International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 4, 2025

Review Article

APPLICATION OF INHALATION THERAPEUTICS FOR LUNG CANCER TREATMENT: AN UPDATED REVIEW

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Received: 16 Apr 2024, Revised and Accepted: 23 Apr 2025

ABSTRACT

Non-communicable Disease (NCDs) are the cause of around 71% of the total deaths globally. Lung cancer is one of the most common and serious malignancies throughout the world. According to the World Health Organization (WHO), lung cancer accounts for 2.2 million new cases annually, representing 11.7% of all cancer cases and 1.8 million deaths, representing approximately one-fifth of all cancer deaths, significantly more than those of breast cancer. The inhalational route for the delivery of drugs has received much attention in recent decades. This route can potentially increase and maintain drug concentration at the site of action. Targeting the chemotherapeutic agent leads to a decrease in dose and further decreases the systemic side effects. The pulmonary route also aids in reducing the drug dose variability due to its passage through the gastric environment. In this study, we have discussed various chemotherapeutic agents that exhibited better results when administered as micro-nanoparticles through an inhalational route. However, the delivery of drugs through inhalation also faces some challenges. The article reviewed all the barriers to inhalational therapy and the strategies to overcome these barriers.

Keywords: Lung cancer, Inhalation, Barriers, Application

DOI: https://dx.doi.org/10.22159/ijap.2025v17i4.53291 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

In 2020, 1.3 million people were diagnosed with lung cancer. Exposure to poor lifestyle choices such as tobacco usage, exposure to harmful radiation and air pollution, increased intake of high-calorie foods, and reduced exercise in the growing population of the world has increased the burden of non-communicable diseases such as cancer. The globally increasing tobacco use accounts for a rise in lung cancer mortality all over the world, notably in Asia, as predicted by the World Health Organization (WHO) [1]. The incidence of lung cancer varies widely worldwide, with the highest rates observed in Western countries such as the United States, Canada, and Europe and lower rates observed in developing countries [2]. About half of the world's smokers live in Asia [3]. As per the GLOBOCAN 2018 report, lung cancer was ranked the fourth leading cause of cancer (5.9% cases) in India, in all ages and sexes. Furthermore, 63,475 of all cancer-related deaths (8.1%) were attributed to lung cancer (cumulative risk 0.60), making it the third leading cause of cancer-related mortality [4]. The International Agency for Research on Cancer predicts that by 2035, there will be over 1.7 million cases of cancer in India [5]. As per the Global Adult Tobacco Survey-2 [GATS]-2 in 2016–2017 [6], approximately 28.6% of the Indian population uses tobacco products accounting for an estimated 267 million tobacco users in the country. The National Tobacco Control Program [7] was launched by the Government of India from 2007 to 2008 to raise awareness of the deleterious effects of tobacco [8]. The data of cancer statistics of India for the year 2022 [9, 10] is summarized in table 1. The paper reviewed all the studies from the last 15 years on various chemotherapeutic agents that were administered as micro-nanoparticles through an inhalational route for lung cancer treatment. The keywords to search include lung cancer, inhalation, pulmonary route, microspheres, nanoparticles etc. The article is prepared using medical and research-focused articles from search engines like PubMed, Google Scholar, Science Direct, MedlinePlus, Bentham etc.

Table 1: Cancer statistics of India

Number of new cancer cases	1.4 million	References
Cancer deaths	850,000	[9, 10]
increase in cancer incidence by 2025 expected	12.8%	
Lung cancer mortality	81,800	
Lung cancer	82,737	
Males	72,510	
Females	39,000	

Lung cancer

Based on histopathology, two broad categories of lung cancer are (i) Small Cell Lung Cancer (SCLS)) and (ii)) Non-small cell lung cancer (NSCLC) accounts for 85 percent of all primary lung malignancies, whereas small cell lung cancer (SCLC) accounts for 15 percent [11]. Owing to its high proliferative and metastatic ability, SCLC is highly malignant, and its sensitivity to radiotherapy and chemotherapy is relatively good. NSCLC, on the other hand, is more common and is less sensitive to radiotherapy and chemotherapy [12]. Reduction in cell doubling time and critical progress of metastasis in connection with both systemic and lymphatic systems are the basic characteristics of SCLC. Among all the types of lung cancers, the highest malignancy is expressed in patients suffering from SCLC, resulting from the ability of SCLC to expand quickly and prematurely to other sites. Irrespective of exhibiting a good response to the anticancer drugs, there is always a chance of relapse which makes SCLC management cumbersome. Histologically, there is no relation found between SCLC and NSCLC and thus, both of them exhibit the effects of treatment strategies very differently [13]. Lung cancer is highly heterogeneous and can arise in many different sites in the bronchial tree, therefore presenting highly variable symptoms and signs depending on its anatomic location. 70%

of patients diagnosed with lung cancer are present with advanced-stage disease (stage III or IV). The degree of lung cancer patients in developing nations has grown from 31% to 49.9% over the past20 years [14]. Based on the anatomic location of the lung cancer, it can also be categorized as (i) Squamous Cell Lung Cancer(SQCLC) represent about 25%–30% of all lung cancers (ii) Adenocarcinomas (Adeno CA) account for approximately 40% of all lung cancers (iii) Bronchioalveola Cancer (BAC), now reclassified into Adenocarcinoma Insitu (AIS) and (iv) minimally invasive Adenocarcinoma(MIA) [15-17] Imaging methods such as chest radiography computed tomography following contrast material injection, and/or positron emission tomography employing Radiolabelled Fluorodeoxyglucose18F-FDG are commonly used to identify pulmonary malignancies. An overview of the type of lung cancer is given in table 2 [15-17].

Table 2: Lung cancer type

Lung cancer type	% Of all lung cancer	Anatomic location	References
Squamous cell lung cancer (SQCLC)	25-30 %	Arise in the main bronchi and advance to the carina.	[15-17]
Adenocarcinomas (AdenoCA)	40%	Arise in peripheral bronchi.	
Large cell anaplastic carcinomas LCAC)	10%	Tumourlack the classic glandular or squamous morphology.	
Small cell lung cancer (SCLC)	10-15%	Derive from the hormonal Cells Disseminate into submucosal lymphatic vessels and regional lymph nodes almost without a bronchial invasion.	

Inhaled chemotherapy

Inhaled cytotoxic chemotherapy is a viable treatment option for confined pulmonary malignancies [11, 18]. It has the advantage of accumulating the drug locally to treat lung cancer [19-21]. The delivery of chemotherapeutic agents to the tumour tissues locally instead of systemically by inhalation treatment can increase efficacy and reduce harmful effects on the system [22]. Additionally, inhalable therapy removes first-pass metabolism and improves patient comfort with treatment because it is non-invasive [23]. Systemic chemotherapy has been linked to side effects and disadvantages that are not directly connected to chemotherapy. For example, intravenous Paclitaxel (PTX) has been linked to hypersensitivity reactions and neurotoxicity due to a solubilising combination of Cremophor EL and dehydrated alcohol. Such toxicity is dose-limiting and may result in therapeutic failure [24]. Aerosol chemotherapy, as compared to systemic administration, has the potential to provide three major advantages for lung cancer therapy [25, 26]. First, for beginners, inhalation treatment for lung disorders has strong pharmacokinetic benefits. Inhalation permits large dosages of chemotherapy or targeted therapy to be delivered directly to the lung tumour site, reducing systemic distribution and toxicities. These benefits, when combined, considerably improve the therapeutic ratio [27, 28]. Second, because of the significant reduction in systemic toxicities, inhalation might lessen treatment pauses that are responsible for tumour cell repopulation [29]. Third, by keeping the anticancer drug's concentration gradient greatly enhanced medication in the lung tumour site, these inhalation techniques may promote drug penetration into the lung tumour [30]. Furthermore, pulmonary medication administration allows the medicine to target solid lung tumours via the local circulation [31]. The anticancer medication can enter the local circulation. Once it has been embedded into the respiratory system. Additionally, anticancer medications breathed might enter the lymphatic system, for example, in surgically removed lymph nodes. Among other things, lymphatic drainage eliminates tiny foreign particles (up to 500 nm in diameter) from the alveoli. This approval opens a new pharmacological avenue for inhaled nanomedicine in lung cancer. A colloidal nanoscale drug-delivery system made of pharmaceuticals and polymeric and/or lipid material that enhances the biokinetics and biodistribution of these medications is used to create nanocarriers [32]. Nanocarriers are nanosized formulations like liposomes, dendrimers, metal nanoparticles, polymeric nanoparticles, etc. and are widely used invarious diseases, especially cancer [33]. Nanomedicine has several advantages in cancer treatment, particularly in the pulmonary administration of anticancer medications [33-35]. Bioavailabilityhasbeen enhanced by nanocarriers [36]. The capacity to enhance local drug bioavailability, get past biological barriers (mucus, cell membranes, etc.), prolong pulmonary residence time (either prevent or minimise drug degradation), accumulate drug preferentially into tumours, enhance drug internalisation by cells, and selectively and specifically recognise cancer cells are some benefits of inhalation therapeutics [37, 38].

Barrier to inhaled chemotherapy

There are two basic reasons why medication delivery by inhalation is relatively complicated. First, defensive systems designed to keep inhaled compounds out of the lungs have developed in the respiratory tract. Once inhaled, they are either removed or rendered inactive. Secondly, a patient must utilize an inhaler device appropriately. Common issues include not following inhaled treatment regimens and misusing DPIs and pressurized metered dosage inhalers. Pulmonary medication delivery was generally ineffective until the second half of the 20th century, which can be partially explained by a lack of awareness of difficulties about both lung defence systems and inhaler usage. These days, the pulmonary route has several benefits over other routes for respiratory disease; thus, it is worth addressing the issues it presents. On the other hand, if these difficulties are effectively resolved, they provide enormous potential that frequently satisfy unfulfilled therapeutic demands. As previously stated, despite the obvious benefits as of now, there is no anticancer chemotherapy available for inhalation; only aerosol chemotherapy is available. The major observations can explain this. To begin, Lung toxicity is a side effect of 10–30% of standard chemotherapy treatments for lung cancer. Higher concentrations of these medications in the lungs, according to scientists and physicians, would result in greater pulmonary toxicities. As a result, the development of these medications for inhalation has been significantly hampered [39]. It is critical to choose a medication candidate that does not cause considerable lung damage. Second, the anticancer drug's residence duration near the lung tumour may be too brief to create efficient antitumor action. The particles are eliminated from the lungs quickly after being inhaled and deposited, the placement of the deposits in the respiratory tract varies based on their physicochemical characteristics and the respiratory condition. Either alveolar macrophages from the respiratory zone or mucociliary clearance from the conducting zone (80–90% of inhaled material expelled from the upper and central lung within 24 h) remove the particles from the conducting zone and move them towards the upper airways (optimal phagocytosis for 1.5-3 m particles or dissolved [40]. Third, nebulizers did not provide sufficient medication Dose Limiting Toxicity [DLT] in phase I clinical studies. This is due to their ineffectiveness in terms of lung deposition and their lengthy administration duration. Cisplatin had no systemic limiting toxicities at the maximum administered dose (60 mg/m^2) in phase I. This dosage was supplied throughout two cycles of three consecutive inhalation days (cycle interval of two weeks) in a total nebulization period of more than 6 h. Finally, another concern is the prevention of environmental contamination and the protection of medical personnel during the manufacture of this inhalation chemotherapy and its delivery to patients [41].

Mechanical barrier

The lungs are a complex network of branching airways known as the bronchial tree. If a particle is to enter the alveolated area to access the big epithelial target location, it must transit via several airway bifurcations where it may be deposited. The position is also critically dependent on inhalation parameters, particularly inhaled flow rate, inhaled volume, and breath-hold interval. The inhaled flow rate should be slow for drugs delivered via pMDI. Drugs delivered via DPI, a 'quick,' 'fast,' or 'forceful' inhalation is generally recommended in patient instruction leaflets because the shear

forces created by such inhalation are used to disperse the drug powder and ensure a sufficiently high respirable dose [42].

Chemical and immunological barriers

Unfortunately, drugs may be susceptible to the effects of substances such as proteolytic enzymes (proteases) and surfactants in the lungs. Proteolytic enzymes such as neutral endopeptidase and cathepsin H have been shown to hydrolyze peptides and proteins in the lungs, resulting in their inactivation. Undissolved drug particles may me*et al.* veolar macrophages, the primary phagocytic cells that protect against inhaled particles. Alveolar macrophages form an immune barrier that does not distinguish between potentially hazardous and potentially helpful compounds [43, 44].

Inhaled particles are eliminated largely by three mechanisms, depending on their geographical distribution and particle properties: mucociliary clearance, phagocytosis, and systemic absorption. In the upper airway, mucociliary clearance is the major clearance mechanism. The mucus is secreted by the ciliated columnar epithelium, which traps particles deposited in the upper airways. These entrapped particles are driven in a proximal direction by the action of beating cilia, leading them to be coughed up or ingested. The bulk of insoluble particles larger than 5 m in size are deposited in the upper airways and removed by mucociliary clearance. Although macrophages are found in the upper airway, phagocytosis is less prevalent in this location. The deep lungs' clearance processes are highly complicated and rely on particle qualities such as dissolution kinetics [45]. Slowly dissolving or insoluble particles in the lungs may interact with epithelial and immune cells and be eliminated by mucociliary clearance, phagocytosis via alveolar macrophages, and endocytosis [46, 47]. The clearance process in the deep lungs is thought to be phagocytosis by alveolar macrophages. Phagocytosis by macrophages is primarily responsible for the clearance of particles ranging in size from 1 to 5 µm. Due to their tiny size and/or quick absorption by epithelial cells, particles with a size less than 200 nm are not detected by macrophages.

Behavioral barriers

What patients do or do not do with their inhaler devices significantly impacts pulmonary medication delivery. Adherence is defined as the number of doses consumed compared to the number of doses given. Cultural influences and misunderstandings influence adherence levels to the treatment. In India, for example, a poll found that 85% of patients thought using an inhaler was a social disgrace, and a similar number wrongly assumed inhalers were only useful for treating chronic ailments [42]. Poor inhaler technique has long been considered an obstacle to inhaled drug delivery. Major errors in the pMDI inhaler technique include not actuating the inhaler while breathing in (lack of coordination) and failing to inhale deeply and gently. The most common issues with DPIs include not inhaling with enough force, as well as device-specific handling and preparation faults, such as wrong device alignment. Although most nebulizers may be used with relaxed tidal breathing, patients can nevertheless misuse them by coughing, breathing through the nose, holding a facemask away from the face, and not properly installing the nebulizer equipment. Inadequate inhaler training predisposes individuals to poor inhaler technique [48].

Lack of adherence and poor inhaler technique leads to inadequate and extremely unpredictable lung deposition, which can lead towards less well-controlled ailment and more recurrent visits to the emergency department as well as an enhanced financial strain on the healthcare system [49].

The combined effect of mechanical, chemical and immunological barriers is that pulmonary bioavailability (for locally acting drugs) and systemic bioavailability (for systemically acting drugs) are low for drugs delivered by most inhalers, and the development of novel, more efficient inhaler systems may be desirable to mitigate the effects of these barriers. However, the high costs of specialized nebulizer or inhaler device, formulation development and their stability issues increase research and development costs.

Strategies to overcome the barriers

The mucociliary clearance can be prevented by using mucoadhesive agents. The deposition of particles can be targeted to alveoli by formulation particles of D_{ae} of 1.8-2.8 µm. Another strategy to overcome drug absorption can be attained by micro- or nanoencapsulation of the drug. Various strategies to overcome one or more clearance mechanisms are described in table 3.

Table 3: Formulation strategies developed to overcome lung clearance mechanisms

Lung clearance mechanism to be overcome	Strategy	Formulation characteristic or composition	References
Mucociliary clearance	Deposition of aerodynamic targeting in the alveoli mucoadhesion.	Aerodynamic diameter between 1.8 and 2.8 µm, compositions based on mucoadhesive agents (Hyaluronan, HPMC, chitosan, etc.)	[50]
Drug absorption	Encapsulation on a micro-or nanoscale of the medication	Lipids-and polymer-based micro-and nanoparticles.	[51]
Macrophage clearance	Changes in the size of the particles. Changes in the shape of the particles. Features of stealth and surface alteration.	Trojan particles, large porous particles, and nanoparticles. Different geometric forms of particles (such as spheres, rectangular discs, and elliptical discs). PEGylation	[52]
Physicochemical, enzymatic degradation	Degradation inhibitors, complexation, and encapsulation	Protease inhibitors, cyclodextrins complexation, and liposome encapsulation	[53]

Inhalation therapeutics in lung cancer

Doxorubicin

Doxorubicin, an anthracycline antibiotic, is frequently used to treat lung cancer. However, cardiotoxicity, hair loss, and other hazardous side effects of DOX treatment are important to consider. Doxorubicin is effective against a variety of tumour forms when used alone. Although it has not been widely used in humans due to the heart toxicity associated with doxorubicin in people with additional cardiovascular disease risk factors, it is potent in vitro against NSCLC cell lines.

Roa *et al.* formulated inhalable doxorubicin (DOX)-loaded nanoparticles and studied its therapeutic effect in a cancer-bearing mouse model (BALB/c model). It was found in the study that the cancer-bearing mice treated with inhalable DOX nanoparticle powder survived for longer periods and exhibited lesser cardiotoxicity when compared with the same dose of drug administered through the IV route [54]. Doxorubicin (DOX)-loaded nanoparticles were incorporated as a colloidal drug delivery system using a spray-freeze-drying technique. A549 cells exhibited reduced sensitivity to the free DOX treatment when compared with H460 cells. At its highest concentration, DOX nanoparticles showed increased toxicity in both the cell lines when compared to the blank nanoparticles and free Dox. Confocal laser scanning microscopy was performed to study cell uptake of free DOX and DOX nanoparticles [55]. Also, Kim *et al.* [56] formulated highly porous PLGA microparticles loaded with Doxorubicin using a w/o/w double

emulsification method. During the study, in vitro cytotoxicity to B16F10 melanoma cells was examined and deposition of the drug in the lung was studied in C57BL/6 mice. Dox PLGA microparticles were administered through the pulmonary route and were studied for their anti-tumour efficacy in a mouse model of B16F10 melanoma metastasis. Their study revealed that Dox PLGA microparticles were very porous. The microparticles possess very high encapsulation efficiency and good aerosolization characteristics. After pulmonary administration of the microparticles, the drug released gradually from the formulation over 14 days and remained in situ for up to 2 w. When tested in vitro, the formulation eliminated B16F10 cells in less than a day. Research on animals revealed that the mass and quantity of tumours in mice with B16F10 implants were significantly reduced upon application of Dox PLGA microparticles. The researchers believed that the above-said formulation has a greater perspective as an inhalation drug with sustained release for the treatment of lung cancer. In another study by a group of researchers, it was found that in H226 cell-induced metastatic tumour in BALB/c nu/nu mice, nanoparticles of albumin on which TRAIL (apoptosis-inducing ligand) were adsorbed and coupled with DOX exhibited acceptable lung pharmacokinetics and antitumor activity when administered through pulmonary route. The study [57] showed that inhalable nanoparticles exhibited synergistic effects on cell killing and its deposition in the lung was found to be increased significantly. The formulation remained in the site in the lungs for over 3 days and continuously released the DOX from the formulation. Acombinational noninvasive and patient compliance formulation was prepared in which hollow paramagnetic nanospheres were fabricated using PEG, which is used as a nanocarrier to deliver methotrexate and doxorubicin simultaneously. Through the pulmonary route [58]. The efficiency of carriers loaded with MTX-DOX was studied using DAPI staining and MTT assay. The effectiveness of nanoparticle-embedded microsphere aerosol formulation was evaluated using a next-generation impactor. The polymeric nanoparticle formulation showed acceptable loading capacity for both MTX and DOX (48%). The drug-loaded nanoparticles were found very efficient and specific to lung cancer A549 cell lines and the safety of blank nanoparticles was confirmed by cytotoxicity assay reports. The inhalation formulation of DOX-MTX nanoparticles dry powder exhibited acceptable aerosolization efficacy. This study concluded that the prepared formulation was efficient and successful in the combined administration of DOX and MTX to the cancer-causing tissues [58]. On comparing the efficiency of the drug when administered through either intravenous or pulmonary route, it was found that direct administration of the drug to the cancer cells in the lungs exhibits better results. Lung toxicity and bolus release of the drug were observed when the cytotoxic drug was administered uncomplexed or unencapsulated. So, to overcome this problem, the researchers formulated a PEGylated polylysine dendrimer conjugated with doxorubicin, which is intended to give controlled and prolonged release of cytotoxic drug [59]. The results of an animal study performed on rats reported that around 60% of the dendrimer was cleared from the lungs in 24 h through mucociliary clearance and absorption into the blood. A comparative study was performed to study the anticancer activity of the formulation when administered through intravenous and pulmonary routes using a syngeneic rat model in which breast cancer metastasised in the lung. The reports suggested that after giving the dose twice weekly through the tracheal route, there was approximately a 95% reduction in tumour burden whereas only a 30-50% reduction was seen in IV administration. The data from the study suggested that PEGylated dendrimer formulation given in inhalable form aids in elongating the exposure time of lung resident malignancies to chemotherapy medications and augments the anti-tumour efficacy. To overcome major issues related to traditional chemotherapy i. e., the development of drug resistance and severe side effects of the drugs, nanoparticle-mediated multidrug combinational therapy was found to be a potential strategy [59].

Gong, H Y *et al.* [60] formulated pH-responsive polymeric vesicles using Methoxylpoly(ethylene glycol)-poly(aspartyl(dibutyl ethylenediamine)-co-phenylalanine)-amphipathic block polymer (mPEG-P(Asp(DBA)-co-Phe)). Using these vesicles, they delivered cancer-related inhibitors of afatinib and doxorubicin hydrochloride (DOX) via Epidermal Growth Factor(EGFR) treatment of enhanced non-small cell lung cancer (NSCLC). The in vitro studies revealed that there was medication release into tumour cells quickly and increased apoptotic cell death when delivered using pH-responsive nanovesicles. After performing in vivo studies, results revealed that co-delivery of DOX and afatinib through pH-sensitive nanoformulations was a propitious approach for the treatment of NSCLC. O. Taratula *et al.* [61] recently developed lung cancer therapy using a medication delivery system based on Mesoporous Silica Nanoparticles (MSN) using inhalable formulation. The developed system was very effective in delivering the drug (doxorubicin and cisplatin) inside the cancer cells and these drugs were combined with siRNA, which are designed to reduce pump and non-pump cellular resistance by targeting MRP1 and BCL2 mRNA in NSCL carcinoma, respectively. This delivery system delivers the drugs locally into the lungs and prevents their movement into the systemic circulation and to other healthier organs. Consequently, the proposed MSN of drugs (doxorubicin and cisplatin) and siRNAcurrentl targeting the lung carcinoma cells has high efficiency for lung cancer treatment. Another study was performed by a group of researchers [62] in which bioresponsive inhalable chitosan microspheres loaded with substrate stimuli, doxorubicin, soluble curcumin (Cur-2-HP-β-CD complex), and elastin were used. The results of the study showed that microspheres released appreciably higher amounts of Dox at pH ~ 5.5 in the presence of elastase enzymes. It was also seen that soluble curcumin exhibited pH-independent release from the bioresponsive microspheres in the presence of elastase enzymes. A better therapeutic profile of the formulation is possible due to increased medication release and subsequently improved exposure of A549 cells to the drug. This results in drug release from the stimuli-responsive formulation, leading to apoptosis phenomena in A549 cells. Thus, this formulation demoy rnstrated an acceptable method for delivering a high load of chemotherapeutic drugs to non-small cell lung cancer cells. An inhalable drug delivery system employing Nanostructured Lipid Carriers (NLCs) loaded with doxorubicin, SiRNA, and conjugated LHRH peptide demonstrated superior control of cancer cells over intravenous administration in different research [63]. Ghosh *et al.* [64] investigated the efficacy of co-loading vincristine and doxorubicin onto a PEGylated liposomal formulation in the treatment of non-small cell lung cancer. The A549 cells' viability was much lower in the dual drug formulation compared to the single drug formulation of liposomal doxorubicin, and the former demonstrated superior cellular absorption. The DPI of the formulation (NLC, Cremophor EL) did not appear to cause any tissue damage to the animals who received it. The development of nanoparticles and liposomal formulation will enhance targeted delivery and improve therapeutic precision as per the research [65]. Table 4 lists some research on inhalation delivery of doxorubicin to treat lung cancer.

Gemcitabine

Gemcitabine, an anti-metabolite medication, is widely used to treat a range of malignancies. It is third third-generationnovel deoxycytidine analoguewith structural similarity to cytosine arabinoside. [72]. Gemcitabine is supplied as a hydrochloride salt through gradual intravenous infusion in three or four-week cycles. Despite being considered a "front-line" chemotherapeutic drug, its efficiency is impeded by inadequate target cell selectivity, insignificant cellular absorption, fast clearance from circulation, the development of chemoresistance, and unwanted side effects. It is a nucleoside analog of deoxycytidine thus inhibiting cell proliferation [73]. A group of researchers carried out a study [74] tested the possibility of gemcitabine (Gem Loaded Gelatin Nanocarriers (GNCs) cross-linked with genipin (Gem-GNCs) for nebulized lung cancer therapy. DSC and PXRD analysis of lyophilized Gem-GNCs revealed that the Gem and excipients were both molecularly distributed and amorphously structured. Non-Fickian diffusion was evidenced by Gem-GNCs and efficient delivery of the formulation was obtained due to erosion of a matrix leading to a reduction in dosing intervals. It was found that the prepared formulations effectively protect Gem from degradation and specific delivery of Gem within tumor cells was also possible to exhibit anti-cancer activity. The study revealed

that at pH 5.4–7.4, gem-GNCs were stable for a full 72 h. The Mass Median Aerodynamic Diameter (MMAD) for nebulized Gem-GNCs came to be 2.0-0.161m, fine particle fraction (FPF) of 75.2% – 2.4% and Geometric Standard Deviation (GSD) of 2.7 – 0.16. Recently, in another study [75], researchers developed a Multifuctional Dual Drug Loaded Nanoparticle (MDNP) intended to target a folate receptor. MDNP is composed of Poly Lactic Glycolic Acid (PLGA) core and a shell of poly(N-isopropylacrylamide)-carboxymethyl chitosan resulting in augmented specific chemo-radiotherapy to treat lung cancer effectively. A potential radiosensitizer, NU744I, and Gemcitabine were released from the formulation in a controlled fashion for lung cancer chemo-radiotherapy. The formulation exhibited biphasic NU744I release, and the release of gemcitabine was dependent on the pH of the surrounding. These MDNPs were acceptably stable, hemocompatible, and showed excellent cytocompatibility with alveolar Type I cells when performed *in vitro* testing. Hence, a novel nanocarrier with a multifunctional ability and biodegradable nature was developed, having the ability to actively target lung cancer cells that overexpress the folate receptors. Also, the novel formulation releases two dissimilar therapeutic agents that provide non-invasive and efficient lung cancer chemo-radiotherapy. A group of researchers formulated gemcitabine and cisplatin combinational niosomal formulation (NGC) containing a lower dose [76]. The heating method was used to prepare NGC and the formulations were further optimized using a D-optimal mixture design. The study revealed that the optimized NGC formulation exhibited acceptable stability and was found to be homogenous against phase separation at various temperatures when stored for 90 days. The optimized formulation exhibited a controlled release of drugs; the study revealed the formulation is safe and inhibits the growth of A549 lung cancer cells. The study also demonstrated that the prepared NGC formulation is potent enough to be used for the treatment of cancer and showed acceptable entrapment efficiency and aerosol output. Cascade impactor analysis further confirmed the deposition of the formulation in the lungs via inhalation. As high as 54% of the synergistic response rate was demonstrated by the Gem-Cis combination formulation in NSCLC. Gandhi M and his group [77] converted the anticancer liposomal formulation into dry powder using the lyophilisation technique. The DPI formulation was evaluated for various tests, including solid-state characteristics and aerosol performance. The optimized formulation has undergone investigations with in vitro cell lines, in vivo experiments, and stability studies. The optimized formulation exhibited favourableaerodynamic properties with an FPF value of 56.12% and MMAD being 3.92µm. Also, the LDPI formulation reduces the higher dose of the drug significantly as the gemcitabine-HCl metabolism is avoided by this formulation, which further reduces the side effects associated with the higher doses. Gemcitabine LDPI exhibited better uptake by A549-human adenocarcinoma cell lines than plain DPI formulation [77]. Various research has been done to deliver Gemcitabine via inhalation route to treat lung cancer as shown in table 5.

Table 4: Doxorubicin delivery via inhalation to treat lung cancer

Drug	Device and test model	Nanoproduct	Size	Observation	Reference
Doxorubicin and ellagic acid	BALB/c mice with dry powder insufflator	Inhalable Lactoferrin-chondroitin nanocomposite	192 nm	The nano complex was converted into inhalable nanocomposites via spray drying.	[67]
Doxorubicin	BALB/c Nebulizer Mice	Epidermal Growth Factor(EGF)-Modified Gelatin Nanoparticles (EGNP)	~120 nm	90% reduction in tumour volume. 100% chance of survival.	[68]
Doxorubicin	A desiccated powder inhaler C57BL/6 rodents	PLGA porous nanoparticles	14 µm	50% reduction in lung tumours with metastases.	[56]
Doxorubicin+TRAIL	A desiccated powder inhaler Nu/nu mice of the BALB/c strain	Doxorubicin-loaded porous PLGA microparticles with surface attached TRAIL	11.5 µm	Doxorubicin-liposome inhalation group showed a synergistic decrease in metastases and caused apoptosis	[69]
Doxorubicin	A desiccated powder inhaler Mice of the BALB/c strain	Inhalable doxorubicin-loaded nanoparticles.	145 nm	Minimized metastasis, reduced cardiac toxicity, Long-term effect	[54]
Doxorubicin+ TRAIL	Aerosolizer with a micro spray,BALb/c nu/nu mice	TRAIL/Dox HAS (human serum albumin)-NP(nano-particle)	~340 nm	Doxorubicin nanoparticles, showed apoptosis and reduced lung metastasis synergistically by approximately 40%.	[57]
Doxorubicin, cisplatin	Tiny sprayer, C57BL/6 rodents	Doxorubicin and cisplatin co-loaded nanoparticles	40-65 nm	High absorption by cells, suppresses the spread of tumours, no indication of toxicity	[70]
Doxorubicin/paclitaxel (2:1)	A desiccated powder inhaler C57BL/6 rodents	Doxorubicin and paclitaxel by porous PLGA microspheres	11.5 µm	Reduced lung tumourlesions	[71]
Doxorubicin/cisplatin	NCR Nebulizer naked mice	Mesoporous Silica Nanoparticles(MSN)	180 nm	Increased lung retention (73%) in contrast to administration by intravenous (5%), decreases buildup in other organs, such as the liver (17%) and kidneys (9%), and systemic circulation	[61]

Paclitaxel

Paclitaxel, being a hydrophobic drug, promotes the assembly of microtubules and inhibits aggregation from disassembly, leading to cell apoptosis, it promotes tubulin polymerization stabilizing microtubules by preventing their depolymerization [79]. Recently, a study was carried out by a group of researchers [80] in which they formulated inhalable nanospray using different surfactants aiming to enhance the antitumor activity of the drug. The solvent evaporation method was used to create paclitaxel and doxorubicin Nano Lipid Carrier (NLCs) in which different surfactants (Cremophor EL, Tween 80, and Tween 20) were used. The formulation was then spray-dried and was assessed for its aerodynamic and medicinal qualities. The results showed, in comparison to Tween 80 and Tween 20, cremophor EL-based nanocarriers had the lowest particle size dispersion (394.1±5.6 nm). In vitro studies indicated that the optimized Cremophor EL DPIs improve cell uptake, and the efficacy of transfection is also improved in lung adenocarcinoma A549 cells, which have raised P-gp. From the in vivo studies, it was confirmed that there is an enhancement in retention and drug accumulation in the lung without any abnormality to the tissues, which further leads to a reduction in

toxic consequences in non-target issues. This leads to a reduction in doses of drugs to achieve a desirable therapeutic response [80]. Another group of researchers [81] has developed and characterized dry powder aerosol of Paclitaxel (PTX) nanocomposite microparticles (PTX nCmP) for lung cancer treatment. PTX-loaded nanoparticles were formulated using a single emulsion or solvent evaporation technique and the drug was encapsulated in acetylated dextran (Ac-Dex). The study results showed the effective uptake of PTX nanoparticles in A549 cells. When compared with free PTX, PTX NP had a greater effect on 2D cells. An acceptable in vitro distribution and lung deposition were exhibited by the formulation using a Next Generation Impactor [82]. Another study carried out recently [81], prepared a naïve delivery method that releases paclitaxel plus afatinib in two stages. This system is intended to treat the first line of inhalation-based EGFR-TKI-resistant NSCLC. The system is intended to deliver drugs in combination with afatinib and paclitaxel. Firstly, afatinib solid lipid nanoparticles were prepared using stearic acid and then these nanoparticles, along with paclitaxel were loaded in poly-lactide-co-glycolide-based porous microspheres (AFT-SLN-PTX-pMS). The formulation showed acceptable particle size, high drug encapsulation efficiency, better aerosolization properties, fine porous structure as well as appropriate safety. From the in vitro release studies it was found in just two days, nearly all of the paclitaxel was released from the AFT-SLN-PTX-pMS and afatinib exhibited sustained release for two weeks. H1975 and PC9/G cells experiment revealed the synergistic effect of both the drugs and the formulation showed better therapeutic outcomes in NSCLC cells resistant to drugs. The tissue distribution, pharmacokinetics and biocompatibility studies showed that AFT and PTX in the prepared formulation showed 96 h of a two-stage release and higher lung concentration. Also, the formulation does not distribute to other critical organs significantly. It was found that Solid lipid particles for inhalation enclosed in PLGA porous microspheres can increase lung targeting and preserve different drug release behaviours [81]. Wing-Hin Lee *et al.*, [83] formulated a simple dry powder inhalation formulation that included paclitaxel and curcumin, which have antioxidant activity and thus protect damage to healthy lung cells while taking an anticancer medication directly into the lungs. DPI was prepared using the co-jet-milling process to get suitable MMAD (2.64–3.12 µm) and high FPF values (60–70%). The combination formulation inhibited the proliferation of cells and cell apoptosis very strongly and started arresting the cell cycle of lung cancer. It was found that the effect is more pronounced as the amount of curcumin rises in the formulation. The study also exhibited that curcumin and paclitaxel actions were connected to the oxidative stress associated with mitochondria. The induction of G2/M cell cycle arrests and apoptosis/necrotic cell death in both A549 and Calu-3 cells showed that the CUR/PTX combination had a more effective cytotoxic impact on lung cancer cells. It was found during the study that curcumin neutralizes the PTX's cytotoxic impact on healthy Beas-2B cells, which varies with dosage. This research reported that a simple DPI formulation of and PTX and CUR combination resulted in selective and enhanced anticancer activity against cancer cells and simultaneously also protects healthy cells from irreversible damage [84]. Regarding the local distribution of chemotherapeutic medications for the lungs, the group has formulated novel polymeric micelles of tocopherol succinate-polyethylene glycol 1000 and 5000 Da and were loaded with Paclitaxel (PTX) [83]. The optimized micelles were then co-spray-dried with a lactose carrier. It was found in the cytotoxicity assay that there was an increased cytotoxic activity of the micelle formulation in contrast to the free medication. The in vitro deposition test results demonstrated that inhalable powder with a high fine particle fraction (60%) was produced when the PTX-loaded micelles were spray-dried with lactose [83]. Another very interesting formulation prepared [85] was microparticles prepared from fatty acid and containing iron oxide nanoparticles and paclitaxel. The microparticles after inhalation, are guided by an external magnetic field to the selected location and the release of the compound is triggered by local hyperthermia. The release and transfer of the components of microparticles were confirmed by isothermal titration calorimetry. It was depicted in the studies that microparticles loaded with 5% paclitaxel suppressed the growth of malignant lung epithelial cells (A549) effectively at concentrations as low as 0.125µg/ml while unloaded microparticles were not cytotoxic for cells [85]. The inhalation route offers direct lung access, but penetration of the medication into lung cancers was still a matter of concern. So this group of researchers has developed [86] micelles made of Folate Polyethylene Glycol Hydropobically Modified Dextran (F-PEG-HMD) for the effective delivery of drugs to the lung and also penetrate lung tumors and cancer cells. When orthotopic MI09-HiFR lung tumour transplanted mice by inhalation, the produced micelles were shown to be able to infiltrate HeLa and Mi09-HiFR, folate receptor-expressing cell lines in both the in vitro and in vivo investigations. In vitro investigations have demonstrated deposition patterns of the formulation with a fine particle percentage of up to 50%, and the micelles re-disperse readily in the physiological buffer. Furthermore, no indication of lung damage or inflammation was noted in the mice in good condition [86]. Table 6 lists some research on the inhalation delivery of paclitaxel to treat lung cancer.

Table 5: Gemcitabine inhalable formulations to treat lung cancer

Drug	Device and test model	Formulation	Size	Observation	Reference
Gemcitabine	Nebulizer Humans	Aerosol	-	Lung deposition dosage is 42%. Little systemic cytotoxicity	[77]
Gemcitabine	Nebulizer A549 and H460 cell lines	Aerosol of Gemcitabine Loaded Gelatin Nanocarriers (GNCs) cross-linked with genipin (Gem-GNCs)	178 – 7.1 nm	Gem-GNCs caused a 40% decrease in the human bronchial fluid's complicated viscosity. At 48 and 72 h, Gem-GNCs performed approximately five times better in H460 than the Gem IC50 decrease.	[74]
NU7441 and Gemcitabine	Nebulizer Sprague Dawley rats athymic nude mice	Folate receptor-targeting Multifunctional Dual Drug Loaded Nanoparticles(MDNP)	average diameter of 289±49 nm	Exhibited biphasic NU7441 release, and pH-dependent release of gemcitabine. good stability, excellent hemocompatibility, and outstanding *in vitro* cytocompatibility with alveolar Type I cells dose-dependent caveolae-mediated*in vitro* uptake by lung cancer cells.	[75]
Gemcitabine and cisplatin	Aerosol lung cancer A549 cell lines	Aerosolisedniosomes	166.45 nm	PDI – 0.16, zeta potential-15.28 mV, Stable at 27 °C with no phase separation for up to 90 d. Aerosol output was 96.22%	[76]
Gemcitabine HCl	Dry powder inhaler wistar rats	Liposomal Dry powder inhaler (LDPI)	3.91µm	LDPI metabolism was avoided, and better uptake of LDPI by cell lines, a better pulmonary pharmacokinetic profile of LDPI formulation with lower toxicity to lung tissues than that of drug solution. FPF value was 56.12%,	[77]
Gemcitabine and erbitux	Nebulizer mouse models of human (H226) and murine (3LL)	Aerosol	-	Inhalation in H226 with 10% reduction of lung weight, 40% reduction with gem and 50% with combination therapy nebulized gem demonstrated an 80% decrease in the lung weights and tumour foci	[78]

Table 6: Lung cancer treatment through inhalation delivery of paclitaxel

Drug	Device and test model	Formulation	Size	Observation	Reference
Doxorubicin and paclitaxel	Dry power insufflators Mice B16F10 cells	PLGA porous microspheres	Geometric mean diameter 11.47±2.71 µm MMAD of 3.52±0.83 µm	Fewer tumour lesions and more healthy alveoli than the single drug-treated group. Long-acting effects.	[66]
Paclitaxel (PTX) and Doxorubicin (DOX)	DPI Wistar rats	nano-lipid carriers	394.1±5.6 nm	A greater drug dispersion in the lungs than plain drugs. No sign of tissue damageorinflammatory reaction	[87]
Paclitaxel	DPI-A549 human epithelial adenocarcinoma lung cancer cells	Nanocomposite Microparticles (nCmP)	200 nm	Reached the distal regions of the lungs, effective cellular uptake in A549 cells	[86]
Afatinib and paclitaxel	Dry powder inhaler Sprague–Dawley rats	PLGA porous microspheres	<50µm	Showed a synergistic impact in drug-resistant NSCLC cells, and codelivery of both medicationsdemonstrated a better therapeutic outcome. Afatinibisreleasedmoreslowly than PTX	[81]
Paclitaxel and Curcumin	Dry powder inhalation aerosol A549 and Calu-3 cells	DPI formulation	Curcumin particle size ~22 µm. PTX particle size ~42 µm	The combination showed a more potent cytotoxic effect against lung cancer cells, induction of necrotic cell death and apoptosis. Both Calu-3 and A549 cells experience G2/M cell cycle arrests. Curcumin counteracts PTX's cytotoxic effects against Beas-2B-positive healthy cells.	[84]
Paclitaxel	Dry powder inhaler A549 pulmonary cell line (human alveolar epithelial lung adenocarcinoma cell line)	Surfactant-based carriers composed of synthetic phospholipids, dipalmitoylphosphatidylcholine, (DPPC) and dipalmitoylphosphatidylglycerol (DPPG)	1.9 to 2.3 µm	Exhibited high in vitro aerosol performance, high drug loading, sustained drug release overweeks, enhanced PTX *in vitro* cytotoxicity on lung cancer cells	[88]
Paclitaxel	DPI-HeLa and M109-HiFR cancer cell lines Orthotopic M109-HiFR lung tumour grafted mice	Folate Polyethlene Glycol Hydrophobically Modified (F-PEG-HMD) micelles	~50 nm	Loaded micelles reduced HeLa and M109-HiFR cell growth with half-maximal inhibitory concentrations of 37 and 150 nm respectively. No sign of lung toxicity and/or lung inflammation	[86]
Paclitaxel	Spray-dried inhalable powder Human lung cancer cells, A549.	Novel mixed polymeric micelles	102 to 196 nm	Increased cytotoxic activity of PTX-loaded mixed micelles compared to the free drug, High fine particle fraction (60%)	[83]
Paclitaxel	Dry powder inhaler A549 human lung epithelial cells	Fatty acid-based microparticles containing iron oxide nanoparticles	1.9–3.6 µm.	Effectively suppressed the proliferation of A549 human lung epithelial cells of malignant origin, targeted delivery	[89]

Curcumin

Curcumin is a yellow-colored natural substance obtained from *Curcuma longa*. It has been used for the treatment of numerous diseases, such as rheumatoid arthritis, asthma, inflammatory bowel disease, chronic obstructive pulmonary disease, and many cancers. It is highly safe for humans and is unambiguously effective in eliminating solid tumors [90]. Research indicates curcumin may be effective in preventing lung cancer development, inhibiting tumor cell proliferation, and potentially reducing metastasis by modulating crucial signallingpath ways involved in lung cancer progression [91] Curcumin exhibits anticancer activity ascribed by its use for the management of pancreatic cancer and lung cancer, colorectal cancer, and many others. Many in vitro and in vivo studies have shown the efficient anti-inflammatory and antioxidant characteristics of curcumin. Despite the promising therapeutic effects of curcumin, its therapeutic efficiency is restrained due to its very poor solubility in water and so reduced systemic concentration after oral administration [92]. Furthermore, curcumin is not stable in the chemical environment of the gastrointestinal tract. Administration of curcumin via inhalation is a novel approach as given in Table 8. In a study [93] curcumin is formulated as a sustained-release dry powder formulation intended to alleviate the local delivery of high doses of curcumin in various pulmonary diseases. A very novel dry powder polymeric carrier was formulated allowing simultaneous delivery of the drug to the lung, circumventing macrophage uptake, and allowing sustained release through the formulation. PLGA nanoparticles loaded with curcumin and grafted with chitosan were synthesized using a spray drying technique. The hydrogel microspheres encasing the PLGA nanoparticles loaded with curcumin and the nanoparticles themselves were found to have an average size of 3.1-3.9 µm and 221-243 nm, respectively. The studies reported that within a few minutes, the carriers attained high swelling and exhibited low moisture content as dry powders. Itbiodegradesat desirable rates. The drug loading efficiency of the formulation was quite high (up to 97%) and better sustained release. It also exhibited good aerosolization characteristics when studied using a next-generation impactor. The respirable/swellable nano-micro particles exhibited strong biointeractionsdetermined by cytotoxicity, in vitro TNF-α tests, and in vitro macrophage uptake investigations. The prepared nano-micro particles are developed as potent carriers for delivering the drug in a sustained release manner through the pulmonary route [93]. Another recent study [94] was carried out in which inhalable powders of curcumin were prepared using PVP and HPbCD as excipients in binary and ternary systems via the SCF anti-solvent method ARISE. It was revealed that the ternary system curcumin-PVP-HPbCD's ARISE processing exhibited significantly enhanced aerodynamic qualities compared to both physical combinations of raw curcumin and excipients. About 49.1% FPF was reported by the formulation it is suitable for inhaling dry powder. The formulation was tested for its cytotoxicity activity. The curcumin formulations exhibited higher toxicity for HI299 cells compared to MRC-5 cells, the IC50 for cancer cells was 1.5–2.0 times lower. The flow cytometry results and confocal microscopy showed that the curcumin-PVP-HPbCD particles were readily uptake by both HI299 and MRC-5 cells [94]. The study depicted that the dry powder formulation was delivered to the lungs efficiently and dissolved in bodily fluids while simultaneously protecting curcumin's anticancer qualities [95]. Curcumin, owing to hydrophobic results in less therapeutic activity so to overcome this problem a group of researchers has developed a porous composite particle in which the drug is loaded into mesoporous material SBA-15[96]. The formulation was intended to be delivered to the lungs via inhalation. The aerodynamic performance was confirmed by FT-4 and NGI and

the drug included in the host material was confirmed by the reduction in surface area and diameter of the pore of the composite material. Good biocompatibility at 10-400µg/ml was exhibited by the mesoporous material which was assured by phagocytosis experiments on RAW264.7, toxicity tests on BEAS-2B cells, and the hemolysis experiments. The B16F10 melanoma metastatic lung mouse model was used to investigate the therapeutic effect of the drug after inhalation. The results indicated that the body weight of the group to which curcumin composite particles were administered increased more slowly and the lung disease grew at a slow rate compared to the curcumin crude drug group. These composite particles possess acceptable aerodynamic characteristics, and encapsulation efficiency, and can escape phagocytosis. Compared to curcumin, these composite particles decrease metastatic lung tumours in C57BL/6 mice implanted with B16F10 cells [96]. In a study [97], freeze-dried small unilamellar cationic niosomes loaded with curcumin (Cur-C-SUNS) were prepared using the reverse-phase evaporation method. The formulated Cur-C-SUNS exhibited acceptable inhibition in the A549 lung cancer cells proliferation at the IC_{50} of 3.1µM which is remarkably lesser than 7.5µM of Cur-SUNS and curcumin suspension (<32µM). Furthermore, the accumulation of Cur-C-SUNS was significantly higher than that of Cur-SUNS and curcumin suspension. In vitro, cellular uptake studies exhibited that endocytosis of Cur-C-SUNS was very high compared to the other two formulations. The reason is the electrostatic interaction between the oppositely charged nanovesicles and the plasma membrane of A549 cells [97]. Another team [98] created a Liposomal Curcumin (LCD) dry powder inhaler for primary lung cancer. The curcumin liposomes were freeze-dried and converted to LCDs with MMAD of 5.81µm and FPF of 46.71%. It was reported that the uptake of liposomal curcumin by the human lung cancer A549 cells was remarkably higher and faster when compared to the free curcumin. It was also revealed that curcumin liposomes were selectively highly cytotoxic to A549 cells but less cytotoxicto BEAS-2B normal human bronchial epithelial cells resulting in an increased selection index partially due to augmented cell apoptosis. LCDs exhibited significantly higher anticancer effects than the curcumin powder and gemcitabine when they were sprayed directly into the rat's cancerous lung through the trachea and this was a result of the expression of many cancers related markers including VEGF, malonadialdehyde, caspase-3, BCL-2 and TNF-α. The study confirms that curcumin exhibited its anti-lung cancer mechanism through its strong anti-inflammatory and anti-oxidative properties and increased apoptosis contributes to its anticancer impact [98].

Table 7: Role of curcumin in lung cancer via inhalation delivery

Drug	Device and test model	Formulation	Size	Observation	Reference
Curcumin	Nebulizer	Nanoemulsion and Microemulsion	7.1 to 5.7 µm	Superior *in vitro* aerosolized performance independent of drug concentration, nontoxic exhibited much better fine particle fractions (FPF),deeper particle deposition, improved inhalation rate	[99]
Curcumin	Dry powder particulate Raw 264.7 macrophage cells	Swellable biocompatible microparticle	221–243 nm and 3.1–3.9 µm	Continuous curcumin administration to the lungs	[93]
Curcumin	Nebulizer A549 and Calu-3	Nanoparticles	28 to 200 nm	Higher cytotoxicity effect on lung cancer cell lines A549 and Calu-3. non-toxic to normal healthy cells (BEAS-2B).	[100]
Curcumin	Breath simulator BEAS-2B cells B16F10 melanoma metastatic lung mouse model	Porous composite particles using mesoporous material SBA-15	15 to 20 µm	Inhibitory effect on tumours, high encapsulation, and phagocytosis escapement characteristics.	
Curcumin	Dry powder inhaler human lung epithelial carcinoma cells A549	Nano-in-Microparticles	3.02 ±0.07 µm	Exhibited a dose-dependent photocytotoxicity, efficient encapsulation, good dispersibility, excellent compatibility with the lung surfactant	[101]
Curcumin	Nebulizer, human lung carcinoma (A549) and human lung adenocarcinoma (Calu-3).	Curcumin miceller nanoparticles	4.8-5.2µm	Non-toxic to healthy lung cells (BEAS-2B) Induce apoptosis and cause G2/M arrest in both A549 and Calu-3 cell lines. More effective in suppressing the expression of the inflammatory marker, Interlukin-8 (IL-8).	[102]
Curcumin	Nebulizer A549 lung cancer cells	Small unilamellarniosomes	97.4±8.3 nm,	Capable to deliver high therapeutic concentration of curcumin higher endocytosis of Cur-C-SUNS as compared to Cur-SUNS	[97]
Curcumin	Dry powder inhaler human lung cancer A549 cell and rats	Liposomes	5.81 µm	Strong anticancer activity attributed to curcumin's anti-oxidative, anti-inflammatory, and improved apoptotic properties. Liposomes enhanced cell endocytosis.	[98]
Docetaxel and curcumin	Aerosol	Nanoemulsion	<5µm	High colloidal stability, drug entrapment efficiency, sustained drug release, excellent stability against extreme conditions, more than 95% aerosol output and greater than 75% inhalation efficiency	[103]

Cisplatin

Cisplatin is primarily used for non-small lung carcinoma treatment, in combination with many other medications such as vinorelbine, etoposide, paclitaxel, docetaxel, or gemcitabine. Its anticancer properties are demonstrated by its ability to impede DNA transcription and replication as well as induce programmed cell death [104]. As a part of the "doublet chemotherapy", cisplatin is delivered for the treatment of both small cell and non-small cell lung cancer. Recently, a preclinical investigation was conducted to study the intensification of the therapeutic efficacy of the drug when a cisplatin dry powder inhaler was administered along with intravenous cisplatin-based treatment. The formulation consists of 50% pure API and was developed using lipid excipients through high-pressure homogenization and spray drying at high speeds. The results depicted that there were significantly higher i. e., seven-fold, increase and decrease in Cmax in the lung and plasma, respectively, when compared with cisplatin solution administered into mice through the IV route. Also, the formulation showed acceptable aerodynamic performance with FPF of ~ 55% and MMAD of size ~ 2 µm. Finally,

when the CID-DPI-50 was added to the standard cisplatin/paclitaxel iv combination, it increased the therapeutic effect by about 67%, reduced the growth of the tumor, and enhanced the median survival to 31 d from 21 d in the M109 lung carcinoma model [105]. Another study was carried out in which two different techniques were combined i. e., HSH and HPH, along with the spray-drying process to formulate cisplatin microcrystals and, further, powders for Dry Powder Inhaler having high drug loading efficiency. *In vitro* studies exhibited increased lung deposition and high dispersion properties of the cisplatin microcrystals embedded into solid lipid microparticles. The formulation also showed the release of the drug in a controlled manner for more than 24 h when studied in lung fluid-simulated media. The stealth abilities of the formulation against macrophages were potentially brought by the addition of PEGylated excipients to the lipid portion of the dry powder formulation. The formulation provides a substitute to the systemic treatment of lung cancer, which is dose-limiting and offers interesting outlooks as a supportive treatment in both SCLC and NSCLC at later stages or as a localized therapy explicitly intended against the cancer recurrence [104]. Table 9 gives an overview of the inhalation of cisplatin to treat lung cancer.

Table 9: Inhalational delivery of cisplatin to treat lung cancer

Drug	Device and test model	Formulation	Size	Observation	Reference
Cisplatin and gemcitabine	Micro AIR nebulizer normal lung (MRC5) and lung cancer (A549) cell lines	niosomes	166.5 nm	Showed controlled release for both drugs up to 24 h penetration, reduced cytotoxicity effects against both MRC5 and A549, good entrapment efficiency and aerosol output.	[106]
Cisplatin	Dry powder inhalation A549 human lung cancer cells	Chitosan microspheres	5.2±1.19µm D_{aero} 2.71µm	Showed higher IC50, higherFPF value, and a two-phase release pattern that started with a blast effect and with a more gradual release.	[107]
cisplatin	Dry powder inhaler, Mice	Solid lipid microparticles	<5µm	Decreased toxicities through lower exposure of non-targeted organs.	[108]
Cisplatin	M109 lung carcinoma model CD1 mice and BALB/cAnNRj mice	microparticle	~2µm	Good aerodynamic performance, seven-fold increase and decrease in C_{max}in the lungs and plasma, respectively when compared with iv cisplatin solution.	[105]

Resveratrol

Resveratrol (RSV, trans-3,5,4′-trihydroxystilbene), is a polyphenol found in red wine, grapes and peanuts. It can impede the three main stages of carcinogenesis i. e., initiation, promotion and progression as a possible antitumor agent. Studies reported that it could activate the tumoursuppressor p53 and silent mating type information regulation 2 homolog I (SIRTI) [109]. RSV stimulates apoptosis by triggering the mitochondrial apoptotic pathway and hinders the proliferation of cancerous cells along with the augmentation of the sensitivity of the cancer cell lines. Despite these pharmacological properties, its use is still restricted due to its low solubility in water and instability in the physiological medium. RSV has poor permeability and bioavailability. It is unstable and has substantial metabolism before reaching the systemic circulation [110]. In a recent study [111], to overcome the problems related to RSV, Sulfobutylether-β-cyclodextrin (CD-RSV) complex was created and subsequently incorporated upon nanoparticles of polymers. The CD-RSV was formulated to investigate increment in the antioxidant and anti-cancer activity of the drug against NSCLC. The results exhibited that the CD-RSV complex raised the solubility of RSV in water up to 66-fold. The developed nanoparticles also exhibited potential for aerosolization with a 2.20µm mass average aerodynamic diameter. From the *in vitro* studies, it was found that CD-RSV nanoparticles exhibited augmented cytotoxicity when compared with free RSV and it also maintains its antioxidant effects. The 3D spheroid studies showed an increase in the accumulation of particles in the lungs. Therefore, an enhancement in the therapeutic efficacy of the inhalable formulation was expected [111]. In another study [112], RSV microsponges (RSV-MS) were formulated successfully by the quasi-emulsion solvent diffusion method and then converted to a porous inhalable carrier. The RSV-MS showed potential FPF and MMAD of 2.13±0.21 µm and 48.54±0.25%, respectively, along with increased lung deposition compared to the conventional form of RSV DPI. Additionally, the *in vitro* and *in vivo* investigations revealed a two-fold rise in the FPF and improvements of 4.4, 14.12, and 1.94 times in the Area Under Curve (AUC), mean Residence Time (MRT), and Cmax, respectively [112]. A group of researchers have investigated pharmacokinetics, RSV distribution in the tissues and metabolic profile of RSV from RSV inclusion complex with hydroxypropyl-β-cyclodextrin (HP-β-CD). The formulation was intended to augment the hydrophilicity of the poorly soluble drug. Further, in vitro studies using rat liver microsomes and lung microsomes investigated the metabolic profiles of the formulation through the pulmonary route. Compared to oral delivery, better absorption and bioavailability (92.95%) of resveratrol was reported in rats after pulmonary delivery. Studies also reported that after pulmonary administration, RSV accumulated in lung tissues very fast and in higher concentrations i. e. more than 100 times those of oral delivery. The study depicted effective delivery of resveratrol both for potential systemic and local effect; the pulmonary route is most suitable [113].

Miscellaneous drugs used for inhalational therapy of lung cancer

Apart from the drug discussed above, various anticancer drugs that are investigated for lung cancer in the form of inhalation are summarized in table 10.

Clinical development

Some clinical research based on inhalable chemotherapeutics is given in table 11.

Table 10: Application of inhalable therapeutics in lung cancer

Drug	Device and test model	Formulation	Size	Observation	Reference
5-azacytidine	Dry powder inhaler, orthotopic rat lung cancer mode	DPI	<10µm with 50% of the particles<3.3 µm	Showed superior pharmacokinetic properties in lung, liver, brain and blood, reducing tumour burden by 70–95%.	[114]
Amodiaquine (AQ)	Nebulizer, A549 cell lines	Inhalable nanoparticulate	4.7±0.1 µm	Significant reduction in IC50 values with AQ-loaded nanoparticles compared to plain drug. Significant cell migration inhibition (scratch assay) and reduced % colony growth (clonogenic assay) in A549 cells with AQ NP.	[115]
Docetaxel Trihydrate	Inhaler, A549 lung Cancer cell lines	Liposome	135.0±0.289 nm	*In vitro* anticancer study against A549 lung cancer Cell lines revealed IC50 of 188.67 mcg/ml, lower	[116]

Drug	Device and test model	Formulation	Size	Observation	Reference
				than the pure drug.	
Docetaxel (DTX)	Dry powder inhaler, A549 lung cancer cell lines	Nano Embedded Microparticles (NEM)	3.74±0.11 µm	Exhibited suitable flowability and aerodynamic behaviour. DTX-NEMs DPI formulation showed great potential for use in the localised delivery of DTX molecules to the lung, for passively targeting NSCLC.	[117]
Erlotinib (ETB)	Dry powder inhaler human alveolar adenocarcinoma epithelial A549 cells	Solid Lipid Nanoparticle (SLN) spray dried into microparticles	1-5 µm	Displayed suitable flowability, aerodynamic traits, and deep inhalation pattern of the formulation. Exhibited sustained drug release profile and enhanced the efficacy of ETB in the A549 cells. ETB-SLNs showed high anticancer activity in lung cancer cells.	[118]
Etoposide and Berberine	Dry powder inhaler A549 lung cancer cells and male Albino mice	Nanocomposites	200 nm	Enhanced cytotoxicity and internalization into A549 lung cancer cells, demonstrated deep pulmonary deposition, and superior anti-tumour efficacy of the inhalable nanocomposites.	[119]
Gefitinib (Gef) loaded glucosamine	Dry powder inhaler A549 lung cancer cells	SLN	187.23±14.08 nm, Microparticles have dia_{ae} 4.48 µm	Showed significantly higher cytotoxicity activity against A549 cells than free Gef.	[120]
Temozolomide	Dry powder inhaler	Dry powder formulation	Between 2.82 and 4.46 µm.	Fast drug release, good dispersion properties low moisture content promote the long-term stability of the formulations.	[121]
Temozolomide	Dry powder inhaler	Nanomicelles	~50 to ~60 nm	Increased local concentrations in the tumour site, and showed wide pulmonary deposition in the lower respiratory tract.	[122]
Sorafenib (SF)	Nebulizer Human NSCLC cell lines A549, H4006, H460, H358, H157; and human embryonic kidney cells (HEK 293)	Catatonically-modified polymeric nanoparticles (NPs)	<200 nm dia_{ae} ~4 µm	Exhibited enhanced cellular internalization and cytotoxicity (~5-fold IC50 reduction vs SF) in various lung cancer cell types. Superior ability to inhibit cancer metastasis. SF NPs have a significant effect on *in vitro* tumor cytotoxicity while cationic modifications to the NPs resulted in better cellular internalization.	[123]
Oridonin	Dry powder inhalers lung cancer rat models	PLGA porous microspheres	2.1±0.1 µm	Exhibited efficient lung deposition in vitro and *in vivo* because of their ideal aerodynamic diameters. Showed a high anti-lung cancer effect after pulmonary delivery according to CT images and pathology.	[124]
Telmisartan (Tel) and Losartan (Los)	Nebulizer, NSCLC cell Lines A549 and H1650 A549 orthotopic and metastatic tumour models	Fluorescent polystyrene NPs	~200 nm	Tel treatment attenuated 2.23 and 1.70 fold Collagen 1 expression compared to untreated control and Los groups, respectively. Tel (at four times less dose) was 1.89 and 1.92-fold superior in anticancer activity to Los, respectively in A549 orthotopic and metastatic tumor models (p b 0.05) when given by inhalation route.	[125]
Melatonin (MLT)	Dry powder inhaler A549 lung cancer cells, normal human bronchial cells (BEAS-2B) and lung cancer rat models	Liposomal Mela Tonin Dry Powder Inhaler(LMD)	6.73µm	At the same drug concentration, the inhibitory effect of LMD on A549 lung cancer cells was significantly higher than that of MLT raw materials. Compared with the model group, the treatment group showed significantly fewer tumour nodules and inflammatory cells.	[126]

Table 11: Clinical development on inhalation therapeutics for lung cancer

Drug	Phase	Device and formulation	Dosage	Disease response (n or proportion)
5FU	Pilot	Ultrasonic wave nebuliser, iv solution	2.5 mg/kg 2h before surgery (for operable patients)	Complete response (2/10), partial response (4/10) and no improvements (4/10)
9 nitro-20(S) campothecin	I	Jet nebulizer, liposome dispersion	6.7 to 26.6 µg/kg/d for 5 cons. d for 1, 2, 4 or 6 w (+2 w of rest) 13.3 µg/kg/d, 5 cons. d/w for 8 w (+2 w of rest)	Partial remission and stable disease
Cisplatin	I	Jet nebulizer, liposome dispersion	Dose escalation: 1.5 to 60 mg/m^2 1–4 cons. d in 1–3 w (= 1 cycle) for 1–8 cycles	Stable disease or progressive diseased
Gemcitabine	I	Vibrating mesh nebuliser, iv solution	Dose escalation: 1 to 4 mg/kg 1 d/w for 9 w	Minor response, stable disease, progressive disease
Carboplatin	I/II	Jet nebuliser+10 litres of oxygen solutions	CAR 160–230 mg/d (inh); CAR (iv) 2/3: 320–460 mg or CAR (iv) 3/3: 550–700 mg+DOC (iv) 100 mg/m^2, GA: chemoT iv (CAR+DOC on d1) GB: chemoTinh CAR 1/3 (d1) and iv CAR 2/3+DOC (d1), GC: ChemoTinh CAR (d1–3)+iv DOC (d1)	Survival: GB vs GA (275±13 d vs 211±13 d, p < 0.001) GC vs GA (250±7 d vs 211±13 d, p ≥ 0.05) Complete response (GA: 0, GB: 2, GC: 1), partial response (GA: 5, GB: 6, GC: 4), stable disease (GA: 8, GB: 3 and GC: 5) and progressive disease (GA: 7, GB: 9, GC: 10)
Doxorubicin	I	Breathe-enhanced jet nebuliser, solution pH 3 with 20% ethanol.	Dosage escalation: 0.4 to 9.4 mg/m2 every 3 w (= 1 cycle)	Partial response (1), stable disease (8) and progressive disease (2)

CONCLUSION

Delivery of therapeutic agents through the lungs is a promising way to provide better therapeutic outcomes for drugs. Inhalation routes provide direct delivery of drugs to the lungs without any systemic side effects. However, this area needs more clinical research to provide better insight into the advantages and challenges of inhaled chemotherapeutics. The development of sophisticated inhalers for user-friendly delivery of medicine consistently and efficiently is

necessary. Formulation optimization is essential for proper particle size distribution and efficient lung deposition. Finding a safe pulmonary profile, administering therapeutic doses in a reasonable amount of time, maintaining therapeutic drug concentrations in the tumour site for an adequate amount of time, and limiting environmental contamination by the aerosol during an inhalation session must considered while developing inhaled chemotherapy. The combination of inhalation therapeutics with nanoformulation and other drug delivery systems has immense potential to treat lung cancer.

ACKNOWLEDGEMENT

None

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Written by NP and TB. Edited and Reviewed by VJ and JT

CONFLICT OF INTERESTS

Declared none

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