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Review Article

Dry powder inhaler in mechanical ventilation and influence of ventilator circuit-related factors on aerosol delivery during mechanical ventilation

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ABSTRACT

Patients on mechanical ventilation need aerosolized therapy through an endotracheal tube and a ventilated circuit. In the critical care setting, patients received inhalation therapy in the form of wet aerosols via nebulizers or pressurized metered-dose inhalers (pMDI). However, an ineffective and inconsistent aerosol delivery due to drug loss in a ventilated system is a major problem for aerosolized therapy in these patients. Dry powder inhaler (DPI) has been a promising inhaler that has no 'rain-out' of wet aerosol on the circuit. This review will summarize the state of the art for aerosol delivery to mechanically ventilated patients with special emphasis on emerging opportunities for dry powder aerosols. Beside inhaler itself, drug delivery to mechanically ventilated patients depends on the ventilator circuit-related factors such as the pattern of inspiration, the volume of inhalation and the volumetric flow rate. Patients on mechanical ventilation differ from patients who can breathe by themselves (unassisted spontaneous breathing) or patient who receive direct-to-mouth inhalation. Drug delivery during mechanical ventilation is affected by the factors that directly related to ventilator circuit that controls a patient's breathing. Thus, these ventilator circuit-related factors that play an important role in drug delivery efficiency will be discussed in this review.

1. INTRODUCTION

Inhalation therapy has been used to treat respiratory disorders for centuries[1, 2]. Over the last 50 years, inhaled drug therapy has slowly been integrated with delivering pulmonary administered drugs to mechanically ventilated patients. Despite periodic successes, aerosolized therapies often fail due to ineffective and inconsistent aerosol delivery. One potential shortfall of current inhalation therapy is the lack of devices specifically designed for drug delivery through ventilator circuits, rather many of the current delivery devices and methods discussed in this review have been developed for standard inhalation therapy and retrofitted for ventilator respiratory therapy. Despite these challenges, a clinical need for improved inhaled therapeutics for mechanically ventilated patients exists.

Table 1 Dry powder inhalers (DPIs) [3-5]

Dry powder inhalers (DPIs)	Definition	Advantages	Disadvantages
The first generation DPIs *Single-unit dose devices* e.g. Spinhaler™, Rotahaler™, Handihaler™	• Each dose is loaded into a capsule, which is inserted into the device before use. After use, the capsule has to be removed before a new one can be placed in the device. • The drug delivery issues were related to particle size and deagglomeration of drug–carrier agglomerates or drug–carrier mixtures delivered by patient's inspiratory flow.	• More effective than multi-dose reservoir devices as they ensure dose consistency and avoid the effects of moisture in the powder reservoir. • The isolation of each dose, which facilitates storage stability.	• Inconvenient for patients compared to multi-dose DPIs because the capsule has to replace before for each use.
The second generation DPIs *Multi-dose reservoir devices* e.g. Easyhaler™, clickhaler™, Taifun® Twisthaler™,Novolizer™,	• Patients dispense the dose at each use. • Measure the dose from a powder reservoir	• Relatively lower cost and ease of use	• Lack of dose uniformity during inhalation and stability of formulations, if it is not protected from environ- mental degradation.
Multi-unit dose devices e.g. Diskhaler™, Diskus™, Eclipse™	• Disperse individual doses, which are premetered, into blisters, disks, dimples, tubes and strip by the manufacturers. • Individual pre-metered doses sealed in the device	• Reproducibility of the formulation compared to that of multi-dose reservoir. • More effective than multi-dose reservoir devices as they ensure dose consistency and avoid the effects of moisture in the powder reservoir. • Isolation of each dose, which facilitates storage stability.	• More complex due to the need to reload the device with a new cartridge/pack and patients (especially in the aged population) need appropriate education to operate the device. • Generally less favored than multi-dose reservoir designs.
The third generation DPIs *Active device* e.g.Exubera®, Aspirair™	• Employ compressed gas or motor driven impellers or use electronic vibration to disperse drug from the formulation.	• More sophisticated but user-friendly. • Enable respiratory force indepen- dent dosing precision and reproducible aerosol production. • Useful for aged people.	• The powder dispersion from active DPIs is limited to the physical or electrical mechanism (vibration, compressed air, impact force and impellers available in the device

The cornerstone of inhalation therapy in mechanically ventilated patients in the critical care setting is in the form of wet aerosols via nebulizers or pressurized metered-dose inhalers (pMDI). Advances in both nebulizer and pMDI delivery methods have been made in the last 20 years; however, both delivery devices have their own challenges associated with ventilator integration. The third type of inhaler, dry powder inhalers (DPI) have also been explored by several investigators for integrative use with mechanical ventilators to improve inhalation therapy. There are over 20 DPIs in the market and more than 25 in development (Table 1). However, none of the DPIs on the market have been specifically designed or approved for use with ventilator

Table 2 Novel inhaler devices [5-9]

Device	Advantages	Disadvantages
Nebulizer *Breath-activated nebulizer* e.g. AeroEclipse	• Deliver medication only during inhalation • Less medication wastes	• Need sufficient flow to trigger • Have longer delivery time • More expensive
Breath-controller nebulizer	• Deliver the medication at the beginning of inhalation • Improve dose precision and decrease upper-airway deposition • Low residue volume • Reduce delivering time by allowing a lower dosage	• More expensive
Breath-enhanced nebulizer e.g. Adaptive aerosol delivery (iNeb) AKITA	• Targeted delivery • Less wasted medication • Delivery adapts to patient's breathing • Can monitor patient adherence	• Very expensive • Not ventilator enabled • Incorrect use is concerned
Vibrating-mesh nebulizers e.g. Aeroneb Go, Pro Omron MicroAir	• Fast, quiet, portable • Self-contained power source • Can optimize particle size for specific drugs	• More expensive • Not compatible with viscous liquids or those that crystallize on drying • Difficult cleaning • Mediation dosage must be adjusted if transition from a jet nebulizer
Meter-dose inhalers (MDIs) *Breath-actuated pMDIs*	• Compact and portable • More than 100 doses available	• Contains propellants • "Cold Freon" effect • Usually low lung deposition but high oropharyngeal deposition
"press and breathe" pMDI plus spacer	• More than 100 doses available • Easier to coordinate • Usually higher lung deposition and less oropharyngeal deposition than pMDIs	• Contains propellants • Not very portable • Not breath-actuated • Plastic spacers may acquire static charge
Dry powder inhalers (DPIs)	• Compact and portable • Breath-actuated (no coordination needed) • Usually higher lung deposition than a pMDI • Do not contain propellants	• Depend on patients' breathing effort • Most types are moisture sensitive • Capsule handling problems for elderly

systems. A list of major advantages, disadvantages, and characteristics of different kinds of inhalers are shown in Table 2. As DPIs have become more popular, researchers have continued to explore the possibility of adapting these new devices with ventilator circuits. This review will summarize the state of the art for aerosol delivery to patients on mechanical ventilation with special emphasis on emerging opportunities for dry powder aerosols.

2. ANATOMICAL DIFFERENCES IN THE VENTILATED PATIENT

The respiratory tract is divided into the upper and the lower respiratory regions. The upper respiratory tract begins at the nasal or mouth cavity leading into the larynx. The larynx transitions into the trachea, which begins the lower respiratory tract and ending at the alveoli. For direct-to-mouth aerosol drug delivery, an aerosol is delivered via oropharynx, larynx, and trachea, whereas aerosol drug delivery for ventilated patients through endotracheal tube cut through these areas and direct to the area of bifurcation of the trachea. The United States Pharmacopeia (USP) induction port (IP) is a 90° bend with uniform circular cross-sections that mimics the oropharynx region for the oral deposition of inhaled drugs[10]. A realistic mouth–throat (MT) model has been developed to replace the USP IP in order to make it more realistic for MT geometry. The airway curvature is a barrier that high volume of orally inhaled aerosols

deposits instead of going to the lungs[11]. On the other hand, ventilated patients are delivered the drug via the tube. Barriers that involved with the tube, the flow in the tube as well as biofilm formation are concerned[12].

3. DRUG DELIVERY IN MECHANICAL VENTILATION

3.1. Ventilator circuit-related factors influencing aerosol delivery during mechanical ventilation

During patient initiated direct-to-mouth inhalation, the mouth and throat can be a major site of drug particle deposition, especially in patients with poor coordination using pMDIs. The portion that deposits on the tongue or the back of the pharynx may be directly swallowed and absorbed in the gastrointestinal (GI) tract and potentially enter systemic circulation via the oral route. In contrast, patients on mechanical ventilation are delivered inhaled drugs through an endotracheal tube, which is inserted into the mouth until just above the first bifurcation; eliminating the potential for deposition in the mouth and throat. While this can be advantageous at preventing un-intended oral exposure, drug loss can be observed in the endotracheal tube [13]. Smaller diameter endotracheal tubes offer more air flow resistance, which at higher flow rates can induce turbulence and aid in dry particle deagglomeration[5]. Furthermore, utilizing shorter and/or smaller diameter tubing can improve delivery yields by decreasing the surface area available for particle impaction. It has also been suggested that electrostatic charge of an endotracheal tube and circuit could be reduced by "priming" the ventilator line with several dose actuation [13]; although a possibly more refined approach may be to utilize endotracheal tubes with low electrostatic charge or to pre-coat the inside of the endotracheal tube prior to placement with a relatively electrostatic inert and non-toxic compound.

3.1.1. Inspiration patterns

The mechanical ventilator controls phases of breathing in either mandatory or spontaneous modes. Normally, inspiration patterns on a ventilator can be categorized into three kinds of waveforms; sine, ramp (decelerating), and square waveform. A sine waveform provides a continuous increase and decrease of flow rate in the form of a sine wave. A ramp waveform generates the highest inspiration flow rate at the beginning of the cycle, and then the flow rate gradually decreases along the cycle. A square waveform provides a constant flow rate throughout an inspiration cycle[14]. In addition to the inspiration cycles, ventilators are programmed with different inhalation modes such as assisted support and full ventilation support, which can include pressure regulation to fit the respiratory needs of the patient.

In terms of drug delivery, research scientists showed that inspiration pattern caused statistically significant differences in nebulizer performance [15, 16]. The square waveform at 30 L/min showed better performance on delivering aerosols through an endotracheal tube compared to ramp waveform at 60 L/min[17]. While it is intuitive to hypothesize that waveform would affect pMDI delivery, few studies have thoroughly evaluated these parameters and current studies are inconclusive and may be affected by other experimental variables [16, 18]. To further complicate ventilation, ventilators can be triggered by several events including flow triggering, pressure triggering, and mandatory breaths. The combination of these variables creates additional challenges to consistently administer inhaled drugs to ventilated patients.

In addition, flow pattern also controlled by selected mode of operation. During mechanical ventilation, volume-controlled ventilation or pressure support ventilation should be selected. A study of aerosol delivery via nebulizer indicated the importance of selected mode to the deposition of aerosols. Volume-controlled ventilation delivered the higher amount of aerosols to the lungs compared to pressure support ventilation[19].

3.1.2. Inhalation volume

Patients with respiratory diseases such as COPD normally have lower inspiratory capacity compared to healthy people[20]. Inhalation volume is a critical parameter that can affect inhaled drug delivery and is strictly controlled by a mechanical ventilator. During ventilation, tidal volume is displayed at the end of exhalation and plays a vital role to ensure sufficient ventilation without causing trauma to the lungs. A study reported that setting the tidal volume at greater than 500 mL in an adult model improved aerosol drug delivery[21]. Although a large tidal volume may increase aerosol deposition efficiency, caution should be used since it also can cause volutrauma if the tidal

volume achieves greater than 8-10 mL/kg [22]. Moreover, some researchers showed an increased incidence of *acute respiratory distress syndrome* (ARDS) with higher tidal volumes; however, the studies were limited by their heterogeneity and high variability in baseline ARDS risk among patients[23]. No definitive recommendations can currently be made concerning the most appropriate tidal volume strategy in patients on mechanical ventilation.

3.1.3. Volumetric flow rate

This factor also alters drug delivery efficiency for inhaled pharmacotherapies. In general, high flow rates can increase turbulent flow and the inertial impaction of aerosols. Some studies suggested that a lower inspiration flow rate (e.g. 40 versus 80 L/min) improved aerosol delivery in both non-ventilated patients and ventilated patients[24, 25]. The volumetric flow rate is also important for aerosol delivery when using DPIs. For passive DPIs, performance is typically flow-rate dependent[5]. The dispersion of drug powders depends on the inspiration effort of the patient and the resistance within the inhaler. Turbulence has an important effect on powder dispersion, resulting in an increased dispersion of the dry powder. The effect of the flow rate on DPI, is thus, an important parameter when delivering the drug-aerosol to ventilated patients; however, to date, there are limited studies evaluating the effect of flow rate on experimental DPIs integrated into ventilator circuits[26].

For nebulizers, aerosol delivery has a direct correlation with the duty cycle (inspiratory time (T_I)/duration of total breathing cycle (T_{TOT})). Investigators have found that increasing the duty cycle (T_I/ T_{TOT}) can improve lower-respiratory-tract aerosol delivery and total aerosol inhaled per each breath [16, 27]. Additionally, greater albuterol delivery to the bronchi can be achieved with a T_I/T_{tot} of 0.50 than of 0.25 when delivered via MDIs. For routine clinical use, a slower inspiratory flow rate was preferred to excessively long inspiratory times to maximize aerosol delivery clinicians should 'go slow with the flow'[28].

3.1.4. Humidity

Traditional ventilator circuits are humidified and heated although the use of heat and moisture exchangers as a source of humidity has become more common in the hospital setting due to their relatively low cost and ease of replacement. Humidity has long been a major challenge for delivering drugs to the lungs of ventilated patients. It has been estimated that 40-50% of drugs can be lost when heated/humidified ventilator circuits are used [29, 30]. As nebulizers add more humidity to the circuit, this can overwhelm the heating elements and lead to 'rain-out' of drugs into a condensate on the circuit tubing wall. This may be due to increasing particle impaction or sedimentation in the ventilator tubing. Increasing humidity may also promote hygroscopic particle growth, which could reduce the delivered fine particle fraction. Studies on pMDIs have also noted increased drug loss in ventilator circuits when humidity levels are high[31]. Although the new design spacer such as Combihaler® and ACE® was applied with pMDIs, the aerosol delivery still decreased in humidified condition compared to non-humidified one[32].

The loss of drug aerosol can be reduced by turning off or bypassing the ventilator humidifier during aerosol administration. Bypassing the humidifier for a long time; however, can harm the airway mucosa, which could be exacerbated in the case of some nebulizers that require up to 35 minutes to complete aerosolization[29]. De-humidifying the ventilator air increases the risk for thick and sticky mucus secretions at the end of the endotracheal tube, but also runs the human risk of forgetting to re-introduce humidity after the drug administration period.

Relative humidity is also known to affect dry powder aerosols. Lower drug delivery efficiency was achieved in both excessively dry and humid environments depending on the physicochemical nature (e.g. hygroscopicity) of the drug[33]. For example, drug delivery efficiency can be decreased because of capillary force between the particles in a humid environment[34, 35] or due to static charges between the particles in a dry environment[36]. These studies suggest that a balance of humidity in the ventilator circuit may provide for a more ideal dry powder delivery environment, whereby some humidity may mask relative surface charge of particles, but excessive humidity may accelerate particle-particle interaction of highly hygroscopic drug formulations.

3.2. Device-related factors influencing aerosol delivery during mechanical ventilation

Device placement plays a key role in drug delivery efficiency of inhaled aerosols. As traditional nebulizers are in 'on' or 'off' mode for minutes at a time, studies have shown that placing the nebulizer farther away from the circuit Y-connector integrated into the inhalation line leads to increased drug delivery efficiency as it reduces the amount of drug that diffuses into the exhalation line[19, 37]. In one study, placing the nebulizer prior to the humidifier increased the amount of drug delivered, suggesting that this placement method may help control 'rain-out' due to better regulation of the circuit humidity[37].

Another way to minimize drug diffusing to the ventilator line is to intermittently control the nebulizer, which is more efficient than continuous nebulization [38]. Aeroneb® Pro and Aeroneb® Solo, for example, are vibrating mesh nebulizers with a specially designed CPAP adaptor which allows for aerosol delivery just below the "Y" connector for effectively treating mechanically ventilated patients (Figure 1). It is microprocessor driven and exploits a pressure transducer to identify changes in airway pressure, detect inspiratory time, and deliver aerosols only during a specified portion of the inspiration. Currently, researchers are exploring the clinical outcomes (ventilator-associated events (VAEs), length of stay (LOS) in intensive care unit (ICU) and total days on mechanical ventilation) when using a traditional jet nebulizer versus a newer generation of vibrating mesh nebulizers during mechanical ventilation; automated innovations such as these look promising to the field of inhaled therapeutics [39-42]. A study showed high efficiency of vibrating mesh nebulizer compared to jet nebulizer[43]. Vibrating mesh nebulizers also provided smaller residual volume and relatively constant temperature of medication compared to ultrasonic devices[44]. Although a study reported independence of drug delivery efficiency from the design of vibrating mesh nebulizers, delivered dose variation still found due to the drug-device compatibility[43]. Nowadays, drug-device combinations have been promising in the area of development that should provide high and consistent delivery performance[45].

Delivery of drugs through pMDIs also suffers from variability due to different circuit placement[46]. In addition to placement, the market is filled with a myriad of commercially available in-line actuators and in-line actuator/spacer chambers to help improve drug delivery. Inhalation synchrony is also important for pMDI administration as a reduction of inhaled mass by 35% was reported when actuation was not synchronized with inspiration[29]. Furthermore, a study showed at least 40% higher dose was administered when the pMDI was actuated at the onset of inspiration compared to actuation during expiration[47]. Future ventilator actuators that include automation may dramatically improve dosing consistency between different health care providers.

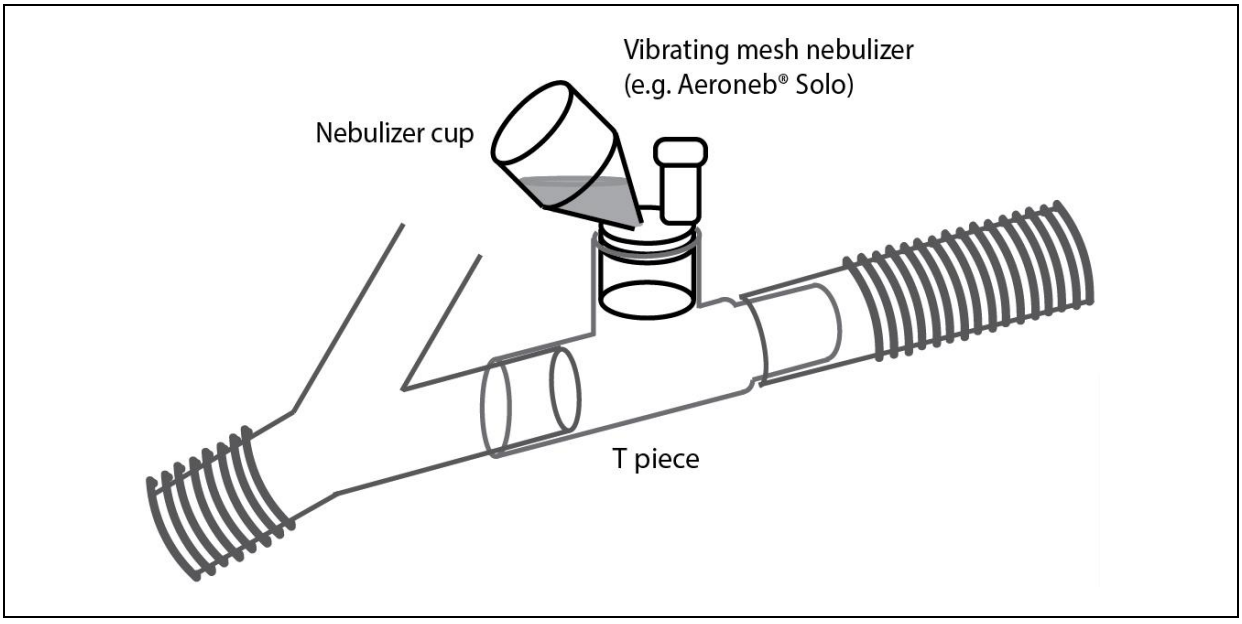

Figure 1. Aeroneb® Solo, a vibrating mesh nebulizer, in ventilator circuit.

3.3. Dry powders with DPIs in mechanical ventilation

The variability of drugs delivered to the lungs due to the low efficiency of pMDI and nebulizer liquid formulations beckons the development of dry aerosol powder technology for ventilated patients[48]. To date, dry powder inhalers have only been explored experimentally in ventilator circuits, with limited success. This might be due to the fact that few devices have been specifically designed to be integrated and/or to perform optimally under various ventilator conditions. In addition, DPIs pose new challenges such as powder dispersion, humidity effects (e.g. hygroscopic powders), and dose actuation. A DPI could be easily adapted to ventilator circuits, either by using the ventilator's inspiratory airflow to create an aerosol or utilizing a power source to first generate an aerosol from the DPI and then enter the drug particles into the ventilator circuit[26, 49].

In an earlier trial using a commercial DPI in a ventilator circuit, Pulmicort Turbuhaler® was modified by removing the outer covering of the device and putting it in a closed chamber that connected to the ventilator circuit[48]. The researchers suggested that dry powder drug delivery was worthy of further improvement, especially in the intensive care setting, even though some drug was lost in the endotracheal tube. The percent of drug lost should be reduced when a dry endotracheal tube and non-humidified system are applied[12, 22]. An in-line delivery system was studied with adapting Monodose® inhaler that disconnection of patients from mechanical ventilator did not require during dry powder delivery[50]. A novel in-line DPI has been developed to apply with the in-line delivery system[51]. Lately, a novel dry powder inhaler has been designed to fit with ventilator connection and to be suitable for delivering dry powder aerosols to ventilated patients (Figure 2). This inhaler has been proposed based on the understanding of the de-agglomeration process of powders in the inhaler and the ease of use of the inhaler[26]. The new inhaler device provided the convenience of connecting with the ventilator and endotracheal tubing while maintaining efficient aerosol delivery compared to the direct-to-mouth Monodose® inhaler[26, 49].

Since breathing can be firmly controlled by ventilator settings, drug formulations and inhaler devices are the primary design metrics that would affect DPI performance. Advances in particle engineering compel efforts to explore drug powder formulations owing to enhanced drug delivery efficiency during mechanical ventilation. To increase powder deposition in the central airways and peripheral areas of the lungs, the size of drug particles should be within 1–5 μm, while simultaneously reducing the cohesive and adhesive forces that negatively affect powder dispersion [52].

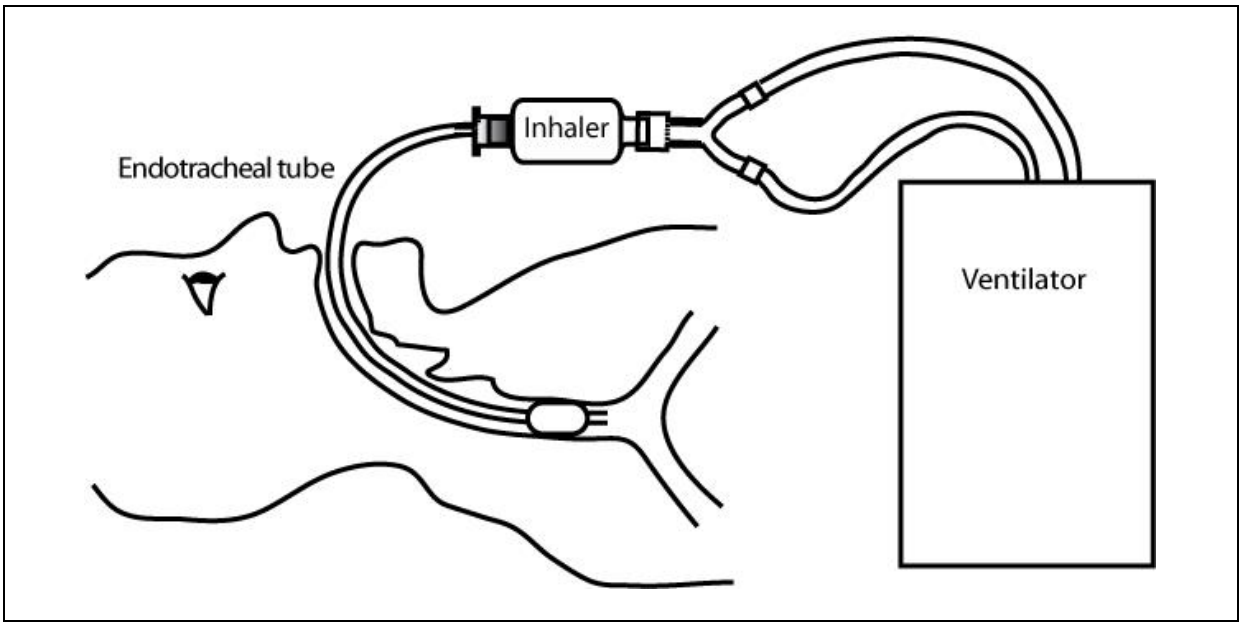

Figure 2. Direct connection of an inhaler device within the ventilator circuit. Here, the inhaler is placed between the ventilator tubing and the endotracheal tube. Aerosols may be generated using an external energy source (e.g. ultrasound) or by utilizing the energy supplied by the ventilator.

Pulmonary formulations composed of nanomaterials have been extensively examined. Emerging methods in particle fabrication such as spray drying, wet milling, and others have allowed the formulation of dry powders with decreased density, increased surface area, and increased flowability. Formulation scientists have also begun to experiment with several anti-static agents that may aid in the dispersion properties of fine powder aerosols. Tobramycin podhaler (TOBI®) is a currently approved inhaled therapeutic that utilizes spray drying technique to form easily dispersed hollow spherical particles. Additionally, another approach is to wet mill micronized drug into NanoClusters [12, 26, 53]. NanoClusters are the formulation that combined the properties of micronized particles and nanosized particles. The micronized particles provide the suitable size for drug deposition, while the agglomerated nanoparticles improve the flowability of particles traveling along the airways, especially passing through the upper airway. Nanoparticle agglomerates yielding micron-sized 'clusters' that require very little airflow to effectively deliver fine aerosol particles. Despite the approach, identifying a precision particle fabrication and/or formulation of dry inhaled powders with ideal dispersion characteristics would accelerate the process of inhaler device design and ventilator integration.

4. FUTURE DIRECTIONS

To date, pharmaceutical aerosol technologies have focused on direct-to-mouth aerosol delivery with far fewer initiatives to deliver aerosols to ventilated patients. Although nebulizer technology has advanced, many drugs cannot be dissolved in water, which complicates nebulizer formulations. Additionally, nebulization times can be long. Introducing these wet aerosols into the ventilator circuit can lead to poor or inconsistent aerosol delivery to the lungs of ventilated patients. Dry powder aerosols represent an attractive alternative to formulate poorly water-soluble drugs, even drugs with low potency requiring a large delivered dose. Improvements must be made to existing dry powder formulations and devices in order to be used in ventilated patients.

Since device components and formulation are interlinked, new designs require careful evaluation when changes are made to any single element. For passive DPI design, the device has to be designated with reasonable resistance since the resistance influences powder dispersion in the device and the resulting aerosol quality. The resistance across the device must also be balanced, as increased resistance limits the flow rate of air at a given pressure and modern ventilators will shut off at high resistance (high circuit pressure) to protect patients from injury. Most marketed DPIs loaded with micronized drug (e.g. Advair®, Symbicort®, Pulmicort®, Flexhaler™) require high device resistance to deagglomerate and aerosolize the dry powder. This suggests that particle engineering methods (e.g. NanoCluster, spray drying, others) that create new formulations of dry powder drugs to easily disperse into fine aerosols at low resistance and/or flow rates will be essential for passive DPIs integration into ventilator circuits.

An alternative to the integration of passive DPIs is to create ventilator-specific active DPIs ($_{Act}$DPI). $_{Act}$DPI would have all the benefits of passive DPIs, but would have several advantages. First, the limitation of internal device resistance which is essential for dry powder dispersion, but it is limited by ventilator settings, could be eliminated entirely by utilizing an external high-pressure power source to shear the powder through the device similar to pMDIs. Second, as high shear can be created using an external power source, a single high shear $_{Act}$DPI could be designed to deliver multiple formulations of drugs. This could lead to a (more) universal $_{Act}$DPI that could easily be managed by inhalation therapy caregivers through eliminating the need for independent DPI devices and ventilation integration adapters for each unique drug/drug formulation. Third, similar to new electronically controlled vibrating mesh technologies, ventilator-specific $_{Act}$DPIs could easily be automated by triggering off of ventilator air flow/pressure or could be assimilated into the ventilator software itself, triggering at a specific series of inhalation events and eliminating the human error associated with 'timing' inhalation. Automation has yet to be introduced into standard pMDI delivery and could also increase delivery of established inhaled pMDI therapeutics.

Additionally, the internal geometry of the device including the shape and dimensions of the air channels should be investigated to deagglomerate drug powders while minimizing aerosol velocity to prevent impaction during entrainment into the ventilator circuit. Effective design of the device geometry can optimize fluidization and deagglomeration of powders

after they come out of the capsule, blister, or chamber and can help powder travel through the airstream with minimal powder loss in the connection. Decreasing the contact surface between the powder and surface of the device may reduce the static particle-particle and particle-device interactions, leading to increased delivery efficiency. Moreover, the shape of the air channels (e.g. spirals, angles) can alter the dispersion of powder independent of device resistance. In sum, devices should be designed specifically for ventilated patients, rather than attempting to retro-fit direct-to-mouth DPIs.

New DPIs should be explored and designed with the intent for potential therapeutic integration with a ventilator circuit. The ideal inhaler has to fit with current ventilator connections and circuitry to provide ease of use without 'breaking' the circuit connection every time drug is administered, which can increase the risk of ventilator line contamination and patient infection. Moreover, as more hospitals begin to use heat and moisture exchangers to provide ventilator humidity, an inhaler device that could be integrated into both types of ventilator circuit routing would help standardize inhaled therapeutic therapy. To accomplish this goal, a ventilator by-pass circuit could be introduced. This circuit could use a standardized suction port elbow with an endotracheal tube suction port, which is routinely used for endotracheal suction of secretions accumulated in the endotracheal tube. Adapting endotracheal suction catheters for drug administration could also eliminate much of the secretions, condensate, and humidity associated with the endotracheal tube itself if a fresh suction tube (catheter) is used.

Finally, other factors influencing aerosol delivery during mechanical ventilation should continue to be studied to optimize aerosol delivery to ventilated patients. In addition, different disease conditions impact the clinical approach to ventilation, depending on the state of the disease. For example, maintaining a positive pressure throughout the breathing cycle may be desired to keep airways open when lungs are plugged with mucus. Such factors should be considered when designing pharmaceutical aerosol delivery systems for the ventilated patient.

5. CONCLUSIONS

Inhalation therapy is an important drug administration modality for patients on mechanical ventilation. Drug formulation, device design, and ventilator circuit integration conditions all influence the efficiency of aerosol drug delivery. Continued improvement in particle engineering and device technologies such as NanoClusters technology and new automated vibrating mesh nebulizers show great promise for improving drug delivery to ventilated patients. New dry powder inhaler designs with an optimized connection to the ventilator circuit would improve convenience and optimize the delivery of fine aerosols to the lungs of patients in critical care. With the incorporation of a smart ventilator circuit using standard valve suction catheter ports, delivering inhaled therapeutics through fresh endotracheal tube catheters could dramatically: 1) minimize the effect of humidity/condensation, 2) eliminate or reduce stagnant drug stuck to the side of the ventilator circuit and endotracheal tube, 3) easily be used for standard humidified ventilator circuits and with circuits utilizing heat/moisture exchangers that would block drug delivery, and 4) be used for both adult and pediatric indications as standardized endotracheal tube suction catheters are routinely used in both patient groups. Properly combining engineered dry powders with devices specifically designed to aerosolize the drug into the ventilator circuit will enable new paradigms for treating respiratory diseases of ventilated patients and potentially opening up a new avenue to deliver other drugs locally, e.g. thrombolytic agents for acute pulmonary embolism, which could improve the therapeutic index over intravenously (systemically) administered formulations. The goal of achieving accurate and reproducible aerosol delivery independent of ventilation parameters requires advances in both applications of aerosols/devices and transport of aerosols throughout patient lungs.

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