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Pulmonary Nano-Drug Delivery Systems for Lung Cancer

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ABSTRACT

Pulmonary route of drug delivery gaining much importance in the present day research field as it enables to target of the drug delivery directly to lung both for site-specific and systemic treatment. Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide. Yet the disease is almost entirely preventable with tobacco smoke exposure consistently recognized as causative in the majority of cases. Pulmonary drug delivery of lung cancer therapy has been only partly explored decades even though it could represent an alternative route of administration of drug-based therapies, including chemotherapy among the benefit it can enhance the therapeutic ratio significantly by decreasing severe systemic toxicities and increasing anticancer therapies. Nanoparticles, although considered a topic of modern medicine, actually have an interesting history. Currently, advances in nanomedicine hold great promise as drug carrier systems for sustained release and targeted delivery of diverse therapeutic agents. Nanocarrier systems provide the advantage of sustained-drug release in the lung tissue resulting in reduced dosing frequency and improved patient compliance.

INTRODUCTION:

The delivery of the drug through the respiratory tract is called pulmonary drug delivery. In the case of broncho-dilating drugs, this is advantageous as a drug will deliver directly to the region where its action is required so that the drug effect will be faster and a low dose of the drug can be administered through this delivery system and so the side effects can be decreased[{1}].

A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states. The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases using drugs such as short and long-acting β sympathomimetics, corticosteroids, and anticholinergic agents[{2}]. Drugs like sodium carmoglicate are absorbed to less extent when given orally And some other drugs like isoprenaline are metabolized in the liver. These types of drugs can be administered through pulmonary route[{1}]. Over the decade certain drugs have been sold in compositions suitable for forming drug dispersion for pulmonary delivery to treat various conditions in humans. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient of a drug dispersion so that the active drug within the dispersion can reach the lung. It has been found that certain drugs within the dispersion can reach the lung. it has been found that certain drugs given by the pulmonary route are readily absorbed through the alveolar region directly into blood circulation [{3}] for the treatment of lung cancer. Recent advances in nanotechnology open a door for enhancing the efficacy of inhalation treatment of lung cancer. The application of nanotechnology to the design of drug delivery systems for effective delivery of therapeutics specifically to tissues and cells affected by the disease allows for enhanced treatment outcomes and prevention of severe adverse side effects upon tissues and cells, including those in the lungs, as well as entire organs. This review also focused on the pulmonary nano-drug delivery system for lung cancer.

ANATOMY OF LUNGS

Lungs are responsible for the gas exchange and supply of oxygen to all the cells. The lungs consist of a total of five lobes, the right lung consisting of three, and the left lung of two lobes. The large surface area of the human lung, along with its rich blood supply, rapid onset of drug action with high bioavailability, and other physiological advantages, make it a potential route for treating asthma, COPD, lung cancer, and other pulmonary disorders. The

human lung consists of 5 lobules and 10 bronchopulmonary segments. Arranged adjacent to each segment are lung lobules composed of 3–5 terminal bronchioles. Each bronchiole supplies the smallest structural unit of the lung, the acinus, which consists of alveolar ducts, alveolar sacs, and alveoli. The alveolar wall is made up of two types of alveolar epithelial cells, namely (pneumonocytes) Type I and Type II. Between the capillaries and the alveolar epithelium, there exists a single endothelial layer. The distance between the alveoli and capillaries is so small, about 0.5 µm, that owing to this extreme thinness of the blood-gas interface, gas exchange is facilitated by diffusion at the interface. The alveoli are coated with a layer of alveolar fluids and mucus, which is majorly composed of phospholipids and surface proteins. This phospholipid surfactant layer at the alveoli reduces the surface tension and is essential for the proper functioning of the gas exchange. These distal respiratory passages are supported by a thin layer of connective tissue. This layer is surrounded by different cells, like macrophages, fibroblasts, nerves, as well as lymph vessels. While this morphologic arrangement readily facilitates the exchange, it can still represent a major barrier to large molecules [2,4,20].

PULMONARY NANO-DRUG DELIVERY SYSTEMS FOR LUNG CANCER

Lung cancer is the most commonly diagnosed cancer (11.6% of all the cases), and the leading cause for cancer deaths (18.4% of all cancer deaths) among both men and women worldwide. Lung cancer is a heterogeneous disease that arises when genetic and epigenetic alterations happen in lung epithelium. Most lung tumors are the result of frequent exposure to tobacco smoke. However, exposure to exogenous carcinogens, such as diesel exhaust, radon, household fumes, and radiation in domestic and occupational environments, has been estimated to cause 10 – 25% of lung cancers in non-smokers. Based on clinical and therapeutic characteristics, lung cancer is broadly divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is further divided into squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large cell carcinoma (LCC). SCLC usually found peripheral on the main bronchus while SCC initiated on main stem lobar or segmental bronchi. ADC and LCC emerge on peripheral lung tissues. These NSCLC forms are histologically distinct from each other. It is responsive to the chemotherapy; however, their response differs against a specific therapy. On the other hand, SCLC rarely occurs but shows fast metastasis and aggressive growth, with an average survival of merely 4 months if not treated. Pathophysiology of SCLC indicates that it commences from neuroendocrine tumors,

and therefore it contains neurosecretory vesicles and neurofilaments. While SCLC is very aggressive, its treatment by radiation and chemotherapy has better responsiveness than NSCLC[5,6].

Surgery, chemotherapy, and radiation are standard treatment options for lung cancer depending on the stage of malignancy, resectability, and overall performance. Chemotherapy is the first-line treatment for the advanced stage of lung cancer in which chemotherapeutic drugs are usually administered intravenously for systemic circulation. The use of the chemotherapeutic drug is based on the principle of toxic compounds to inhibit the proliferation of cells growing at an abnormal rate. A combination of gemcitabine (FDA approved chemotherapeutic agent) with cisplatin has been widely used for first or second-line treatments of patients with advanced or metastatic lung cancer. Also, common chemotherapeutic drugs such as paclitaxel, docetaxel and gemcitabine, and vinorelbine are widely used in combination with platinum-based drugs (i.e. cisplatin) improve therapeutic index. However, it should be noted that the majority of chemotherapy drugs are associated with side effects such as pain, nerve damage, and skin allergic reactions. Therefore, minimizing the side effects of chemotherapy drugs remains a challenge in the field of cancer chemotherapy[7].

Treatment complexities and the cytotoxicity of anticancer drugs to normal cells often results in therapeutic failure. Considering the challenges associated with conventional chemotherapy, targeted and local delivery of chemotherapeutics via nanoparticle (NP) carriers to the lungs is an emerging area of interest. Recent studies and growing clinical application in cancer nanotechnology showed the huge potential of NPs as drug carriers in cancer therapy, including in lung carcinoma for diagnosis, imaging, and theranostics. Researchers have confirmed that nanotechnology-based inhalation chemotherapy is viable and more effective[5,6]. nanocarriers have been investigated, including liposomes, polymeric micelles, polymeric NPs, solid lipid NPs, and inorganic NPs for inhalation treatments of lung cancer. Yet, the toxicity of such nanomaterials to the lungs tissues and further distribution to other organs due to systemic absorption on inhalation delivery is a debatable concern. The major advantages of nanoparticle-mediated drug delivery to the lung are attributed to the unique pharmacokinetic and pharmacodynamic properties of the system. Nanoparticles are particulate drug carrier systems that incorporate a certain drug to coat, protect, and increase its function.

Table No. 1: Current lung cancer therapeutics, their mechanism of action and common side effects[5]

Drug	FDA approval	Mechanism of action in lung cancer	Side effects
Adenocarcinoma			
Cisplatin	1978	Induction of oxidative stress Formation of DNA adducts Induction of apoptosis	Nephrotoxicity Ototoxicity Neurotoxicity
Carboplatin	1989	Formation of interstrand and intrastrand DNA cross-links Inhibition of DNA synthesis	Anemia Neutropenia Thrombocytopenia
Crizotinib	2011	Inhibition of ALK, hepatocyte growth factor receptor Inhibition of ROS1 Suppression of growth Induction of apoptosis	Pneumonitis Bradycardia Vision disorders
Atezolizumab	2016	Inhibition of the interaction between PD-L1 and PD-1 receptor Induction of T-cell antitumor activity	Fatigue Diarrhea Nausea
Bevacizumab	2006	Fusion with VEGF Inhibition of VEGF activity Prevention of endothelial cell proliferation Suppression of angiogenesis	Hypertension Wound healing complications
Ceritinib	2006	Inhibition of autophosphorylation of ALK, insulin-like growth factor 1 receptor and ROS1	Abdominal pain Diarrhea Hyperglycemia
Squamous cell carcinoma			
Paclitaxel	2012	Fusion with β-tubulin Stabilization of microtubules Inhibition of cell cycle at mitotic phase	Neutropenia, Nausea and vomiting Arthralgia
Methotrexate	2014	Inhibition of the synthesis of purine nucleotides Suppression of DNA synthesis Inhibition of cell proliferation	Hepatotoxicity Osteonecrosis Soft tissue necrosis

Nanoparticle drug delivery of lung cancer therapy

Nanoparticles have attracted attention to nano biomedical technology because of the presence of smaller size which has a huge amount of energy and allows the particle to adsorb and carry the hydrophilic and hydrophobic macromolecules to the target site. Nanoparticles are structured size ranging from 1 to 100 nm[9]. The major clinical advantage of nanocarrier-based strategies over free drugs is the specific delivery of large amounts of chemotherapeutic agents by favorably altering their pharmacokinetic properties, resulting in increased tumor localization, improved antitumor effects, and decreased nonspecific toxicities[17,16]. Both the hydrophobic as well hydrophilic drug can be encapsulated in nanostructures which offer the controlled release of the drug. The nanocarrier strategy is used for its accurate targeting

which is highly important in targeted chemotherapy. Two important mechanisms are followed for site-specific targeting i.e., active and passive mechanisms. Nanoparticles offer several advantages of include:

(a) Specific targeted drug delivery,

(b) improves stability and eradicates toxicity,

(c) both active and passive drug targeting can be achieved by reducing the size

(d) controlled release drug delivery,

(e) Better image and diagnostic tool for the earlier detection of cancer cells in the biological system.

(f) Less amount of dosage form is required,

(g) More rapid onset of therapeutic action.

There are three types of nanoparticles have been used in the treatment of Lung cancer (a). Natural and semi-synthetic nanoparticles, (b). Synthetic (organic) Nanoparticles, (c). Synthetic (In-Organic) Nanoparticle.

Natural and semi-synthetic nanoparticles

- **Liposomes**

Liposomes are an attractive drug delivery system, especially for pulmonary applications, as it is prepared primarily from phospholipids, which are inherent in the lungs. They are prepared using lung surfactants, phospholipids, cholesterol, etc. Liposomes possess sustained-release properties, which enable the maximum drug effect over a prolonged period [{20}]. The liposomes are First described in 1965, liposomes are one of the first nanoparticle platforms to be applied in medicine. Today, there are more than 11 formulations that are approved for clinical use, with many more in clinical and preclinical development[{21}]. A typical liposome consists of a single bilayer lipid membrane (unilamellar liposomes) or several bilayer lipid membranes (multilamellar liposomes). The outer surface of liposomes is often modified by polymer (mainly poly (ethylene glycol), PEG). Such coating performs several functions. It adds STEALTH properties to the liposomes and allows for conjugating additional

components of the delivery system (e.g. targeting moiety) to the distal end of the polymer [22]. So Liposomes possess sustained-release properties, which enable the maximum drug effect over a prolonged period. Currently, two liposomal products in the last stage of clinical development are dry powder liposomes, Arikace® (amikacin, Insmed, Monmouth Junction, NJ, USA), and Pulmaquin (ciprofloxacin, Aradigm Corp., Hayward, CA, USA), for the treatment of lung infections[20].

- **Solid lipid nanocarrier**

Solid lipid nano-carriers are composed of solid lipids, surfactants, and water. carriers, as shown in different studies: *in-vitro*, *ex-vivo*, and *in-vivo*. Their main use is represented by lung cancer treatment and TB (tuberculosis) vaccine delivery. Recently, solid lipid nanoparticles (SLNs) have gained huge notice for the delivery of drugs, particularly poorly water-soluble drug candidates. They offer improved properties by combining the benefits of liposomes, NPs, and nanoemulsions. They are usually prepared by high-pressure homogenization or micro emulsification technique, where the drug is efficiently entrapped in a lipid matrix. Solid lipid nano-carriers represent a multifunctional strategy in which a single molecule allows detection, diagnosis, imaging, cell destruction, and delivery of drugs, decreasing drug-related side effects. SLNs overcome the general limitations of polymeric systems by exhibiting low toxicity due to the presence of biodegradable lipids. The inhalational treatment of paclitaxel-loaded SLNs was more efficient in reducing the number and size of lung metastases in comparison to iv delivery of the same drug. The SLN is quite more stable than liposomes in a biological system. Considering the dimensions in the nanometre range of the SLN said to be a zero-dimensional nanomaterial. The SLN is used as the colloidal carrier of hydrophobic chemotherapeutic for the long circulation of the bloodstream. Cationic SLN is amphiphilic nature where the presence of two hydrophobic fatty acid chains and hydrophobic amino groups with the linker[2,8,9].

- **Chitosan**

Chitosan is a natural, polysaccharide-based cationic polymer derived from chitin. It is widely used in many biomedical applications because of its biocompatibility and biodegradability and can be easily modified with targeting ligands[14]. They are approved by the US FDA and EMA for tissue engineering, drug delivery, and also gene delivery. Mumper et al first reported the use of chitosan for in vitro gene delivery [15]. Chitosan is one of the best

candidates for nucleic acid delivery because of its amine groups with a positive surface charge. Protonation of the chitosan amine groups occurs at a pH below its p*K*a value of 6.6. This strong pronation of amines enhances the electrostatic interaction between chitosan and nucleic acids to form complexes of nanoscale dimensions [14]. The excellent biocompatible and biodegradable nature of chitosan makes it useful in various drug delivery applications. The structure of chitosan is highly favorable for effortless functionalization with its primary hydroxyl and amino groups that also improve the physical and biological properties of chitosan during the conjugation process. The hydrophilic nature of chitosan aids an easy conjugation of a hydrophobic moiety which in turn leads to the formation of self-assembled nanoparticles that are useful for targeted drug delivery applications [16]. The unique characteristic of chitosan is non-toxic, renewable, high affinity to proteins, modification of cell wall permeability.

Dendrimers

Dendrimers (also known as dendritic polymers) are nanoparticles that resemble a series of tree-like branches surrounding a central core an inner dendritic constitution of extremely branched polymers, and an exterior of multivalent functional groups (figure 1). The multi-factional surface shell and hyper-branching tree-like interior with cavities facilitate conjugation or encapsulation of drug molecules. The functional group on their surface gets incorporated with charged polar compounds by electrostatic interaction, whereas the uncharged, nonpolar compounds get embedded in the hydrophobic interior[5,6]. A recent study illustrated the use of dendrimer-targeting peptide conjugates as a carrier for drugs towards NSCLC. These dendrimer-peptide conjugates when administered to a lung tumor-bearing athymic mouse model were efficiently taken up by the cancer cells demonstrating their potential as a drug carrier for the treatment of lung cancer. For instance, doxorubicin was conjugated to a 56 kDa PEGylated poly-lysine dendrimer and studied for anticancer efficacy. In a related study, a newly designed PEGylated dendrimer nanoparticle showed promising application as an aerosol-inhaled drug delivery modality. The smaller dendrimer particles are reported to enter the bloodstream via inhalation while larger particles are sequestered in the lung for an extended period of time[10,11].

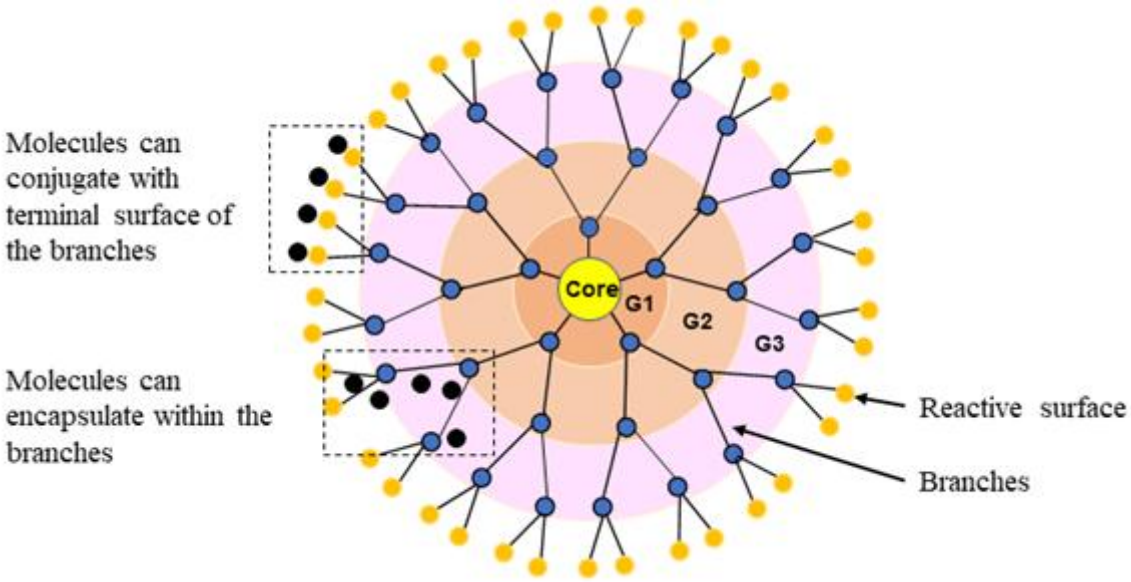

Figure No. 1: Dendrimer architecture. Dendritic nanoparticles are composed of three different sections; core, at the center, interior, branched cell amplification region, and surface, terminal reactive groups. Branches are attached to the core as shells and nomenclature as generations (G1, G2, G3, etc.) that build by repeating a series of chemical reactions. The spherical branching structure or the number of layers of a dendrimer can expand up to the desired size (macromolecular structure).

Organic nanoparticles

- **Polymeric Nanoparticles**

Polymeric NPs are extensively explored nowadays for their remarkable potential as a drug delivery system for anticancer compounds. They are prepared either by encapsulation, dissolution, and entrapment of drugs in biodegradable polymers or by embedding drugs in polymeric matrix[6]. Polymeric nanoparticles are composed of biodegradable or biocompatible materials such as polylactic acid, alginic acid, gelatin, and chitosan, which results in prolonged drug release. They are currently used in several chronic pulmonary diseases such as asthma, tuberculosis (TB), and pulmonary hypertension[8]. Polymers are gaining rapid importance for pulmonary drug delivery. Several polymers have been investigated for pulmonary application. Polymers have numerous advantages, like modified surface properties, high encapsulation of the drug and protection of the drug from degradation, prolonged drug delivery, and a long shelf life[12]. More recently, biodegradable

polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic) acid (PLGA), gelatin, albumin, chitosan, polycaprolactone and poly-alkyl-cyanoacrylates have gained popularity in use because of their controlled and sustained release properties, subcellular size, and biocompatibility. For instance, Abraxane, an FDA-approved albumin-based nanoparticle carrying paclitaxel, is indicated for first-line treatment of locally advanced or metastatic NSCLC in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy{13}. The main disadvantage is Owing to the lack of enzymes to break down polymeric materials, the toxicity remains an issue.

- **Polymeric micelles**

The polymeric micelles represent a potential nanocarrier for the efficient delivery of anticancer agents. A polymeric micelle is principally formed when the hydrophobic part of the block copolymer is driven to the interior, which can encapsulate a poorly soluble drug, whereas the hydrophilic portion of the block copolymer faces outward to form the shell{14} (figure 2).

They are prepared by dissolving individual polymeric chains in the aqueous solution above a threshold concentration (critical micelle concentration; the concentration of surfactant in water which initiates the formation of micelles) and solution temperature (critical micelle temperature; the lowest temperature, at which surfactants form micelles in water). Most micelles are made up of amphiphilic polymers such as polyethylene glycol (PEG) and polyethylene oxide (PEO), which are FDA-approved excipients{5}. Gill et al produced polyethylene glycol (PEG) 5000–di-stearoyl phosphatidylethanolamine (PEG_{5000}–DSPE) micelles bearing paclitaxel through solvent evaporation technique{15}. Their observations showed that the PEG_{5000}–DSPE micelles administered intratracheally were capable of maintaining maximum paclitaxel concentrations in the lungs for a long duration{14,16}. Intratracheal-delivered polymeric micelles containing paclitaxel exhibited the highest aggregation of paclitaxel in the lungs, with $AUC_{0–12}$ (area under the plasma concentration-time curve from 0 to 12 hours) in lungs 45 times greater than iv-administered formulation and 3 times greater than intratracheally administered taxol. The concentration of paclitaxel in other tissues and plasma was found to be considerably low{14,16}.they also found that altered pharmacokinetics of paclitaxel through encapsulation in PEG‑lipid micelles decreases the

exposure of paclitaxel to non-targeted organs. Thus, it can be concluded that PEG5000-DSPE micelles are suitable as pulmonary drug carriers[16].

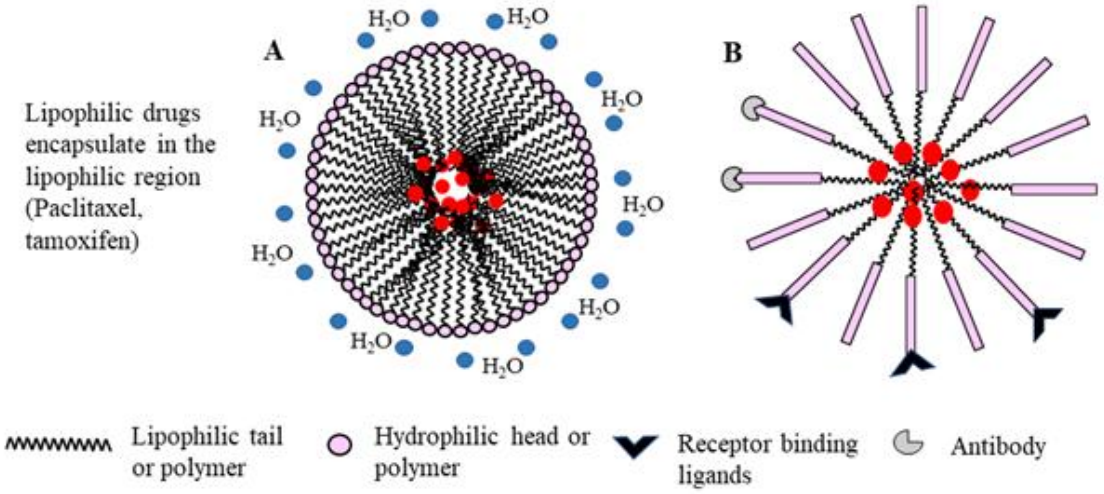

Figure No. 2: Schematic representation of micelle formation by amphiphilic surfactants (A) or copolymers (B). In aqueous systems, micelles are formed spontaneously by orienting the hydrophobic tailor polymer away from water molecules, while the hydrophilic head or polymer interact with polar water molecules, resulting in a spherical molecule. Conjugation of receptor binding ligands or antibody targets on the micelle shell enhances targeted drug delivery. Alternatively, modification by PEGylation enhances the micelle longevity *in-vivo*.

Inorganic nanoparticles

Inorganic nanoparticles exhibit different material properties and hence have many potential applications. The optical and magnetic properties of inorganic nanoparticles have paved the way for their usage in cancer therapies. They also exhibit features such as fluorescence, near-infrared (NIR) absorption, and Raman enhancement making them extremely useful in image-guided therapies. Nanoparticles made of Au or Ag conjugated with polyethyleneimine (PEI) have also been used to deliver genes. Functionalization of Au NPs with PEG and coumarin were found to efficient incorporation capacity into breast cancer cells without any observed toxicity to other normal cells. A major limitation of using inorganic nanoparticles is that their long-term toxicity and clearance have not been evaluated sufficiently.

- **Magnetic nanoparticles (MNPs)**

The magnetic NPs (MNPs) are prepared by either entrapping drug into magnetic micro/nanosphere or embedding as a magnetically-active disc and they are distinctively different from other typical nanoparticles due to their unique magnetic property. In magnetic targeting, the liberation of the drug in blood circulation is controlled by applying a strong magnetic field. Different magnetic materials with a variety of magnetic properties are available, such as magnetite, iron, nickel, cobalt, neodymium-iron-boron, and samarium-cobalt. Furthermore, some liquids can also be strongly magnetized in a magnetic field known as ferrofluids. Ferrofluids are principally colloidal suspensions of nano dimension ferromagnetic particles. Currently, commonly used MNPs are made of iron oxide due to its biodegradability, biocompatibility, superparamagnetic effects, and capability to act as a contrast agent in magnetic resonance imaging[15,6].the (Fe_3O_4) NPs used for the localized hyperthermia-induced cancer cells, killing, diagnosis, and targeted delivery of chemotherapeutics to the cancer region under the influence of magnetic field[18]. Verma et al produced magnetic core-shell NPs by a surface coating of Fe_3O_4 MNPs, with a polymer PLGA intended for nebulized drug delivery for the treatment of lung cancer[19]. As of now, chemotherapy, radiotherapy, and medical procedures are considered the three clinically accessible treatments in tumor management. The main drawbacks of these treatments are the side effects as they are not specific. As an alternative to this, thermotherapy is being used to kill a tumor cell with principles based on the higher the-sensitive nature of cancer cells than normal cells.

CONCLUSION:

Lung cancer is the leading malignancy worldwide, accounting for more than one million cases diagnosed annually. The treatment of lung cancer continues to be very challenging for oncologists. Currently, the field of "Lung cancer nanotechnology" is under intense development for applications in lung cancer imaging, molecular diagnosis, and therapy. The basic rationale is that nanomaterials(such as liposomes, micelles, SLNS, magnetic and metal-based nanocarriers, dendrimers) have novel functional and structural properties that are not encountered at either molecular or macroscopic levels. Pulmonary drug delivery for lung cancer treatment is also becoming more and more important. This is basically due to the specific physiological environment of the lungs as an absorption and treatment organ. Numerous exciting achievements in the field of oncology based on nanotechnology await us

shortly. We expect that in the future, different nanotechnology-based drug carriers would serve as "Trojan horses" in the field of lung cancer diagnostics and its treatment.

CONFLICT OF INTESREST:

The authors confirm that this article content has no conflict of interest.

REFERENCES:

1. Dr. Satheesh Madhav NV, Girish Dwivedi. Pulmonary drug delivery; a review Pharmatutor –art -1700
2. Shah ND, Shah VV, Chivate N. Pulmonary Drug Delivery: A Promising Approach. JAPS 2012;02 (06):33-37
3. Siraj Shaikh, Sayyed Nazimi, Tarique Khan, Afsar Shaikh, Mohammad Zameeruddin. Recent advances in pulmonary drug delivery system: a review. IJAP 2010;02(04)
4. Mohammed Ali in handbook of non-invasive drug delivery system. Science direct. Pulmonary Drug Delivery System.2010;209-246
5. Madumani Amararathna, Kerry Goralski, David W. Hoskin, H. P. Vasantha Rupasinghe Pulmonary Nano-Drug Delivery Systems for Lung Cancer: Current Knowledge and Prospects, Journal of Lung Health and Disease.
6. Ahmad J, Akhter S, Rizwanullah M, Amin S, Rahman M, Zaki Ahmad M, Rizvi MA, Kamal MA, Ahmad FJ: Nanotechnology-based inhalation treatments for lung cancer: state of the art. PMC.2015; 8: 55—66
7. Wing-hinleeching-Yeeloo Daniela Trainipaul M. Young. Inhalation of nanoparticle-based drug review. AJPS.2015;10(06)
8. Teodora G. Alexescu1, Simina Tarmure, Vasile Negrean, Maria Cosnarovici, Victoria M. Ruta, Ionela Popovici1, Ioana Para, Mirela G. Perne1, Olga H. Orasan1, Doina A. Todea. A Review Nanoparticles in the treatment of chronic lung diseases. JMMS.2019;6(2):224-231
9. Raahulan Sivarajakumar, Dhamini Mallukaraj, Madhurya Kadavakollu, Niveditha Neelakandan, Sandhya Chandran, Saravanan Bhojaraj, Veera Venkata Satyanarayana Reddy Karri, Nanoparticles for the Treatment of Lung Cancers: J Young Pharm. 2018;10(3): 276-281
10. Anish Babu, Amanda K. Templeton, Anupama Munshi, Rajagopal Ramesh. Nanoparticle-Based Drug Delivery for Therapy of Lung Cancer: Progress and Challenges Journal of Nanomaterial.2013;11
11. Andriy Kuzmov, Tamara Minko. Nanotechnology approaches for inhalation treatment of lung diseases Journal of Controlled Release. Science direct.2015;219:500-518
12. Mukta Paranjpe and Christel C. Müller-Goymann. Nanoparticle-Mediated Pulmonary Drug Delivery: A Review.PMC.2014;15(4):5852-5873
13. A. Z. Wang, K. Yuet, L. Zhang et al. Chemo Rad nanoparticles: a novel multifunctional nanoparticle platform for targeted delivery of concurrent chemoradiation, *Nanomedicine*.2010;5(3):361–368
14. Narsireddy Amreddy, Anish Babu, Ranganayaki Muralidharan, Anupama Munshi, Rajagopal Ramesh. Polymeric Nanoparticle-Mediated Gene Delivery for Lung Cancer Treatment.PMC.2017;375(2):5852-5873
15. Dhrisya Chenthamara, Sadhasivam Subramaniam. Therapeutic efficacy of nanoparticles and routes of administration. PMC. 2019;23:20
16. Patel MP, Patel RR, Patel JK. Chitosan mediated targeted drug delivery system: a review. J Pharm Pharm. NIH.2010;13(4):536-57
17. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discovery.NIH.2005;4(2):145-60
18. Akhter S, Ahmad Z, Singh M, et al. Cancer targeted metallic nanoparticle: targeting overview, recent advancement and toxicity concern.NIH.2011;17(18):1834-50
19. Verma NK, Staunton KC, Satti A, Magnetic core-shell nanoparticles for drug delivery by nebulization. J Nanobiotechnology.NIH.2013;11:1

20. Mukta Paranjpe, Christel C. Müller-Goymann. Nanoparticle-Mediated Pulmonary Drug Delivery: Review. Int J Mol Sci.PMC.2014;15(4):5852-5873
21. Ankita Dadwal, Ashish Baldi, Rajkumar Narang. Nanoparticles as carrier for drug delivery in cancer.Artificial cells, Nanomedicine and biotechnology An international journal.2018;46:295-305
22. Andriy Kuzmov, Tamara Mink. Nanotechnology Approaches for Inhalation Treatment of Lung Diseases. Journal of Controlled Release. 2015;219:500-518