Review Article

Exploring targeted pulmonary delivery for treatment of lung cancer

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Abstract

Lung cancer is the most malignant cancer today. The treatment of lung cancer continues to be a challenge for oncologists. The direct delivery of chemotherapeutic agents to the lungs could represent a novel therapeutic approach for patients with pulmonary metastases. The large alveolar surface area, the low thickness of the epithelial barrier, and an extensive vascularization make the pulmonary route an ideal route for administration of oncolytics. This paper reviews the research performed over the last and current decades on the delivery of various oncolytics for pulmonary delivery for the treatment of lung cancer. Inhaled drug delivery devices in cancer therapy are also discussed in the present manuscript.

Key words: Lung cancer, oncolytics, pulmonary route

INTRODUCTION

The chronic diseases of the airways and lungs, such as lung cancer, chronic obstructive pulmonary disease, tuberculosis, asthma, idiopathic pulmonary fibrosis, and pulmonary hypertension, impose enormous human suffering globally but their impact is far greater on developing countries and deprived population. These diseases will become one of the leading causes of death worldwide in the near future.[1] The rapid changes in life style, urbanization, and environmental degradation, smoking habit, increasing elderly population in developed countries etc., are all contributing toward the increase in patients with airway diseases.[2] Although significant progress has been made, currently available treatments are not as satisfactory as one would like. Pulmonary disorders can be efficiently treated if high and prolonged drug concentrations are maintained in the lungs and delivered via pulmonary route of drug delivery, which involves the delivery of drugs to the respiratory tract either for the treatment or prophylaxis of airway diseases, or for systemic absorption for the treatment or prophylaxis of other diseases.[3]

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Rationale for pulmonary drug delivery in lung cancer

Lung cancer is one of the most lethal cancers and the second most common cancer in both men and women. The long-term survival rate of lung cancer patients treated by conventional approaches such as surgical resection, radiation, and chemotherapy remains far from satisfactory.[4] Systemic drug delivery is rarely successful because only a limited amount of the chemotherapeutic drugs target lung tumor sites, even when administered at high dose. Most of the chemotherapeutic drugs act on normal cells, inhibiting their growth which makes the patient extremely weak and can even result in death.[5] Improved drug delivery can play a key role in the fight against cancer by delivering anticancer drugs locally to the tumor site in lungs and thus decreasing systemic exposure to the drugs.

In recent years, there is an extensive interest in formulating drugs for pulmonary delivery for reasons that remain significant. The interest in this approach has been stimulated by the potential utility of the lung as a portal for the entry of drugs including peptides and proteins. In fact, the lungs are an efficient port of entry for drugs to the bloodstream due to the large surface area available for absorption (about 100 m^2), the very thin absorption membrane (0.1-0.2 μm), and the elevated blood flow (5 L/min), which rapidly distributes molecules throughout the body. Moreover, the lungs exhibit relatively low local metabolic activity and unlike the oral route of drug administration, pulmonary inhalation is not subject to first-pass metabolism.[6] Pulmonary delivery has been used to treat local pulmonary diseases such as asthma and microbial infections as well as systemic diseases like diabetes and it has a great potential for gene delivery, but its application to the treatment of cancer is also giving promising results.[7] In primary or metastatic lung cancer, administration of oncolytics via inhalation could increase exposure of lung tumor to the drug, while minimizing systemic side effects.[8]

Drug carriers in cancer therapy

Over the last decade, there has been an increasing interest in developing pulmonary drug delivery systems suitable for cancer therapy. With the approval of Pfizer's Exubera® (human insulin [rDNA origin]) inhalation powder, the promise of pulmonary delivery has been delivered and this advance has opened up the possibility of other drug candidates for pulmonary delivery. A number of micrometer and nanometer-sized drug carrier systems such as liposomes, polymer conjugates, polymeric micelles, microparticles, and nanoparticles (NPs) have been investigated to selectively deliver various anticancer bioactives at the tumor site and are discussed in the following subsections of the manuscript.

Inhalable nanoparticles

Nanoparticle technology had emerged on the commercial scale when the first product using NPs, Abraxane®, an injectable suspension of albumin NPs with bound paclitaxel was used for cancer therapy, and became available in 2005.[9] NPs with their special characteristics such as small particle size, large surface area, and the capability of changing their surface properties have several advantages compared to other delivery systems.[10] Intavenous injection of nanosized carriers results in their accumulation in the liver which significantly reduces the dose that reaches the tumor site.[4] Therefore, targeted aerosolized NP delivery to the lungs is an emerging area of interest which will bypass the presystemic metabolism.

Solid lipid nanoparticles

Videira *et al.* carried out the preclinical evaluation (in experimental mouse mammary carcinoma) of a pulmonary delivered paclitaxel-loaded lipid nanocarrier for an antitumor effect.[11] The paclitaxel-loaded solid lipid NP treatment was more effective in decreasing the number and size of lung metastases, in comparison with the treatment using intravenous administration of the same drug using the conventional formulation.

Lipid nanocapsules

Hureaux *et al.* developed lipid nanocapsules (LNCs) for the aerosol delivery of paclitaxel.[12] The structure, drug payload, and cytotoxicity of nebulized LNCs were compared with fresh LNCs. The results showed that LNC dispersions could be made into aerosols by using mesh nebulizers without altering the structure of LNC.

Polymeric nanoparticles

A dry powder formulation of doxorubicin (DOX) encapsulated in NPs was developed by Azarmi *et al.* This vector was produced by a method of polymerization/emulsion and then dried. After being re-dissolved in deionized water, the particles had an average size of 173 ± 43 nm. The DOX-loaded NPs showed enhanced cytotoxicity compared to free DOX.[13]

Tseng *et al.* presented gelatin NPs with biotinylated epidermal growth factor set at the outside of the structure to allow the active targeting to the EGF receptor for lung cancer targeting.[5] These NPs had a diameter between 200 and 300 nm and could encapsulate cisplatin. Aerosol droplets of the novel formulation developed were generated using a nebulizer and delivered to mice model of lung cancer. They determined that aerosol droplets formed using these NPs were deposited at the lower respiratory tract and observed that these droplets accumulated in the cancerous lung tissue by using a live imaging procedure for monitoring aerosol deposition. They also demonstrated that the gelatin NPs delivered by inhalation did not cause lung inflammation and were thus safe for use.

Roa *et al.* incorporated DOX-loaded NPs into inhalable effervescent and non-effervescent carrier particles using a spray-freeze drying technique [Figure 1]. The prepared inhalable powders were tested in a tumor bearing Balb/c mouse model. They observed that the animals treated with effervescent NP carrier showed longer survival times than animals treated with non-effervescent NP carrier and also the lungs of animals treated with inhalable effervescent DOX NPs showed fewer and much smaller tumors compared to the control groups as visualized by MRI imaging [Figure 2]. Their study demonstrated that inhalable effervescent DOX NPs are an effective way to treat lung cancer.[4]

Lipid-coated nanoparticles

Hitzman *et al.* formulated an *in vivo* pulmonary delivery of 5-fluorouracil (5-FU) in lipid-coated nanoparticles (LNPs) system to a hamster model.[14] The 5-FU LNPs consisted of a core composed of 20% (w/w) 5-FU, 20% (w/w) FITC-dextran, and 60% (w/w) poly-(glutamic acid) with a shell composed of 33% (w/w) cetyl alcohol and 67% (w/w) tripalmitin. The LNPs were suspended at 5 mg/mL in a 0.01% Pluronic F68 aqueous solution and atomized into droplets using an ultrasonic driver. The produced droplets were dried and then directed into a nose-only rodent aerosol exposure chamber for inhalation by hamsters at a dose of 30 mg LNPs/kg body

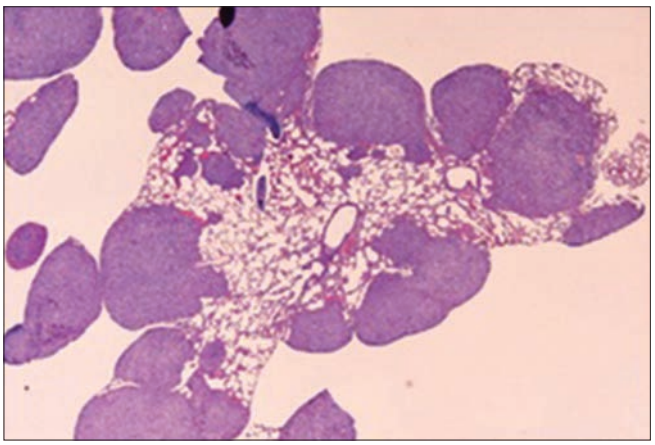

Figure 1: Lung section of a mouse treated with a doxorubicin solution intravenously. Bulky tumor nodules are easily observed (20× magnification, hematoxylin and eosin staining). "Reprinted from Journal of Controlled Release, 150, Roa *et al.*, Inhalable nanoparticles, a non-invasive approach to treat lung cancer in a mouse model, 49-55, 2011, with permission from Elsevier"

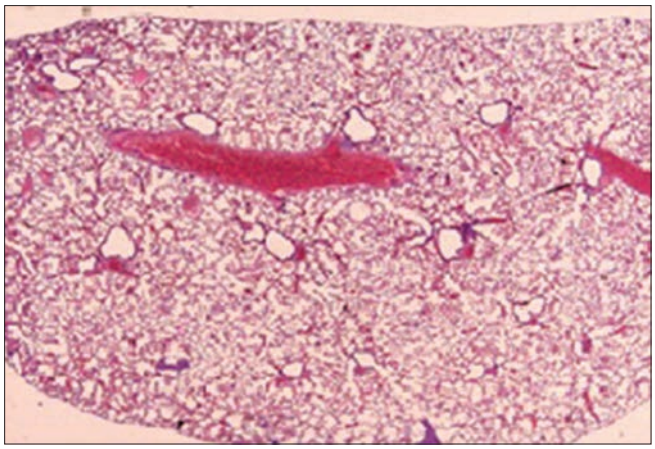

Figure 2: Lung section of mouse treated with effervescent doxorubicin nanoparticle powder (20× magnification, hematoxylin and eosin staining). "Reprinted from Journal of Controlled Release, 150, Roa *et al.*, Inhalable nanoparticles, a non-invasive approach to treat lung cancer in a mouse model, 49-55, 2011, with permission from Elsevier"

weight (1.5 mg 5-FU/Kg body weight). The pharmacokinetics of the 5-FU LNPs and total 5-FU in the lung, trachea, larynx, esophagus, and serum were studied. It was found that effective local targeting as well as sustained efficacious concentrations of 5-FU in the expected tumor sites were achieved. The results suggested the use of 5-FU containing LNPs for treating squamous cell carcinoma of the lung.

Nanostructured lipid carriers

Patlolla *et al.* prepared celecoxib-nanostructured lipid carrier (Cxb-NLC) NPs by the hot melt homogenization technique.[15] The particle size and entrapment efficiency of the formulation were 217 ± 20 nm and >90%, respectively. Cxb-NLC showed dose and time-dependent cytotoxicity against A549 cells. Based on the results of pulmonary administration of the formulation to Balb/c mice, it was proved that most of the nebulized NPs were able to deposit in the alveolar region of the mice lungs and also enhanced the Cxb lung residence time resulting in improved Cxb pulmonary bioavailability compared to solution formulation.

Nanocomposite particles

Tomoda *et al.* prepared the PLGA NPs with the anticancer drug (TAS-103) in the form of nanocomposite particles by the spray drying method with trehalose as an excipient.[16] It was observed that cytotoxicity of the prepared formulation against A549 cells was higher than that of free drug. When the nanocomposite particles were administered in rats by inhalation, drug concentration in lungs was higher than that after intravenous administration of free drug.

Liposomal drug delivery system

For pulmonary delivery, liposomes have many advantages over other vehicles as they are less toxic and show good compatibility with lung surface cells because they are prepared with phospholipids endogenous to the lung as surfactants. They can also serve as a biodegradable pulmonary reservoir with enhanced pulmonary residence time, decrease mucociliary clearance of drugs, prevent local irritation, and increase drug potency.[17] However, the major drawback associated with conventional liposomal formulations is long-term instability. Thus, liposomes can be freeze-dried or spray-dried to improve the stability and can be formulated as liposomal dry powder for inhalation which is a useful inhalational technology for pulmonary delivery.

Anabousi *et al.* carried out *in vitro* assessment of transferring-conjugated DOX-loaded liposomes as drug delivery systems for inhalation therapy of lung cancer.[18] They observed that the novel formulation showed enhanced cytotoxicity toward cancerous human pulmonary epithelial cell lines (A549 cell line, Calu-3 cell line, and 16HBE140 cell line) in comparison to non-cancerous human alveolar AT I/AT II cells in primary culture. The study suggested that such delivery systems might have the potential to selectively target transferring receptor-bearing tumor cells and to spare non-tumor cells, when applied topically as an aerosol to tumor-diseased lungs.

Zhang *et al.* investigated *in vitro* release, *in vivo* distribution (in mice) and severity of damage (in rat lungs) following pulmonary delivery (intratracheal instillation) of 9-nitrocamptothecin (9-NC) liposomes.[7] Their results demonstrated that 9-NC liposomes have great potential by the pulmonary route to act as local sustained release reservoir and were safe and non-irritating to the lungs.

Microparticles

Alipour *et al.* prepared biodegradable paclitaxel loaded alginate microparticles (for pulmonary delivery) by the emulsification/gelation method and characterized them.[8] They assessed the *in vitro* cytotoxicity activity of paclitaxel loaded microparticles using human non-small cell lung cancer cell lines (A549 and Calu-6). The results showed that exposure of cells to pure paclitaxel and paclitaxel-loaded microparticles effectively inhibited the growth of A549 and Calu-6 cells similarly in a concentration- and time-dependent manner.

Polymeric micelles

Gill *et al.* evaluated the potential of paclitaxel-loaded micelles fabricated from PEG_{5000}-DSPE as a sustained release system following pulmonary delivery.[19] PEG_{5000}-DSPE micelles containing paclitaxel were prepared by the solvent evaporation technique. They investigated tissue distribution and plasma pharmacokinetics of the PEG-lipid micelles after intratracheal and intravenous administrations, in addition to intratracheally administered taxol to male Sprague-Dawley rats. Toxicological profile of PEG_{5000}-DSPE was also demonstrated. Intratracheally administered polymeric micellar paclitaxel showed highest accumulation of paclitaxel in the lungs with AUC_{0-12} in lungs being 45-fold higher than intravenously administered formulation and 3-fold higher than intratracheally delivered taxol. Toxicity studies showed no significant increase in levels of lung injury markers in the PEG_{5000}-DSPE-treated group as compared to the saline-treated group. 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 PEG_{5000}-DSPE micelles are suitable as pulmonary drug carriers.

Inhalation gene therapy

Gene therapy refers to the transfer and expression of genes for therapeutic applications in the target cell.[20] It is a novel approach in treatment of genetic disorders including lung disorders and cancer. Currently, more than 65% of gene therapy clinical trials have been aimed to cure cancer.[21]

Jiang *et al.* prepared and evaluated Folate-Chitosan-graft-polyethylenimine (FC-g-PEI) copolymer as a lung cancer cell-target small hairpin RNA (shRNA) carrier.[22] They prepared FC-g-PEI copolymer by an imine reaction between periodate-oxidized folate-chitosan and amine groups of low-molecular-weight PEI. The composition of FC-g-PEI copolymer was characterized using ^1H nuclear magnetic resonance while the condensation capability of the copolymer with shRNA was evaluated using 1% agarose gel electrophoresis. It also showed low cytotoxicity compared to PEI 25K control in three different cell lines, i.e. KB, A549 and HeLa. They had also demonstrated that aerosol delivery of FC-g-PEI/Akt1 shRNA complexes suppressed lung tumorigenesis in a urethane-induced lung cancer model mouse through the Akt signaling pathway.

Mohammadi *et al.* reported that Chitosan-DNA-Fibronectin Attachment Protein of *Mycobacterium bovis* (Chitosan-DNA-FAP-B) NPs are good candidates for targeted gene delivery to FAP-B receptors of the lung epithelial cell membrane.[23] The prepared NPs were nebulized to mice using air jet nebulizer and it was observed that nebulization did not affect the physicochemical properties of NPs with respect to DNA binding ability, size, and zeta potential. Through this study, it was concluded that the level of gene expression of chitosan-DNA-FAP-B NPs in the mice lungs was 16-fold higher than chitosan-DNA NPs.

Okamoto *et al.* formulated two reporter genes, i.e., pCMV-Luc (luciferase expression plasmid driven by the cytomegalovirus promoter) and pEGFP-F (plasmid DNA encoding farnesylated enhanced green fluorescent protein) in mannitol powders (as a dry powder carrier) with chitosan (as a non-viral vector) to investigate gene expression and distribution in normal and tumorous tissues in the lungs.[24] The powders of pCMV-Muβ encoding murine interferon-β were intratracheally administered to mice burdened with lung metastasis. It was observed that the genes expressed in both normal and tumorous tissues and the intratracheal powder resulted in higher expression than the intravenous or intratracheal solution. They also reported that at the lowest dose (1 μg), the intratracheal solution, and powder were more effective at suppressing lung weight and the number of pulmonary nodules than the intravenous solution. Thus, their study suggested that the intratracheal pCMV-Muβ powder was more effective at suppressing the growth of lung metastasis than the intravenous or intratracheal pCMV-Muβ solution.

Jinturkar *et al.* developed and assessed comparative enhancement in cytotoxicity of liposomal etoposide and docetaxel in non-small cell lung cancer cell lines (H-1299 and A-549) after pre-treatment and co-administration of the p53 tumor suppressor gene.[21] Liposomes were prepared by the thin film hydration method. The developed liposomes and lipoplexes (liposome-DNA complexes) demonstrated enhanced cytotoxicity of 13-28% after p53-drug co-administration and 41-63% after p53 pre-treatment. All the formulations when developed as dry powder inhalers (DPIs) showed a significant *in vitro* lung deposition pattern in the Anderson cascade impactor.

Miscellaneous

Wauthoz *et al.* compared the efficacy of local delivery of temozolomide (alkylating agent) by inhalation to intravenous delivery in a B16F10 mouse melanoma metastatic lung model.[25] They formulated suspension of the drug and an endotracheal administration device was used to aerosolize the suspension. They observed that the global *in vivo* antitumor activity of the inhaled temozolomide provided a median survival period similar to that for intravenous drug delivery and 3 out of 27 mice survived with almost complete eradication of lung tumors.

Xie *et al.* synthesized hyaluronan-cisplatin (HA-Pt) conjugate which was delivered via endotracheal instillation to female Sprague-Dawley rats.[26] They observed that the total platinum level in the lungs of the HA-Pt lung instillation group was 5.7-fold and 1.2-fold higher than the cisplatin intravenous (i.v.) group at 24 and 96 h, respectively. They found that in the brain and kidneys, the cisplatin i.v. group had higher tissue/plasma ratios compared to the HA-Pt lung instillation group. They also performed cell toxicity studies in the human lung cancer cell line A549 and observed that HA-Pt conjugates had similar toxicities as compared to cisplatin which suggested that the antitumor activity of cisplatin was fully preserved after conjugation to hyaluronan.

Van Putte *et al.* compared the drug uptake of gemcitabine and carboplatin during selective pulmonary artery perfusion (SPAP) and intravenous infusion (IV). They used female Dutch Landrace pigs for the study and observed higher pulmonary gemcitabine peak concentrations and AUC after SPAP gemcitabine and gemcitabine/carboplatin compared to IV.[27] They also observed that SPAP carboplatin and gemcitabine/carboplatin resulted in higher pulmonary carboplatin peak concentrations compared to IV while AUC was higher after SPAP gemcitabine/carboplatin. Based on this pharmacokinetic study, they concluded that SPAP is a more efficient technique of drug delivery for the treatment of primary lung cancer compared with intravenous infusion.

Mahesh *et al.* administered 5-azacytidine (5-Aza) solution directly into the trachea in imprinting control region (ICR) mice and in nude mice bearing orthotopic human lung cancer xenografts.[28] Based on *in vitro* results, it was concluded that 5-Aza inhibited the growth of human lung cancer cell lines H226, H358, and H460 in a dose-dependent manner, while the animal studies revealed that the intratracheal 5-Aza was about

3-fold more effective than intravenous 5-Aza in prolonging the survival of mice bearing orthotopic H460 and H358 x enografts, and did not cause any detectable toxicity.

Inhaled drug delivery devices

For any drug to be delivered to the lungs by inhalation, it has to be formulated as an aerosol.[3] Aerosol preparations are stable dispersions or suspensions of solid materials and liquid droplets in a gaseous medium. Drug delivered by aerosol is deposited in the airways by gravitational sedimentation, inertial impaction, and diffusion as summarized in Table 1. By the aerosol method, oncolytics can be efficiently and noninvasively delivered to lung cancer area by inhalation. Thus, the drug can directly exert its effects on lung cancer cells before it gets degraded or metabolized. Targeted aerosol delivery can also increase the retention time of the drug in the lungs resulting in improvement of the pulmonary receptor occupancy at the expense of systemic exposure, thereby reducing the systemic side effects of the drug. Inhalation treatment is a noninvasive approach that can be performed at home under supervision, thus reducing the frequency of clinical visits and yielding greater patients compliance.[5] There are two primary modes of pulmonary aerosol administration, i.e. nasal and oral inhalation. As the nasal inhalation is limited by anatomical features such as narrower airway lumen, therefore oral inhalation of compounds is generally preferred.[29]

Although there is a large number of devices which can be used to generate particles [Table 2], the most commonly used pulmonary delivery devices are pressurized metered-dose inhalers (pMDI), nebulizers, and DPIs.[29] A good delivery device should generate an aerosol of suitable size (0.5-5 μm) and provide reproducible drug dosing. It must protect the physical and chemical stability of the drug formulation. It should also be a simple, convenient, inexpensive and portable device.[6]

Table 1: Mechanism of aerosol deposition (Yang *et al.*, 2008)[30]

Site	Size (μm)	Mechanism
Large airways	5-9 (slow inhalation), 3-6 (fast inhalation)	Impaction
Smaller airways	1-5	Gravitational sedimentation
Respiratory bronchioles	1-3	Gravitational sedimentation
Alveoli	≤0.5	Brownian diffusion

Table 2: Devices for generating particles (Groneberg *et al.*, 2003)[29]

Device	Particle size (μm)
Metered-dose inhaler	1–35
Jet nebulizer	1.2–6.9
Ultrasonic nebulizer	3.7–10.5
Spinning disc	1.3–30
Dry powder	Flow-related
Vibrating orifice	0.5–50
Condensation	1.1
Solid particle	0.1–4

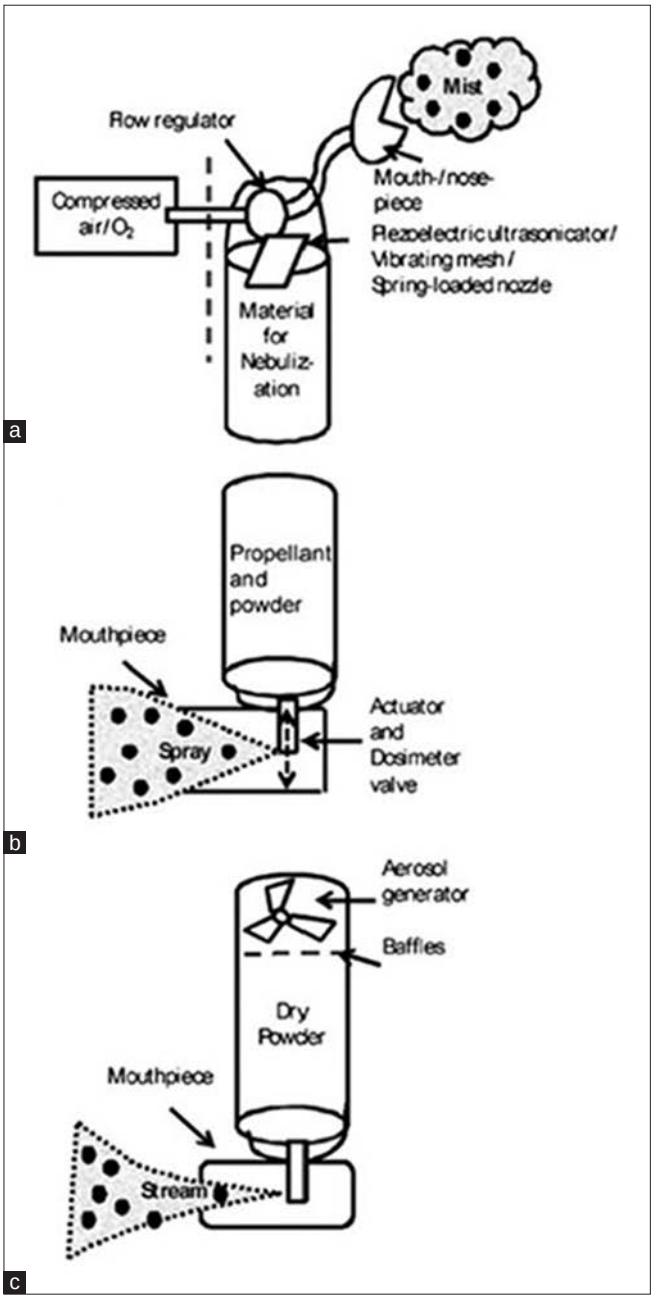

Figure 3: Schematic illustration of therapeutic aerosol delivery. (a) A nebulizer may achieve atomization of droplets by a stream of compressed air, or through piezoelectric sonication, or by mechanical means such as vibrating mesh or spring-loaded nozzle. (b) A pMDI uses a dose-metering valve to deliver medicament suspended in a propellant spray. (c) A DPI delivers a more gentle stream of inhalant through indrawn breath. "Reprinted from Tuberculosis, 91, Misra *et al.*, Inhaled drug therapy for treatment of tuberculosis, 71-81, 2011, with permission from Elsevier"

Nebulizers

Nebulizers were the first devices developed for inhalation therapy market. These utilize compressed air or ultrasonic power to break up a formulation containing drugs into inhalable aerosol droplets.[31] This technique consists of dispersing solid or phase-separated drug delivery systems into droplets suspended in a small amount of medium.[32] The patient is required to inhale

the mist through the nose and mouth [Figure 3a]. Compared to pMDI and DPIs, nebulizers are usually bulkier, require longer administration time, and have lower delivery efficiency.[33]

Pressurized metered-dose inhalers

The most familiar technique of administering medication to the airways and lungs is the pressurized metered-dose inhaler.[31] pMDI contains active substance, dissolved or suspended in a propellant system, which contains at least one liquefied gas in a pressurized container that is sealed with a metering valve [Figure 3b]. The actuation of the valve delivers a metered dose of the medicament in the form of an aerosol spray, which is directed by a suitable actuator for administration via oral or nasal inhalation.[3] pMDIs are portable, multi-dose, and usually have fairly uniform dosing but application of pMDI technology is limited by the requirement of breath coordination, high oral deposition, and limited dose per actuation.[31]

Dry powder inhalers

To overcome the problems encountered with nebulizers, alternative simple and small inhalers that do not use propellants were developed. DPIs are aerosol systems in which drugs are inhaled as clouds of fine particles. The drug is either pre-loaded in an inhalation device or filled into hard capsules or foil blister discs which are loaded into a device prior to use [Figure 3c]. DPIs are portable, easy to operate (breath actuated), inexpensive, propellant free (ozone friendly) and show improved stability of formulation as a result of the drug state.[3] However, due to strong interparticle forces, drug delivery by DPI is highly dependent on inspiratory flow rate, which varies greatly and also moisture ingress can create stability issues.[31]

CONCLUSIONS

Pulmonary drug delivery is becoming more and more important. This is due to the specific physiological environment of the lung as an absorption and treatment organ. The development of inhalable insulin can be seen as a milestone in pulmonary drug delivery.

Effective drug delivery is essential in achieving improved therapeutic outcome when treating lung cancer. The integration of nanotechnology and pulmonary delivery of drug aerosols represents a new and exciting frontier for pharmaceutical dosage form design to increase the bioavailability and patient compliance, as supported by the results of studies using NPs as a therapeutic agent for lung and systemic diseases.

Advancement in areas of biotechnology, device design, and a greater understanding of delivery barriers in the lung will undoubtedly lead to an expanse of opportunities for fully exploiting the pulmonary route for drug delivery.

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