

Review

Pulmonary drug delivery: Implication for new strategy for pharmacotherapy for neurodegenerative disorders

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ABSTRACT: Innovative drug delivery in the treatment of brain neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) has the potential to avoid many unwanted side effects over current medications. Advances in understanding of these diseases and their treatments have led to the search for novel modes of drug delivery. In this review, we have highlighted new strategies and future prospects for pulmonary delivery of drugs for the management of these important neurological disorders. The advancement of knowledge on pulmonary drug delivery will provide novel therapeutic formulations for better management of the PD and AD patients throughout the world.

Keywords: Pulmonary drug delivery, Dry powder inhaler, Metered dose inhaler, Nebulizer, Parkinson's disease, Alzheimer's disease

1. Introduction

Pulmonary delivery, a non-invasive route of drug delivery is becoming a route of choice for most drugs. Pressurized metered dose inhalers (pMDI) and nebulisers (liquid jet and ultrasonic) are the preliminary devices to deliver drugs into lung; however, currently, breath actuated dry powder inhalers (DPI) are designed to deliver medicaments as a powder form through the airways in the lung to achieve both systemic and local effects.

Direct delivery of drugs into the pulmonary regions of the lung enables lower doses with an equivalent therapeutic action compared to oral or parenteral

routes because of the large surface area (~100 m²) of the lungs. Advantages of DPI formulations over other dosage forms (*i.e.*, parenteral and other liquid dosage forms) are solid dosage form stability, ease of use, less expensive, painless and user friendly. The inhaled route allows the delivery of small doses of drug directly to the alveoli attaining a high concentration of drug in the local area and minimizes systemic side effects resulting in a high therapeutic ratio of drugs compared with that of systemic delivery administered either by oral or parenteral routes. Oral tablets and capsules need to be swallowed which is sometime difficult for some patients especially for children. Respiratory delivery also offers effective therapy with minimum adverse effects by using small doses of drugs through inhalation and allows substantially greater bioavailability of polypeptides (1).

Currently, delivery of drugs for the management of neurological disorders especially PD and AD are done by oral, parenteral and transdermal routes. Pulmonary delivery of drugs is well established in the management of asthma and COPD (chronic obstructive pulmonary disorder). However, no DPI drugs are approved yet for the management of other diseases like AD and PD. This mini-review discusses advantages of pulmonary delivery of drugs, pulmonary delivery technologies, and current situations and future trends in managing major AD and PD by delivering drugs into the deep lung *via* DPI or MDI devices.

2. Pulmonary delivery technology

Aerosol delivery of drugs, formulated as liquid solutions, suspensions, emulsions or micronized dry powders, are aerosolised *via* some commonly used different types of delivery devices (nebulizer, pMDI, and DPI). In this section both the formulations as well delivery devices are discussed.

2.1. Nebulisers

Nebulisers are probably one of the oldest forms of pulmonary drug delivery, deliver large volumes of

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drug solutions or suspensions and are frequently used for those drugs which can not be formulated into pMDIs or DPIs. Currently, two categories of nebulisers are available on the market include air jet and ultrasonic nebulisers. Air jet nebulisers can generate both smaller particles (mass median aerodynamic diameter 2-5 μm) and coarse aerosols, and deliver medication quickly; however, it produces high oropharyngeal deposition of drugs. Most jet nebulisers operate by forcing pressurised gas (air or oxygen) through a nozzle or jet at high velocity so that the nebulizer solution is atomized. On actuation the gas expands resulting in the generation of a negative pressure which draws the liquid formulation into the gas stream. The aerosol mist impacts against a baffle, drains back into the reservoir incorporated with the nebuliser and recirculates. The ultrasonic nebulisers do not require compressed gas. The solution formulation is atomised by an energy source, piezoelectric crystal transducer, which vibrates at high frequency and these devices can generate slightly larger aerosols. However, the overall efficiency of the piezoelectric driven ultrasonic nebulisers is more or less similar to that of air-jet nebulisers. Patients who are seriously affected with obstructive lung conditions prefer to use nebuliser therapy. Nebulisers are suitable for drugs with high dose and little patient co-ordination or skill; however, treatment using nebuliser is time consuming and less efficient, resulting in the waste of active medicaments. They are not portable devices and have been limited to the treatment of hospitalised patients. A number of nebulisers include AeroDose[®] (Aerogen), AeroEclipse[®] (Trudell Medical International), Halolite[®] (Medic-Aid Limited), RespiMat[®] (Boeinger Ingheim),

etc are currently available on market to deliver various types of drugs.

2.2. Pressurised metered dose inhalers

Pressurised metered dose inhalers (pMDIs), also known as metered dose inhalers (MDIs), are the most commonly used delivery devices. In this device (Figure 1), drug is either dissolved or suspended in liquefied propellants (or a mixture of propellants) with other excipients and presented in a pressurised canister fitted with a metering valve. On actuation of the valve, a predetermined amount of drug is released as spray. Aerosol formulations are packed in tin-plated steel, plastic coated glass or aluminium containers. The propellants used in pMDI formulations are liquefied gases of chlorofluorocarbons (CFC), which are not environmentally friendly. This is the reason why currently hydrofluoroalkanes (HFAs), which have no remarkable effects on the ozone layers, are used in the formulation for MDIs. At room temperature and pressure these are gases but they are liquefied by applying high pressure or by lowering temperature. On spraying, drug formulation with propellants are expelled and aerosolised. Although pMDIs are widely used in respiratory drug delivery, some problems have been associated with these devices, including the need for coordination of inspiratory inhalation with valve actuation and the use of a propellant, which has possible adverse effects on the stratospheric ozone layer as mentioned before. Currently there are a good number of pMDIs available on the market such as Ventolin (albuterol, GlaxoSmithKline), Azmacort (triamcnenolone acetate, Aventis Pharma), Symbicort

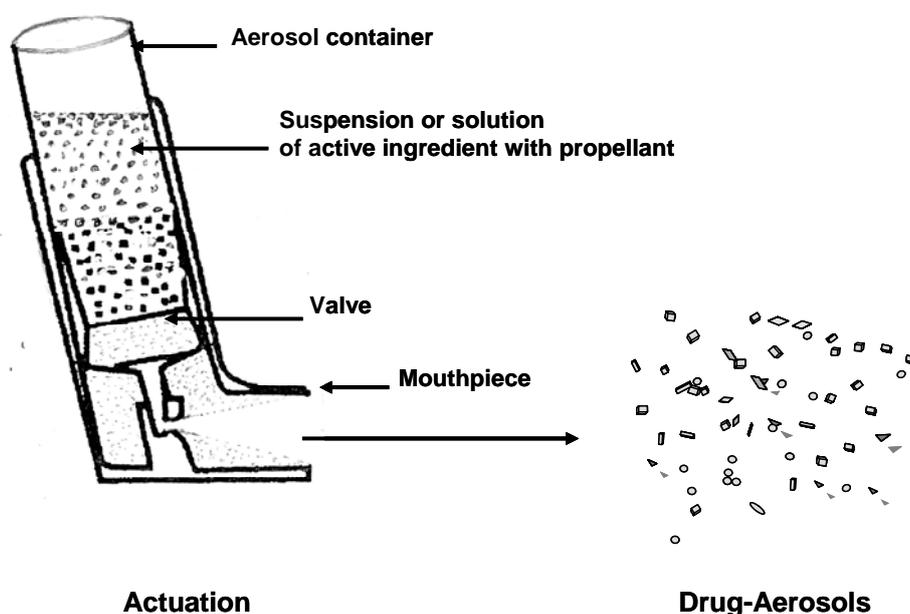


Figure 1. Schematic diagram of aerosol delivery of drugs from pMDI. Modified form Dalby *et al.* (2).

(Budesonide and formoterol, AstraZeneca), Flovent (Fluticasone, GlaxoSmithKline), *etc.* for the treatment of asthma.

There are some breath actuated and microprocessor controlled MDIs available on the market (Autohaler[®], Respimat[®]). These devices ensure the patient receives the drug at the correct point in the inspiration, and by slow inhalation with an indicator light to inform the patient whether the dose is inhaled or not. Anyway, as mentioned above, pMDIs have some disadvantages such as oropharyngeal deposition of drugs due to high velocity of propellants. The particles aerosolised from the MDIs have a high velocity, which exceeds the patients' inspiratory force, therefore, a large number of particles deposit onto the oropharyngeal areas. Thus a small fraction of drug deposits into the patients lungs (3) due to a lack of co-ordination between actuation and inhalation. To overcome this difficulty several inhalation aids like spacers incorporated with MDIs have been developed (4,5).

2.3. Dry powder inhaler (DPI) system

Dry powder inhalers contain the drug in a powder formulation, where drug particles (< 5 µm) are blended with a suitable large carrier (*e.g.* lactose) to improve flow properties and dose uniformity (6,7) and drug powders are delivered into the deep lung *via* a device known as dry powder inhaler (DPI). Powder de-agglomeration and aerosolisation from these formulations are achieved by the patient's inspiratory airflow, which needs to be sufficient to create an

aerosol containing respirable drug particles for lung deposition. Good flow properties of the formulation are necessary to ensure accurate dose metering of the drug. Advantages of DPI over other inhaler systems (pMDIs) are independence of breathing co-ordination with dose actuation, the absence of propellants, low innate initial velocity of particles (reducing inertial impaction at the back of the throat) and solid state drug stability. There are two types of DPI formulations; one is loose agglomerates of micronized drug particles having controlled flow properties, and the second one is carrier-based interactive mixtures (Figure 2) which consist of micronized (< 5 µm) drug particles mixed with larger carrier particles (8). Drug dispersion from the interactive mixtures can be enhanced by the addition of fine excipients (lactose) in the formulation (9,10). Drug particle size and powder formulation, breathing patterns and complex physiology of respiratory tract are major factors affect delivery of drugs into the deep lung. The redispersion of drug particles depends upon the interparticulate forces within the powder formulation. DPIs are highly portable, breath activated and relatively less expensive. Since drugs are kept in solid state in DPIs, they exhibit high physicochemical stability of drugs particularly proteins and peptides. In DPI formulation the device is an important factor in achieving adequate delivery of inhaled drug to lungs. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing.

There is a wide range of DPI devices, single, multi-unit or multiple dose devices, breath activated and

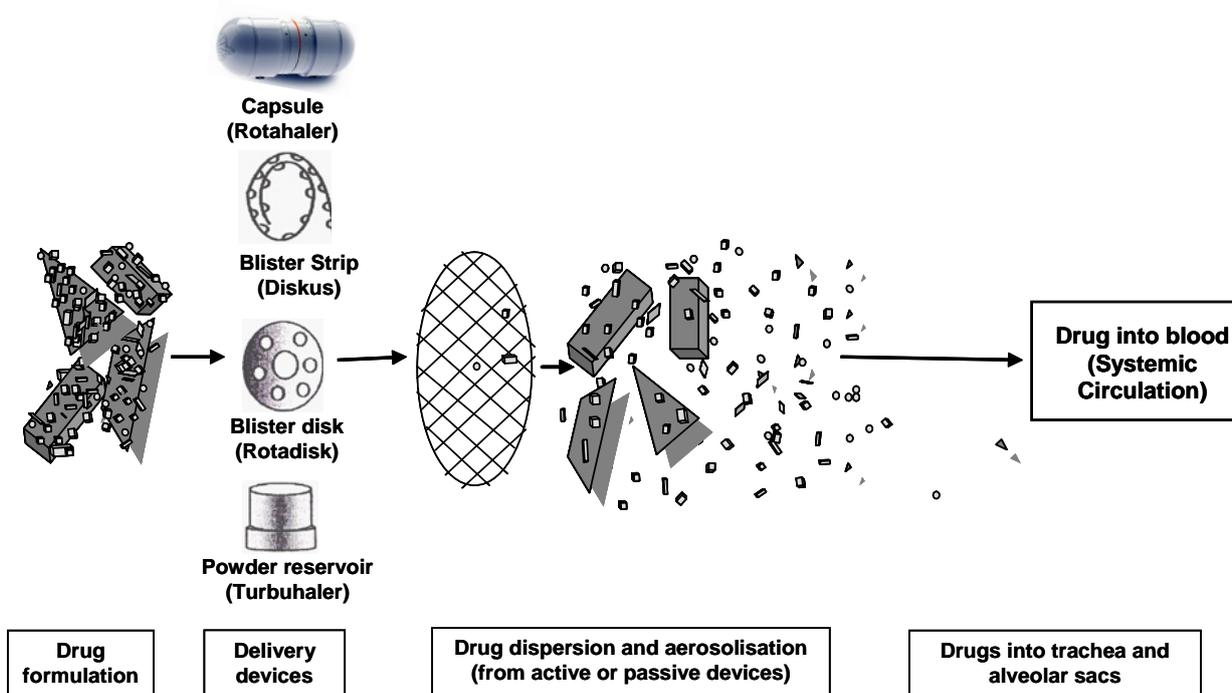


Figure 2. Schematic diagram of the pulmonary delivery of drugs from DPI formulations. The formulation consists of micronized drugs adhered on the surface of large carrier particles. Drug particles detached from the surface of large carriers and deposits into the patients airways by inhalation. Modified from Telko and Hickey (11).

power driven, available on the market; however, no devices showed efficiency in maximal drug delivery. Currently, based on the design, DPI devices may be classified into three broad categories *i.e.*, the first generation DPIs, the second generation DPIs and the third generation DPIs. The first generation DPIs were breath activated single unit dose (capsule) *i.e.*, the Spinhaler[®] and Rotahaler[®]. The second generation of DPIs use better technology *i.e.*, multi-dose DPIs (they measure the dose from a powder reservoir) or multi-unit dose (they disperse individual doses which are premeasured into blisters, disks, dimples, tubes and strip by the manufacturers) and multi-unit dose devices are likely to ensure the reproducibility of the formulation compared to that of multi-dose reservoir. The third generation DPIs, also known as active devices, which employ compressed gas or motor driven impellers or use electronic vibration (12,13) to disperse drug from the formulation. The very first approved active device (Exubera[®], Pfizer) with compressed air to aerosolise drug formulation for DPI insulin delivery was available on market; however, due to some unknown reasons, the production has been discontinued.

3. Mechanisms of drug deposition from aerosols

To achieve a desired therapeutic effect from aerosols, an adequate amount of drug must reach the alveolar sacs of the respiratory airways. The dynamic behavior of aerosol particles is governed by the laws of aerosol kinetics (14). The dominant mechanisms of depositing aerosol particles into the respiratory tract include inertial impaction, sedimentation (gravitational deposition), Brownian diffusion, interception and electrostatic precipitation (15). Inertial impaction and sedimentation are the most important for large particle deposition ($1\ \mu\text{m} < \text{MMAD} < 10\ \mu\text{m}$). A brief description of each mechanism of deposition is given below:

Inertial impaction: This is the main deposition mechanism at the tracheal bifurcation or successive branching points of airways. The airflow changes its direction at branching of the airways. The aerosol particles continue to move in their original direction and impact on any obstacle on the way. The deposition of aerosol particles by impaction increases with increasing air velocity, frequency of breathing and particle size (16). Large particles ($> 5\ \mu\text{m}$) with high velocity are mainly deposited by impaction (17).

Sedimentation: Sedimentation occurs when the gravitational force exerted on a particle overcomes the force of the air resistance. Particles of smaller size ($0.5\text{-}3.0\ \mu\text{m}$), which have tendency to escape from deposition by inertial impaction, may be deposited by sedimentation. Deposition of small particles by sedimentation mainly occurs in the smaller airways and alveolar regions and increased sedimentation

is observed during breath-holding or slow steady breathing (17).

Diffusion: Deposition of aerosolized particles less than $0.5\ \mu\text{m}$ occurs by diffusion due to Brownian movement. Deposition of aerosols by diffusion is independent of the density of particles but increases with decreasing size. Generally, the deposition of particles larger than $1.0\ \mu\text{m}$ is dominated by inertial impaction and particles smaller than $0.1\ \mu\text{m}$ are deposited by diffusion. Both sedimentation and diffusion are important for the particle size ranging between $0.1\text{-}1.0\ \mu\text{m}$ (18).

Interception: Although particle deposition by interception is not common, the deposition of elongated particles (particles large in one dimension but with small aerodynamic diameters) is believed to occur by this mechanism. Deposition of particles in the respiratory airways by interception is important when the dimensions of the anatomic spaces of airways become comparable to the dimensions of the particles (17).

Electrostatic precipitation: Electrostatic charges may be generated in a DPI on particles of an aerosol. Particles are inhaled immediately after charge generation and before neutralisation of the charge can occur. A charged particle may induce an image charge of opposite polarity on the airway walls. This image charge attracts the particle which is subsequently deposited by electrostatic precipitation (17,19). Only fibrous particles are believed to be deposited by this mechanism, therefore, this mechanism may not be significant for DPI formulations.

4. Pulmonary delivery of various drugs

4.1. Current drugs

Currently, local delivery of medicaments to the alveoli of lungs from both DPIs and pMDIs are mainly used for the treatment of lung disorders including asthma and bronchitis and a limited number of therapeutic compounds such as β -adrenoceptor agonist, muscarinic agonist, corticosteroids and mast cell stabilizers are available. Recently certain combinations of drugs are also formulated due to a synergistic therapeutic benefit. Corticosteroids and long acting β -adrenoceptor agonists formulations are available as both pMDIs and DPIs (20). Zanamavir, an antiviral agent has been introduced in the market as an aerosol product for the treatment of influenza (21). Aerosol delivery of recombinant human deoxyribonuclease (rhDNase) and tobramycin are available as nebuliser for the treatment of cystic fibrosis (21,22). The very first approved aerosol delivery of insulin as DPI formulation (Exubera[®], Pfizer) was introduced in the market; however, the production of this drug has been discontinued from market in early 2008 due to some unknown reasons.

Table 1. Drugs administered as aerosols against various diseases

Indication	Drug substances	Delivery method	References
Cystic fibrosis	Amiloride	Liquid	98,99
	Tobramycin	Powder	100,101
	DNAse	Powder	102,103
	Colistin sulphomethate	Powder	53
Cancer	Doxorubicin	Powder	104,105
Diabetes	Insulin	Microparticle/Liquid	106-108
Osteoporosis	Calcitonin	Microparticle	24,25
Sexual dysfunction	Apomorphine, Phosphodiesterase type 5 (PDEs) inhibitors	Microparticle	71,109
Vaccines	Malarial vaccine	DPI/ Microparticle	45
	Measles vaccine	Microparticle	44
	Influenza vaccine	Microparticle	46,47
	Zanamivir	Microparticle	110,111
Endometriosis, Pubertus praecox, Prostate carcinoma	Leuprolide	Powder/Liquid	26,27
Hormone replacement therapy	Testosterone	Liquid/Oral AREx	112
Immunosuppressor	Cyclosporin A	Microparticle/Liquid	113,114
Thrombosis and emphysema	Heparin	Microparticle	115,116

4.2. Drugs delivered as aerosol

Aerosol delivery offers the greatest potential to deliver drugs into the lower airway of the lungs of a wide range molecule for systemic diseases. A list of various drugs administered *via* pulmonary route has been presented in the Table 1.

Aerosol delivery of macromolecules is a potential non-invasive way of administering drug, to avoid frequent injections. Lung delivery of insulin has already been established; however, insulin loaded chitosan nanoparticles (23); nanoparticles of calcitonin (24); and nanospheres of elcatonin coated with chitosan (25), have been demonstrated for successful deep lung delivery. Aerosol delivery of leuprolide has been investigated as both MDI and DPI formulation for the management of prostate cancer (26,27). Dry powders of other proteins like parathyroid hormone for osteoporosis (28,29), glucagone (30), growth hormone (hGH) for dwarfism (31), vasoactive intestinal peptide (VIP) for pulmonary diseases like asthma (32) have been successfully investigated.

Lung delivery of genes that directly target the regions of interest by avoiding problems associated with intravenous delivery has been developed. Recently, successful gene delivery into lungs for cystic fibrosis has been demonstrated (12,33). Using nebuliser, delivery of liposomally encapsulated adenoviral vectors containing genes have been investigated; however, efficiency in low gene transfer at the cellular level has

been demonstrated (34,35). Lung delivery of genes complex with cationic lipids (lipoplex) and polymer-based (polyplex) are in progress (36,37) and a cationic lipid coupled with plasmid DNA (lipoplex), showed efficient lung delivery of gene (38). In another study, aerosol delivery of p53 and cytokine (IL-12) delivered *via* a nebuliser have been reported for therapeutic responses with reduced toxicity in animal lung tumor model (39-41). Based on the above mentioned researches it seems that there is a potential future of pulmonary gene therapy for various types of clinical applications.

Aerosol delivery of vaccines is an another area of interest and inhalation of measles vaccine was showed to be both safe and effective (42) and nebulised measles vaccine in human model found to produce better immunity with reduced side effects compared to that of subcutaneous injection (43). Dry powder inhaler formulation of measles vaccine (44), mucosal vaccination for influenza virus (45), malarial vaccine (46), and siRNA (47) have been investigated with significant success. Very recently, aerosol delivery of human immunodeficiency virus (HIV) treatments in infected patients found to be therapeutics with reduced toxicity and improved patient compliance (48). Therefore, it seems that pulmonary delivery of various genes is progressing and in future the world will see suitable vaccines against many pulmonary pathogens like *Mycobacterium tuberculosis*, respiratory syncytial virus (RSV), and severe acute respiratory syndrome (SARS).

Inhaled rifampicin antibiotic, and rifampicin loaded poly(lactide-co-glycolide) microparticles (49), colistin sulphate (50,51), and mucoactive agent Nacystelyn (52) have been found to be promising against cystic fibrosis (CF). Moreover, DPI formulation of colistin (53), gentamicin (54), azithromycin (55), tobramycin (56), have been effective method of treating CF. Furthermore, deep lung delivery of amphotericin B desoxycholate, liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion *via* nebulizers has been shown to be valuable in the prophylactic treatment of pulmonary aspergilosis (57). A nebulised dispersion of amorphous itraconazole nanoparticles (300 nm) produced by ultra-rapid freezing technique, showed improved bioavailability in mice (58). This outcome offers the application of itraconazole nanoparticles for the efficient treatment of fungal infections.

Lung delivery of aerosolised chemotherapeutic agents for the direct local treatment of lung tumors has been explored and found advantageous over other methods of drug delivery systems. Pulmonary delivery of aerosolised 9-nitrocamptothecin (9-NC) and cisplatin in patients with lung cancer have shown safety and promising antitumor effect (59,60). In addition, lung delivery of doxorubicin (61), paclitaxel (62), celecoxib and docetaxel (63,64), gemcitabine (65), liposomal camptothecin (66), *etc.*, has also been investigated and reduced toxicity was demonstrated. Recently, doxorubicin-loaded nanoparticles in dry powder aerosol form showed significant cytotoxicity in lung cancer (67). The researchers have indicated the potential of inhalation delivery of anticancer drugs in the treatment of lung cancer; however, further details investigation has been warranted.

Very recently, Dames and his co-workers developed targeted delivery of colloidal iron oxide nanoparticles (super magnetic iron oxide) (68), suspension of tocopherol nanoparticles coupled with biodegradable polymers for delayed release (69) and liposomal encapsulated cannabinoid for a prolonged psychoactive effect (70) have been demonstrated. In another study, aerosol delivery of apomorphine for sexual dysfunction (71), morphine and fentanyl for pain management (72), and ergotamine for migraine headaches (73,74). Furthermore, using nebuliser, aerosol delivery of radiopharmaceutical, ^{99m}Tc with phosphate buffer for lung ventilation imaging purposes is widely used (75). Inhalation of radiolabeled sulfur colloid (SC) aerosol (^{99m}Tc -SC, 0.2 μm) for studying particle uptake by airway surface macrophages has been demonstrated (76).

The aforementioned findings show the wider application of aerosol delivery of drug-aerosols; which offers the greatest potential to deliver drugs into the lower airway of lungs of a wide range of molecules (*i.e.*, antibiotics, genes, peptides and proteins, antibodies and

oligonuclides) for systemic diseases and put forwards the most promising inhalable platform for efficient systemic administration.

5. Inhaled drugs for neurodegenerative disorders

Pulmonary delivery of drugs for the management of neurological diseases is not currently approved. As deep lung delivery of different drugs showed potential benefit, researchers are now focusing to expand research on delivering drugs into the deep lungs *via* DPIs/MDIs. Some drugs administered as aerosols for the treatment of neurological disorders are shown in Table 2.

5.1. Pulmonary delivery of drugs for Parkinson's disease (PD)

PD is a chronic and progressive movement disorder (77). Millions of people suffer from PD in the developed and developing world (77). It is estimated that approximately 15 percent of people with PD are diagnosed before the age of 50 with incidence increasing with age. Evidence suggests that PD occurs when trouble sprouts in the basal ganglia, a segment of brain areas known for their contribution to movement. In general, nerve cells in the brain substantia nigra inexplicably die or become impaired. Normally these cells communicate *via* the chemical dopamine (DA) with cells in another one of the areas, the striatum, which includes subareas called the putamen and the caudate nucleus. Without DA, the striatum can't send out the electrical signals needed for normal movement, and consequently PD develops. Recently, a number of studies also indicate that the basal ganglia are involved with some of the cognitive problems that PD patients experience (78). Although there is presently no effective cure, there are many treatment options such as medication and surgery to manage the PD symptoms.

Levodopa is considered to be a temporary solution for minimising PD symptoms (79,80). Research suggests that the drug enters the brain and is transported into cells that can convert it into DA in the striatum. At first, symptoms diminish, but symptoms return in three to five years. Thus far, research suggests that the cells that convert levodopa die off. Higher doses of levodopa can make up for the decreasing number of cells but may cause jerking movements of the limbs, trunk and head as well as hallucinations. However, a number of attempts have been made to improve on the levodopa treatment by creating drugs that mimic DA by using DA agonists. Low doses of the DA agonists in combination with levodopa create less severe side effects and work for longer periods of time. Scientists are now taking this step further to determine if the drugs that mimic DA can replace levodopa altogether (81). At this point, researchers have developed drugs

Table 2. Drugs administered as aerosols against neurological disease

Indication	Drug substances	Delivery method	Details of delivery method	References
Pain, dyspnea	Opioids/Morphine	Powder	Micronized powders and aqueous formulation aerosolized	117-119
	Fentanyl/alfentanil and morphine	Liquid	Liposomal fentanyl delivered via a nebulizer and MDI	72,120
Smoking cessation	Nicotrol [®] Nicorette [®] (Nicotine)	Nicotine cartridge/ Liquid	Nicotine cartridges in an inhaler; pMDI	121,122
Migraine, Vascular cephalgia	Dihydroergotamine mesylate	Liquid	HFA 134a based suspension delivered by MDI	73
	Ergotamine tartrate	Liquid	Pulmonary delivery method is unavailable	123
	Detorelix	Liquid	Intratracheal (<i>i.t.</i>) instillation of Liposomal drugs	124
Parkinson's disease	Dopamine D-1 agonist, ABT-431	Liquid	HFA based drug formulation was delivered by MDI and AERx	85,86
Parkinson's disease	L-Dopa/ L-Dopa + agonist	Powder/liquid	Alkermes AIR, delivery of small or large molecules to the deep lung; Drugs in propellant delivered by MDI	83,84,89

Note: pMDI is pressurised metered dose inhaler; MDI: metered dose inhaler; HFC is hydrofluoro alkane; AERx is a DPI device that deliver aerosolised drugs from a dosage form that consists of liquid drug formulation and a nozzle array.

that each target a specific DA receptor site such as D1 or D2 (82). The drugs that are acting at D2 sites appear not to work effectively alone. But preliminary research on rodent models shows drugs that act on D1 sites work better than when administered without levodopa. Thus, these new drugs appear to work better than the use of levodopa alone because they continue to show benefits over time and cause lesser side effects. More importantly, several investigators have discovered other DA receptors sites such as, D3, D4, and D5. It is likely that in the future drugs could be developed that would act on these receptor sites (80-82).

Overall, levodopa (L-dopa) provides better therapeutic advantage for most early stage PD patients and current treatments of PD are primarily with oral formulation, such as levodopa/carbidopa, bromocriptine, selegiline, benzotropine and trihexyphenidyl; however, the efficacy of orally administered formulations becomes problematic with the progression of disease condition and due to a lost ability to control L-dopa's poor pharmacokinetics. Majority of the drugs approved and currently available on the market are oral (Tablet/capsules), some are parenteral (IV, IM, SC) and only one is a transdermal patch; however, no pulmonary delivery products been not developed.

Deep lung delivery of levodopa particles for treating a patient with PD has been reported (83); however, no further data is available for the readers.

Using MDI, delivery of a DA agonist to the airways has been demonstrated and the authors indicated that the inhalation route provided effective delivery of the drug to the receptor (84). Pulmonary administration of a drug (ABT-431, a selective D1 receptor agonist) was found to be significantly greater than that of oral administration (85). For example with intratracheal instillation of the drug solution, bioavailability of the drug was 75% in dogs and tetrafluoroethane (HFC-134a) based MDI formulation showed 40% bioavailability. The lung bioavailability of the aerosolised drug was 34% compared to intravenous injection in the same dogs. The authors emphasised that a single rising dose in human study demonstrated that the absorption of ABT-431 following oral inhalation administration (bioavailability 25%) resulted in a dose-dependent increase in the AUC (area under the curve) versus time profile at dosages from 3.3 mg to 13.2 mg. sing a novel delivery device (AERx), Okumu and his associates (86) delivered ABT-431 (a selective dopamine D-1 receptor agonist) to healthy male volunteers and plasma samples were analysed following lung delivery and intravenous administration and 82-107% of pulmonary bioavailability was observed. This outcome demonstrated that the aerosol inhalation of this drug was a proficient means for systemic delivery.

Dugs for pulmonary delivery for the management of PD have not currently been approved; however,

only one formulation containing L-dopa has been investigated (83,87). The inhalation data for pulmonary delivery of L-dopa showed at least two fold less dose compared to that of oral dose (88). In another study, demonstrated aerosol delivery of L-dopa dry powder formulation in a rat model and pulmonary administered L-dopa showed rapid and higher plasma levels ($C_{max} = 4.8 \pm 1.10$ mg/mL at 2 min) compared to that of oral administration where the drug produced delayed and lower plasma level ($C_{max} 1.8 \pm 0.40$ mg/mL) at 30 min (89). The authors acknowledged that an inhalable formulation of L-dopa may provide PD patients with effective form of rescue therapy as well as replacement for first-line oral therapy. However, this formulation is in preclinical stage. Innovative drug delivery in treating PD has the potential to reduce many adverse effects of currently available drugs. Pulmonary delivery of current drugs, genes and liposomes will help encourage patient specific treatment for PD. Improved treatments with pulmonary delivery system may involve drugs that target one specific site or a combination of sites for better pharmacotherapeutics. Therefore, these advances, along with investigations into gene transfer, surgical and transplantation techniques, hold great promise for those with PD.

5.2. Pulmonary delivery of drugs and Alzheimer's disease (AD)

Dementia is a brain disease that significantly affects a person's ability to carry out daily routine activities. It is well established that the most common form of dementia among older people is AD, which initially involves the various parts of the brain that control thought, memory, and language (90,91). In recent years some progress has been made, however, the causes of AD remain unknown, and there is no effective cure. Like PD (see above), it is estimated that millions of people worldwide suffer from AD (91). Previous research has found that other brain changes in people with AD. For example, brain neurons die in areas of the brain that are vital to memory and other mental abilities, and connections between neurons are disrupted. Furthermore, AD may impair thinking and memory by disrupting neuronal transmissions and functions. AD is a slow disease, starting with mild memory problems and ending with severe brain damage. The course the disease takes and how fast changes occur vary from person to person. On average, AD patients live from 8 to 10 years after they are diagnosed, though some people may live with AD for as many as 20 years (90,91).

Given the complex disease process with AD, there is no better therapeutic strategy to reduce or minimize AD. However, some drugs such as, tacrine, donepezil, rivastigmine, or galantamine may help prevent some symptoms from becoming worse for a limited time in some people in the early and middle stages of the

disorder (92,93). Furthermore, memantine has been marketed to treat moderate to severe AD, although it also is limited in its therapeutic benefits. There are some formulations that may help control behavioral symptoms of AD such as insomnia, agitation, anxiety, and depression. Despite the complexity of the symptom pattern in AD, treating these symptoms often makes patients more comfortable and makes their care easier for caregivers. In addition, many researchers have begun to search for ways to block the formation of amyloid deposits, an important biomarker for AD. In a recent study, investigators used the amyloid protein as a vaccine to prevent and clear existing plaques in mice that were engineered to develop large numbers of the deposits (93). Although it remains unclear, the vaccine appears to involve the immune system and clearing amyloid. Future human studies will test the level of the plaques' contribution to AD. More importantly, the research has the potential to show that the vaccine method can influence the clinical signs in patients. A number of research groups are investigating slight variations of the vaccine strategy (94). For example, one group found positive results with an amyloid vaccine that was delivered to mice in the form of nasal drops. It is suggested that other therapeutic strategy may help prevent plaques. Several investigators have uncovered some evidence that the estrogen hormone may influence the development of AD. A number of human studies demonstrated that older women who take estrogen supplements can reduce their risk of developing AD. It is possible that estrogen's benefits, at least in part, may result from an ability to reduce the levels of amyloid protein. In a recent study, estrogen reduced the levels of amyloid protein made in a cell culture model. Recently, a long-sought enzyme, beta-secretase which makes one of the cuts that leads to the formation of amyloid protein has been identified (95). The researchers plan to develop drugs that can inhibit the enzyme. Additionally, an enzyme involved in the formation of amyloid is gamma-secretase, which has not yet been purified. Overall, these significant discoveries shed light on AD treatment strategy and provide hope that amyloid plaque-directed therapies for humans may soon become available.

However, no specific medications have been formulated yet to deliver drugs into deep lung for the treatment of AD. Using nebuliser, pulmonary delivery of apolipoprotein, amphipathic compounds and apolipoprotein were found to efficiently reach the systemic circulation through the lung (96); however, no further data are available for the readers. The author claimed that pulmonary delivery of drugs can be used for the treatment of AD as well as cardiovascular disease. Most drugs for the treatment of AD are oral (very slow absorption) or parenteral (expensive) and aerosol formulations have not been studied. Thus, it would be worthwhile for the researchers to focus on

pulmonary delivery of drugs for the management of AD. Like PD, current treatments of AD are primarily with oral formulation as described above. Improved treatments with pulmonary delivery system may involve drugs that target one specific site or a combination of sites for better pharmacotherapeutics.

6. Future directions

Lung delivery of drugs offer the greatest potential to deliver drugs into the lower airway of the lungs and the delivery of a powder form of a wide range of molecules (*i.e.*, antibiotics, peptides, proteins, antibodies and oligonucleotides) to the deep lung for systemic diseases put forwards the most promising inhalable stage for increasing systemic administration. Pulmonary delivery of large molecules for chronic diseases is advancing tremendously and may become successful in the near future. Therefore, pulmonary drug delivery needs to focus not only on lung diseases but also on conditions in which fast onset is desirable such as cancer pain, allergic reactions, brain disorders, cardiovascular disorders, and sexual dysfunction. It has been reported that more than 40 drug formulations for widely varying designs of DPIs are in the pipeline for drug delivery into the deep lung; however, only four inhaled products (for the treatment of asthma only) include a long acting bronchodilator, two corticosteroids and a combination formulation (97). In addition, anticancer drugs, steroids, beta2 receptor agonists, antimuscarinics, antihistamines and anti-inflammatory agents, which are primarily administered by oral or parenteral route, may be considered for pulmonary delivery. Therefore, there is a promising future for lung delivery of drugs for the management of other systemic disorders along with pulmonary diseases. Local and systemic delivery of different drugs for chronic systemic diseases needs to be more focused on the use of aerosol formulations, which have a lot of potential. In future, biotechnology products will produce very small amount of potent drugs which will require smart devices that deliver drugs efficiently into the lower airway of lungs. The current trend in pulmonary drug delivery and potential benefits of this route will enable the continued development of smart but reliable DPI technology to enhance deposition of drugs into deep lungs with a better patient compliance.

7. Conclusions

Pulmonary delivery of various drugs by aerosolisation has been used for centuries to treat respiratory tract diseases and the pressurised metered-dose inhaler was the only delivery device of choice. Currently, aerosol therapy is expanding with the advancement of science and technology specially in developing dry powder inhaler formulations to target the systemic circulation

for the delivery of proteins and peptides, gene therapy, and influenza and measles vaccines. Moreover, advances in all of these areas have led to pulmonary delivery of medicaments being a route of choice for many drugs, not only for respiratory diseases but also for systemic delivery of drugs for other disorders. Now a days, mental health disorders and cardiac diseases are increasing with the changing world; however, pulmonary delivery of neuroactive and cardio active drugs has not been explored. Most drugs for treating AD or PD are in oral dosages forms (tablets, capsules and solutions); forms where drug absorption is very slow and only 70-90% is bioavailable. The longer range future of DPIs does include non-invasive and efficient delivery of large molecules for systemic conditions with improved patient compliance. Therefore, pulmonary drug delivery of drugs would extend the new era of drug delivery research, which will eventually extend the life of drugs (solid state stability), increase patient compliance, and reduce the total cost not only for brain neurodegenerative disorders but also for other chronic human diseases.

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