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# Nanoparticulate Drug Delivery Systems in Lung Cancer: Advances, Clinical Translation, and Emerging Targeting Strategies

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**Keywords**

*Nanoparticulate drug delivery systems; Lung cancer; Nanomedicine; Targeted drug delivery; Enhanced permeability and retention (EPR) effect; Polymeric nanoparticles; Liposomes; Clinical translation.*

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## Abstract

Lung cancer remains to be a major contributor to cancer–related deaths across the globe, primarily due to late-stage diagnosis, tumour heterogeneity, metastasis, and the systemic toxicity associated with conventional therapies such as chemotherapy and radiotherapy. Nanoparticulate drug delivery systems (NDDS) have emerged due to rising to elevate the treatment efficiency while lessen the adverse effects. A wide range of nano carrier system such as polymeric nano particles, liposomes, dendrimers, solid lipid nano particles inorganic nano particles and metal based platforms, have been widely explored for the treatment of lung cancer. These Nano systems improve drug solubility, enable controlled and sustained release, prolong systemic circulation, and enhance the drug's preferential accumulates in the tumur through passive targeting such as the enhanced permeability and retention (EPR) effect, as well as active ligand-mediated targeting strategies. Additionally, advancements in surface engineering, inhalable nano formulations, and Thera-ostics platforms have further expanded the clinical potential of nanomedicine in lung oncology. Despite encouraging preclinical outcomes and the approval of selected Nano formulations, clinical translation remains limited due to biological barriers, immune clearance, Tumur microenvironment complexity, manufacturing challenges, and regulatory constraints. This review provides a comprehensive overview of current nanoparticle-based drug delivery systems for lung cancer, highlighting their design principles, therapeutic advantages, existing clinical applications, and translational challenges, while outlining future perspectives for precision nanomedicine in pulmonary oncology.

## INTRODUCTION:

Cancer is the unrestricted growth and development of tumour cells in the body, it ranks among the leading causes of death globally. In the current scenario, Russia is developing an mRNA cancer vaccine and will distribute it to the public in 2025[1]. Single-drug treatment for cancer has also developed. Specific treatments are needed to

cure the cancer. One of the solutions for treating cancer is radiotherapy, which destroys and eliminates the cancer cells in a permanent manner. In India, they predicted cancer affliction is expected to rise to 29.8 million [2]. The highest burden is expected to be in the north and northeast regions. The strategies for cancer treatment include: immunotherapy, targeted therapy, surgery, chemotherapy, hormonal therapy, radiation therapy, stem cell transplant, photodynamic therapy, laser therapy, gene therapy, and Cryotherapy [3]. Cancer's multistep process includes metastasis, initiation, and promotion progression. The genetic mutations that occur during cancer development involve proto-oncogenes, tumour suppressor genes and senescence genes. Tumour cells can evade apoptosis [4]. Tumour cells evade the immune system's recognition and response to survive and develop into metastatic tumours. Although several conventional methods are available. On the other hand, side effects will also occur due to damage to healthy cells or the removal of organs during surgery. Over the last few decades, nanotechnology has been widely used in medicine, including diagnosis, treatment [5], and tumour targeting in a safer and more effective manner. Nanotechnology's role in cancer therapies was to reduce toxicity in healthy tissues, increase bioavailability, deliver anticancer drugs to tumour tissues, and improve pharmacokinetics. The genetic mutations that occur during cancer development involve proto-oncogenes, tumour suppressor genes, and senescence genes. Tumour cells can evade apoptosis. Tumour cells evade immune recognition and response, survive, and develop into metastatic tumours [6].A Carcinogenic drug, peptides, sugars, Tumor- specific antibody and some of the hormones are the targeting moieties of the tumour. An anti-carcinogenic chemotherapeutic agent has tested for specificity. NPs are better than drug delivery systems because they have Nanoscale receptors on their surfaces. In cellular immunity, T cells are the primary cells responsible for directly recognising and killing tumour cells. Immune cells and major CD8 T-cells kill infected cells [7].

***DIFFERENTTYPEOFNANOPARTICLES:***

● POLYMERIC NANOPARTICLES:

In past, it was widely act as the carrier for drug delivery. Polymeric nanoparticles are

made from biocompatible synthetic polymers such as poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), and poly (ethylene glycol) acid[8].

PLGA is the most widely used method. Polymeric nanoparticles can be nanocapsules or nanospheres.

● ***NANO SPHERES:***

They are solid polymers embedded in the drug's polymeric matrix. Encapsulation of the drug into a nanosphere enables controlled drug release and allows it to penetrate intracellular and extracellular spaces.

***POLYMER MICELLES***

The drug delivery system is formed through the self assembly of amphillic blocks co-polymers in liquid media. The water repelling core center that entraps poorly water-soluble drugs and a hydrophilic outer shell that enhances stability in biological fluids. This core–shell architecture improves drug solubility, protection, and circulation time. Polymeric micelles preferentially gathered in tumor tissues due to enhanced vascular permeability. Surface modification with targeting ligands further improves site-specific drug delivery to cancer cells. It is a prevalently used polymers include polyethylene glycol (PEG), polylactic-co-glycolic acid (PLGA), and chitosan (CS). These materials provide a favorable biocompatibility and biodegradability profiles. Polymeric micelles have been widely investigated for cancer therapy and analytical applications. They offer advantages such as controlled drug release and reduced systemic toxicity. However, challenges including limited stability and leakage of premature drug remain concerns for clinical translation.

***LIPOSOMAL DRUG DELIVERY SYSTEM:***

Liposomes are tiny spherical vesicles composed of a phospholipid bilayer. Liposomes are lipid-based drug delivery systems used for cancer treatment. Liposomes are a nano-carrier formed by a lipid-based membrane designed to deliver a drug to tumours. In liposomes, Doxorubicin hydrochloride can be loaded effectively as a chemotherapeutic agent. Liposomes have a hydrophobic tail and a hydrophilic head as a bilayer. The most commonly used polymer coating to improve liposome surface properties was PEG coating. Liposomes reach the tumour through the bloodstream

and migrate through leaky tumour vessels. Due to their distinct size, liposomes can penetrate the vasculature of tumours but not normal healthy cells. This is called the enhanced permeation and retention effect. Over time, liposomes accumulate in tumour tissue and then enter the interior of tumour cells via endocytosis in the acidic endosomal compartment. The encapsulated doxorubicin sulphate within the liposomes becomes available to act on tumour cells, inducing a controlled form of tumour cell death. Liposome nano drug based on many liposome drugs such as DepoCyt, Exparel, Depo-Dur, Marqibo and DaunoXome. This drug has been approved for clinical research. PEG coating modifies liposomal function and prolongs circulation time [9].

***INORGANICNANOCARRIERSFORDRUGDELIVERY***:

Inorganic nanocarriers are used in biomedicine and other fields due to their structural and functional properties. They are an excellent prospect for targeted drug delivery[10].

**MAGNETIC NANOCARRIER:**

Magnetic hypothermia treatment is one of the promising non-invasive approaches for thermal activation therapy for cancerous tumours. Upon exposure to an external alternating current magnetic field, magnetic nanoparticles can generate heat through the oscillation of their magnetic moments. Magnetic hyperthermia can destroy cancer cells by raising their temperature to 40-50 °C with minimal injury to normal cells. Magnetic hyperthermia-based heating system to be employed either for the controlled release of a drug from a caged drug delivery system or killing the tumour cells, or both. The most commonly used material for magnetic hypothermia is ferrite nanoparticles (Buxton, 2009), particularly magnetite (PHA-304), with particle sizes ranging from 0 to 100. Nanometre magnetic iron oxide nanoparticles possess several beneficial properties, including excellent chemical stability, low cytotoxicity, strong magnetic behaviour, and the ability to be easily surface-modified and functionalized. When compared to other types of magnetically susceptible materials, such as certain metals, iron, nickel or cobalt or metal alloys.

Cobalt or metal alloys' heat generation mechanism

- Good aqueous solubility of drugs
- To overcome multidrug resistance

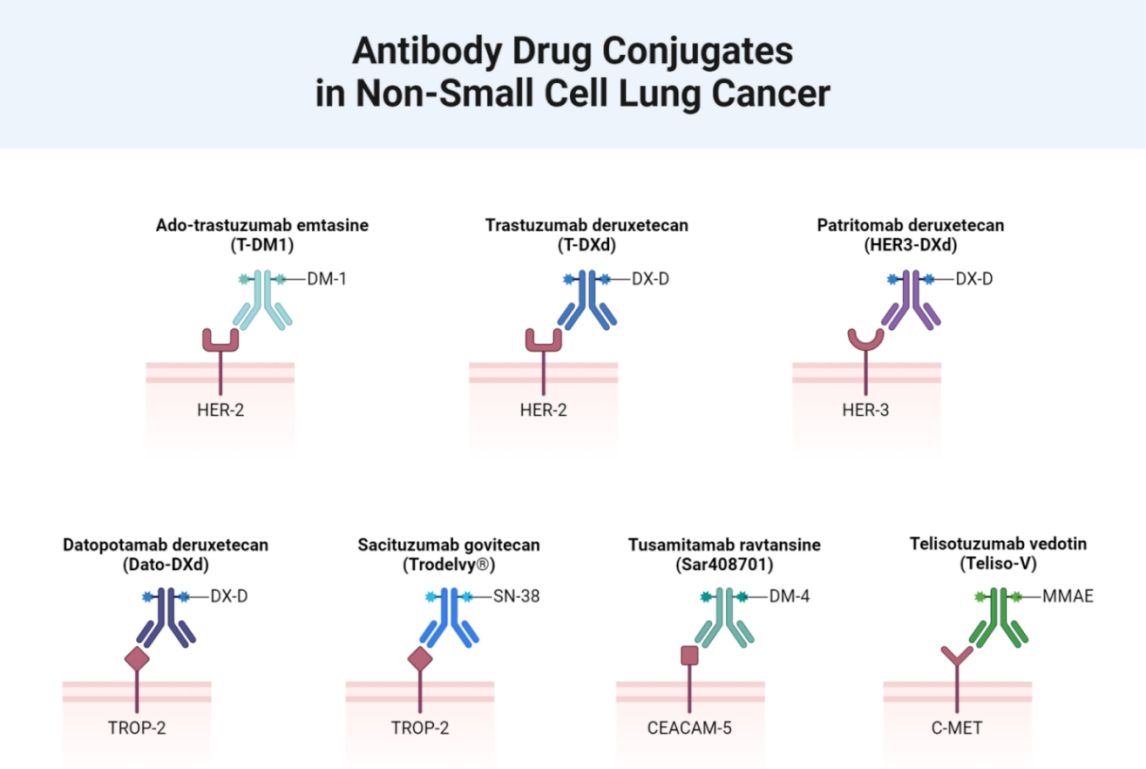


**FIGURE 1.** Antibody-drug conjugates in Non-small cell Lung cancer targeting the HER2, HER3, TROP-2, CEACAM-5, and c-MET, with precise antibody targeting and a cytotoxic agent for targeting tumour cells.

***DIFFERENT TYPE OF NANOPARTICLES DRUG DELIVERY***:

**1. Polymer-based delivery**:

Polymeric-based drug carriers are colloidal solid particles made from biodegradable polymers and are known as polymeric nanoparticles, whether natural or synthetic. Polymers composed of repeating monomer units offer a wide range of chemical functionalities,enabling the use in various nano particle utilization, including drug delivery and surface modification. They can successfully enter cells through capillaries because of their small size (50 to 300nm), which increases the concentration and

therapeutic mediation at the site of action. Natural polymers such as polysaccharides and proteins are typically derived from biological sources, making them biocompatible and biodegradable [11]. Synthetic polymers are valued for their ease of production and lower risk of contamination. Each polymer type exhibits unique properties based on its molecular structure. For example, polyethene glycol (PEG) is known for its bioinert nature and is frequently used to modify nanoparticle surfaces. PEGylation has been shown to reduce immune recognition of nanoparticles and improve their penetration through respiratory mucus, owing to its inert properties. Polyethyleneimine (PEI), a cationic polymer, binds well to nucleic acids because of its strong electrostatic interactions. PEI-based nanoparticles have demonstrated effectiveness in delivering genes to treat chronic lung conditions. In recent years, the utilisation of biodegradable polymers, including polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), albumin, chitosan, polycaprolactone, and poly alky-cyanoacrylates, has increased. These materials provide controlled, sustained drug release, possess nanoscale dimensions, and exhibit excellent biocompatibility. An example is Abraxane, a nanoparticle formulation of paclitaxel conjugated to albumin, approved by the FDA. It serves as treatments for individuals with locally advanced lung cancer. Polymer-based nanoparticles utilizing polycaprolactone chitosan coated for oral delivery chemotherapy delivery in lung cancer treatment. The therapeutic effect is achieved by selectively targeting cancer cells that exhibit elevated mucin levels compared to normal cells.

***2. Dendrimer nanoparticles***:

Dendrimers are intricate three-dimensional macromolecules featuring a central core from which several branched polymer chains emerge in an organised manner. The attributes of dendrimers, including their dimensions and surface architecture, can be modified by varying the number of generations during synthesis. In gene therapy, dendrimer nanoparticles that incorporate positive or negative charged polymers are frequently utilized to form complexes with nucleotides via , electrostatic binding, thereby improving stabilization and delivery. Due to presence of numerous amide and amine groups on their polymer chains, dendrimers composed of polypropylene imine (PPI) and

poly(amidoamine)(PAMAM) are extensively utilized in gene therapy applications due to their abundance of amide and amine groups in their polymer chains. Recent research on dendrimers has revealed the promise of dendrimer-linked peptide compounds as targeted drug-delivery systems for non-small cell lung cancer. PEGylated dendrimer nanoparticles demonstrated efficacy as inhalable aerosols for pulmonary medication administration. Smaller particles were observed to penetrate the bloodstream through inhalation more readily, whereas larger particles persisted in the lungs for extended periods[12].

***3. Polymeric micelles:***

Polymeric micelles comprise a functional core encased by a surrounding shell. The core comprises the hydrophobic segments of an amphiphilic block copolymer, where the shell is constituted by hydrophilic segments. Alternatively, these micelles are formed from water-soluble block copolymers that incorporate both neutral polymer chains and charged segments. When block copolymers self-assemble via electrostatic interactions to form structures termed polyion complex micelles [13]. These interactions occur between ionic components of the copolymer and molecules with opposing charge. In gene therapy, negatively charged nucleotides are used with these hydrophobic ones. Polymeric micelles have effectively delivered in gene therapy, where DNA or RNA molecules are typically enclosed within the core, and the outer shell plays a critical role in influencing pharmacokinetics.

4. ***Lipid-based drug delivery:***

Liposomes are spherical vesicular structures formed from phospholipid bilayers. They are extensively utilised to transport both hydrophobic and hydrophilic substances by integrating them into the lipid bilayer or by encapsulating a hydrophobic drug within their watery core. Minimising the lipid bilayer quantity decreases liposome dimensions, thereby promoting their transformation into nanoscale particles. Liposomes prolong drug circulation time and enhance tumour-targeted delivery. Liposomes often agglomerate, leading to diminished stability in biological systems and accelerated breakdown by the reticuloendothelial system (RES). The surfaces of liposomes are coated with innocuous hydrophilic polymers, such as polyethene glycol(PEG)[14]. This coating improves liposomes' stability, creates a protective barrier that delays RES recognition, and prolongs their circulation

time in the bloodstream [15]. Liposomes are gaining popularity in anticancer therapy due to their excellent biocompatibility. Liposome-based drug delivery is largely due to their potential to improve pharmacokinetics and suppress the adverse effects associated with certain cancer therapies. In recent years, liposome technology has advanced to include various types, including cationic liposomes, virosomes, and temperature-responsive liposomes. Only two liposome drugs have received FDA approval. In lung cancer, liposomes offer a promising approach for delivering therapeutic agents and genes [16]. Cisplatin is a standard drug for non-small cell lung cancer. Cisplatin causes kidney damage in about 20 per cent of patients at high doses. Liposomal version of cisplatin called lipoplatin. Lipoplatin shows lower nephrotoxicity than conventional therapy. Paclitaxel is commonly used in lung cancer treatment.

***5. Solid lipid nanoparticles****:*

Solid lipid nanoparticles (SLNs) are nanoscale colloidal drug deliver system. They range in dimension of 50 to 1000 nm. They are formulated using physiological lipids and are stabilized in an aqueous surfactant medium . These nanoparticles are usually formed from substances such as triglycerides, beeswax, and cholesterol. They are widely employed as carriers for hydrophobic chemotherapeutic agents, enabling prolonged circulation in the bloodstream. Cationic (SLNs) have an amphiphilic nature, incorporating two hydrophobic fatty acid chains and a hydrophobic amino acid group connected. These hydrophobic amino acids can bind with negatively charged DNA plasmids to create stable complexes. Cationic SLN-DNA complexes can reach the damaged tissue through intratracheal administration or aerosol inhalation. Benefits of using SLNs are their ability to minimise drug leakage into the bloodstream compared to liposomes, thereby improving drug circulation and providing controlled release[17].

***6. ANIONIC LIPOSOMES***:

In the anionic liposomes for gene delivery. They have low efficiency in encapsulating DNA or RNA nucleotides. This issue often arises during the formation of liposome-nucleotide complexes or systems in which nucleotides are enclosed within liposomes [18]. To improve nucleotide encapsulation, positively charged helper molecules, such as calcium and chloride, and amino acids, such as polylysine or arginine-rich oligomers, are

frequently employed. These cationic agents assist in forming complexes with the nucleotides, aiding their incorporation into or around the anionic liposomes.

### *7. INORGANIC NANOPARTICLE:*

Inorganic nanoparticles, including gold, iron oxide, and silica nano particles, are used for their distinctive magnetic and plasmonic properties. Inorganic nanoparticles are commonly employed in diagnostic imaging for various diseases. Metal-based nanoparticles made from gold. Gold has attracted significant attention for gene delivery. This is largely because positively charged metal ions readily interact with negatively charged DNA and RNA molecules. Inorganic nanoparticles have shown limited effectiveness in treating persistent lung conditions[19]. Gold nanoparticles were delivered to lung epithelial cells in chronic obstructive pulmonary disease. Positively charged gold nanoparticles can interact with negatively charged proteins in the bloodstream, and gold nanoparticles with polyethene glycol can help minimise aggregation. The slow clearance of gold nanoparticles from the body presents a barrier to their longer-term use and clinical relevance. There is only a limited drug loading capacity. Challenges must be thoroughly addressed before inorganic nanoparticles are introduced into clinical trials.

### *8. METAL-BASED NANOPARTICLE*:

Metallic nanoparticles composed of gold and iron oxide have been widely recognized for their potential in drug delivery. Metals such as gold and silver have been widely used in various medical applications, particularly in advanced diagnostic techniques for detecting and identifying lung cancer. Lung cancer types and subtypes, as well as distinguishing normal and cancerous cells namely,small cell lung cancer and non-small cell lung cancer. Gold nano particles have been utilized to facilitate the delivery of anticancer drugs, thereby enhancing therapeutic outcomes. For example, methotrexate typically suffers from poor tumour retention due to its high water solubility, which is particularly problematic given its properties, including low toxicity, excellent biocompatibility, and chemical stability. They can be easily prepared and modified, and their high surface reactivity enables easy surface modification or attachment of functional polymers and biomolecules. Gold nanoparticles have also been incorporated into complex drug delivery platforms alongside other carriers.

To enhance gene delivery efficiency, gold nanoparticles have been combined with nucleotides coated with polymers or used as cores for dendrimer structures. Gold nanoparticles were chemically modified with carboxylic acid groups and coated with polyethyleneimine, a pH-responsive, polyelectrolyte to control the release of small interfering RNA (siRNA) and extracellular DNA following PH changes inside endosomes[20].

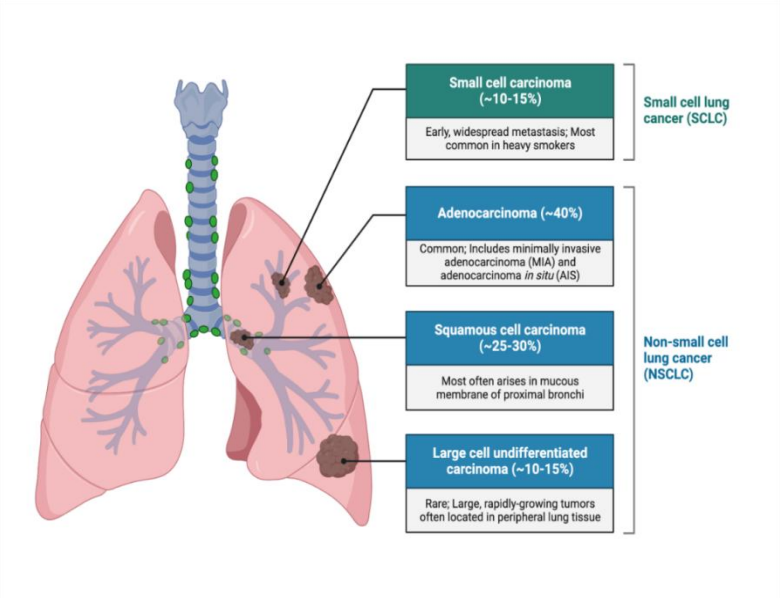


**FIGURE 2:** Schematic representation of metal-based nanoparticles in lung cancer therapy.

Iron oxide nanoparticles are extensively utilised in the biomedical field due to their superparamagnetic characteristics. These nanoparticles have both diagnostic and therapeutic applications, including magnetic resonance imaging (MRI) and magnetic field-triggered drug delivery. Iron oxide nanoparticles typically serve as the core, while cationic polymers or lipids are applied to the surface to enable nucleotide binding [21].

***Table 1: ADVANTAGES AND DISADVANTAGES OF NANO DRUG DELIVERY SYSTEM***;

| NANOCARRIER | ADVANTAGES | DISADVANTAGES |
|---|---|---|
| **LIPOSOME** | Eco-friendly consistent. Ability to digest and delivery polar. Protects involved drugs and provides sustained release. | **I**nstability Difficulty targeting tumours It may be allergic |
| **GOLD NANOPARTICLES** | Easy for combination or mixture and fusion of multiple bioactive agent Large surface area | Non-biodegradable Cost and toxicity Regulatory challenges |
| **CARBON NANO PARTICLES OR NANOTUBES** | Ability to digest and delivery various type of drugs of bioactive agents Increase drug accumulation and drug circulation time low toxicity at cellular level strong absorption in the NIR range biocompatibility | Can be toxic Low solubility in water Poor pharmacokinetics toxicity and non-biodegradable cancer oxidative DNA damage |
| **QUANTUM DOT** | Exceptional fluorescence property for highly sensitive imagining. Control particle size determination Potential for target delivery | Toxicity and pharmacological issues mainly from heavy metal and colloidal instability Air sensitivity Nano particulate accumulation |
| **POLYMERIC NANOPARTICLES** | Best stability Accumulates tumour EPR Allowing for controlled release | Toxic side-effects Low polymer concentration in organic phase |

| | | |
|---|---|---|
| | for anticancer drug Potential overcome for drug resistant | Agglomeration |
| **DENDRIMERS** | Soluble in water and biocompatibility<br>It used to deliver photosensitizers to tumour cells which can destroy them theragnostic capabilities<br>Flexibility in conjugation | Rapid elimination<br>Bio distribution<br>Toxicity |

**ADVANTAGE'S**

**Targeted Nanocarrier Systems for Enhanced Anticancer Drug Delivery**

The use of targeted moieties, for specifically ligands, nucleic acids, peptides target has emerged as a highly effective approach to enhance the selective transport for anticancer agents. These targeting components are designed to recognize and binds specifically to hyperactive receptors or antigens present on top of the cancer cells. By attaching these moieties to therapeutic compounds, drug delivery systems can achieve greater specificity, minimizing toxicity to healthy tissues while enhancing the therapeutic efficacy against malignant cells.[22]To facilitate this targeted delivery, a variety of nanocarriers have been extensively explored[23]. These **include liposomes, gold nanoparticles, carbon nanotubes, quantum dots, polymeric nanoparticles**, and dendrimers. Each of these nanocarriers can serve multiple roles—not only as drug delivery vehicles but also as tools **for diagnostics and imaging**, thereby integrating treatment and monitoring into a single platform, a concept known as therapeutics [24]. The performance of nanocarrier-based drug delivery systems is influenced by several critical factors, including drug loading efficiency, physiological stability, circulation time, targeting specificity, and encapsulation efficiency. Drug loading efficiency determines the amount of therapeutic agent that can be incorporated within the nanocarrier, thereby affecting its therapeutic potential. Physiological stability ensures that the nanocarrier maintains its structural

integrity during systemic circulation until it reaches the intended target site. It influences residence time in the blood stream and the duration of drug availability and enhances tumour accumulation. Targeting specificity improves selective recognition and binding to cancer cells, reducing non-targeted effects. on healthy tissues. Encapsulation efficiency reflects how effectively the drug is entrapped within the nanocarrier, contributing to controlled and sustained drug release. Optimising these parameters is essential to enhance therapeutic efficacy, minimise systemic toxicity, and improve the overall safety profile of cancer treatment strategies.[25].

**DISADVANTAGEs.**

Particles of very small size possess the ability to penetrate various biological membranes within the body. Besides this, it is an advantage of cancer treatment, but it's a main disadvantage because of the potential harm to cells. DNA nanoparticles can cross the blood-brain barrier (BBB). Making them a valuable method for delivering drugs directly to the brain to treat various neurodegenerative disorders. However, there are drawbacks, as Nano drug formulation used for treating other disorders, such as cancer, can penetrate and cause brain and life-threatening effects. Since the irritation occurs in the lung tissue and the airways due to the accumulation in the lungs. Natural compounds are being explored in multiple clinical trials for the treatment of lung cancer. The production of anti-cancer nanodrugs is complex and time-consuming, which may entail significant financial expenditure [26]. It might have many advantages, but it also has certain problems.

***EXISTING LUNG CANCER NANODRUG DELIVERY SYSTEM:***

The purpose of nanotechnology in cancer treatment has become one of the most exciting, fast-growing and rapidly changing areas of biomedical research. Cancer is a notable example of a disease in which nanotechnological approaches have substantially enhanced both diagnostic techniques and treatment options, as mentioned in previous sections [27]. As well as nanomedicine and nanobased drug delivery systems, future development seems very promising; they still have a long way to go before they can help people with lung cancer. The overall impact of these new technologies on lung cancer treatment in the healthcare system, including how they can

be used to treat the disease, remains relatively limited.

**Recent advancements in nano-enabled cancer drug delivery systems encompass the following developments**:

● STING ACTIVATORS: These kinds of medicines are given with chemotherapy drugs to make the tumour microenvironment less resistant to pharmaceuticals, which helps drugs develop at tumour sites[28].

● HYBRID NANOPARTICLES: In hybrid Np, either natural or synthetic materials are combined to form different carrier forms.

● SURFACE – ENGINEERED NANOPARTICLES: Have a targeting middle layer and a hydrophobic internal core.

● ENZYME – RESPONSIVE PEPTIDE DRUG CONJUGATES: Use a targeting ligand and an enzyme – Responsive linker[29].

NDDS (Nano drug delivery system) are a crucial treatment for cancer. They can:

● Improve drug targeting

● Prolong drug circulation

● Break through the Tumor cell membrane

● Minimise side effects

● Increase drug efficacy

● Reduce drug metabolism

● Improve the dissolution capacity of water insoluble drugs.

● Allow to manage & site specified drug release .

The FDA has approved many drugs to treat cancer, including targeted therapies, drugs for a specific type of cancer and drugs for solid tumours. Below are some examples of FDA-approved drugs for lung cancer treatment [30].

**Table 2:FDA-approved drugs for lung cancer therapy, including their molecular targets and corresponding brand names.**

| ***DRUG*** | ***TARGET*** | ***APPROVED*** | ***BRANDS*** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Everolimus | Blocking MTOR | FDA | A finitor zortress |
| Doxrubicin hydrocholide | Blocking topoisonerase II | FDA | Vepesid |
| Etoposide | Topoisomerase II | FDA | Imfinzi |
| Durvalumab | PD-LI | FDA | Imfinzin |
| Methotrexate sodium | Dihydrofolate reductase (DHFR) | FDA | Trexall Xatmap |
| Nivolumab | Bind and block protein PD-1 | FDA | Opdiro |
| Lurbinetedin | Oncogenive transcription | FDA | Zepzelca |
| Topotecan HCL | Topoisomerase -I | FDA | Hycamtin |

[28]

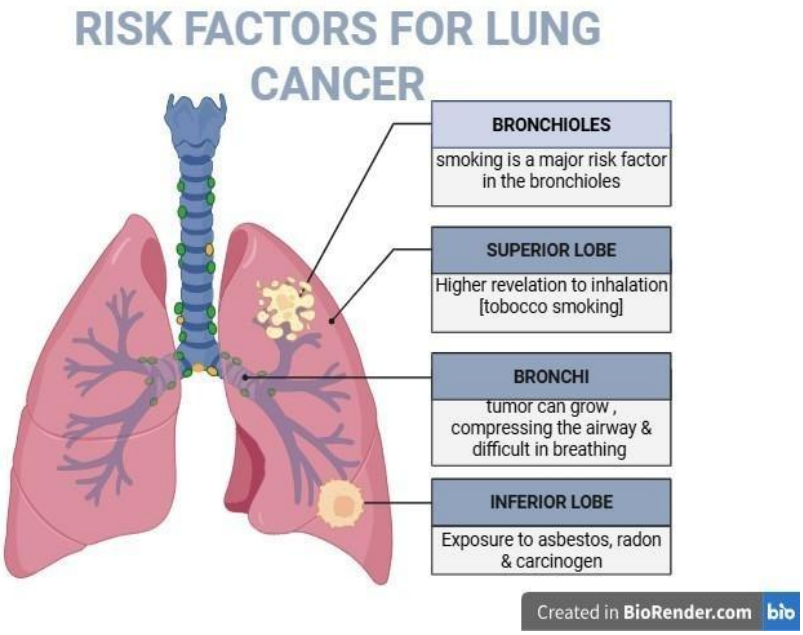

**Figure 3:** Anatomical distribution of major risk factors associated with lung cancer across different lung regions.

**Table 3:Correlation between anatomical lung regions, predominant histological subtypes of lung cancer, and recently used therapeutic agents.**

| **LUNG REGION** | ***COMMON TYPES*** | ***RECENTLY USED DRUGS*** |
|---|---|---|
| Bronchi | Squamous NSCLC | Durvalumab, Amivantamab |
| Bronchioles | Adenocarcinoma | Osimertinib, Sotarasib |
| Superior lobe | Smoking related NSCLC | Nivolumab, ADCs |
| Inferior lobe | Environmental exposure | Bevacizumab, Pembrolizumab. |

[28]

**CHALLENGES FACED BY CANCER THERAPY:**

Thousands of studies suggested that Nanomedicine can treat several cancers. However, only a limited number of nanocarrier-mediated anticancer formulation have progressed to clinical evaluation. Therefore, it is important to overcome the existing barriers in order to design and develop optimized nanomedicine systems suitable for successful clinical application . Thus, it is very significant to address the challenge in developing optimised nanomedicine products for clinical use. However, designing effective cancer therapies using nanoparticles remains a major challenge, and only a few nano formulations have entered clinical trials. Nanoparticles can be engineered to selectively target tumour cells by reducing the harm to healthy cells and tissues. Despite the potential benefits, several challenges are addressed[31]. Since its initial identification, it has been recognized that macromolecules preferentially accumulate within tumor tissues owing to the presence of fenestrated endothelial vasculature. This phenomenon, widely regarded as a fundamental gateway

for targeted drug delivery, has enabled the experimental and clinical approval of numerous nano anti cancer formulation. These nanotechnology-based drug delivery systems generally exhibit prolonged systemic circulation and preferential tumor localization compared to normal tissues, thereby reducing off-target distribution and associated adverse effects. . These NDDs usually have prolonged systemic circulation and accumulate less in normal organs than in tumour tissue [32], which reduces side effects. When using nanoparticles to target the tumor cells, the primary challenge includes biological barriers[33], tumor microenvironment and nanoparticle property and major challenges include poor penetration in to the tumor due to the dense extra cellular matrix (ECM), rapid clearance by the immune system, difficulty in achieving specific targeting the tumor cells, potential systemic toxicity and the complex tumor microenvironment which can hinder NDDs and distribution.[34]

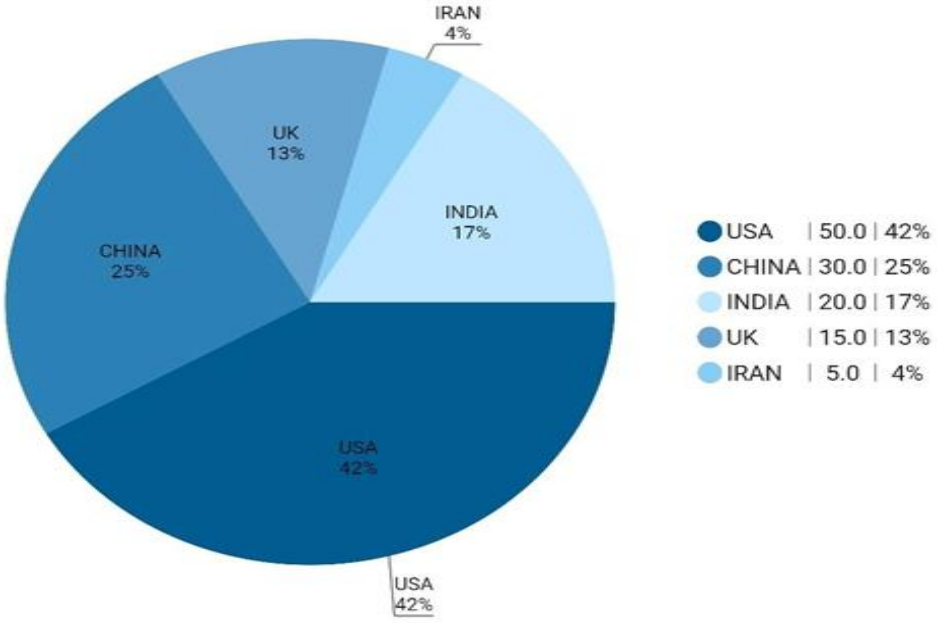


**FIGURE 4: This figure illustrates the global distribution of research contributions in nanotechnology for cancer oncology across countries. This distribution highlights the dominant role of developed and emerging economies in advancing research and innovation in this area.**

In the course of recent decades, the field of nanocomposite-based drug delivery systems has experienced major progress. Current research efforts are directed towards the development of safe, efficacious, and clinically translatable nanomedicine that enables highly sensitive diagnostic imaging and improves therapeutic outcomes [35]. Describe this advancement and technology-driven approach that continues to encounter significant challenges in the translation of nanoparticles into clinically approved nanomedicine. Diverse nanoparticles have shown significant therapeutic promise in both preclinical and clinical settings. Despite this progress, a key challenge in nanomedicine is translating rapidly emerging innovations into practical clinical applications. [36]Effective drug delivery to the lung using nanotechnology is essential for these delivery systems to overcome several challenges. These include avoiding antibodies, reducing clearance from circulation, improving target efficiency, and crossing biological barriers. Addressing this hurdle is critical for the successful clinical application of Nanoparticle-based therapeutics. Agents are being employed to treat lung cancer patients in the coming years [37]. Given that just 20% of patients experience long-term survival beyond five years, cancer is still linked to a poor prognosis or an undesirable outcome. Nonetheless, considerable advances have been achieved in understanding its molecular and genetic process, which has improved the accuracy of diagnosis and led to the development of comprehensive treatment plans that include radiotherapy, surgery, and targeted therapies such as immunotherapy, chemotherapy, and targeted agents. Overall survival outcomes have not significantly improved as a result of these advancements[38]. One popular kind of FDA-approved nanocarrier therapeutic intervention lung cancer is liposomes. They are composed of lipids, including polyethene glycol, cholesterol, and phospholipids, which come together to form a single-layer vesicle structure that can hold medicinal medications[39]. Because of their design, drugs can be delivered more effectively, cause less harm, and target cancer cells more precisely. The nanoparticles used in lung cancer are gold nanoparticles, silica nanoparticles, liposomes, dendrimers, carbon nanotubes, quantum dots, and lipid-based nanoparticles (bio-Nanoparticle). Technologies used for lung cancer are surgical therapy, chemotherapy, and targeted

treatment therapy. These lipids on a particle are used in lung cancer treatment for drug delivery and diagnosis [40].

**Targeted Nanocarrier Systems for Enhanced Anticancer Drug Delivery**

The use of moietied targeting — for examples are ligands, nucleic acids, peptides, or small molecules—has developed a highly effective process for improving the selective delivery of anticancer agents[41]. These targeting components are designed to recognize and associate specifically to enhanced receptor expression or antigens present on the membrane of cancer cells. By attaching these moieties to therapeutic compounds, drug delivery systems can achieve greater specificity, minimizing toxicity to healthy tissues while enhancing the therapeutic efficacy against malignant cells. To facilitate this targeted delivery, a variety of nanocarriers have been extensively explored. These include **liposomes, gold nanoparticles, carbon nanotubes, quantum dots, polymeric nanoparticles**, and **dendrimers**. Each of these nanocarriers can serve multiple roles as drug delivery vehicles tools for **diagnostics and visualization**, thereby integrating treatment and monitoring into a common platform, a concept termed as therapeutic diagnostics[5]. The performance of nanocarrier-based drug delivery systems is governed by several critical parameters, including drug loading efficiency, physiological stability, circulation time, targeting specificity, and encapsulation efficiency. Drug loading efficiency determines the amount of therapeutic agent that can be incorporated within the nanocarrier, directly influencing dosing capacity and therapeutic outcome. Physiological stability ensures that the carrier maintains its structural integrity during systemic circulation until it reaches the target site. Persistence in the blood stream, affects the duration of drug availability and tumor accumulation, particularly through mode of action they had enhanced permeability and retention (EPR) effect. Targeting specificity enhances selective binding to cancer cells, prevent the non specific binding, toxicity to healthy tissues. Encapsulation efficiency reflects the effectiveness of drug entrapment within the nanocarrier system, contributing to controlled and sustained release. Optimisation of these interconnected parameters is essential to enhance therapeutic efficacy, improve safety profiles,

and advance the clinical translation of nanocarrier-based cancer treatments.[42]

## CONCLUSION

Nanoparticulate drug delivery systems (NDDS) represent a remarkable advancement in the diagnosis of lung cancer by resolving the insufficient association with standard treatment such as chemotherapy, radiotherapy, and systemic drug administration. Various nanocarriers, including polymeric nanoparticles, liposomes, dendrimers, solid lipid nanoparticles, inorganic nanoparticles, and metal-based systems, have demonstrated improved drug solubility, enhanced permeability and retention (EPR)-based tumor accumulation, controlled and sustained release, and reduced systemic toxicity. Surface modification strategies such as PEGylation and ligand-based site specific targeting further elevate circulation time and tumor specificity. Despite encouraging preclinical findings and the availability of several FDA-approved nano formulations, the clinical translation of nanoparticle-based therapies remains limited due to biological barriers, the complexity of the tumor microenvironment, immune clearance, potential toxicity, manufacturing challenges, regulatory constraints, and high production costs. Future research should focus on stimuli-responsive systems, inhalable nanoformulations for localised pulmonary delivery, hybrid nanoplatforms, and Theranostics integration to facilitate the translation of laboratory research into the clinical use. innovation and clinical application. With on going progress nano technology and precision targeting strategies, NDDS hold substantial promise for improving therapeutic efficacy, minimising adverse effects, and enhancing survival outcomes in lung cancer management.

## ABBREVIATIONS

NDDS – Nano Drug Delivery System

NPs – Nanoparticles

NSCLC – Non-Small Cell Lung Cancer

SCLC – Small Cell Lung Cancer

EPR – Enhanced Permeability and Retention

FDA – Food and Drug Administration

PLA – Polylactic Acid

PLGA – Poly (lactic-co-glycolic acid)

PEG – Polyethene Glycol

PEI – Polyethyleneimine

SLNs – Solid Lipid Nanoparticles

PAMAM – Poly (amidoamine)

PPI – Polypropylene Imine

siRNA – Small Interfering RNA

DNA – Deoxyribonucleic Acid

RNA – Ribonucleic Acid

RES – Reticuloendothelial System

ECM – Extracellular Matrix

BBB – Blood–Brain Barrier

MRI – Magnetic Resonance Imaging

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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