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Developments in Nanotechnology for Lung Cancer Treatment: A Comprehensive Strategy

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ABSTRACT

Lung cancer is a significant worldwide health concern that demands novel approaches to its management. The field of nanotechnology has shown great promise for revolutionizing the treatment of this illness. An overview of the many applications of nanotechnology in lung cancer treatment is given in this abstract. For the treatment of lung cancer, drug delivery has been transformed using nanotechnology. Chemotherapy medicines can be specifically and precisely released at the tumor location by using nanoparticles that have been designed to encapsulate them. Patients receiving treatment benefit from this focused approach's dual benefits of minimizing systemic toxicity and increasing therapeutic effect, all of which improve patient quality of life. Furthermore, a major obstacle in the treatment of lung cancer is drug resistance, which nanoparticles help to overcome. The role of important receptors as well as the targeting types have also been discussed. Nanotechnology provides fresh ways to counter resistance mechanisms and boost treatment regimen efficacy through the creation of creative medication formulations and combination therapies.

KEYWORDS: Nanocarrier , Non-small cell lung cancer, Hydrogels, nanotechnology, liposomes, active targeting

INTRODUCTION

Lung cancer is a life threatening disease which is caused due to the uncontrolled division of cells in the lungs. Smoking is known to be the major cause of lung cancer [1]. One of the leading causes of death globally, cancer has more than 200 different kinds. 18.4% of all cancer-related deaths are caused by lung cancer, which is also the most common type with the worst prognosis worldwide. About 70% of patients with lung cancer have advanced disease at the time of diagnosis, and only 15% of patients are still alive five years following diagnosis [2]. Lung cancer, which ranks third and second in terms of incidence and fatality rates among all malignant tumors, is more common in males than in women. Twenty percent of cases of lung cancer are small cell lung cancer (SCLC) and eighty percent are non-small cell lung cancer (NSCLC), which together make up about 80% of all cases of lung cancer [3, 4]. A combined PET-CT scan is typically used to determine the location and size of lung tumors, facilitate accurate disease staging, and identify unclear lung nodules[5]. As per a recent report by the World Health Organization (WHO), lung cancer ranks as the sixth most prevalent cause of death, accounting for around 1.8% of all fatalities [6]. Many therapeutic approaches, including surgery, radiotherapy, radiosurgery, chemotherapy, and immunotherapy, are commonly used to treat lung cancer. Lung cancer can be treated with several fundamental ways, each with limitations of its own. Advanced-stage lung cancer can be treated with any of these therapies [7]. Furthermore, cancerous cells and healthy tissues are equally harmed by radiation therapy and chemotherapy. Recent advances in drug nanotechnology have effectively overcome the drawbacks of traditional chemotherapy medications. Man-made particles, known as nanoparticles, are typically less than 100 nm in size and are derived from metals such as gold, lipids, or polymers[8, 9]. The different applications of nanoparticles in lung cancer therapy are shown in Figure 1.

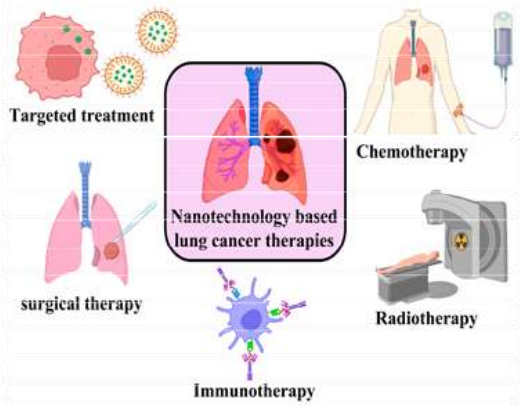

Figure 1. Applications of nanotechnology-based therapeutic approaches in lung cancer.

Nanomedicine is a relatively new therapeutic modality that focuses on replacing drug delivery and addressing therapeutic effects while minimizing adverse effects on normal tissues [10, 11].

THE DISADVANTAGES OF CONVENTIONAL LUNG CANCER TREATMENT

The goal of any cancer treatment is to eradicate or eliminate the malignant cells while sparing healthy cells. Surgery, radiation therapy, and chemotherapy are the most often utilized conventional therapeutic modalities. These treatments can be used singly or in combination[12]. Surgical resection is the most reliable and efficient method of treating individuals with lung cancer. Surgery is regarded as the best course of treatment for NSCLC. A shorter hospital stay, less initial postoperative discomfort, and less impairment of pulmonary function are all linked to the use of video-assisted thoracoscopic surgery (VATS) by some surgeons [13, 14]. These days, surgery is only an option for those with SCLC whose disease was detected early and is locally restricted. Patients with stage I lung cancer may not be able to have surgery if their health is not well. Because of their compromised lung function, some patients—even those with stage I/II NSCLC—do not make good candidates for surgical resection. The standard of care in these situations is RT [15].

Patients who were unable to undergo surgery have found relief by radiotherapy; however, the rate of cure is significantly lower than that of surgical excision. It is commonly recognized that radiation therapy damages the cells in the surrounding area, which greatly reduces the ability of the lungs to operate. Therefore, patients with a seriously impaired pulmonary system might not be a good fit for this technique. High-energy radiation, such as x-rays, or particles are used in radiation therapy (RT) to kill cancer cells [16]. RT is frequently advised for individuals with limited-stage SCLC during treatment [17, 18].

Anti-cancer medications are administered intravenously or orally as part of chemotherapy. For SCLC, chemotherapy is the primary treatment choice. This is because, by the time SCLC is discovered, it has already spread, making it impossible for surgeries and radiation therapy to treat every part of the cancer. Preoperative treatment, however, may reduce the size of the tumor, improve operability, and get rid of micro metastases. Conversely, preoperative chemotherapy has the potential to postpone surgery and, in the event that it is unsuccessful, render malignancies incurable [19, 20].

OVERLY ACTIVE RECEPTORS

[1] Epidermal Growth Factor Receptor (EGFR)

The progression of carcinoma is significantly aided by the overexpression of the transmembrane protein EGFR. It is composed of an extracellular region containing the ligand-binding region in charge of controlling tumor growth (invasion, angiogenesis, metastasis, and cell proliferation) and an intracellular portion containing tyrosine kinase activity[21]. Ligand binding to the attachment region results in conformational changes. Tyrosine kinase activity and ligand binding further cause auto phosphorylation, which in turn causes changes in the Signaling pathways. These tyrosine kinase inhibitors work better on cancers with mutated EGFR [22]. Over activation of EGFR can result in mutations that change the signal transduction pathways. Anti-apoptosis and cell multiplication are further induced by the attachment of ligands located on the cell's exterior[23].

[2] Folate Receptors

Folate receptors exhibit a higher affinity for binding folic acid. Folate Receptor Alpha (FRA), Beta (FRB), Gamma (FRG), and Delta (FRD) are the four distinct forms that it comes in. Known as FOLR-1 or folate binding protein (FBP), FRA is a glycosylphosphatidylinositol-anchored glycoprotein that is located on the cell surface and helps transport 5-methyltetrahydrofolate (5-MTF), an active form of folate[24]. In lung-like solid tumor types, overexpression of the FRA has been observed, and folate absorption—whether direct or indirect—proves to be beneficial for the proliferation of cancer cells. The increased levels of overexpressed FRA in NSCLC have been documented in a number of investigations. The United States Food and Drug Administration (FDA) has approved a number of methods aimed at FRA[25].

[3] **Vascular Endothelial Growth Factor Receptor (VEGFR)**

It was initially discovered that VEGFRs are a factor in vascular permeability that, when released by tumor cells, causes vascular leakage. Three main forms of tyrosine kinase receptors that only bind to mammalian VEGFR are FLT-1 (VEGFR1), FLK-1 (VEGFR2), and FLT-4 (VEGFR3). The seven extracellular immunoglobulin-like domains present in these receptors are activated by ligand-mediated dimerization. These receptors are known to play a role in the angiogenesis, proliferation, and metastasis of tumor cells and are often overexpressed in non-small cell lung cancers (NSCLCs) [26, 27].

[4] **Cluster of Differentiation (CD44)**

The membrane glycoprotein receptor CD44 is involved in several processes, including adhesion, differentiation, homing, and migration of normal and cancerous stem cells [28]. It does this by attaching to hyaluronic acid. In lung cancer, CD44 overexpression was discovered in type II pneumocytes and squamous metaplasia. NSCLC patients' lymph node metastases have been connected to the 44v6 Cluster of Differentiation [29].

[5] **Integrin**

Integrins are members of the transmembrane heterodimeric glycoprotein family, which includes alpha and beta subunits that are not covalently bound. There are 24 different integrin receptors, and they are dependent on the orientation patterns displayed in the middle of the 18 α and 8 β subunits[30]. Almost 82% of patients with NSCLC have identified integrins, irrespective of the kind or degree of differentiation. Conversely, only 13% of SCLCs showed signs of an overexpressed A3β1. The high severity and potential for spread of SCLC have been linked to down regulated levels of integrin expression[31].

[6] **Sigma receptor**

The protein sigma receptors Σ1 (sigma-1) and σ2 (sigma-2) are membrane-bound and have different pharmacological profiles. A significant overexpression of σ2Receptors has been seen in 12 out of 15 human SCLC samples and 6 out of 15 human Adenocarcinoma samples. Numerous investigations carried out on σ2 have indicated that it is a biomarker with great promise that could be utilized as a novel target for chemotherapy [32].

[7] **Others**

An overview of the key participants in the field of lung cancer therapy helped by nanomaterials is provided. There are still some novel receptors or treatments that merit an update [33]. Figure 2 highlights various targets on lung cancer cells.

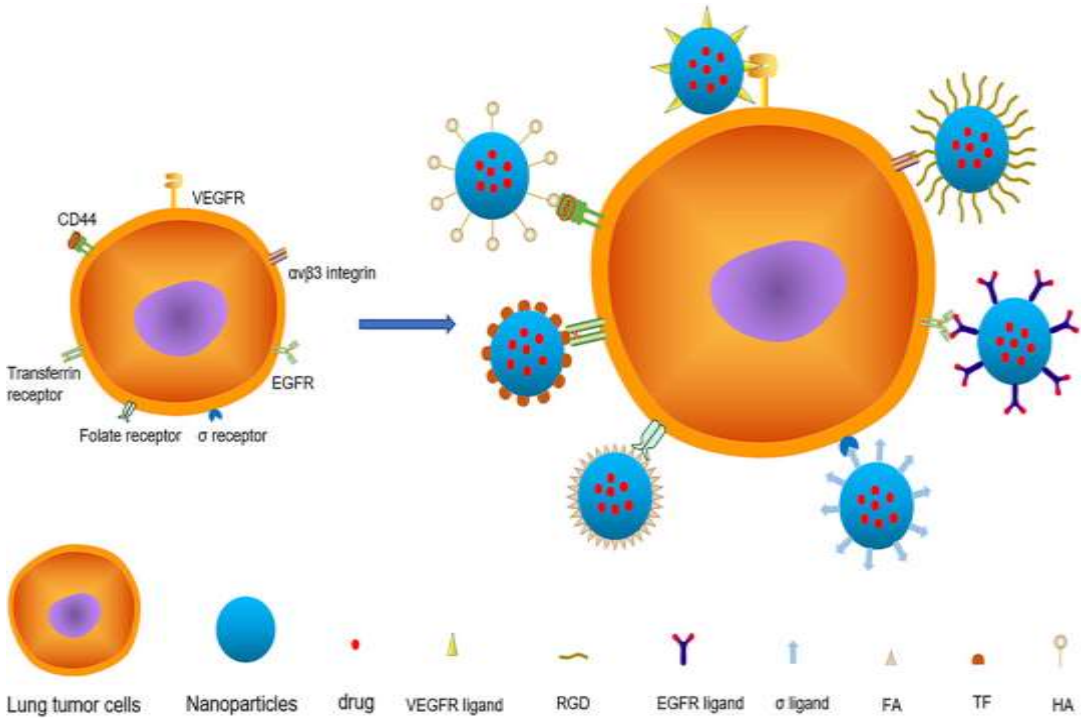

Figure 4. Various targets on lung cancer cells

TARGETING STRATEGY USING NANOCARRIER

Different targeting tactics for lung cancer treatment are made possible by nanotechnology. Figure 3 vividly covers the types of targeting used in Nanotechnology.

1. **Passive targeting**: Because of damaged lymphatic drainage and leaky blood arteries, nanoparticles can take advantage of the increased permeability and retention (EPR) effect to aggregate in tumor tissues. The permeability of tumor tissues is exploited by passive targeting.

Chemotherapeutic medicines can be passively targeted by taking advantage of the leaky and faulty vasculature found in rapidly proliferating malignant tumors. This is known as the EPR effect, or enhanced permeation and retention effect[34]. The EPR effect is seen in most polymer NPs. An illustration would be the passive targeting of paclitaxel-laden poly(lactic acid)-blockpoly(ethylene glycol) polymeric micelle formulations loaded with genoxol-PM.A phase II trial involving patients with advanced non-small cell lung cancer has examined this nanocarrier system[35].

2. **Active Targeting**: Lung cancer cells are the precise target of functionalized nanoparticles. Ligands, antibodies, or peptides that identify specific markers on cancer cells can do this. In order to enable the preferential accumulation of a chemotherapy medication in the tumor tissue, within individual cancer cells, or even within intracellular organelles, active targeting is typically accomplished by conjugating the NP to a targeting moiety. Targeting moiety/ligands include proteins (Transferrin), tiny molecules (Folate molecules), aptamers, and antibodies (mAbs). In a recent study, mice with A549-luc-C8 lung tumors received intravenous injections of PGA nanoparticles loaded with paclitaxel palmitate and deco-rated with cetuximab Abs for targeting These mice had a significantly higher survival rate than the control group[36, 37].

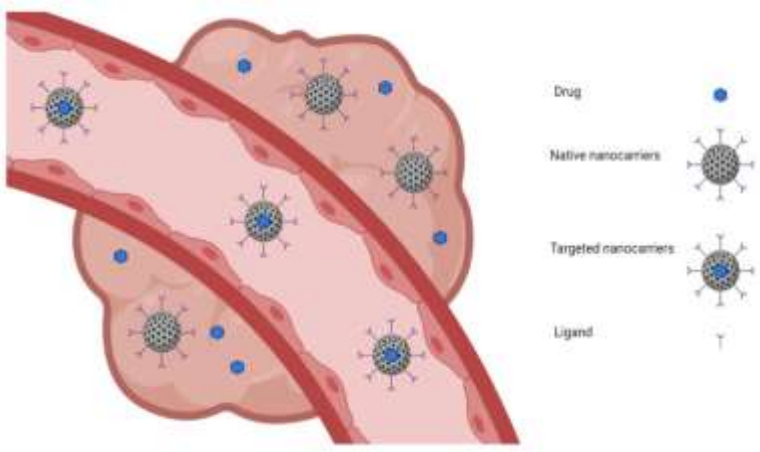

Figure 3. Passive and Active targeting

NANOCARRIER MEDIATED DRUG DELIVERY SYSTEM

[1] Liposomes

Liposomes are spherical delivery systems made of hydrophobic and hydrophilic molecules contained within amphiphilic lipid bilayers, which can trap hydrophilic molecules in the watery core[38]. Liposomes possess various distinctive characteristics, including their non-toxic nature, surface reactivity to external stimuli, physical stability, high vascular density, and extended retention duration at the intended location. A liposome's structure consists of an aqueous core, cholesterol, and phospholipids. The US FDA approved Doxil, the first formulation of Nano liposomes containing doxorubicin, in 1995 to treat Kaposi's sarcoma associated with AIDS[39]. Additionally, nanoliposomes may extend the medication's circulation, improve the stability of the integrated drug in vivo, and easily alter the size and surface of the drug to raise its therapeutic index. Nevertheless, batch-to-batch volatility, high production costs, and poor stability at ambient temperature owing to drug encapsulation leaking during storage are some of the drawbacks of nanoliposomes.

Targeted delivery mechanisms such as active, passive, pH-responsive, magnetic, stimuli-responsive, and thermo-responsive liposomes are employed by synthesized liposomes to deliver medicinal compounds. Lipids and cholesterol make up liposomes, sometimes referred to as conventional liposomes. The opsonins and reticulo-endothelial system assist these liposomes to be easily removed from the blood, which is an added advantage. Overcoming these obstacles, “intelligent liposomes” can be a useful drug delivery method for the treatment of lung cancer[40].

[2] Hydrogels

Three-dimensional mesh made of polymeric materials called hydrogels have the ability to hold a sizable amount of water inside their fibres. Poly(2-hydroxyethyl methacrylate), or P-HEMA, was the first hydrogel to be created. Hydrogels can be cross-linked physically (via hydrogen bonding) or chemically (through ionic, covalent, and atomic bonding)[41].

Typically, polymers (PEG-PCL-PEG/DDP, PECE/DDP) with a polymeric micellar mixture of paclitaxel and cisplatin are used to functionalize hydrogels (sol−gel−sol). Hydrogels exist as solutions at room temperature; however, they solidify into gels at body temperature. The main way that this gel form fights cancer is by creating a drug depot that allows the medication to slowly diffuse throughout. The thermosensitive polymer releases cisplatin, while the adjacent malignant tissues gradually absorb micellar paclitaxel through the gel state. Hydrogel compositions both extend the life of the organism and

prevent carcinogenesis. Drug combinations in the form of hydrogels may be used to treat lung cancer. Researchers have created an intravenous medication delivery device based on hydrogel to treat non-small cell lung cancer[42].

[3] Dendrimers

A distinct family of polymeric nanoparticles known as dendrimers was initially described in the late 1970s. Dendrimers are artificially produced polymeric macromolecules that are bifurcated and branched, with a size range of 10-100 nm. Since they often have a globular shape and functional groups on their surface, they are great options for drug administration. Chemical synthesis of dendrimers is achieved by a controlled polymeric process that combines hydrophobic and electrostatic interactions. It is possible to optimize both the surface and biodegradability of these nanocarriers. Because of their symmetrical structure, biocompatibility, ease of biodegradability, high payload, and many conjugation points that facilitate surface modification, these nanocarriers have shown promise as a helpful tool in cancer therapy[43].

[4] Polymeric micelles

Polymeric micelles are frequently employed for the targeted delivery and controlled release of hydrophobic anti-neoplastic medicinal drugs. Copolymers or amphiphilic surfactants self-assemble into polymeric micelles (PMs) with a diameter of 10–100 nm when they are dissolved in water above their critical micellar concentration. PMs are made up of a hydrophilic shell structure around a hydrophobic inner core[44].

Therefore, it is possible to encapsulate hydrophobic and amphiphilic medications in the core and regulate their release. The particle can avoid the reticular endothelial system because the hydrophilic shell stabilizes the core. In turn, this increases the time that particles are in the blood, which may promote the build-up of particles in the tissues around tumors. Because polymeric micelles aggressively evade renal exclusion and RES, their smaller size (diameter less than 100 nm) makes them an excellent drug delivery method. They even permit themselves to progressively enhance the endothelium barrier's penetration in the tumor-dominated region. Particle agglomeration, opsonin linkage, and protein linkage are all inhibited by the hydrophilic barrier that surrounds the hydrophobic center of the micelle. These break down in the blood vessels before they reach the intended area. This approach's main advantage is that it uses biodegradable drug delivery technologies that can be employed for both cancer and ocular drug administration[45].

[5] Solid lipid nanoparticles

Submicron-sized (50–1,000 nm) natural or synthetic lipid-based medication delivery systems are known as solid lipid nanoparticles (SLNs). Triglycerides, emulsifying wax, beeswax, acetyl alcohol, cholesterol, and cholesterol butyrate are a few standard solid lipids used to create SLNs. Because SLN naturally increases the bioavailability of water-insoluble medications, it has been successfully used as a carrier to transport a variety of anticancer medications, including doxorubicin, idarubicin, and etoposide. By avoiding first-pass effects, the lungs provide a large surface area. The incredibly thin alveolar walls in the deep lung also aid in the quick absorption of aerosolized medications (in the 1 to 3 μm size range). In addition to delivering anticancer drugs, SLNs have been effectively utilized as a gene delivery mechanism in vitro for lung cancer cells (A549). It has been observed that solid-lipid nanoparticles with a large surface area can hold a considerable amount of medication. Additionally, it boosts the drug's bioavailability and shields it from the environment. Solid-lipid nanoparticles are the best nano-carrier system for targeted drug administration because they combine the qualities of polymeric nanoparticles, liposomes, and fat emulsion carriers[46, 47].

[6] Polymeric Nanoparticles

Drugs are encapsulated in various polymers, forming a class of nanoparticles called as polymeric nanoparticles. By tying the target tumor cells or tissues to the ligand, these polymeric nanoparticles (NPs) improve the drug's stability and affinity. Polymeric nanoparticles are in high demand for their ability to target cancer cells in both active and passive ways. Polymer nanoparticles can be synthesized using a variety of polymers. Poly(lactic acid) (PLA), Poly(lactide-Co-glycolide) (PLGA), etc. Lactic acid is used to make PLA, a biodegradable polyester. Polylactic-co-glycolic acid (PLGA), a copolymer of glycolic and lactic acids, is biocompatible and biodegradable.PLGA has been validated as a medication delivery vehicle for parenteral administration by the European Medicines Agency (EMA) and the U.S. Food and medication Administration. Positive results are seen when polymeric nanoparticles are used to treat lung cancer [48]

For the treatment of non-small cell lung cancer (NSCLC), polymeric nanoparticles comprising polymers such poly-lactic-acid-co-glycolic acid (PLGA), poly-lactic-acid (PLA), chitosan, and polycaprolactone have been thoroughly studied. In addition to being biocompatible and biodegradable, polymeric nanoparticles (Figure 1d) have several advantages for drug delivery, such as the ability to encapsulate different active molecules (such as drugs, peptides, and oligonucleotides) and be easily modified for controlled and sustained release, easily nanosized, easily cellular uptake, and the ability to avoid reticuloendothelial clearance. Moreover, they have better storage stability than formulations based on lipids[49].

[7] Metal based Nanoparticles

Numerous metal-based nanoparticle classes, including quantum dots, carbon nanotubes, gold, and silver, have been studied as potential drug delivery agents for the treatment of non-small cell lung cancer. The research on metal-based nanoparticles has grown exponentially, mainly because of their easy alteration of surface properties and good biocompatibility. Their ability to extinction of visible light has rendered them appropriate for intracellular tracking.

A carbon monolayer organized in a hexagonal honeycomb lattice, graphene is also attracting a lot of interest because of its exceptional ability to load drugs due to pi-pi stacking that occurs between graphene sheets. However, a thorough understanding of graphene's physicochemical properties is

currently lacking in order to optimize its use in drug delivery systems[50, 51]. Different types of nancarrier-mediated drug delivery systems used in nanotechnology are displayed below in figure 4.

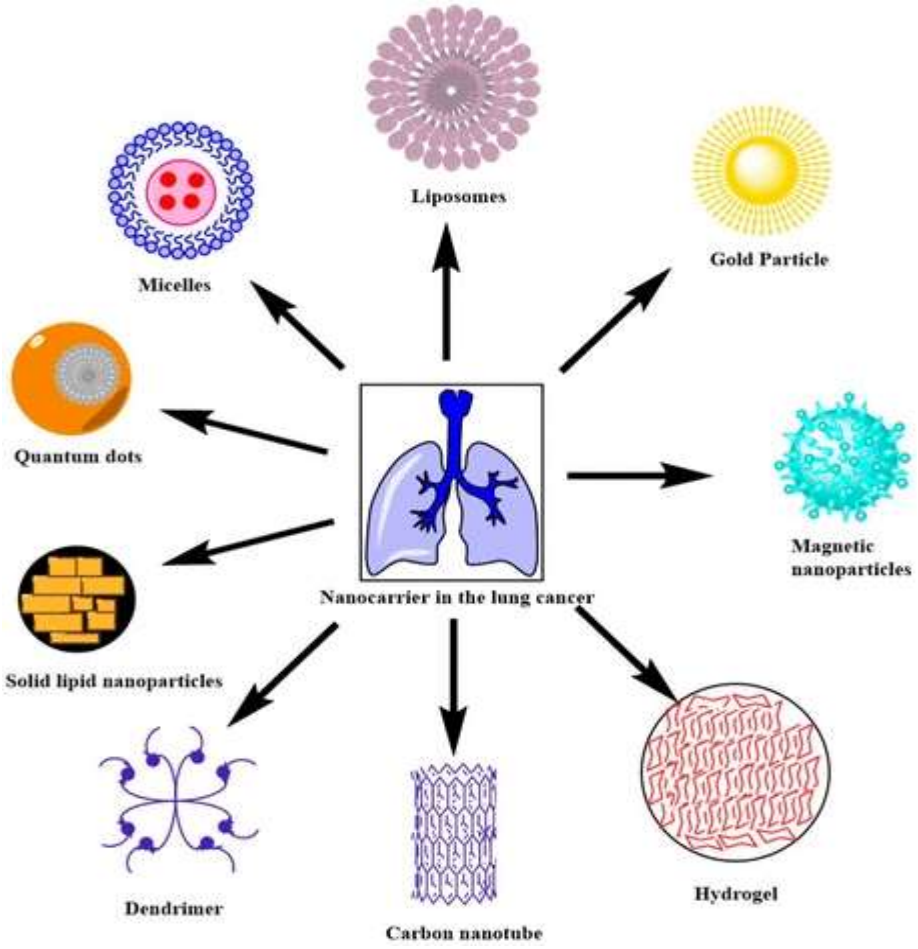

Figure 4. Different types of nano-carrier mediated drug delivery system

Outlook For The Future And Conclusion

Nanotechnology has a lot of potential for the treatment of lung cancer in the future. We can expect a revolution in lung cancer diagnosis and therapy due to the continuous progress in nanomaterials and their applications[52]. Future developments include targeted medication delivery, enhanced imaging, early detection using ultrasensitive nanoparticles, and customized treatment plans. Several other unique characteristics, such as enhanced bioavailability, prolonged drug release, target-specific (tumor) cytotoxicity, and improved pharmacokinetics, can also be added to nanomaterials, making them useful in the medical industry[53]. Moreover, the possibility of minimally invasive surgery made possible by nanorobots and theranostic methods that integrate diagnosis and treatment provide a window into a future in which lung cancer treatment will be more accurate and successful. We may be able to improve the quality of life as well as prolong the lives of people with lung cancer by utilizing nanotechnology.In summary, the use of nanotechnology to lung cancer research and clinical settings offers a promising avenue for more individualized and efficient treatment of this difficult illness[54].

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