical and fascinating solutions to issues concerning drug design by encouraging the discovery of novel drugs with desired physicochemical characteristics. The main targets for development in nano biotechnologies in drug delivery: reducing toxicity even while utilizing therapeutic drugs, improving both biocompatibility and safety, delivering drugs with more precision, faster development of new safe medicine (Mottaghitalab et al. 2019; Holowka and Bhatia 2016; Sultana et al. 2022; Farokhzad et al. 2006; Nagpal et al. 2010; Felgner et al. 1987; Hirsch et al. 2003).

Systems for drugs delivering have become increasingly important. These systems are easy to build and could promote the body's customized delivery of the active ingredients. It's interesting to note that different drug polarities can be delivered by a variety of methods using chemical or physical contacts, including such electrostatic, Van der Waals forces of attraction, covalent bonds, and hydrogen bond. Superparamagnetic iron oxide nanoparticles (SPION) are organic substances like fatty acids, phospholipids, peptides, polysaccharides, polymers and surfactants or that is coated with silica or gold on top of iron oxide cores that are inorganic particles. Nanoparticlesmay be heated when an applied alternating magnetic field from the exterior because they have magnetic characteristics that allow for collecting in a specific region. When coated with antibodies or peptides, nanoparticles can attach to specific

cells to cure or image diseases. These nanoparticles are appealing due to their property for range of application as magnetic hyperthermia, drug delivery, MRI, and magnetically assisted cell transfection. The nanoparticles are between 50 and 160 nm in size. Clinical trials now use organic-coated particles as MRI contrast agents to diagnose liver cancers and differentiate between inflammatory and metastatic lymph nodes (Fais et al. 2016; Sahu et al. 2021; Sowjanya 2015; Mitchell et al. 2021; Davis et al. 2010; Hirsch et al. 2003).

Nanomaterials are also used as nanocarriers that interact with biological systems and how quickly the active ingredient is released into the body. Although there are many different nanocarriers with unique drug release mechanisms, profiles are being created to strengthen the distinctiveness of the nanostructures focus on selected places of the organism, to reduce their chemical functionalization or coating with various compounds, like polymers, to increase their immunogenicity natural polysaccharides, a cell's membrane, antibodies, as well as tunable surfactants, peptides, etc. In rare circumstances, medicines do not show binding and alignment with a particular target or avoid crossing. A number of barriers, including the blood–brain barrier and ligand-modified proteins, crossed the cerebrospinal fluid. Table 13.1 gives insight into Nanomaterial based drug delivery systems (Farhood et al. 1994; Farokhzad et al. 2006).

Nanocarriers were used to enter the cell and enable the distribution of a specific drug in a membrane-specific environment. Numerous nanocarriers have included hyaluronic acid as a ligand with encouraging findings for intra-vitreal delivery. An extracellular matrix polymer called hyaluronic acid boosts the anticancer activity of cancer stem-like cells, breast cancer cells, and lung adenocarcinoma cells. Although time-consuming, the creation of ligand-appended drug delivery systems necessitates a variety of targeted designs that consider physiological aspects, involving tissue structure, blood flow, and disease severity. The lesson in such situations is that we need to examine what the body actually requires; possibly working in conjunction with the body's natural processes is preferable to working against them (Hirsch et al. 2003; Hainfeld et al. 2004; Meng et al. 2009).

The important factors to be considered for the nanomaterial-based drug delivery system.

- Increased blood flow and accumulation with passive or active targeting
- Increased depth of penetration in target tissue
- Delivery of the payload into the cytoplasm under control
- Conquering drug resistance in target tissue

Table 13.1 Details about the nanomaterial-based drug delivery system, active molecules, drug administration and disease target

Nanomaterial based drug delivery system	Active molecules	Name	Drug administration	Disease target	Routinely used components	References
Liposomes	Daunorubicin	DaunoXome	Intravenous	Acquired immunodeficiency syndrome AIDS-related	Small interfering RNA /DNA	Farhood et al. (1994), Puri et al. (2009), Tran et al. (2009), Ragelle et al. (2017)
	Morphine	DepoDur	Epidural	Pain relaxation		
Protein-based F Protein nanoparticle	RSV	RSV-F vaccine	Intravenous	Respiratory syncytial	Small interfering RNA /DNA	Ragelle et al. (2017), Sharma et al. (2012)
Polymer-based-PLGA nanoparticle	Rapamycin	SEL-212	Intravenous	Gout (common/ complex arthritis)	Delivery of proteins, peptides, vaccines,/ imaging	Ragelle et al. (2017), Farokhzad et al. (2006), Nagpal et al. (2010)
PEG polyamino acid nanoparticle	Cisplatin	NC-6004	Intravenous	Solid tumors		
Lipid-based Lipid nanoparticle	TTR siRNA	Patisiran (ALNTTR02)	Intravenous	TTR-mediated amyloidosis	Small interfering RNA /DNA	Ragelle et al. (2017), Felgner et al. (1987)
	MYC siRNA	DCR-MYC	Intravenous	Hepatocellular carcinoma		
Metal-based Au metal shell silica core nanoparticle	Laser irradiation	AuroShell	Intravenous	Prostate cancer	Thermal ablation/ imaging/antimicrobial drug delivery	Hirsch et al. (2003), Hainfeld et al. (2004)
Hafnium oxide nanoparticle Silver nanoparticle	Radiotherapy	NBTXR3	Intrahepatic/ intra-arterial	Liver cancers		
Magnetic iron NP	Magnetic field	–	Intratumoral	Prostate cancer	Magnetic targeting/ thermal ablation/MRI contrast agent	Meng et al. (2009)

13.3 Basic Principle and Mechanism of Nanotechnology in Drug Delivery

Drugs with low solubility have a number of biopharmaceutical issues, including accessibility and bioavailability after intake through mouth, require high dose intake and creates unwanted side effects. However, by incorporating nanotechnology into the drug delivery process, all of these issues might be resolved. Numerous research organizations worldwide have researched the use of nanoparticles as medication carriers extensively since it is the most cutting-edge technology. Solubility, diffusivity, bioavailability, drug release patterns, and immunogenicity are some of these properties of the nano carriers are easily tunable. This makes them a convenient route of drug administration with a prolonged pharmacological life cycle, lower toxicity, and less adverse effects with improved biodistribution (Mirza and Siddiqui 2014).The formation of nanoparticle basically involves the spontaneous self-assembly of building blocks in to well-defined patterns or structure (Lu et al. 2016). The therapeutic agents may be attached to the nanoparticle surface or stored inside the spherical shape of the nanoparticle. The therapeutic chemicals may release from the nanoparticle through swelling, erosion, diffusion, or disintegration once they reach the target site.

13.3.1 Drug Delivery Strategies Using Nanostructures

The designed drugs delivery systems are either target to deliver the drug to a targeted sites are planned for controlled drug molecule release. Usually, nano carrier delivers the drugs via two ways: (i) passive and (ii) self-delivery (Patra et al. 2018; Lu et al. 2016).

13.3.1.1 Passive Delivery

In passive delivery drugs are integrated into the inner chamber of self-assembled nano structures through covalent interactions (mainly the hydrophobic effect) between the carrier and drug molecule, medicines. Many nanocarriers, including porous nanoparticles, nanomicelles, and nanocapsules, have a hydrophobicity to stabilize the medicinal molecules they are encapsulating (Chung et al. 2014). Drugs will be released at the target site after the nano carrier is disassembled. However, very less drug loading inside the hydrophobic compartments of the nano carrier is observed in physical encapsulation, mostly weight range from 2 to 5% (Lin et al. 2013).

13.3.1.2 Self-delivery

The drugs are effectively linked to the nanocarrier during self-delivery. The conjugation between the carrier and drug molecule should be easily cleavable at target sites. In this process, the releasing time of drug molecule from the carrier is very crucial. If the medicine is released before it reaches the intended place, its activity and effectiveness will be reduced. This procedure, called "burst release," will cause the body to immediately remove the drugs (Keith and Cui 2014). Therefore, it's essential to design the drug's and its nanocarrier's conjugation in a balanced way.

Notably, each drug delivery systems have their unique physical, chemical and morphological features. Depending upon their chemical interactions or physical interactions with drug molecules they may have their own affinity for different drugs. Addition to this, various other parameters, like the nanocarriers' chemical composition and the mode of association of drug with them are also important parameters for understanding the drug delivery system (Siepmann et al. 2008; Mattos et al. 2017). Further, numerous investigations were done to determine how these nanocarriers release drugs. Solvent, diffusion, and chemical reactions are a few examples of the mechanisms that might indicate the release of drugs from nanocarriers (Fig. 13.2) (Lee et al. 2010; Ding and Li 2017). For instance, neem bark extract loaded biogenic silica has a greater drug release profile than neem bark extract encapsulated silica nanoparticle (Mattos et al. 2017).

Another illustration is the cancer treatment's pH-sensitive medication release from polymeric nanomicelles. In this instance, the polymeric nanocarriers distribute the medication selectively into the tumour cell's acidic pH environment. When polymers with ionizable functional groups are exposed to pH changes, their structure changes, releasing the medicines through structural breakdown. In some cases, acid-labile linker is used between drug and copolymer to accomplishregulated drug release in tumours with an acidic pH. In controlled drug release, acid-labile bonds such oxime, hydrazone, orthoester, imine, and vinyl ether bonds were examined (Wang et al. 2018; Salim et al. 2014).

13.4 Nanomaterials Used in Drug Delivery

Owing to the importance of nanoparticle in drug delivery system, wide libraries of nanoparticles, composed of various size, shape and materials having unique chemical and surface properties have been synthesized already (Yan and Chen 2014; Mudshinge et al. 2011; Lombardo et al. 2019). The nanoparticle can be classified in two broad categories as mentioned below.

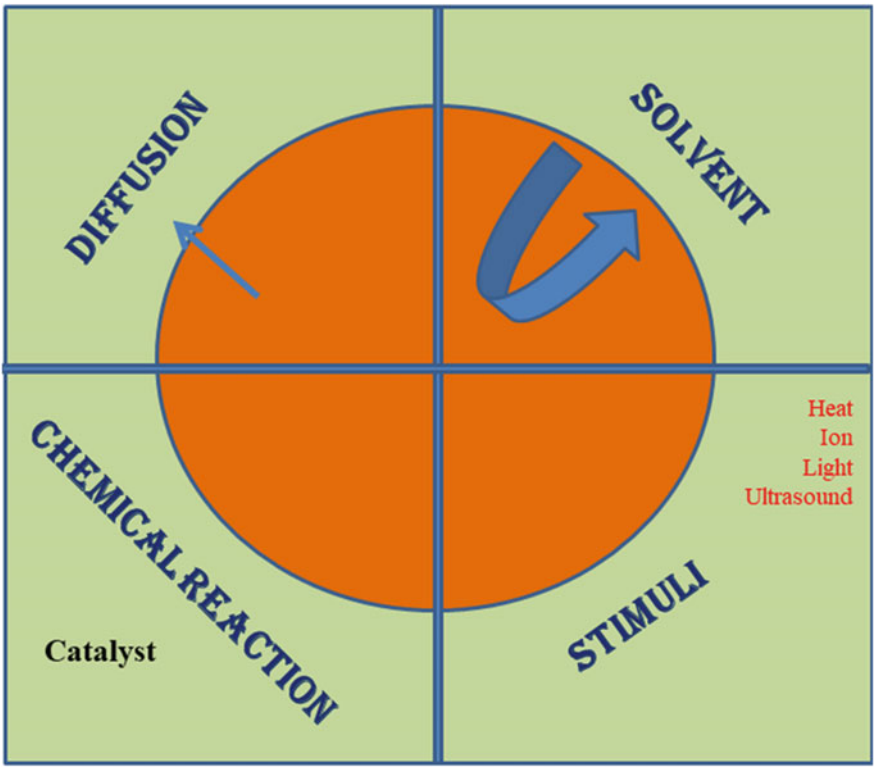

Fig. 13.2 Drug release mechanisms operated in nanocarriers

13.4.1 Organic and Polymer Based Nanocarrier

Recently, interest on organic and polymer-based nanoparticles in drug delivery systems has increased. They include chitosan, cellulose, liposomes, dendrimers, polymeric micelles, protein aggregates etc. The important advantage of organic nanoparticles over inorganic is they are biodegradable, which canovercome the chronic toxicity to cells or tissues. In addition, use of phospholipids in nanoparticles synthesis will improve the biocompatibility and ability to penetrate cell membrane (Fricker et al. 2010).

13.4.1.1 Chitosan Based Nanocarrier

A biocompatible and biodegradable polymer with surface functional groups, chitosan may readily be changed to fulfil certain tasks. Nanocarrier based on chitosan have received extensive research for use in medication delivery applications with different mode of administrations for the treatment of pulmonary diseases, drug delivery

to the brain, gastrointestinal and dermatological disorders (Yoo and Park 2001). Recently, amphiphilic chitosan derived polymeric micelle nanoparticles were synthesized by the grafting of long, hydrophobic acyl chains via self-aggregation in water (KoopaeiM et al. 2014). Self-aggregated amphiphilic micelles of chitosan and polycaprolactone were synthesized and were used as paclitaxel carriers to enhance its pharmacokinetic profile in the gut (KoopaeiM et al. 2014).

In order to increase the amount of medicine in the brain and increase treatment effectiveness, nanoparticles of carboxymethyl chitosan were created and employed as a nanocarrier for the intra-nasal release of carbamazepine (Liu et al. 2018). The nanoparticles have an average diameter of 218.76 ± 2.41 nm, 35% drug loading capacity and 80% encapsulationefficiency. Study indicates that concentrations of carbamazepine in the brain were higher ($P < 0.05$) for an additional 240 min compared to those in the plasma. Another illustration is the oral delivery of 5-fluorouracil (5-FU), which was explored in terms of the drug release profile into the gut from hyaluronic acid-coated chitosan nanoparticles (Fricker et al. 2010; Yoo and Park 2001; KoopaeiM et al. 2014). The 5-FU release profile indicates that the medicine was shielded from discharge in the stomach and small intestine as it travelled from the stomach to the colon. Additionally, the high concentration of drugs at the tumour site might be able to improve antitumor effectiveness while lowering systemic toxicity. Experimental studies show that targeting and bioavailability of drug by chitosan nanocarrier can be improved by chemical modification of nanoparticles.

13.4.1.2 Cellulose Based Nanocarrier

In drug delivery systems, cellulose and its derivatives are frequently utilized as nano carriers, primarily to change the solubility and gelation of the pharmaceuticals that result in the control drug release profile (Sun et al. 2019). Release of repaglinide orally (an anti-hyperglycemic-RPG) was investigated by using cellulose nanocrystals and chitosan nanoparticles (Elseoud et al. 2018). Chitosan nanoparticles had a mean size distribution of 197 nm, whereas hybrid chitosan nanoparticles and oxidized cellulose nanocrystals containing repaglinide had mean diameters of 251–310 nm. Because of the drug's hydrogen bonds with the cellulose nanocrystals, the drug was continuously released. In contrast to nanoparticles derived from native cellulose nanocrystals, those based on oxidized cellulose nanocrystals had a reduced release profile. Acyclovir was used as the drug molecule to study the drug release into the nasal mucosa utilizing nanoparticles of hydroxypropyl methylcellulose, cationic hydroxyethyl cellulose, methylcellulose, and sodium carboxymethyl cellulose (Hansen et al. 2015). The polymers' suitability as excipients for nasal release applications was also evaluated with regard to the frequency of their ciliary beats and their infusion into the tissue system of the nasal passages. It was observed that, thermally induced viscosity was increased by polymer grafted copolymer with the cellulose derivatives. Additionally, the permeability of acyclovir into the nasal mucosa was seen to be enhanced when combined with cationic hydroxyethyl cellulose. As evaluated by ciliary beat

frequency, negative effects on tissues were not observed all the cellulose derivatives (Elseoud et al. 2018; Hansen et al. 2015).

13.4.1.3 Liposomes

Liposomes are spherical vesicles made up of phospholipids and steroids that are generally between 50 and 450 nm in size. Phospholipids are generallyrecognized as safe components and thus minimize the chance of potential side effects. Liposomes are used for the transportation of various molecules in the cosmetics and pharmaceutical industry and one of the most extensively studied methods for delivering drugs. Liposomes are thought to be a superior medication carrier because of how close their membrane structure is to that of the cell membrane. They also make it easier for drugs to be incorporated into them (Bozzuto and Molinari 2015). Experimental studies have shown that liposomes make drug molecule stable, enhance their biodistribution, are also biocompatible and biodegradable and can be used for both hydrophilic and hydrophobic drugs. Additionally, the in vivo stability or the targeting ligand can be increased by functionalization of the liposome surface with 'stealth' material, which also allow liposomes to be delivered preferentially. Liposomes have been effectively employed as effective carriers for several medications, including antivirals, antineoplastics, antibacterial, insulin, and plasmid DNA, thanks to their multifunctional properties. Table 13.2 lists a few of the chosen biomedical uses for liposome nanocarriers.

Table 13.2 Liposomes biomedical application

Liposome	Composition	Drug application	References
Hydrogenated soya, phosphatidylcholine and distearoylphosphatidylglycerol (DSPG)	Amphotericin B	Aspergillus fumigatus	Takemoto et al. (2004)
Dipalmitoyl-phosphatidylcholine (DPPC),cholesterol and dimethylammonium ethane carbamoyl cholesterol (DC-chol)	Benzyl penicillin	Staphylococcus aureus	Kim and Jones (2004)
Stearylamine (SA) and dicetyl phosphate	Zidovudine	HIV	Kaur et al. (2008)
Liposome	Daunorubicin and doxorubicin	Breast cancer	Park (2002)
DC-Chol liposome	Plasmid DNA	Gene transfer insubcutaneous tumor	Whitemore et al. (2001)

13.4.1.4 Dendrimers

Dendrimers are three-dimensional globular formations that are well defined, monodisperse, and extremely divergent. These structures provide ideal drug delivery systems because their surface may be readily and precisely functionalized (Whitemore et al. 2001; Kesharwani et al. 2015). There are two methods for producing dendrimers: the first is a divergent technique, where the synthesis begins in the core and is subsequently extended outward. The other one is convergentwhich starts from the synthesis of outside of the dendrimer followed by extended to words the inside core (Madaan et al. 2014). The presence of amine group in dendrimers limits its clinical use, because the amine groups are either cationic or positively charged, making them toxic. Normally, modified dendrimers are used in order to reduced or eliminate the toxicity. Dendrimers are categorised based on their functionalization moiety such aspolyamidoamine (PAMAM), polyethyleneimine (PEI), polyethylene glycol (PEG), melamine, polypropyleneimine(PPI), poly L-glutamic acid (PG). The mechanisms are used to load drugs into dendrimers: electrostatic interaction, simple encapsulation, and covalent conjugationare some of the mechanisms via which drug is loaded in the dendrimers (Cheng et al. 2008).Basically, dendrimers delivered the drug via two different path ways, (i) in vivo release of drug from dendrimer is possible in presence of suitable enzyme which can cleave the drug dendrimer's covalent bonding; (ii) change in physical environment like pH, temperatureetc.,will also lead to the release of drug (Tripathy and Das 2013). Dendrimers have successfully applied in ocular, oral, transdermal, pulmonary and targeteddrug delivery (Cheng et al. 2008). Few applications of dendrimers in biomedicals are given in Table 13.3.

Table 13.3 Biomedical application of dendrimers

Dendrimer	Composition	Drug application	Refs.
PAMAM (polyamidoamine)	Nadifloxacin, prulifloxacin	Various bacteria	Madaan et al. (2014), Cheng et al. (2008)
PAMAM (polyamidoamine)	Propranolol	Hypertension	D'Emanuele et al. (2004)
Polylysine dendrimer	VivaGel (SPL7013 Gel)	HIV, HSV and sexuallytransmitted infections	Rupp et al. (2007)
PAMAM	5-Fluorouracil	Tumor	Zhuo et al. (1999)
Dendrimer	Isotope of boron (10B)	Cancer	Hawthorne (1993)
Poly(L-glutamic acid),polyamidoamine andpoly(ethyleneimine)	Folic acid	Breast cancer	Kukowska-Latallo et al. (2005)

13.4.1.5 Polymeric Micelles

Amphiphilic copolymers are used to produce polymeric micelles, which self-assemble in aqueous solutions to form a core shell structure. Drugs that are hydrophobic can be loaded into the micelle's hydrophobic core, but the hydrophilic shell renders the system water soluble and remains stable the core. To prevent rapid renal excretion, polymeric micelles typically have a size under 100 nm and a narrow dispersion. Given that these drugs can be accommodated by the micelles' internal core structure, they have a significant potential for hydrophobic drug delivery. As a result, drug stability and bioavailability are increased (Xu et al. 2013). Formation of micelles was affected by many factorssuch asconcentration of amphiphiles, size of the hydrophobic chain in the system of the molecule, temperature, and solvent (Bhushan et al. 2016). The crucial micelle concentration is the lowest concentration at which micelle assembly creation begins (Kulthe et al. 2012). The amphiphilic moleculesremain independent at lower concentration. Drugs can be loaded onto polymeric micelles via the solvent evaporation technique, direct dissolving process, and dialysis procedure (Bhushan et al. 2016; Kulthe et al. 2012).The drug targeting properties of polymericmicelles can be established by different mechanism of action. A few examples of this are the clustering of monoclonal antibodies to the micelle crown, the complexing of a particular ligand to the micelle surface, or enhanced penetrability and holding effect stimuli.

13.4.1.6 Protein and Polysaccharides Nanoparticles

Natural biopolymers such as proteins and polysaccharides are derived from a variety of biological sources, including microbes, animals, plants, and marine sources (Balaji et al. 2017). The majority of protein-derived nanoparticles are biodegradable, metabolizable, and functionalized for attachment to certain drugs and other targeted ligands. Bovine and human serum albumin, as well as gliadin, are examples of water-soluble proteins that can be used to make protein nanoparticles (Bassas-Galia et al. 2017). To deliver the drug at exact cells and tissues, the protein nanoparticles are combined with targeting ligand via chemical alteration of the nanoparticle (Balaji et al. 2017; Bassas-Galia et al. 2017). Likewise, the polysaccharides are composedof monosaccharides bonded through*O*-glycosidic link. The significant disadvantage of polysaccharide nanoparticles for drug administration is their oxidative destruction at high temperatures (beyond their melting point), which is frequently required in industrial procedures. The polysaccharides' inability to be used in any way since they are all soluble in water is another issue (Lohcharoenkal et al. 2014). However, various technique has been established the stability of the polysaccharide chains must be ensured.

13.4.2 Inorganic Nanoparticle as Drug Carrier

Various inorganic nanoparticles, such as metal nanoparticles, Mesoporoussilicananoparticles, quantum dots, and nanotubes possesses unique properties which used for differentbiomedical applications. Some of them are discussed below.

13.4.2.1 Metal Nanoparticle

In recent years, biomedical application of metal nanoparticle in target/sustained drug delivery, biosensors, bio-imaging and photo ablation therapy has been growing drastically (McNamara and Tofail 2017). Further, functionalization and modification of these nanoparticle improve their binding capacity with drugs, other ligands and antibodies, thus making them more promising candidate for biomedical applications (Kudr et al. 2017). Most extensive studies have been carried out with some metal nano particle like gold, iron, silver and copper for their ability as drug carrier. In numerous cases, the stability of polymeric nanoparticles has been increased by covalently bounded them with goldnanoparticles (Aryal et al. 2009).

13.4.2.2 Mesoporous Silica Nanoparticle

Over the last two-decade, application of mesoporous silica for drug delivery have been studied extensively. The diverse properties of mesoporous silica such as tenable pore size, high surface area, monodispersity and diverse functionalization makes them more suitable for drug delivery system. A diverse range of drugs such as paclitaxel, telmisartan, camptothecin, chlorambucil and doxorubicin have been either loaded in mesoporous silica or covalently grafter to it. In order to get enhance drug delivery capacity, functionalized silica nanoparticles are usually used. Forexample, silica nanoparticle functionalized with galactose or mannose shows higher cytotoxicity and efficient target profile to cancer cellsthan unfunctionalized ones (Bharti et al. 2015; Baeza et al. 2016).

13.4.2.3 Quantum Dot

The quantum dots are coreshellnanocrystalscontaining interface amongvarious semiconductor. Usually, the size of quantum dots ranges from 2 to 10 nmin diameterand increases to 5–20 nm after polymer encapsulation (Choi et al. 2007a, b). Hydrophilic therapeuticagents can be immobilized via covalentor non-covalent bondsontothe hydrophilic side of the amphiphilic polymer. This fully designed nano structure will identify the diseased cells and treat it. As Quantum dot nanoparticle emit detectable signals, it helps for real-time monitoring of its trajectory (Qi and Gao 2008).

13.5 Clinical Development and Approved Nano Medicines

13.5.1 Cancer Therapy

Cancer can be viewed as a sickness of many diseases because it is a very complex biological phenomenon. Many patients' lives have been saved by the medicine that is now used to treat cancer. Still, the treatment's severe side effects, which affect every part of the body because of the non-specificity of chemotherapeutics, are also responsible for a huge number of fatalities. Among the qualities of cancerous cells is their ability for replication, which allows them to spread quickly and uncontrolled (Hanahan and Weinberg 2011). The primary goal of the available chemotherapy is to prevent all rapid cell growth. The drawback of this therapy is that it also destroys other quickly dividing cells in the body, such as intestinal epithelial cells and hair follicles, which might have life-altering side effects for the patient (Baudino 2015). Another technique for the delivery of chemotherapeutic drugs is via micelles and liposomes. Moreover, micelles are fantastic how in overcoming the hydrophobic core of insoluble medications and making them soluble shell that is hydrophilic. Suppose the micelle's surface is PEGylated once more through passive diffusion. In that case, it improves the nanocarriers' capacity to penetrate the fenestrated vasculature of malignancies and inflammatory tissue, a greater drug concentration in tumors due to improved medication delivery. There are numerous polymeric micelles on the market now that contain anticancer drugs. The NK105, NK012, NC-6004, NK911, SP1049C and NC-6004 studies are examples of clinical trials and Genexol-PM is one such system (Varela-Moreira et al. 2017).Patients with breast cancer are permitted to take (paclitaxel) there are other types of nanoparticles as well, carbon nanotubes are one of the newest systems that has demonstrated potential when used to treat cancer (Varela-Moreira et al. 2017; Rahamathulla et al. 2021). Carbon nanotubes (CNTs) that fit into the category of a type of carbon with a cylinder-shaped structure that deepens on several sheets in cylinder-shaped concentric circlesfor instance, single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) (Rahamathulla et al. 2021).Because the hollow interior of carbon nanotubes is extremely hydrophobic, drugs that are not soluble in water can be simply added. The expansive area makes it possible to functionalize the outside of objects, particularly for a specific cancer receptor and contrast agents (Hahn et al. 2011).

Last but not least, the anticancer effects of the spherical compound Buckminsterfullerene C60 and its compounds are studied. Fullerene C60 is a potent collector of reactive oxygen species due to its capability to bind up to six electrons (Usenko et al. 2008). Fullerene nanocrystals (Nano-C60) can boost the cytotoxicity of chemotherapeutic medicines, hence future research into a Nano-C60 adjuvant chemotherapy is possible (Zhang et al. 2008). Further research conducted by Prylutska and Skivka (2015) using the Fullerene C60 and Doxorubicin combination showed that the tumour volumes of the treated rats (C60 + Dox) were 1.4 times lower than those of the control group. Additionally, the manner in which the C60 + Dox complex affects tumour cells and its implications on immune regulation.

13.5.2 Diagnostic Testing

Despite extensive study, it is currently impossible for clinical applications to utilize nanoparticles for diagnostic testing (Mitchell et al. 2021; Kolluru and Rizvi 2013). The limitations of fluorescent light hamper diagnostic testing indicators, including color and fluorescence that disappear after usage. Researchers now have a means to get around the problems with matching and limiting the usage of dyes because of a bleeding effect thanks to fluorescent nanoparticles (Wolfbeis 2015).Quantum dots, which can be produced in a large variety of distinctly diverse hues, were discovered, which was a huge advance. They have an adjustable emission spectrum, photo-stability in the visible light spectrum, and an absorption spectrum that ranges from UV wavelengths to high quantum yield. The location of a particular particle inside the spectrum is determined by the size of the nanodot. The nanodot's size dictates where a specific particle is located in the spectrum (Wolfbeis 2015). The advantages of quantum dots are numerous as they may connected to biomolecules that can spend a lot of time investigating a biological system while applying white light they become agitated (Datta and Jaitawat 2006). Recent advances in theranostic nanoparticles, which employed for diagnosis and therapy have drawn a lot of interest. There has been a lot of interest in recent developments in theranostic nanoparticles, which are used for both diagnosis and treatment. Janib et al. (2010) has been used demonstrated that a variety of nanoparticle types, such as surfactants and dendrimers, include drug conjugate aggregates (vesicles and micelles), carbon, and core–shell nanotubes. It is possible to track the path and the positioning of these nanoparticles at the targeted area in addition to the drug taking steps to evaluate therapeutic response by combining a drug and an imaging agent in one ingenious distinct formulation (Bhojani et al. 2010). If the human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) is not treated, the patient's immune system will be almost completely destroyed, and they will die (Bhojani et al. 2010; Vishnu and Aboulafia 2015). Treatment was intentionally developed for this sickness when it started, with most patients taking 30 to 40 pills daily. The previous ten years, therapeutic advances have decreased the need for pills, daily countdown to a select few (Mamo et al. 2010; Haberer et al. 2011; Khalil et al. 2011; Crabtree-Ramirez et al. 2010).Research has proven how to create polymeric nanoparticles that transport antiretroviral (ARV) medicines to increase the effectiveness of this therapy (Mamo et al. 2010; Haberer et al. 2011). In order to prevent HIV infections, this nanotechnology based can also be utilized in conjunction with vaccinations (Mamo et al. 2010; Khalil et al. 2011). Antiretroviral medicines used to treat HIV can be classified according to the stages of the HIV life cycle to which they respond best. To avoid the emergence of tolerance and to actively prevent the progression of HIV, highly effective antiretroviral therapy (HAART), a mixture of several drugs is administered. Using nanotechnology has greatly facilitated the delivery of antiretroviral medications and in increasing compliance. When administered orally or through other non-parental methods, antiretroviral medications mucosal epithelium barrier must be permeable (suppository and patches, etc.) (Crabtree-Ramirez et al. 2010).

13.5.3 Nutraceuticals Delivery

Observable health benefits can be found in nutraceuticals, which are standardized components. They are frequently eaten in tandem with several allopathic treatments to enhance health benefits and lower the risk of particular chronic illnesses (Das et al. 2012). As with any other medicines, food matrix interactions, water solubility, degradation, and epithelial permeability all affect the bioavailability of oral nutraceuticals, and subsequently their effectiveness (Gonçalves et al. 2018). Most supplements are made of lipophilic compounds, such as polyunsaturated lipids, phytochemicals, and fat-soluble vitamins (vitamin E, A, K, and D). Extensive research has been focused on enhancing the nutraceuticals' dissolving processes utilizing combinations with nanoparticles, and nanotechnology once again and offers all-encompassing supports (Crabtree-Ramirez et al. 2010; Das et al. 2012; Gonçalves et al. 2018; Acosta 2009; McClements 2015; Din et al. 2017; Ravichandran 2010). The most well-known and well-researched nutraceutical is curcumin (diferuloylmethane), which has anti-inflammatory, antioxidant, antiapoptotic, and antiangiogenic properties. Curcumin's oral bioavailability was found to be 9 times greater when taken without piperine, an absorption booster (Shaikh et al. 2009). When compared to curcumin powder, a different study utilising colloidal nanoparticles of curcumin called theracurmin shown inhibitory effects against alcohol intoxication as well as a 40 times more surface area under the a 27-fold higher AUCarea under the curve in healthy human volunteers compared to rats (Sasaki et al. 2011).

The Vitis vinifera, Labrusca, and Muscadine grapes are the most prevalent sources of resveratrol, a notable non-flavonoid polyphenol present in many plants. It is universally acknowledged for its anti-inflammatory, anti-cancer, and antioxidant potential (Summerlin et al. 2015). Despite its low solubility and low bioavailability, the body rapidly metabolizes resveratrol and eliminates it (Kapetanovic and Muzzio 2011). The more prevalent and biologically active of the geometric isomers of resveratrol, trans-resveratrol, is photosensitive and transforms into cis-resveratrol when exposed to light. Extensive studies have focused on resveratrol nano-formulations that enhance the pharmacokinetic profile and bioavailability. Bonfanti Santos, polymeric nanoparticles, and zein-based nanoparticles are a few of them. Recent studies have concentrated on zein-based nanoparticles, nano-emulsions, liposomes, cyclodextrins, and dual nano-encapsulation methods. The neuroprotective properties of resveratrol were recently evaluated by developing solid lipid nanoparticles coated with apolipoprotein E (apoE) for low-density lipoprotein (LDL) receptor recognition on the blood–brain barrier (Sessa et al. 2013; Penalva et al. 2015; Neves et al. 2016).

13.5.4 Clinical Approvals and Market Status of Nano Medicines

Market-available nanomedicines come in a variety of forms and are based on the most cutting-edge liposome technology. The other commercially available nanomedicines are based on polymeric micelles, polymeric prodrugs, and nanoparticles. 41 nanocarrier-based formulations are being tested at various stages of clinical development and have gone from the lab to the patient's bedside. Many additional formulations based on nanocarriers are now under preclinical research. Unsurprisingly, to avoid the additional manufacturing, regulatory, financial, and polydispersity challenges associated with active, ligand-receptor-based targeting, the majority of these nanomedicines (37) rely on passive targeting via the increased permeability and retention effect. Only 4 actively targeting nanocarriers, 3 of which use TfR as their target and one of which uses prostate-specific membrane antigen (PSMA) are now being developed clinically. Drugs created at the nanoscale have several physical and biological benefits. These benefits may then result in enhanced therapeutic effectiveness and decreased toxicity. A bigger number of medicines are being researched for a variety of disorders in clinical settings, despite the fact that only about 50 nanotherapeutics have previously reached clinical use (Svenson 2012; Caster et al. 2017). The development of nanomedicines due to incorporating nanotechnology in medicine is changing how diseases are treated. This is especially true for nanomedicines that use lipid nanoparticle (LNP) drug delivery systems because more than the FDA has already approved 10 pharmaceuticals that employ LNPs to deliver treatments to illness sites. Most of these nanomedicines are cancer therapy formulations that function better and have lesser toxicity than the "free" drug (Allen and Cullis 2013). We now have a strong grasp of the criteria for the effective clinical translation of LNP systems for the delivery of small molecules as a result of the clinical success of LNP-based drug delivery systems. Size ranges of 100 nm or below, extremely effective encapsulation methods, a low surface charge, reliable, scalable production procedures, and appropriate product stability are examples of translational parameters (Cullis et al. 1989; Akinc et al. 2019). Table 13.4 gives the details of some nanomaterial based drug, its market status and involvement of active ingredient.

13.6 Advantages of Nanomaterial for Drug Delivery

In general, drugs are taken either through injection or via orally. In this process, the drug circulates all over the patient's body which may causes harmful side effect. Additionally, after oral administration, some of the drugs are poorly absorbed due to their vulnerability across theintestinal epithelium. As a result, high dose of drug is required in conventional drug delivery system to make up the bio-availability of drug

Table 13.4 Nanomaterial based drug, active molecules, disease target and market status

Nanomaterial based drug delivery	Drug product	Active ingredient	Status	Disease target	Company/ Manufacturar	FDA approved date/clinical trial status	References
Liposomes	Doxil_/Caelyx	Pegylated doxorubicin	Marketed	Metastatic breast and ovarian cancers	Janssen Pharmaceuticals/ Orthobiotech, Schering-Plough	November 1995	Svenson (2012), Caster et al. (2017), Pillai (2014)
	Myocet	Liposome-encapsulated doxorubicin	Marketed (EU)	Metastatic breast and ovarian cancers	Cephalon Inc. (EU)/ Sopherion therapeutics (US, CAN)/Elan Pharmaceuticals/ Sopherion Therapeutics	2000 approved in Europe and Canada	
	DaunoXome_	Liposome-encapsulated daunorubicin	Marketed	HIV-associated	Galen Ltd	April 1996	
	EZN-2208	Multi-arm mPEG-SN38 conjugate	Phase 2 NCT01036113b NCT00931840b	Metastatic breast cancer	Enzon Pharmaceuticals Inc	–	Svenson (2012), Cullis et al. (1989)
Polymer based	Genexol-PM	Paclitaxel-loaded polymeric micelle	Marketed	Breast cancer	Samyang pharmaceuticals	Marketed in Europe, Korea	Svenson (2012), Cullis et al. (1989), Akinc et al. (2019), Pillai (2014)

(continued)

Table 13.4 (continued)

Nanomaterial based drug delivery	Drug product	Active ingredient	Status	Disease target	Company/ Manufacturar	FDA approved date/clinical trial status	References
	NK911	mPEG-poly(aspartic acid)-doxorubicin conjugate	Phase 1	Solid tumors	Nippon Kayaku Co., Ltd.	–	Svenson (2012), Pillai (2014)
	XMT1001	Polyacetal camptothecin conjugate	Phase 1 NCT00455052b	SCLC and NSCLC	Mersana Therapeutics	–	
	SPI-077	Stealth liposomal cisplatin	Phase 2 NCT00004083b	Platinum-sensitive ovarian cancer	New York University School of Medicine/Alza	–	
Legend-receptor based	MBP-426	Transferrin-targeted nanoparticles with oxaliplatin	Phase 2 NCT00964080a	Metastatic gastric, Cancer, gastro-esophageal junction	Mebiopharm Co., Ltd	–	Svenson (2012), Caster et al. (2017), Allen and Cullis (2013), Cullis et al. (1989), Akinc et al. (2019)
	CALAA-01	Transferrin-beta-cyclodextrin polymer nanoparticle complexed with siRNA	Phase 1 NCT00689065a	Tumors	Calando Pharmaceuticals, Inc		

inside the body. By using nanoparticles as drug carrier, one can able to tune the parameters such as biodistribution of drugs, solubility, diffusivity, toxicity and pharmacokinetics of the drug molecule inside body (Zhang et al. 2008, 2014). Thus, nanoparticles offer substantial advantages over the conventional drug delivery in terms of high specificity, high stability, efficient drug carrying capacity and controlled drug release. It also has the ability to deliver both hydrophilic and hydrophobic molecules inside the body. These properties of nano carrier offer improved drug bioavailability and less dosing frequency. Nanoparticles possess unique physicochemical properties like functionalizable structure, high reactivity, large surface area to mass ratio and manageable and ultra-small size. They can easily enter through the biological membranes, tissues and organs, whereas large size particle of conventional medicine cannot cross these barriers easily (Yao et al. 2020). The most significant features of nanoparticle drug delivery system is their target specific delivery ability. By this they only affect the diseased tissue, which results in increase drug concentration at target site, improve its efficacy and also reduce the unwanted side effect caused by drug molecule. Due to these advantages, targeted nanocarriers are being highly focused in therapeutic and research. Overall, using nanoparticles as a drug carrier have the following advantages.

- Controlled and target specific release of the therapeutic agent during the transportation which increase the drug efficiency and reduces the side effects.
- Drug can be encapsulated in to the system without any chemical reaction.
- There is no drug wastage, and thus increased the drug bioavailability at target site for prolonged time period and lower the frequency of drug intake.
- By tuning the ligand of nanocarriers, the solubility of poorly water-soluble drugs can easily increase.
- Additionally, it also extends the half-life of drug circulation by decreasing immunogenicity.

13.7 Toxicity and Hazards of Nanoparticles

If nanotechnology is to be utilized in nanomedicine, safety and toxicological risks must be given full attention to resolve. The difference between the doses indicated for clinical efficacy and the levels that result in undesirable pharmaceutical side effects is known as a therapeutic ratio/index. However, these specific compositions also need for a toxicological evaluation. That's also particularly true when medications are delivered via nanoparticles. Particles are intentionally injected into the environment and human body for a variety of purposes, some of which anticipate major improvements in healthcare (Abeer 2012). When toxicologists argued that new science, practises, and protocols are required, opinions began to shift (Krewski et al. 2020). Unlike bulk materials, which are produced for their distinctive features, nanoparticles. These special characteristics need to be looked into from a toxicological perspective because surface contact with bodily tissue is crucial in determining

particle response. When nanoparticles are chosen for their distinct reactive properties, it stands to reason that these properties would also affect how dangerous these particles are. Although there may be several issues related to the usage of these nanoparticles that can be found using existing testing and methodologies in medication and device review, these tests cannot be relied upon to identify all potential dangers, both biological and non-biological in nature.

As compared to micron-sized particles, nanoparticles are fundamentally different in their physico-chemical composition, which may enable them to modify body distribution, cross the blood–brain barrier, and activate blood coagulation pathways. Studies into the (pharmaco) dynamics and dispersion of nanoparticles should get further attention in light of these properties. What is currently lacking is a fundamental knowledge of how nanoparticles behave biologically in terms of in vivo dispersion at the organ and cellular level. Diseased people are primarily affected by combustion-derivednanoparticles in populations exposed to the environment. Typical pre-clinical testing is nearly typically conducted on healthy animals and volunteers, which means that particle concerns may not be discovered until much later. Utilizing nanoparticles as drug delivery systems may lessen the toxicity of the medicine that is added. It is thus impossible to differentiate between the toxicity of pharmaceuticals and that of nanoparticles. When using slow- or non-degradable particles to deliver medications, this is essential since they may build up and remain eventually, the drug delivery site will produce persistent inflammatory reactions (Abeer 2012; Krewski et al. 2020).

13.7.1 Nanoparticle Toxicity Evidence

With PM10 particulate matter with a size below 10 mm, the strongest database on the toxicity of nanoparticles has been created wherein nanoparticle manufacturing has shown to be an influential driving factor for research (Borm et al. 2006). It is crucial to talk about these data in the belief that it would help shed light on the toxicity of synthetic nanoparticles. Several sources support the hypothesis that combustion-derived nanoparticles have a significant role in causing the negative consequences of ambient particle air pollution or PM10. The concept that PM10 contains a component has grown as a result of the assumption that a sizable portion of PM10's mass is non-toxic, with combustion-derived nanoparticles appearing to be a plausible option really because many PM10 particles are believed to be non-toxic, inflammation has developed, and combustion-derived nanoparticle appears to be a potential possibility. Since they make up the majority of particles, nanoparticles may be significant because they have a large surface area per mass while being tiny. According to particle toxicology, a larger particle surface corresponds to a greater level of toxicity for hazardous particles in general. The claim that nanoparticles in PM10 are significant contributors to negative effects is supported by significant data from toxicology and limited information from epidemiology sources (Borm et al. 2006; Pope et al. 2004).

Respiratory disease respondents to indicate fatalities, hospitalizations, and deaths from cardiovascular and respiratory disease are all indicators of the harmful impact of PM on human health (Pope et al. 2004). These negative consequences are linked together by inflammation, making nanoparticles capacity to elicit inflammation one of their key characteristics. It is unclear which nanoparticles effects require lower exposures may have an influence on the consequences of pulmonary inflammation as a precursor than those that cause inflammation. Additionally, there is a chance that pulmonary inflammation will alter membrane permeability, which could then affect the likelihood that particles will spread outside the lung. Some nanoparticles may also have the capacity to directly influence cardiovascular disease. Following the intake of diesel exhaust particles, vascular function was hampered (Hoet et al. 2004; Ehsanifar et al. 2021). Several data are still sparse, and not all nanoparticle investigations have detected a significant transfer of substance from the lung to the blood. Very little translocation has occurred in several studies that are important to understand the kinematics of how ambient air nanoparticles are cleaned in order to realize the potential for adverse effects of inhaling them (Kreyling et al. 2004; Takenaka et al. 2006).

13.7.2 Toxicological Effects of Nanoparticles

Nanoparticles have several extremely unique characteristics that are crucial for the future design and toxicity testing of artificial nanomaterials. The impacts of tiny particles are only quantitatively different in some cases (Fourches et al. 2011). In this situation, nanoparticles might have similar effects to "conventional" nanoparticles (such as lung cancer or inflammation), but they might be more effective due to their large surface area. Nevertheless, nanoparticles may result in new effects that have not before been observed with larger particles (e.g., mitochondrial damage, platelet aggregation, cardiovascular effects). Ligand-coated based nanoparticles researched and used to deliver drugs or for molecular imaging. The ability of nanoparticles to penetrate tissue without impairing tissue function has significantly enhanced. Anionic nanoparticles are generally non-toxic in nature, in contrast to cationic nanoparticles, which have been shown to cause hemolysis and blood coagulation when present, such as Au and polystyrene (Fourches et al. 2011; Tang et al. 2012).Additionally, drug-loaded nanoparticles have been utilized to lengthen half-lives or better understand difficulties, and they have demonstrated which features of the particles need to be changed to permit delivery while remaining biocompatible (Tang et al. 2012).

Identification of hazards is the standard procedure for assessing the safety of healthcare goods, its advised is to include testing based on the intended use and risk classification. Inhalation risks may be associated with some designed nanoparticles that become airborne, while continuous exposures may result from using nanoparticles in cosmetics (Fourches et al. 2011; Tang et al. 2012). Parenteral administration requires careful consideration of systemic distribution, interactions with blood components, and kinetics when employing synthetic nanoparticles as instruments

to deliver drugs to specific target. Each nanoparticle composition needs to be separately investigated using the appropriate techniques, paying close attention to their route of entry. Empty particles' possible harmful (toxic) consequences should also be considered in this context (Tang et al. 2012). A number of fundamental factors must be taken into account when developing testing processes. Although nanoparticles have an effects as "conventional" nanoparticles (such as inflammation and lung cancer), their increased surface area may make them more effective. Additionally, nanoparticles may have brand-new effects that were not previously observed with bulk substances or larger particles. The main issue at hand is whether the testing and categorization procedures used today are sufficient or appropriate. These will be able to spot specific hazardous consequences, as shown by the studies that have already been released. However, it is possible that not all dangers will be found, necessitating more targeted testing. Additionally, nanotechnology encourages the blending of technologies; for instance, similar materials may be used in the automobile and health sciences industries. Data interchange between sectors is advised to promote the manufacturing and marketing of safe nanomaterials (Fourches et al. 2011; Gnach et al. 2015).

13.8 Challenges and Future Scope

The application of nanotechnology to cancer therapy has brought about a new era in cancer treatment. Both organic and inorganic are among the nanoparticles are already used in cancervarious types of treatments. Nanoparticles based drug delivery systems are superior to customary pharmaceuticals in linked with better biocompatibility, pharmacokinetics, stability, and disease targeting, while also contributing in important contribution to lowering systemic toxicity and overcoming resistance to drugs. Due to these benefits, Nanoparticlesbased medications can be broadly used in radiation, targeted therapy, and chemotherapy, gene therapy and hyperthermia. Better platforms are provided by nano material based drug delivery systems for combination treatment, it aids in overcoming drug resistance pathways, including over expression of the tumour microenvironment under hypoxia, impaired apoptotic pathway, and efflux transporter. According to different drugs resistance mechanisms, MDR can be overcome by using loaded nanoparticles that have different targeting agents paired with cytotoxic agents.

As it developed, other types of nanoparticles have display superior delivery qualities and sparked additional interest attention. Additional research in biological traits of identifying certain cancers will result in more focused in the directions of research for these medicines. Additionally, creating hybrid nanoparticles that are designing nanoparticles with targeting moieties that more specifically target cancer cells makes sense for cancer therapy more investigation particularly, the relationships between nanoparticles complicated, as is the immune system (Sailor and Park 2012). In addition, a variety of considerations must be considered to ensure proper execution of a particular drug release and its practical uses in human bodies. For instance, to

obtain an acceptable encapsulation effect the nanocomposites with multi-stimulatory responsive characteristics may be produced as effectively adapted to complicated biological systems. The nanoparticles surface, composition, size, and form are all the elements that influence how nanoparticles interact with the defense mechanism. Although classical immunotherapy has shown greater efficacy than nanovaccines and synthetic APCs, the clinical efficacy of this therapy is still inadequate, and further research into the safety and tolerance of these novel techniques is required. Nanotechnology will undoubtedly continue to progress, and in the near future, non-toxic, biocompatible, and hemo-compatible drug delivery systems will successfully transport therapeutic agents to afflicted locations in human bodies to treat cancer. Additionally, creating nanoparticles laden with immunomodulatory factors may increase the potency of immunotherapy vaccines. Therefore, for drug design and exploration, a deeper understanding of nanotechnology and additional research into the interaction between nanoparticles in drug delivery systems and target disease immunity are required.

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