ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 10, 2023

Online - 2455-3891
Print - 0974-2441

Review Article

AMELIORATION IN APPROACHES FOR ENHANCED PULMONARY DRUG DELIVERY

SURAJ CHOUDHARY*, APARAJITA PATIL

Department of Pharmaceutics, Oriental College of Pharmacy, Navi Mumbai, Maharashtra, India.
***Corresponding author: Suraj Choudhary; Email: surajchoudhary2228@gmail.com**

Received: 12 April 2023, Revised and Accepted: 25 May 2023

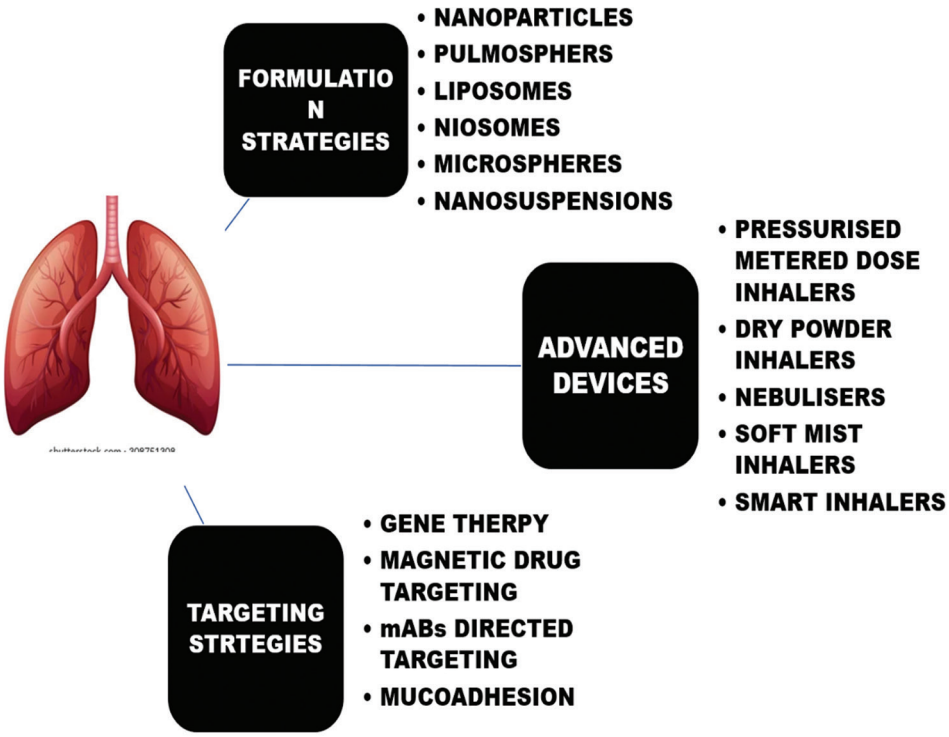
ABSTRACT

Pulmonary disorders including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and other severe conditions like cancer have indeed made pulmonary drug delivery systems, both, an area of interest as well as concern. The mortality rate, around 8%, has enabled researchers to develop novel technologies for efficient drug delivery and reduced side effects. As the drug delivery through inhalation involves two major influencing factors, that is, formulation type and the device used for inhalation, various strategies have been designed with an intent to upgrade the existing drug formulations and devices used. Apart from this, various targeting strategies including gene therapy and magnetic targeting so as to improve the target specificity of the administered drug in the regions of the pulmonary system have been developed. In spite of these advancements, pulmonary drug delivery appears to be challenging in terms of formulation design and animal model design as well as lack of availability of FDA-approved excipients for inhalation. Persistent efforts have been made by the researchers in combining various strategies to negate the drawbacks/limitations of pulmonary drug delivery so as to develop a drug delivery system with improved efficacy and negligible adverse effects.

Keywords: Advanced approaches, Devices, Drawbacks, Formulation, Inhalation, Pulmonary drug delivery system.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i10.48081. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

GRAPHICAL ABSTRACT



An overview of approaches for enhanced pulmonary drug delivery.

INTRODUCTION

Millions of people have indeed been reported to be affected by pulmonary disorders as of today, and the number of patients rises continually. Asthma, bronchiolitis, the common cold, cough, and more severe conditions including cystic fibrosis (CF), lung cancer, and pulmonary hypertension all belong to the category of pulmonary disorders, which constitute the third leading cause of mortality worldwide [1]. The extensive impact rate and elevated mortalities make it obligatory for the researchers to deviate attention toward the betterment of pulmonary drug delivery systems (PDDS) [2,3]. Due to the factors such as high vascularisation, large epithelial surface area, thin alveolar absorptive membranes, and high solute exchange capacity, PDDS proves to be an efficient method for local as well systemic effects, making it an ideal target for drug delivery. Ease of administration, non-invasive method, and surpassing of first-pass metabolism are other key reasons to emphasize the development of PDDS [4].

However, there are several barriers associated in the pulmonary drug delivery, namely, mechanical barrier due to complex network of bronchial tissues, chemical and immunological barrier that includes proteolytic enzymes and alveolar macrophages, and behavioral barrier due to the non-compliance by the patients to the therapy [5]. There exists an impeccable need to overcome these barricades, to enhance the drug delivery in the pulmonary systems. The persistent attempts to broaden the spectrum of efficacious drug delivery in the pulmonary system have been broadly grouped by three approaches [3,6]. The first strategy being the development of formulations such as pulmospheres, liposomes, niosomes, microspheres, nanosuspensions, and lyophilized powders for pulmonary drug delivery, second being target-based strategies including genetically engineered particles, monoclonal antibodies (mAB) directed targeting for enhanced pulmonary drug delivery and lastly the modifications in pulmonary drug delivery devices namely pressurized metered dose inhalers (pMDI), nebulizers, soft mist inhalers (SMI), and smart inhalers [7].

Collectively, the advances in terms of pulmonary drug delivery have been significant; however, they are associated with a set of limitations and challenges. Poor adherence to the inhaled regimen, lack of patient compatibility with the modernized devices, large size, and volume of device, limited number of FDA approved excipients for inhalation, and difficulty in development of animal models for pulmonary formulations are few of the said limitations [8]. Considering the development in the area drug delivery technology, it would be convenient to say that the fate of pulmonary drug delivery will not remain restricted to few diseases, but is prone to expand its applicability over a variety of common conditions including pulmonary fibrosis, lung transplant rejection, and tuberculosis as well as pulmonary aspergillosis, in an attempt to fulfill unmet needs [9,10].

ADVANTAGES OF PDDS

Recent advancements in the molecular and post-genomic era have enabled better understanding of molecular, physiological, and biochemical composition of lung, molecular basis of the lung infections, and various barriers associated with drug delivery. Considering the availability of vital data regarding pulmonary system and its numerous advantages over the other routes, the drug delivery system emphasizing the pulmonary route has gained much attention. Among the several superiority factors, few are listed advantages of PDDS [11]. Due to their extensive surface area (almost 100 m^2), well-established vascular system, and thin alveolar wall, the mucosa of the lungs levels of drug metabolizing enzymes in intracellular and extracellular compartments, pulmonary drug delivery devices bypass the hepatic first-pass metabolism and poor gastrointestinal absorption. For pulmonary drug delivery, several proteins and peptides are viable alternatives [12,13]. The onset of action is significantly rapid, for example, an inhaled drug generally takes 15–30 min to produce action whereas an oral dose of bronchodilator may take around 2–3 h. The drug delivery remains site-specific within the diseased pulmonary system, thereby reducing the overall amount of drug administered by the patient [14]. PDDS are also known for their enhanced efficacy, potentially reduced adverse effects, improved bioavailability of drugs, and reproducible absorption kinetics. Due to their less invasive nature, elevated patient compliance is observed [15].

BARRIERS TO PULMONARY DRUG DELIVERY

Till the second half of the twentieth century, pulmonary drug delivery was an arduous issue due to insufficient awareness about pulmonary defense systems. In spite of the contemporary expansion of research and knowledge in the area of pulmonary system, there exist indisputable barriers, thus making drug delivery through the pulmonary route a strenuous challenge. Pulmonary drug delivery is significantly complicated due to various barriers, namely, mechanical, chemical, immunological, and behavioral barriers [16-18].

Mechanical barriers

The bronchial tree, a complex network of airway tissues present in the lungs, enables drug molecules traveling from the alveolar region to their targets in the epithelial region to deposit themselves anywhere along the airway bifurcation. The mechanical barriers are highlighted in diseased conditions, including inflammation, mucus hypersecretion, or bronchoconstriction, as the airways get narrowed. Mucocilliary clearance of lungs proves to be a significant mechanical barrier [16,19]. The drugs already marketed for the treatment of pulmonary diseases as well as those under clinical trials are described in Table 1.

Chemical and immunological barriers

The chemical and immunological barriers in pulmonary drug delivery are mainly composed of alveolar macrophages, surfactants, and proteolytic enzymes [16]. Alveolar macrophages are described as phagocytic cells that engulf foreign particles and eradicate them from the lungs. Surfactants prevent the inhaled particles from adhering to the epithelial surface of the lungs, making the particles accessible to the macrophages to be engulfed and eliminated by them. The hydrolysis of proteins and peptides occurs in the lungs attributable to the proteolytic enzymes cathepsin H and endopeptidase [16,20].

Behavioural barrier

Behavioural characteristics of the patients like intentional or unintentional non-adherence to the therapy could potentially affect how effectively it works. In addition, variables including patient non-compliance, improper handling of the device during inhalation, inefficient, and varied drug deposition in the lungs may result in inadequate or insufficient therapeutic efficacy [19] (Fig. 1).

FORMULATION STRATEGIES FOR PULMONARY DRUG DELIVERY

Due to its local and systemic effects, the pulmonary route of drug administration has drawn the interest of researchers, who are striving to enhance the drug formulation to achieve greater efficacy and improved therapeutic action [14]. Several more current revelations in drug delivery techniques reduce expected toxicity and boost therapeutic efficacy. To address pulmonary problems, a number of dosage formulations have been developed and evaluated [23].

Nanoparticles

Nanoparticles, with a size range of 1–100 nm, are the particulate systems with distinctive features that are essential for drug delivery for a variety of pulmonary disorders, including lung cancer, tuberculosis, and asthma. Due to the incredibly small size of the nanoparticles, they can effectively be airborne and delivered to the alveoli, making them ideal for the pulmonary delivery of drug [24]. To combat tuberculosis, Sung *et al*. synthesized Rifampicin nanoparticles that were encapsulated in poly lactic coglycolic acid (PLGA) employing the solvent evaporation method. The active pharmaceutical ingredient is dissolved, trapped, and encapsulated in nanoparticles using a variety of techniques, also including polymers or a vector [25]. In regards of pulmonary drug administration, nanoparticles are essential for accomplishing the goal of target specificity. Their larger specific surface area improves the

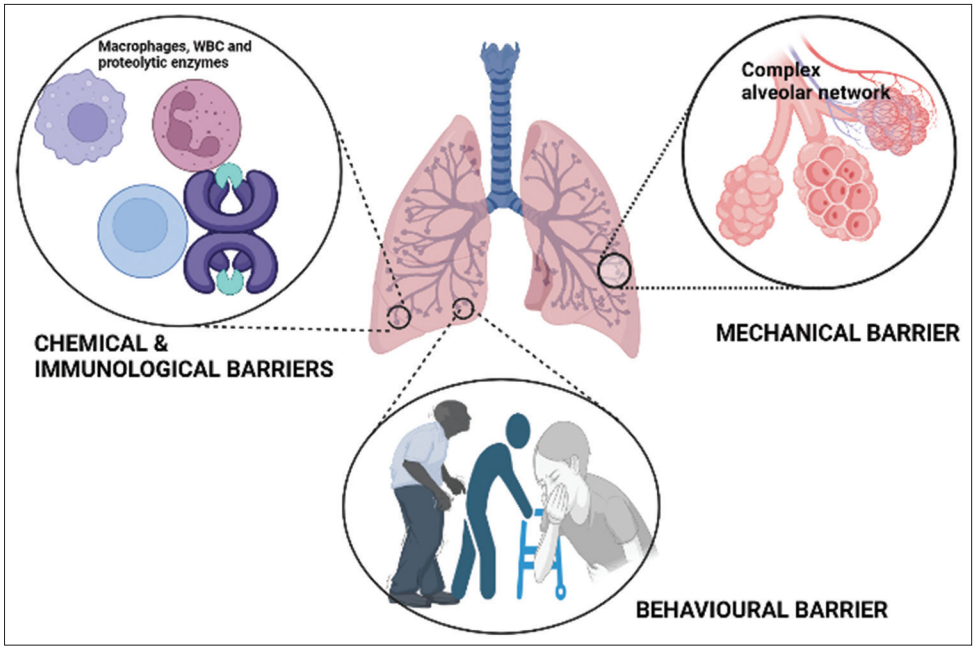


Fig. 1: The figure represents different kinds of barriers for pulmonary drug delivery [16,20-22]. Note: The barriers are categorized into three types namely chemical and immunological barrier, mechanical barrier, and behavioural barrier [11,13-16]

bioavailability profiles as well as solubility of poorly soluble drugs like corticosteroids [26].

Liposomes

Amphiphilic molecules or particles constitute liposomes, which are microscopic or nano vesicles that spontaneously form unilamellar or multilamellar concentric bilayers, partitioned by water compartments. As the tail is made up of a hydrophobic group and the head is made up of a hydrophilic group, they have both lipophilic and hydrophilic characteristics. As a result, liposomes provide the added benefit of making the process relatively simple because of their dual nature [27]. For the treatment of various lung disorders and even using the lungs as a drug depot for systemic delivery, they can be developed with lung endogenous phospholipids as surfactants, having a much wider range of size that can be used to deliver both hydrophilic and lipophilic drugs. In experimental laboratory rats, Bi *et al*. demonstrated an improved pulmonary delivery efficiency employing insulin-loaded liposomes generated by freeze drying process [17,18]. To deliver insulin to the lungs using liposomal carriers, Sun *et al*. developed insulin-encapsulated liposomes which exhibited a 40% maximum encapsulation efficiency [28].

Pulmospheres

Small porous particles with a distinctive sponge-like particle shape, a low particle density of <0.1 g/cm^2, and excellent redispersibility properties constitute pulmospheres [7,29]. They are synthesized using the spray drying technique, which involves rapidly evaporating a liquid feed stock with hot gas to produce a dry powder. There are three ways that drugs can be included in or combined with pulmosphere formulations: Solutions, suspensions, and carrier-based systems. Regardless of their physicochemical features, a wide variety of drugs can be delivered to the lungs by means of pulmospheres [29].

Niosomes

The vesicles termed as niosomes are composed of non-ionic surfactants and self-assembled in aqueous media to form a closed bilayer structure. In this bilayer structure, the hydrophilic head remains in touch with the aqueous solvent while the hydrophobic sections are directed away from it [7,11]. By altering the composition of the vesicles, such as its size, tapped volume, lamellarity, concentration, and surface charge, it is feasible to modify its properties. The use of niosomes in the treatment of malignant diseases, such as lung cancer, has been confirmed to be very effective [11].

Microspheres

The drug is either dissolved or uniformly dispersed in microspheres, which are homogeneous monolithic spherical colloidal particles having particle size smaller than 200 micrometres. Microspheres are one of the potential dosage forms for target-specific delivery in pulmonary disorders, according to reports [30,31].

Nanosuspension

Nanosuspensions are described as colloidal dispersion of pure drug particles with an average particle size between 300 and 700 nm which are stabilized by surfactants. Nanosuspension has been widely used as a target-specific tool in therapeutics due to its advantages over solution formulation, including the need for a miniscule amount of cosolvent, which reduces its toxicological effects and potential *in vivo* interference; a broader dose range because the concentration of nanosuspension is not constricted by solubility in the vehicle; better content uniformity; and enhanced drug penetration in deep lungs and narrower airways [32].

Microemulsions

Microemulsions, comprised of water, oil, and cosurfactant, ranging from 5 to 100 nm, are primarily are often used for controlled drug release and site-specific targeting as well as for reducing the rate of degradation [23,33]. On the basis of the dispersed particles, microemulsions can be water in oil microemulsion, oil in water microemulsion, and bio-continuous microemulsion. They are used as drug delivery vehicles for pulmonary systems as they offer a range of benefits including thermodynamic stability, enhanced drug solubilization, and enhanced bioavailability [13,17]. Lecithin inverse microemulsions were developed by Sommerville *et al*. for pulmonary administration using dimethyl ether and propane as propellants. Polar chemicals have been found to be soluble in the inverse microemulsions (Fig. 2) [33].

ADVANCES IN PULMONARY DRUG DELIVERY DEVICES

In case of the pulmonary system, the efficacy and potency of the drug on the subsequent disease condition are not just narrated by the nature

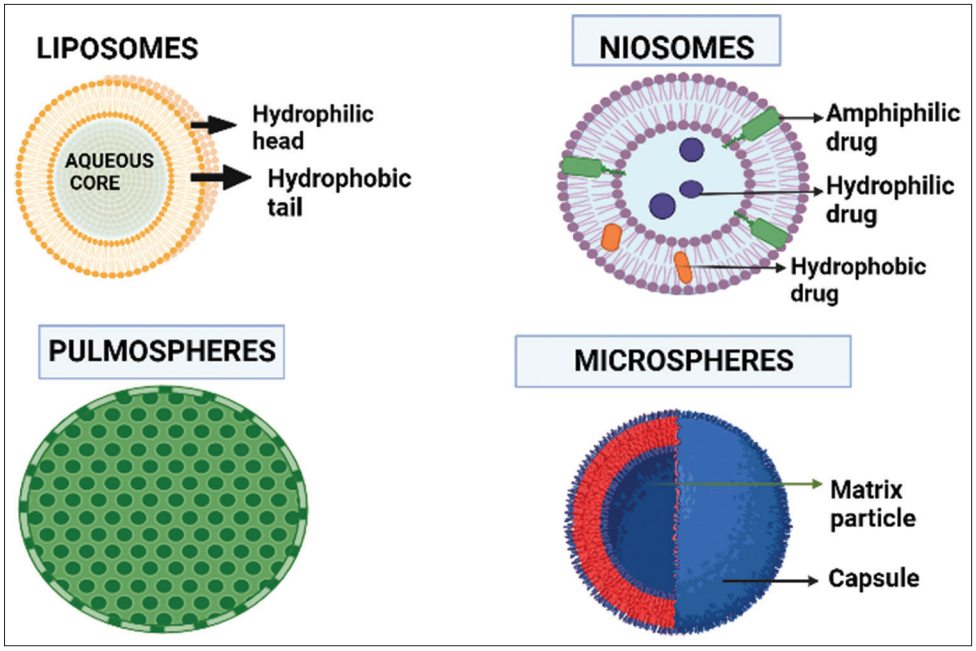


Fig. 2: A figure representing structures of various micro/nano formulations [11,27,29,30]. A figure representing structures of various micro/nano formulations [8,21,22,23]

of the drug, but also the device being used as a tool for drug delivery. As these aspects influence the deposition of inhaled aerosols in the lungs, the selection of an inhaler should take into account the requirements of the patients, inhalation method, and preference [9]. The selection of adequate device for drug delivery remains crucial in inhalation therapy since there exists intense scarcity in availability of an ideal inhaler [38]. The goal of innovation in terms of devices for the management of pulmonary disorders should be to overcome the limitations caused by various pathological conditions. Needless to say, over the past few decades, there has been gradual improvement in the performance of inhaler devices, while few devices with better drug delivery profile are still under investigation [14,18].

pMDI

The metered dose inhalers (MDI) consist of a pressurized medicine canister in a plastic holder with a mouthpiece that, when sprayed, delivers a precise, consistent dose of medication. There are two methods for using MDIs, first and the preferred being using the MDI with a chamber and second, using MDI without a chamber [8] pMDI has offered a set of few vital advantages, namely, multi-dosing, consistent dosing, consistent dosing, rapid delivery, convenience of usage, resistance to bacterial contamination, humidity, and cost-effectiveness [39]. There have been several advancements in pMDI technology, of which the replacement of chlorofluorocarbons (CFC) propellants with hydrofluoroalkane (HFA) propellants. This transition was quite essential as CFC propellants possessed "cold Freon" effect and relatively high throat deposition, causing cough and paradoxical bronchospasm in patients, thus leading to patient incompliance [40,41]. To control drug deposition, which frequently occurs with the formulation of ethanol-free HFA suspension, as well as to reduce drug and canister deterioration, pMDI canisters have been redeveloped. Simultaneously, pMDI valves have been redeveloped to match the newer HFA propellants, to reduce extractables/leachable, increase dosing consistency, and also to overcome the issue of air trapping in the system during storage [42].

The more recent pMDI, also known as breath-actuated pMDI or coordination devices, is developed to bridge the gap between breathing of the patient and inhaler activation. They are breath-synchronized devices, designed to time the pace of inspiration with the release of the dose from the inhaler. With the goal of having an integrated dose tracker, a soft triggering mechanism, and the capacity to activate at low inspiratory flow rates, a new generation breath-actuated pMDI has been devised [43]. Another relatively new breath-activated pMDI, the K-haler device uses a special "kinked-hose valve technology" and delivers lower, more consistent plume force than a normal pMDI in addition to fine particles and pulmonary deposition rate. The coordinated inhalational flow rate between the drug actuation and patient variability can be used to determine the reliability of pMDI [39,44,45].

Dry powder inhalers (DPI)

The DPI demands minimal coordination between the breathing of the patient and device actuation to deliver dry powder medication to the lungs [46]. DPIs are constructed to balance the flow rate and inhaler resistance in the device, which is a limitation. To increase particle deagglomeration, DPIs demand for a faster airflow, and a greater fine particle percentage can be attained through stronger impaction. The disadvantage of the increased flow rate is the accumulation of particles in the oropharynx area, which limits drug delivery to the lungs [46,47].

Since DPI does not need propellants, they have received tremendous attention in recent years. The latest generation of DPI, also referred to as "active" or "power" aided DPI, uses built-in battery-driven impellers and vibrating piezoelectric crystals to dispense medication. As a consequence of the presence of an external energy source, they can be activated even at low flow rates. The development of porous particles with a small geometric diameter and substantial capability for lung deposition is yet another strategy for the improvement of DPIs [46,48]. Despite the convenience by which powder formulations can be fluidized or dispersed at low airflow rates, very few power-assisted DPIs have been introduced due to a number of factors, including complexity, high cost, high susceptibility to failure in the case of discharged batteries, and large device size [49].

Nebulizers

Nebulizers are devices that can transform liquid drugs into a fine mist. They are commonly used to administer pharmaceutical aerosols to patients who have difficulty using a pMDI or a DPI appropriately [50]. The atmospheric air crosses the nebulizer, during inspiration, for the aerosolized delivery while during exhalation the air present inside the aerosol expels the aerosol to atmosphere, which may lead to the leakage of residual drug from the nebulizer. Jet nebulizer, the first technical operation developed for the sake of aerosol production, functions based on the mechanism of utilizing the gas flow from a compressor. The

Table 1: Inhaled marketed formulations or undergoing clinical studies for pulmonary infectious disease treatment

Disease	Formulation		Therapeutics (Brand/registered name)	Development status	References
Bacterial infection with cystic fibrosis	Inhalation solution		Tobramycin (Tobi®, Bramitob®)	Marketed	[34]
			Dornase alfa (Pulmozyme®)	Marketed	[34]
			Levofloxacin (Aeroquin® (formerly MP-376))	Phase III (NCT01270347, NCT01180634)	[35]
	Lyophilized powder for inhalation solution		Aztreonam lysine (Cayston®)	Marketed	[34]
			Colistimethate sodium (Promixin®)	Marketed	[34]
	Inhalable lipid particles (Pulmosphere™)		Tobramycin (Tobi® Podhaler™)	Marketed	[34]
	Inhalable dry powder		Ciprofloxacin (Cipro Inhale (BAYQ3939))	Phase III (NCT01764841)	[35]
	Excipient-free spray-dried powders		Colistimethate sodium (Colobreathe®)	Marketed	[34]
			Mannitol (Bronchitol®)	Marketed	[34]
Mycobacterium avium complex lung disease	Aerosol	Liposomes for nebulization	Amikacin (ARIKAYCE Kit)	Marketed	[34]
	Dry powder	Dry powder inhaler	Budesonide (PULMICORT)	Phase II (NCT04416399)	[35,36]
		Nanoparticle powder for inhalation	Remdesivir (GS-5734™) (VEKLURY)	Phase I (NCT04480333)	[35,37]
		Excipient-free dry powder	Ivermectin	Phase III (NCT04681053)	[35,36]
		Dry powder for nebulization	Melphalan	Phase II (NCT04380376)	[35,36]
		TD-0903	JAK inhibitor	Phase I (NCT04350736)	[35,36]
		Dry powder for nebulization	A synthetic version of Vasoactive Intestinal Polypeptide (ZYESAMI™ (aviptadil acetate))	Phase II/III (NCT04360096)	[35]
	Aerosol	SPRAY	Ciclesonide (OMNARIS)	Phase II (NCT04381364, NCT04330586)	[35,37]
		HCQ01	Hydroxychloroquine sulfate	Phase I/II (NCT04731051)	[35]
		S-1226 (8%)	Carbon dioxide (8%) and perflubron (PFOB)	Phase II (NCT04949386)	[35]
		Inhalation Solution	ILOPROST (VENTAVIS)	Phase II (NCT04445246)	[35,37]
		Nebulizer inhalation solution	Saline containing 0.3% hyaluronic acid sodium salt (Yabro®)	Phase II (NCT04830020)	[35]
		Nasal spray	Ivermectin	Phase II (NCT04510233)	[35]
		Nebulizer inhalation solution	GM-CSF (rHuGM-CSF) (Molgramostim)	Phase II (NCT04569877)	[35]
		Nebulized inhalation solution	Sargramostim (GM-CSF) (Leukine®)	Phase II (NCT04707664)	[35,37]
		BI 767551	Antibody against the coronavirus SARS-CoV-2	Phase II/III (NCT0489447, NCT04822701)	[35]
		DZIF-10c	SARS-CoV-2-neutralizing monoclonal antibody	Phase I/II (NCT04631705)	[35]
		DAS181	Recombinant Sialidase Protein	Phase II/III (NCT04354389)	[35]
		Inhalation Solution	Dornase Alfa (PULMOZYME)	Phase III (NCT04402970)	[35]
Pulmonary tuberculosis	Aerosol	Inhalation solution	Ad5Ag85A	Phase I (NCT02337270)	[35]
	Dry powder	Inhalable dry powder	Amikacin	Phase I (NCT04249531)	[35]

atomization of the formulation takes place through a small aperture in the nebulizer that facilitates the passage of the gas [51]. Air is employed to drive the atomized particles, which include both small and big droplets, toward a baffle. The impaction of the baffles has an impact on the larger droplets, which are subsequently pushed to the other side and intended to be recycled in liquid form inside the nebulizer [15]. In addition, there are three distinct types of jet nebulizers based on the amount of mist they emit when inhaled. In the case of continuous output during the respiratory phases of the patient, standard unvented nebulizers are preferred [50]. Ultrasonic nebulizers are classified into two categories that are frequently employed for inhalation therapy. The typical nebulizers are those where the medication comes into direct touch with the piezoelectric transducer. As a result of the transducer heating, the temperature of the drug rises. However, sterilizing a piezoelectric transducer is challenging [8,52].

Mesh nebulizers can be utilized to deliver suspensions as well as liquid drug formulations, although in the case of suspensions, performance is observed to be affected by the relation between both the mass of inhaled aerosol and the output rate. According to in vitro research, commercial mesh nebulizers reduce nebulization time without affecting drug efficacy [12,53]. The sanitation and disinfection are the elements that may potentially affect how well-marketed mesh nebulizers operate. The delivery of liquid drug formulation inside the nebulizer, which is accomplished by application of force, is greatly simplified by static mesh nebulizers [51]. The liquid drug is delivered through the mesh utilising a vibration mechanism in vibrating mesh nebulizers. By producing aerosolized particles when they are most likely to reach the deep lung, vibrating mesh nebulizers makes use of continuous nebulization technology. Modern portable vibrating mesh nebulizers can offer accurate doses with minimal waste, convenience, and energy consumption, as well as excellent drug localization [2,6,40,45]. The wide cross-sectional area of conical mesh nebulizers and convenience of pumping and loading with drug formulation also alter the droplets that pass through the perforations, which improves the uptake of inhalants through the respiratory system [54]. For the nebulization technique to

be successfully used for pulmonary targeting, both the formulation and the equipment are essential [54,55].

Soft mist nebulizers

The term "soft mist" is used to describe both the characteristics of the aerosol cloud and the process by which they are produced. To overcome the limitations of pMDI and DPIs, SMI that produce aerosols through solution atomization have been developed. This process produces medicinal aerosol without the use of a power source. It is powered mechanically by a coiled spring that the patient may effortlessly compress [56]. An exclusive component called the uniblock forces a metered volume of a propellant-free drug solution through a nozzle or series of nozzles. The uniblock is a silicon and glass-based system with extremely small nozzles and a filter structure. The drug solution disintegrates into inhalable droplets when two small liquid jets collide at a precisely controlled angle, producing a soft misty aerosol that moves slowly (like nebulizers) [57]. There is a lesser possibility of oropharyngeal deposition since the soft mist leaves the nozzle at a speed that is approximately one-tenth that of an aerosol cloud released from a pMDI. To accomplish drug deposition, significant inspiratory flows are not necessary [41,58]. A good example is the Respimat Soft Inhaler, where more than 60% of the drug dose is contained in a fine-particle dose of 5.0 micromete, allowing a better inhalational drug delivery to the patient and a reduction in the nominal drug dose without any appreciable loss of pharmacodynamic effect or clinical efficacy [57,59,60].

Smart inhalers

Smart inhalers enable patients to consume their medications on time and appropriately, which helps the patients adhere to their treatment regimens. They remain vigilant on compliance and provide microprocessor-assisted aid to the patients [12,61,62]. While a few of them utilize bluetooth technology to connect to mobile phones or tablets, others employ it to issue reminders to patients to take their next dose, provide immediate feedback on technique and timing, or record the interaction of environment and individual that ultimately resulted in inhaler use. Some of them monitor the time and duration of inhaler use [63]. Smart inhalers are classified into two categories: add-on devices that have an e-module that is externally attached to the inhaler and devices that were designed with an e-module already installed. The majority of the currently considered or available e-modules are external add-on modules. For pMDIs, DPIs, and SMIs, an example of such add-on device is the propeller sensors [13,40,44]. Using Bluetooth, they are wirelessly connected to a smartphone. Patients, caregivers, and clinicians can use the analytical data to help identify incidents or patterns that can help them with management. Another example of an add-on device that can be mounted on top of a conventional inhaler canister is the CareTRX. It can track all different types of drugs, log symptoms, triggers, and peak flow, display graphs and statistics on activity, and analyze patterns for medication adherence. When used in combination with a smartphone, it makes advantage of the built-in GPS capabilities to monitor location of each inhaler use in and connects patients with healthcare practitioners to facilitate communication [64]. The Inhaler Compliance Assessment digital health device, which is based on acoustical sensing, is designed to process sound measurement. It ascertains whether the patient generates an adequate amount of inspiratory effort, detects whether the patient generated an adequate amount of PIFR to effectively deagglomerate drug particles from the DPI, and also to calculate the amount of drug delivered from DPIs [63]. Furthermore, there are smart nebulizers for customized regulated inhalation. These devices combine flow and/or pressure sensors, a microprocessor, and nebulizer technology to allow bolus aerosol inhalation techniques that can be personalized to the breathing pattern or lung function of the patient (Fig. 3) [64,65]. Table 2 summarizes the commercially available inhalational devices.

TARGETING-BASED APPROACHES FOR PULMONARY DRUG DELIVERY

The PDDS is influenced by numerous factors. Similarly, the intention of enhancing drug efficacy and increasing patient compatibility has to be looked upon with a wider perspective. Formulation modification and advances in drug delivery devices are the two discussed approaches for efficacious treatment in pulmonary disorders. However, apart from them, there are various upcoming therapies and method for increased target specificity, thus reducing the possibility of any adverse effects [16,73,74].

Gene therapy for pulmonary drug delivery

The alteration of genes in the human cells in an effort to treat or manage the severity of a disease comprises gene therapy. The delivery of genes through modernized devices holds a scope of promising treatment for the broad spectrum of pulmonary disorders. Exogenous genes could be administered in vivo to the lungs to treat two genetic disorders which are life-threatening: CF and alpha antitrypsin deficiency [75]. The vectors used for the process of gene transfer are broadly categorized as viral vectors and non-viral vectors. The viral gene transfer vectors include adenovirus and adeno-associated virus, while the non-viral gene transfer includes the use of liposomes, cationic polymers, receptor-mediated gene therapy, endosome scape, and nuclear targeting as well as episomal vectors to serve the purpose [76].

The monogenic and recessive nature of CF gene ignited the development of gene therapy-based strategies. The mutations of CF transmembrane conductance regulator (CFTR) genes were found to be the causative factor for CF. Later, it found that CFTR is the only gene affected and the rectification of just one allele of the two CFTR alleles is sufficient to revert the disease. In contrast to the conventional therapies, gene therapy focuses on targeting the disease at its point of origin, thus leading to prevention of lung diseases or curing them completely if the treatment is initiated early [77]. The cloning of CF gene led to a developed interest of researchers in the delivery of genes directly to the surface of the lungs through inhalation and the earlier efforts were focused on the use of non-viral vectors, specifically cationic lipids. Previously, factors such as inefficient penetration of mucous membrane, as well as inhibitory effects of surfactants and other lung-specific features resulted in a lack of therapeutic effect. However, in recent years, numerous non-viral and even viral vectors have been used for successful drug delivery [76,77].

However, despite extensive research in the gene transfer domain, gene therapy lacks to meet the expected therapeutic effect because of the insufficient knowledge with respect to gene delivery and vector design as well as the natural defense mechanism in the host. Thus, the better understanding of the lung, its physiological functions, and the barriers associated with the pulmonary system may provide a navigation route in the development of novel strategies [75].

Magnetic drug targeting in pulmonary drug delivery

The experiences with magnetic drug targeting in the blood arteries in an effort to treat pulmonary diseases including CF, chronic obstructive pulmonary disease, and asthma locally gave rise to the concept of magnetic drug targeting. According to experts, the magnetic drug targeting method has a substantial amount of potential, particularly for lung cancer [78].

A comprehensive size and shape-specific uniform micro and nanoparticles coated with biocompatible magnet are formulated and a drug solution is formed which is nebulized so as to form aerosol droplets. The aerosolized magnetic nano or micro particles are navigated toward the target cells under the influence of an external magnetic force, applied in two different positions of the lung airways [79]. The magnetic nano and microparticles transport as well deposition in the specific region of the lungs is being studied for a broad range of diameters, ranging from 1nm to 500nm, along with different flow rates [78].

The conventional approach to treat lung cancer with magnetic drug targeting involves the use of a permanent magnetic field which is however, associated with a set of drawbacks and limitations like the creation of field gradient causing particles to settle away from the targeted cells, which would lead to destruction of protective mucus layer present in the inner walls of respiratory tract [80]. Thus, application

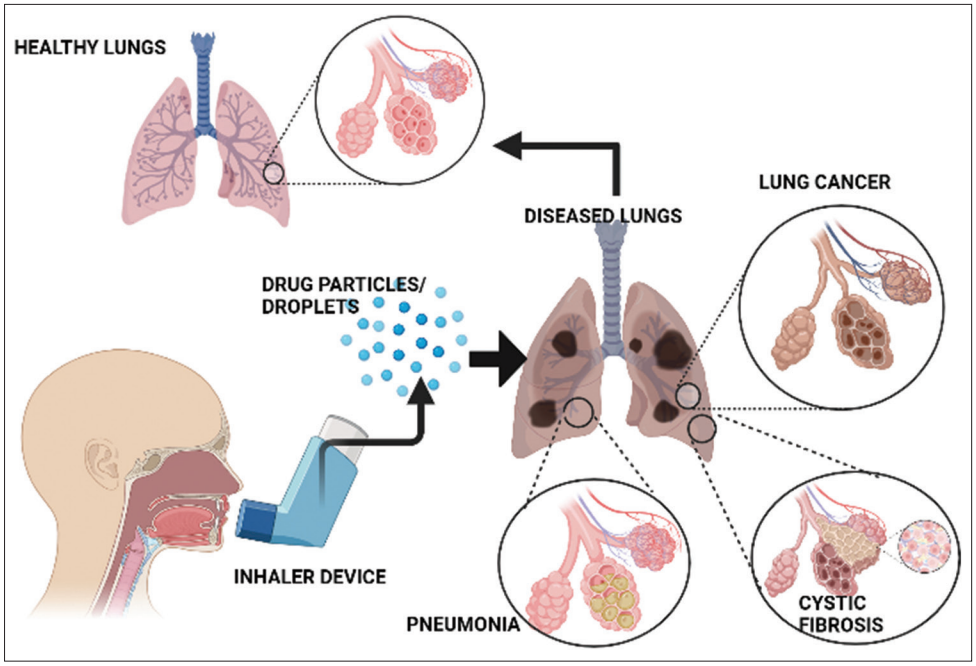


Fig. 3: A general representation about the utilization of inhaler devices for the treatment of various pulmonary diseases [42,43,52,64]. A general representation about the utilization of inhaler devices for the treatment of various pulmonary diseases [32,33,40,48]

Table 2: Examples of marketed formulations of inhalational devices

Type of device	Device name		Company	References
Pressurised metered dose inhalers	Autohaler		3M Pharmaceuticals, St Paul, Minnesota	[66]
	Easibreathe		Norton Healthcare, London, United Kingdom	[66]
	K-Haler		Clinical Designs, Aldsworth, United Kingdom	[66,67]
	MD Turbo		Respirics, Raleigh, North Carolina	[66]
	Smartmist		Aradigm, Hayward, California	[66]
	Xcelovent		Meridica, Melbourne, United Kingdom	[67]
	Easidose		Bespak, Milton Keynes, United Kingdom	[66]
	Breath Coordinated inhaler		Aeropharm, Edison, New Jersey	[66]
	Spacehaler		CelltechMedeva, Slough, United Kingdom	[67]
	Tempo		Map Pharmaceuticals, Mountain view, California	[66]
	BrochoAir		BronchoAirMedizintechnik, Munich, Germany	[66]
Dry powder inhalers	Device name	Sub-type		
	Aerohaler	Multi-unit dose	Boehringer- Ingelheim	[68]
	Diskhaler	Multi-unit dose	GlaxoSmithKline	[69]
	Accuhaler	Multi-unit dose	GlaxoSmithKline, UK	[68]
	Diskus	Multi dose	GlaxoSmithKline	[70]
	Turbuhaler	Multi dose	Astra Zeneca	[68]
	Miat-Haler	Multi dose	Andi- Ventis, Cyprus	[69]
	Maghaler	Multi dose	GGU	[69]
	Skyhaler,	Multi dose	Skye Pharma, London, United Kingdom	[69]
	Taifun	Multi dose	Leiras	[68]
	Chickhaler	Multi dose	Innovata Biomed, ML labs	[70]
	Jethaler	Multidose	PulmoTecGmb/Hochstadt, launch by Ratiopharm and CT Berlin	[70]
	Novolizer	Multidose	ASTA Medica	[68,69]
	Pulvinal	Multi dose	Chiesi	[68]
	Twisthaler	Multi dose	Schering- Plough	[68]
	Eclipse	Unit dose	Aventis	[69]
	Inhalator	Unit dose	Boehringer-Ingelheim	[68]
	Rotahaler	Single dose	GlaxoSmithKline	[70]
	Spinhaler	Single dose	Aventis	[70]
	Cyclohaler	Single dose	Pharmachemie	[69]
	Aerolizer	Single dose	Novartis	[70]
	Handhole	Single dose	Boehringer-Ingelheim	[69]
Nebulizers	AeroEclipse II BAN		Trudell Medical International	[71]
	Apixneb			[72]
	CompAIR		Omron Healthcare	[71]
	Pari LC plus		PARI	[71]
	Side Stream Plus		Philips Respironics	[71]
	Micro AIR NE -U22		Omron Healthcare	[72]

Table 3: List of monoclonal antibodies in various stages of preclinical development against respiratory viral infections

Name	Delivery route	Origin	Mechanism	Target	Disease/ pathogen	Stage	References
Foralumab	Nasal or oral	Anti- CD3 human monoclonal antibody	Anti-inflammatory effect	Interleukin-6 receptor	COVID-19	Phase 2	[87]
Palivizumab	Intranasal	Humanised monoclonal antibody (IgG)	Neutralisation via blocking viral fusion	Antigenic site of the protein of RSV	RSV	Preclinical animal studies	[88]
Genetically engineered IgG Fc domain with enhanced binding affinity to mucin	Nasal spray formulation	Eureka's E-ALPHA phage library	Neutralisation	SARS CoV-2 S1 spike protein	COVID-19	Preclinical animal studies	[89]
Diomat biopolymer loaded with active motif's 414-1 human IgG monoclonal antibodies	Nasal spray	Recombinant human IgG antibodies	Neutralisation	Receptor binding domain	COVID-19	In-vitro stage	[90]
ALX-0171	Nasal spray	Trimeric nanobody	Neutralisation	Antigenic site II of RSV F protein	RSV	Phase I/IIa trial	[91]
Monovalent and bivalent VHN nanobodies (Ablynx)	Intranasal	Llamas nanobodies	Neutralisation	Antigenic site B in H5 hemagglutinin	Influenza A virus	Preclinical studies	[92]
Bispecific nanobody	Intranasal	Alpaca spike immunised immune library	Neutralization	Receptor binding domain	COVID-19	Preclinical studies	[93]
Single domain anti-bodies (nanobodies)	Intranasal	Yeast surface displayed library of synthetic nanobody	Locks spike into inaccessible down state	Spike	COVID-19	In-vitro stage	[94]

of the magnetic field during the termination phase of inspiration will ensure the deposition of particles at the intended site. Another aspect to be considered in magnetic drug targeting is the time-accurate injection of the particles. An aerosol cloud is preferred for the particles to reach the deepest parts of the bronchial tree [81]. This therapy, if proved successful in humans, could also be an economical treatment due to systemic drug distribution in the specific region of the lung [79].

Inhalational monoclonal antibody therapy

With over 50 approved drugs and more than 500 mABs-based therapeutics in clinical development, mABs have established themselves as one of the most useful tools in the healthcare domain. Considering the recently approved biologics, around 90% of them are mAB-based drugs [82]. The growing popularity of mABs can be possible because of their therapeutic safety, high target specificity, and comparatively better pharmacokinetics. The majority of mABs are administered systemically or intravenously, which limits their ability absorption from the site of administration through the bloodstream to the affected organs and, as a result, restricts their ability to be used therapeutically. Viral or non-viral respiratory disease primarily impacts the respiratory system, which limits the absorption of systemically injected mABs [83]. However, scientists are investigating various alternate routes for the administration of therapeutic mABs, one such route potential approach being the use of inhalational route. The sensitive mucosal surface, which is considered to be the primary entry point for pathogens, can rapidly and directly receive protective doses of antibodies through passive assimilation via inhalation. Since the concentration of a drug substance impacts its effectiveness at the site of action, inhaled medications are expected to have a faster onset of action and greater efficacy [84]. Since the mucosal surface of the upper respiratory tract is where the majority of respiratory viral infections begin, mucosal administration of mABs has proven effective not only for defense but also for limiting the spread of virus. In addition, by targeting a protein called vascular endothelial growth factor, systemic administration of certain mABs, such as bevacizumab (Avastin), inhibits the formation of tumor blood vessels. Other side effects, including high blood pressure, slow wound healing, and kidney damage bleeding are the probable side effects. As a result, inhalational therapy seems to be appealing, non-invasive, local, and also convenient in terms of patient compatibility [83,85]. The device must be connected to a depot of mAB that is safe, pharmacologically active and that consistently as well as effectively acts in the targeted region of the lung [83,86]. Table 3 explains various monoclonal antibodies under different stages of clinical trials.

CHALLENGES FOR PULMONARY DRUG DELIVERY

Asthma, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD), which account for more than 400,000 fatalities in the European Union, or approximately 8% mortality rate, are among the greatest health-care obstacles faced by the world [95]. Such high mortality rates indeed emphasize on the increasing need for innovative as well effective treatment approach. Despite the fact that pulmonary medication delivery is gaining significant attention due to its non-invasiveness, researchers still encounter a plethora of challenges with this method of administering medications [14].

Defying conventional drug design wisdom

Agents can be rapidly delivered into the circulatory system by the lungs. However, it is essential for the topically applied drugs to remain and act inside the lungs for treatment of respiratory conditions with extracellular targets. Potential side effects from drug absorption into the body include those that could affect the cardiovascular system, central nervous system, and digestive system, as well as off-target effects. The goal of conventional orally delivered drug design, which was to improve the chemical characteristics of an API so as to enhance absorption and bioavailability within the body, seems to be at variance with this challenge [21]. Lipinski's Rule of 5 is the most considered set of parameters for predicting suitability of molecules as orally administered drugs. However, during the formulation of an extracellular luminal targets, it becomes necessary to defy these rules [96]. For instance, it is relatively difficult for the larger compounds to cross the epithelial barrier; therefore, this results in reduced absorption into the bloodstream. Similarly, poorly lipophilic molecules have a tough time penetrating the lining of the airway, which causes them to remain at the site of action for a prolonged period of time. Developing drugs that are difficult to absorb in the gut, highly plasma protein-bound, and/or quickly metabolized, and eliminated are beneficial at limiting the risk of medication side effects [97].

Formulation challenges

For the administration of drugs to the lungs, MDIs or DPIs have

been proven to be extremely successful at delivering therapeutic agents, either systemically or locally, as aerosols. The development of therapeutic molecules with an appropriate size range continues to be a critical issue. Aerosol particle size must be carefully optimized since it affects both the dose deposition and the distribution of aerosol particles in the lungs [4]. While small particles typically get widely dispersed in the periphery, large-sized particle aerosols tend to deposit on the central airways. The effects of distribution of a particular treatment are strongly impacted by the position of the target receptors inside the lung; therefore, both of these aspects may have a massive effect on therapeutic efficacy [19]. Moreover, drug particles may easily stick to one another in the humid environment of the respiratory system, which could lead to irritation and a decline in efficacy. There are a number of air jet-milling-based micronization technologies that can be utilized to create nanoparticles of the proper size for pulmonary drug administration. The limited number of FDA-approved inhalation excipients that are currently available is a major impediment to the formulation of PDDS [95].

Developing suitable animal models

Since it is essential for animals to breathe while receiving drugs intravenously or intratracheally developing animal models for these techniques necessitates meticulous planning and technical proficiency. Timing, volume, and depth of anesthesia are just a few of the many variables that must be taken into account. Before conducting formal preclinical toxicology investigations, it is essential to understand the *in vivo* action of the drug [97]. Significant time and resources can be saved using simple and qualitative comparisons of candidate drugs early in the drug development process. These basic studies can serve as timely indications of lung irritation or inflammation, and this information can guide development decisions and reduce the risk of an unexpected and expensive failure later on [95].

Patient compliance issues

Many asthma therapies utilize bronchodilators and anti-inflammatories like corticosteroids, which are more efficient when taken in combination. The requirement to take several drugs may make it more difficult for patients to follow their treatment protocols. Developing a single drug molecule that targets several different systems could be a possible approach to overcome this challenge [4]. A novel approach to dual bronchodilator therapy, bifunctional muscarinic antagonist-beta agonists may be more beneficial than single mechanism bronchodilators with equal or better compliance. When combined with a second molecule, like a corticosteroid, similar strategies may potentially provide the opportunity of triple combination therapy. The influence of the disease or effect of age on ability of the patient to inhale the substance is another crucial factor to take into consideration when selecting pulmonary drug delivery approach for the treatment of lung disorders. Some elderly patients may not have the necessary respiratory muscular strength to effectively use DPIs. In certain circumstances, nebulizer inhalation may be recommended [97].

FUTURE PERSPECTIVE

Although there are a variety of roadblocks to successful pulmonary drug delivery, interest in this approach seems to be expanding faster than ever. This presumably indicates that we are well aware of the advantages that pulmonary delivery offers. With a greater emphasis on ensuring adherence and adequate inhaler use, therapies for the treatment of asthma and COPD have evolved significantly in the past few years and are expected to continue to do so. In an attempt to address unmet needs, future developments in topical delivery are much more probable to witness the repurposing of several drugs for inhalation [4]. There are several opportunities for using drugs administered through inhalation to treat both common conditions and rare diseases. Inhaled interferon-gamma is employed to treat idiopathic pulmonary fibrosis, inhaled Cyclosporine to treat lung transplant rejection, inhaled Rifampicin, inhaled Capreomycin to treat tuberculosis, and inhaled Voriconazole to treat pulmonary aspergillosis. Pharmaceutical industries have opted to maximize lung deposition through design of the inhaler device or formulation to optimize inhaled drug delivery for systemic action. This is possible due to the availability of an effective spectrum of delivery systems, although this is not the sole strategy [98]. Future studies could contribute to the employment of additional strategies, such as the incorporation of protease inhibitors into drug formulations, the use of PEGylation, which seems to be able to safeguard drug molecules from natural defense mechanisms within the lungs, or formulations that use immunoglobulin receptors in the airways to facilitate protein transcytosis. There has been a significant interest in extending the duration that drugs remain in the lungs to have a local or systemic effect. Improved adherence to the prescribed treatment regimen could result from the delivery of a twice-daily drug in a controlled-release formulation that enables once-daily dosing [99]. Only liposomal formulations have so far advanced to later phases of clinical trials, despite a variety of controlled release formulations have been evaluated over several decades, including the use of large porous particles containing PLGA [5]. Although the technology of inhaled delivery of nanomedicines is still in its infancy, formulation strategies have encompassed the use of drug-loaded PLGA nanoparticles and the inclusion of nanoparticles into liposomes. Not all respiratory disorders can be treated with inhaled medication, but in some circumstances, inhalation employed as a supplement to oral or parenteral delivery may prove to be extremely beneficial in the future [100].

CONCLUSION

Researchers have turned their attention to this approach as the preferred one for treating a variety of lung disorders as a consequence of a number of technology advancement and innovative targeted approaches [2]. Although, pulmonary route for the delivery of drugs has proved to be efficient due to its varied advantages briefly summarized as improved drug's efficacy, non-invasive, and reduction of systemic side effects, it is undeniably associated with a set of limitations [19]. Future advancements in the treatment of lung infections are expected to concentrate substantially on topical application of antibiotics. To enable *in vitro/in vivo* correlations and predictions in the context of data generation, novel approaches to examine the fate of inhaled drugs should be fundamental [21]. Researchers should focus on the combination of the approaches, namely, formulation development, advancement in devices as well as the targeting-based approach so as to develop a delivery system with negligible limitations. A successful clinical translation of microparticulate inhalational drug delivery would lead to the development of various treatment methods that are more patient-compatible and require less frequent administration.

AUTHORS' CONTRIBUTIONS

SC carried out the literature survey and drafted the manuscript. AP supervised the work and provided critical review to the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

We declare that we have no conflicts of interest/competing interest.

FUNDNG

No funds, grants, or other support was received.

REFERENCES

1. Kaur SS. Pulmonary drug delivery system: Newer patents. Pharm Pat Anal 2017;6:225-44. doi: 10.4155/ppa-2017-0019, PMID 28818001
2. Patil JS, Sarasija S. Pulmonary drug delivery strategies: A concise, systematic review. Lung India 2012;29:44-9. doi: 10.4103/0970-2113.92361, PMID 22345913
3. Groneberg DA, Witt C, Wagner U, Chung KF, Fischer A. Fundamentals of pulmonary drug delivery. Respir Med 2003;97:382-7. doi: 10.1053/rmed.2002.1457, PMID 12693798
4. Newman SP. Drug delivery to the lungs: Challenges and opportunities. Ther Deliv 2017;8:647-61. doi: 10.4155/tde-2017-0037,

PMID 28730933
5. Nikander K. Challenges and opportunities in respiratory drug delivery devices. Expert Opin Drug Deliv 2010;7:1235-8. doi: 10.1517/17425247.2010.525231, PMID 20939686
6. Nanjwade BK, Adichwal SA, Gaikwad KR, Parikh KA, Manvi FV. Pulmonary drug delivery: Novel pharmaceutical technologies breathe new life into the lungs. PDA J Pharm Sci Technol 2011;65:513-34. doi: 10.5731/pdajpst.2011.00704, PMID 22293840
7. He S, Gui J, Xiong K, Chen M, Gao H, Fu Y. A roadmap to pulmonary delivery strategies for the treatment of infectious lung diseases. J Nanobiotechnology 2022;20:101. doi: 10.1186/s12951-022-01307-x, PMID 35241085
8. Newman S. Improving inhaler technique, adherence to therapy and the precision of dosing: major challenges for pulmonary drug delivery. Expert Opin Drug Deliv 2014;11:365-78. doi: 10.1517/17425247.2014.873402, PMID 24386924
9. Liang Z, Ni R, Zhou J, Mao S. Recent advances in controlled pulmonary drug delivery. Drug Discov Today 2015;20:380-9. doi: 10.1016/j.drudis.2014.09.020, PMID 25281854
10. Siekmeier R, Scheuch G. Treatment of systemic diseases by inhalation of biomolecule aerosols. J Physiol Pharmacol 2009;60(Suppl 5):15-26. PMID 20134033
11. Thakkar M, Brijesh S. Opportunities and challenges for niosomes as drug delivery systems. Curr Drug Deliv 2016;13:1275-89. doi: 10.2174/1567201813666160328113522, PMID 27017826
12. Scheuch G, Kohlhaeufl MJ, Brand P, Siekmeier R. Clinical perspectives on pulmonary systemic and macromolecular delivery. Adv Drug Deliv Rev 2006;58:996-1008. doi: 10.1016/j.addr.2006.07.009, PMID 16996638
13. Siekmeier R, Scheuch G. Systemic treatment by inhalation of macromolecules-principles, problems, and examples. J Physiol Pharmacol 2008;59(Suppl 6):53-79. PMID 19218633
14. Ghumman M, Dhamecha D, Gonsalves A, Fortier L, Sorkhdini P, Zhou Y, *et al*. Emerging drug delivery strategies for idiopathic pulmonary fibrosis treatment. Eur J Pharm Biopharm 2021;164:1-12. doi: 10.1016/j.ejpb.2021.03.017, PMID 33882301
15. Rau JL. The inhalation of drugs: Advantages and problems. Respir Care 2005;50:367-82. PMID 15737247
16. Plaunt AJ, Nguyen TL, Corboz MR, Malinin VS, Cipolla DC. Strategies to overcome biological barriers associated with pulmonary drug delivery. Pharmaceutics 2022;14:302. doi: 10.3390/pharmaceutics14020302, PMID 35214039
17. Klingler C, Müller BW, Steckel H. Insulin-micro-and nanoparticles for pulmonary delivery. Int J Pharm 2009;377:173-9. doi: 10.1016/j.ijpharm.2009.05.008, PMID 19446621
18. Wang H, Qin L, Zhang X, Guan J, Mao S. Mechanisms and challenges of nanocarriers as non-viral vectors of therapeutic genes for enhanced pulmonary delivery. J Control Release 2022;352:970-93. doi: 10.1016/j.jconrel.2022.10.061, PMID 36372386
19. Ho DK, Nichols BL, Edgar KJ, Murgia X, Loretz B, Lehr CM. Challenges and strategies in drug delivery systems for treatment of pulmonary infections. Eur J Pharm Biopharm 2019;144:110-24. doi: 10.1016/j.ejpb.2019.09.002, PMID 31493510
20. De Souza Carvalho C, Daum N, Lehr CM. Carrier interactions with the biological barriers of the lung: Advanced *in vitro* models and challenges for pulmonary drug delivery. Adv Drug Deliv Rev 2014;75:129-40. doi: 10.1016/j.addr.2014.05.014, PMID 24880145
21. Ruge CA, Kirch J, Lehr CM. Pulmonary drug delivery: From generating aerosols to overcoming biological barriers-therapeutic possibilities and technological challenges. Lancet Respir Med 2013;1:402-13. doi: 10.1016/S2213-2600(13)70072-9, PMID 24429205
22. Antimisiaris SG, Marazioti A, Kannavou M, Natsaridis E, Gkartziou F, Kogkos G, *et al*. Overcoming barriers by local drug delivery with liposomes. Adv Drug Deliv Rev 2021;174:53-86. doi: 10.1016/j.addr.2021.01.019, PMID 33539852
23. Loira-Pastoriza C, Todoroff J, Vanbever R. Delivery strategies for sustained drug release in the lungs. Adv Drug Deliv Rev 2014;75:81-91. doi: 10.1016/j.addr.2014.05.017, PMID 24915637
24. Pramanik S, Mohanto S, Manne R, Rajendran RR, Deepak A, Edapully SJ, *et al*. Nanoparticle-based drug delivery system: The magic bullet for the treatment of chronic pulmonary diseases. Mol Pharm 2021;18:3671-718. doi: 10.1021/acs.molpharmaceut.1c00491, PMID 34491754
25. Liu Q, Guan J, Qin L, Zhang X, Mao S. Physicochemical properties affecting the fate of nanoparticles in pulmonary drug delivery. Drug Discov Today 2020;25:150-9. doi: 10.1016/j.drudis.2019.09.023, PMID 31600580
26. García-Fernández A, Sancenón F, Martínez-Máñez R. Mesoporous silica nanoparticles for pulmonary drug delivery. Adv Drug Deliv Rev 2021;177:113953. doi: 10.1016/j.addr.2021.113953, PMID 34474094
27. Elhissi A. Liposomes for pulmonary drug delivery: The role of formulation and inhalation device design. Curr Pharm Des 2017;23:362-72. doi: 10.2174/1381612823666161116114732, PMID 27848886
28. Sun L, Fan M, Huang D, Li B, Xu R, Gao F, *et al*. Clodronate-loaded liposomal and fibroblast-derived exosomal hybrid system for enhanced drug delivery to pulmonary fibrosis. Biomaterials 2021;271:120761. doi: 10.1016/j.biomaterials.2021.120761, PMID 33774524
29. Weers J, Tarara T. The pulmosphere^{tm} platform for pulmonary drug delivery. Ther Deliv 2014;5:277-95. doi: 10.4155/tde.14.3, PMID 24592954
30. Athamneh T, Amin A, Benke E, Ambrus R, Gurikov P, Smirnova I, *et al*. Pulmonary drug delivery with aerogels: Engineering of alginate and alginate-hyaluronic acid microspheres. Pharm Dev Technol 2021;26:509-21. doi: 10.1080/10837450.2021.1888979, PMID 33593203
31. Su Y, Zhang B, Sun R, Liu W, Zhu Q, Zhang X, *et al*. PLGA-based biodegradable microspheres in drug delivery: Recent advances in research and application. Drug Deliv 2021;28:1397-418. doi: 10.1080/10717544.2021.1938756, PMID 34184949
32. Arora D, Khurana B, Rath G, Nanda S, Goyal AK. Recent advances in nanosuspension technology for drug delivery. Curr Pharm Des 2018;24:2403-15. doi: 10.2174/1381612824666180522100251, PMID 29788880
33. Ishak RA, Osman R. Lecithin/TPGS-based spray-dried self-microemulsifying drug delivery systems: *In vitro* pulmonary deposition and cytotoxicity. Int J Pharm 2015;485:249-60. doi: 10.1016/j.ijpharm.2015.03.019, PMID 25772421
34. D'Angelo I, Conte C, La Rotonda MI, Miro A, Quaglia F, Ungaro F. Improving the efficacy of inhaled drugs in cystic fibrosis: Challenges and emerging drug delivery strategies. Adv Drug Deliv Rev 2014;75:92-111. doi: 10.1016/j.addr.2014.05.008, PMID 24842473
35. Home, ClinicalTrials.gov. Available from: https://www.clinicaltrials.gov [Last accessed on 2022 Apr 28].
36. Daley CL, Winthrop KL. *Mycobacterium avium* complex: Addressing gaps in diagnosis and management. J Infect Dis 2020;222(Suppl 4):S199-211. doi: 10.1093/infdis/jiaa354, PMID 32814943
37. Sharma SK, Upadhyay V. Epidemiology, diagnosis and treatment of non-tuberculous mycobacterial diseases. Indian J Med Res 2020;152:185-226. doi: 10.4103/ijmr.IJMR_902_20, PMID 33107481
38. MacLoughlin R, Telfer C, Clark A, Fink J. Aerosol: A novel vehicle for pharmacotherapy in neonates. Curr Pharm Des 2017;23:5928-34. doi: 10.2174/1381612823666170918122136, PMID 28925894
39. Sanders M, Bruin R. A rationale for going back to the future: Use of disposable spacers for pressurised metered dose inhalers. Pulm Med 2015;2015:176194. doi: 10.1155/2015/176194, PMID 26491563
40. Laube BL. The expanding role of aerosols in systemic drug delivery, gene therapy, and vaccination. Respir Care 2005;50:1161-76. PMID 16122400
41. Debnath SK, Debnath M, Srivastava R. Opportunistic etiological agents causing lung infections: Emerging need to transform lung-targeted delivery. Heliyon 2022;8:e12620. doi: 10.1016/j.heliyon.2022.e12620, PMID 36619445
42. Ram FS, Brocklebank DM, White J, Wright JP, Jones PW, Lasserson TJ. Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma. Cochrane Database Syst Rev 2002;2002:CD002158. doi: 10.1002/14651858.CD002158, PMID 11869625
43. Ooi J, Traini D, Boyd BJ, Gaisford S, Young PM. Determination of physical and chemical stability in pressurised metered dose inhalers: Potential new techniques. Expert Opin Drug Deliv 2015;12:1661-75. doi: 10.1517/17425247.2015.1046834, PMID 26067386
44. Cooney D, Kazantseva M, Hickey AJ. Development of a size-dependent aerosol deposition model utilising human airway epithelial cells for evaluating aerosol drug delivery. Altern Lab Anim 2004;32:581-90. doi: 10.1177/026119290403200609, PMID 15757496
45. Mortensen NP, Hickey AJ. Targeting inhaled therapy beyond the lungs. Respiration 2014;88:353-4. doi: 10.1159/000367852, PMID 25277464
46. Noriega-Fernandes B, Malmlöf M, Nowenwik M, Gerde P, Corvo ML, Costa E. Dry powder inhaler formulation comparison: Study of the role of particle deposition pattern and dissolution. Int J Pharm 2021;607:121025. doi: 10.1016/j.ijpharm.2021.121025, PMID 34418472
47. Liu X, Sulaiman M, Kolehmainen J, Ozel A, Sundaresan S. Particle-

based coarse-grained approach for simulating dry powder inhaler. Int J Pharm 2021;606:120821. doi: 10.1016/j.ijpharm.2021.120821, PMID 34171427
48. Allan R, Canham K, Wallace R, Singh D, Ward J, Cooper A, *et al*. Usability and robustness of the WixelaInhub dry powder inhaler. J Aerosol Med Pulm Drug Deliv 2021;34:134-45. doi: 10.1089/jamp.2020.1603, PMID 32865454
49. Son YJ, Miller DP, Weers JG. Optimizing spray-dried porous particles for high dose delivery with a portable dry powder inhaler. Pharmaceutics 2021;13:1528. doi: 10.3390/pharmaceutics13091528, PMID 34575603
50. Stein SW, Thiel CG. The history of therapeutic aerosols: A chronological review. J Aerosol Med Pulm Drug Deliv 2017;30:20-41. doi: 10.1089/jamp.2016.1297, PMID 27748638
51. Martin AR, Finlay WH. Nebulizers for drug delivery to the lungs. Expert Opin Drug Deliv 2015;12:889-900. doi: 10.1517/17425247.2015.995087, PMID 25534396
52. Sorino C, Negri S, Spanevello A, Visca D, Scichilone N. Inhalation therapy devices for the treatment of obstructive lung diseases: The history of inhalers towards the ideal inhaler. Eur J Intern Med 2020;75:15-8. doi: 10.1016/j.ejim.2020.02.023, PMID 32113944
53. Sznitman J, Heimsch T, Wildhaber JH, Tsuda A, Rösgen T. Respiratory flow phenomena and gravitational deposition in a three-dimensional space-filling model of the pulmonary acinar tree. J Biomech Eng 2009;131:031010. doi: 10.1115/1.3049481, PMID 19154069
54. Bos AC, Tiddens HA, Minh KT, Heeres I, Overweel-Uijterlinde JL, Kok AE, *et al*. Daily observations of nebuliser use and technique (DONUT) in children with cystic fibrosis. J Cyst Fibros 2016;15:645-51. doi: 10.1016/j.jcf.2016.03.005, PMID 27052127
55. Dubus JC, Becquemin MH, Vecellio L, Chaumuzeau JP, Reychler G, GAT (Groupe aérosolthérapie de la Société de pneumologie de langue française). Good practice for aerosol therapy by nebulization in 2020. Rev Mal Respir 2021;38:171-6. doi: 10.1016/j.rmr.2020.11.010, PMID 33288396
56. Eudaley ST, Dabbs WS, Chamberlin SM. YouTube as a guide for Respimat® soft Mist™ inhaler technique. J Pharm Pract 2021;34:40-3. doi: 10.1177/0897190019853988, PMID 31232147
57. Iwanaga T, Tohda Y, Nakamura S, Suga Y. The Respimat® soft mist inhaler: Implications of drug delivery characteristics for patients. Clin Drug Investig 2019;39:1021-30. doi: 10.1007/s40261-019-00835-z, PMID 31377981
58. Kumbhare U, Yelne P, Tekale S. Therapeutic use of an inhaled drug delivery in pulmonary hypertension: A review. Cureus 2022;14:e30134. doi: 10.7759/cureus.30134, PMID 36381737
59. Perriello EA, Sobieraj DM. The respimat soft mist inhaler, a novel inhaled drug delivery device. Conn Med 2016;80:359-64. PMID 27509644
60. Keating GM. Tiotropium Respimat(®) soft mist™ inhaler: A review of its use in chronic obstructive pulmonary disease. Drugs 2014;74:1801-16. doi: 10.1007/s40265-014-0307-4, PMID 25300412
61. Chono S. Development of drug delivery systems for targeting to macrophages. Yakugaku Zasshi 2007;127:1419-30. doi: 10.1248/yakushi.127.1419, PMID 17827922
62. Chono S, Tanino T, Seki T, Morimoto K. Pharmacokinetic and pharmacodynamic efficacy of intrapulmonary administration of ciprofloxacin for the treatment of respiratory infections. Drug Metab Pharmacokinet 2007;22:88-95. doi: 10.2133/dmpk.22.88, PMID 17495415
63. Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild-to-severe asthma: A network meta-analysis. Eur Respir J 2020;56:2000625. doi: 10.1183/13993003.00625-2020, PMID 32430423
64. Zabczyk C, Blakey JD. The effect of connected "smart" inhalers on medication adherence. Front Med Technol 2021;3:657321. doi: 10.3389/fmedt.2021.657321, PMID 35047916
65. Lin J, Zhou X, Wang C, Liu C, Cai S, Huang M. Symbicort® maintenance and reliever therapy (SMART) and the evolution of asthma management within the GINA guidelines. Expert Rev Respir Med 2018;12:191-202. doi: 10.1080/17476348.2018.1429921, PMID 29400090
66. Singh A, Malviya R, Sharma K. Pulmonary drug delivery system: A novel approach for drug delivery. Curr Drug Ther 2011;6:137-51. doi: 10.2174/157488511795304930
67. Pritchard JN. The climate is changing for metered-dose inhalers and action is needed. Drug Des Dev Ther 2020;14:3043-55. doi: 10.2147/DDDT.S262141, PMID 32801643
68. Fernandes SD, Koland M. Understanding the essentialities in establishing the bioequivalence of oral inhalation drug products to be marketed in the USA. Ther Innov Regul Sci 2020;54:738-48. doi: 10.1007/s43441-019-00007-3, PMID 32557296
69. Kuribayashi R, Yamaguchi T, Sako H, Takishita T, Takagi K. Bioequivalence evaluations of generic dry powder inhaler drug products: Similarities and differences between Japan, USA, and the European Union. Clin Pharmacokinet 2017;56:225-33. doi: 10.1007/s40262-016-0438-8, PMID 27461251
70. Muralidharan P, Hayes D, Mansour HM. Dry powder inhalers in COPD, lung inflammation and pulmonary infections. Expert Opin Drug Deliv 2015;12:947-62. doi: 10.1517/17425247.2015.977783, PMID 25388926
71. Barjaktarevic IZ, Milstone AP. Nebulized therapies in COPD: Past, present, and the future. Int J Chron Obstruct Pulm Dis 2020;15:1665-77. doi: 10.2147/COPD.S252435, PMID 32764912
72. Chandel A, Goyal AK, Ghosh G, Rath G. Recent advances in aerosolised drug delivery. Biomed Pharmacother 2019;112:108601. doi: 10.1016/j.biopha.2019.108601, PMID 30780107
73. Chono S, Tanino T, Seki T, Morimoto K. Efficient drug targeting to rat alveolar macrophages by pulmonary administration of ciprofloxacin incorporated into mannosylated liposomes for treatment of respiratory intracellular parasitic infections. J Control Release 2008;127:50-8. doi: 10.1016/j.jconrel.2007.12.011, PMID 18230410
74. Morimoto K. Designs of optimized microbial therapy systems of respiratory infections. Yakugaku Zasshi 2013;133:81-92. doi: 10.1248/yakushi.12-00256, PMID 23292024
75. Villate-Beitia I, Zarate J, Puras G, Pedraz JL. Gene delivery to the lungs: Pulmonary gene therapy for cystic fibrosis. Drug Dev Ind Pharm 2017;43:1071-81. doi: 10.1080/03639045.2017.1298122, PMID 28270008
76. Laube BL. Aerosolized medications for gene and peptide therapy. Respir Care 2015;60:806-21; discussion 821. doi: 10.4187/respcare.03554, PMID 26070576
77. Kim YD, Park TE, Singh B, Maharjan S, Cho KS, Park KP, *et al*. Image-guided nanoparticle-based siRNA delivery for cancer therapy. Curr Pharm Des 2015;21:4637-56. doi: 10.2174/13816128213115103192327, PMID 26486148
78. Goetz SM, Dahmani C, Rudolph C, Weyh T. First theoretic analysis of magnetic drug targeting in the lung. IEEE Trans Bio Med Eng 2010;57:2115-21. doi: 10.1109/TBME.2010.2051032, PMID 20515705
79. Dahmani C, Götz S, Weyh T, Renner R, Rosenecker M, Rudolph C. Respiration triggered magnetic drug targeting in the lungs. Annu Int Conf IEEE Eng Med Biol Soc 2009;2009:5440-3. doi: 10.1109/IEMBS.2009.5332476, PMID 19963644
80. Price DN, Stromberg LR, Kunda NK, Muttil P. *In vivo* pulmonary delivery and magnetic-targeting of dry powder Nano-in-microparticles. Mol Pharm 2017;14:4741-50. doi: 10.1021/acs.molpharmaceut.7b00532, PMID 29068693
81. Manshadi MK, Saadat M, Mohammadi M, Kamali R, Shamsi M, Naseh M, *et al*. Magnetic aerosol drug targeting in lung cancer therapy using permanent magnet. Drug Deliv 2019;26:120-8. doi: 10.1080/10717544.2018.1561765, PMID 30798633
82. Respaud R, Marchand D, Pelat T, Tchou-Wong KM, Roy CJ, Parent C, *et al*. Development of a drug delivery system for efficient alveolar delivery of a neutralizing monoclonal antibody to treat pulmonary intoxication to ricin. J Control Release 2016;234:21-32. doi: 10.1016/j.jconrel.2016.05.018, PMID 27173943
83. Torphy TJ, Li L, Griswold DE. Monoclonal antibodies as a strategy for pulmonary diseases. Curr Opin Pharmacol 2001;1:265-71. doi: 10.1016/s1471-4892(01)00047-9, PMID 11712750
84. Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular targets for biological therapies of severe asthma. Front Immunol 2020;11:603312. doi: 10.3389/fimmu.2020.603312, PMID 33329598
85. Ku TJ, Ribeiro RV, Ferreira VH, Galasso M, Keshavjee S, Kumar D, *et al*. *Ex-vivo* delivery of monoclonal antibody (rituximab) to treat human donor lungs prior to transplantation. EBiomedicine 2020;60:102994. doi: 10.1016/j.ebiom.2020.102994, PMID 32950000
86. Mümmler C, Munker D, Barnikel M, Veit T, Kayser MZ, Welte T, *et al*. Dupilumab improves asthma control and lung function in patients with insufficient outcome during previous antibody therapy. J Allergy Clin Immunol Pract 2021;9:1177-85.e4. doi: 10.1016/j.jaip.2020.09.014, PMID 32980583
87. Karnam A, Rambabu N, Das M, Bou-Jaoudeh M, Delignat S, Käsermann F, *et al*. Therapeutic normal IgG intravenous immunoglobulin activates Wnt-β-catenin pathway in dendritic cells. Commun Biol 2020;3:96. doi: 10.1038/s42003-020-0825-4, PMID 32132640
88. NTR7403. Nasal Administration of Palivizumab to Prevent

RSV Infection. Available from: https://trialsearch.who.int/trial2.aspx?trialid=NTR7403
89. Halwe S, Kupke A, Vanshylla K, Liberta F, Gruell H, Zehner M, *et al*. Intranasal administration of a monoclonal neutralizing antibody protects mice against SARS-CoV-2 infection. Viruses 2021;13:1498. doi: 10.3390/v13081498, PMID 34452363
90. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q *et al*. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J Virol 2020;94:e02015-19. doi: 10.1128/JVI.02015-19, PMID 31826992
91. Mora AL, Detalle L, Gallup JM, Van Geelen A, Stohr T, Duprez L, *et al*. Delivery of ALX-0171 by inhalation greatly reduces respiratory syncytial virus disease in newborn lambs. mAbs 2018;10:778-95. doi: 10.1080/19420862.2018.1470727, PMID 29733750
92. Ibañez LI, De Filette M, Hultberg A, Verrips T, Temperton N, Weiss RA, *et al*. Nanobodies with *in vitro* neutralizing activity protect mice against H_5N_1 influenza virus infection. J Infect Dis 2011;203:1063-72. doi: 10.1093/infdis/jiq168, PMID 21450996
93. Wen J, Zhao S, He D, Yang Y, Li Y, Zhu S. Preparation and characterization of egg yolk immunoglobulin Y specific to *Influenza B virus*. Antiviral Res 2012;93:154-9. doi: 10.1016/j.antiviral.2011.11.005, PMID 22127067
94. Schoof M, Faust B, Saunders RA, Sangwan S, Rezelj V, Hoppe N, *et al*. An ultra-potent synthetic nanobody neutralizes SARS-CoV-2 by locking Spike into an inactive conformation. bioRxiv 2020;370:1473-9. doi: 10.1126/science.abe3255
95. Omri A. Pulmonary drug and vaccine delivery: Therapeutic significance and major challenges. Expert Opin Drug Deliv 2015;12:853-5. doi: 10.1517/17425247.2015.1044277, PMID 25990662
96. Lipinski CA. Lead-and drug-like compounds: The rule-of-five revolution. Drug Discov Today Technol 2004;1:337-41. doi: 10.1016/j.ddtec.2004.11.007, PMID 24981612
97. Smaldone G, Berkland C, Gonda I, Mitchell J, Usmani OS, Clark A. Ask the experts: The benefits and challenges of pulmonary drug delivery. Ther Deliv 2013;4:905-13. doi: 10.4155/tde.13.76, PMID 23919470
98. Kim SY, Wong AH, Neel EA, Chrzanowski W, Chan HK. The future perspectives of natural materials for pulmonary drug delivery and lung tissue engineering. Expert Opin Drug Deliv 2015;12:869-87. doi: 10.1517/17425247.2015.993314, PMID 25522669
99. Alastruey-Izquierdo A, Cadranel J, Flick H, Godet C, Hennequin C, Hoenigl M, *et al*. Treatment of chronic pulmonary aspergillosis: Current standards and future perspectives. Respiration 2018;96:159-70. doi: 10.1159/000489474, PMID 29982245
100. Rubin BK, Williams RW. Emerging aerosol drug delivery strategies: From bench to clinic. Adv Drug Deliv Rev 2014;75:141-8. doi: 10.1016/j.addr.2014.06.008, PMID 24993613