Formulation technology to repurpose drugs for inhalation delivery

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Inhalation of drugs for both medicinal and recreational purposes has occurred for centuries. Over the last two decades, a variety of new formulation technologies and inhaler devices have been developed to repurpose drugs given by other routes of administration as superior inhalation products with improvements in safety, efficacy and convenience for patients. These efforts have been particularly successful for drugs for the treatments of diseases of the respiratory tract. The delivery precision, safety, tolerability and efficacy of many different drugs given by inhalation for systemic effect using these modern inhalation delivery technologies was shown to equal or exceed that for the parenteral route of administration. It is expected that more wide-spread use of this route for systemic delivery will be accepted as some of the products currently in late stage development reach the market.

Introduction

Drug repurposing can be a very attractive path for drug development compared to the traditional pharmaceutical drug discovery path as the latter is relatively slow, expensive and risky even in late-stage development [1,2]. The challenge with development of new chemical entities (NCEs) is that many molecules may show in vitro activity, but subsequently fail in preclinical efficacy models, or later in the more expensive and time-consuming preclinical (animal) safety studies prior to entry into clinical development. Manufacturing, stability and compatibility problems may not become apparent until large scale batches have been prepared and investigated over prolonged periods of time. Even the development of analytical methods for in vitro and in vivo studies is costly for an NCE. Often, systemic side effects are not observed with NCEs until late stage clinical trials, or post-approval. For those few NCEs that do enter human clinical development most fail to reach the market, with respiratory NCEs as a class burdened with the highest failure rates of nearly 85% and total cost exceeding $1.1 billion in 2006 [3].

By contrast, reformulating existing marketed drugs for inhalation delivery to treat lung conditions or for systemic uptake through the lung should be faster, cheaper and involve less risk as much of the information about the drug and its biological effects are already known. Since the established drug has already satisfied a significant number of safety and pharmacology studies, it can bypass much of the early cost and time needed to bring a drug into clinical development. However, stability of the new formulation, its performance in an inhalation device and inhalation safety will still need to be established.

Rationale for pulmonary administration

The most obvious justification for pulmonary delivery is for drugs to treat diseases of the lung as was true for the ‘repositioning’ of early asthma medications: epinephrine, selective beta 2 agonists and corticosteroids (Table 1) [4–6]. As very little of the dose administered orally or by injection typically
reaches the lung, higher doses must be administered to be effective. The unnecessarily high drug dose may have cost and side effect implications. The amount of the same drug that needs to be inhaled can be orders of magnitude lower yet still achieve a comparable lung dose with equivalent potency, or a higher lung dose can be delivered with superior efficacy. The latter is particularly attractive if systemic side effects are dose-limiting, provided that the high local concentrations of the drug do not cause respiratory tract side effects.

A second scenario is when the drug is already approved to treat medical conditions in other parts of the body but the same condition may also affect the respiratory tract (for example, treatment of fungal and bacterial infections in the lung, lung cancer, and prevention of organ (lung) rejection by the inhalation route) [7]. Alternatively, the drug may treat a pulmonary condition but act by a completely different mechanism in the respiratory tract than for its original indication elsewhere in the body (e.g. the anti-depressant amitriptyline, by blocking ceramide levels, has the potential to treat inflammation and infections in the respiratory tract [8]).

A third scenario, and one which has been used by tobacco smokers and recreational drug users for millennia, is to inhale the drug not for local action in the lung, but rather for entry into the systemic circulation (Table 2). The advantages include ease of use and complete absorption within a few minutes in the case of small lipophilic molecules (e.g. fentanyl, nicotine and testosterone), as well as small hydrophilic drugs (e.g. morphine) [9–12], and thus rapid pharmacodynamic effect for conditions such as pain relief. For peptides and proteins, the key reason is to replace injections [13], although reduction of side effects [14] and modified pharmacodynamics [15] may also be attractive. While pulmonary bioavailability may only be a fraction of that of subcutaneous injection, which may affect the cost of goods (COGs), the pharmacokinetic (PK) and pharmacodynamic (PD) precision can be equal to or superior to parenteral treatment with the correctly designed delivery systems combining particle size control with management of the respiratory maneuvers [9,12].

**Topical lung treatment: asthma and COPD**

Several therapeutic classes of compounds can be inhaled to treat asthma or COPD including beta-agonist bronchodilators, corticosteroids, mast cell-stabilizers (e.g. sodium cromoglycate) and anticholinergics. Only sodium cromoglycate was developed solely as an inhaled product so the other classes all represent repositioned inhaled medications, long before the term ‘repositioned’ was in common use in this regard. In many instances within each drug class, molecules with superior properties were designed specifically for the inhaled route.

**Beta-agonists**

The beta-adrenergic agonist class of bronchodilators were probably first ingested orally in herbal preparations containing ephedrine thousands of years ago. The first synthetic beta-agonists, epinephrine and ephedrine, were also given orally in the early 1900s [5]. These compounds are non-selective and also stimulate the alpha adrenergic receptors, which causes side effects like increased blood pressure. Changing the administration route of these drugs and subsequently development of more selective drugs specifically for the

### Table 1. Reasons to reposition of a drug for administration by inhalation for the treatment of diseases of the respiratory tract

<table>
<thead>
<tr>
<th>Reason</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>More convenient delivery</td>
<td>Drugs with poor oral bioavailability, for example, some antibiotics and most macromolecules</td>
</tr>
<tr>
<td>Fewer systemic side effects</td>
<td>Prostacyclin analogs for the treatment of pulmonary arterial hypertension; antibiotics for respiratory infections; corticosteroids for treatment of asthma</td>
</tr>
<tr>
<td>Faster onset of action</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>Improved therapeutic response</td>
<td>Asthma medications such as bronchodilators, and steroids</td>
</tr>
<tr>
<td>Improvement of partitioning of drug or biologic from blood to lung</td>
<td>Muscarinic receptor antagonists such as tiotropium bromide, and biologics acting on the epithelial side of the lung, such as alpha-1-antitrypsin [40]</td>
</tr>
<tr>
<td>Reduction of cost of goods</td>
<td>Biologics acting on the epithelial side of the respiratory tract, such as alpha-1-antitrypsin [40]</td>
</tr>
</tbody>
</table>

### Table 2. Reasons to reposition of a drug for administration by inhalation for systemic delivery

<table>
<thead>
<tr>
<th>Reason</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>More convenient delivery</td>
<td>Drugs with poor oral bioavailability, for example, peptides and proteins</td>
</tr>
<tr>
<td>Overcoming side effects at administration site</td>
<td>Cytokines (e.g. interferon alpha) at injection site; drugs that have gastro-intestinal side effects</td>
</tr>
<tr>
<td>Faster onset of action</td>
<td>CNS drugs, for example, treatment of pain, craving for cigarettes</td>
</tr>
<tr>
<td>Better therapeutic response</td>
<td>Immunization via respiratory mucosa</td>
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</table>
inhaled route (e.g. albuterol and terbutaline) enabled lower doses and resulted in faster onset of bronchodilatation and at least as long-lasting effect as for the oral route, with fewer systemic side effects [5]. The onset-of-action for most inhaled short-acting bronchodilators (SABAs) is typically 5–15 min after dosing with peak effect in 30–60 min and a duration of action of 2–3 hours. Beta-agonists are currently available in the nebulizer, metered dose inhaler (MDI), dry powder inhaler (DPI) and soft mist inhaler (SMI) formats.

Steroids
The use of oral prednisone and intravenous hydrocortisone in the late 1940s provided dramatic improvement in asthmatic symptoms but their prolonged use led to a host of now well-understood systemic side effects. Early attempts to develop effective inhaled steroid therapy failed due to the use of steroids with low topical anti-inflammatory potency or too high systemic effect. Success was achieved by selecting more lipophilic steroids with higher affinity for the glucocorticoid receptor and which upon systemic absorption were rapidly metabolized in the liver to species with lower receptor affinity thus reducing systemic side effects [6]. These include beclomethasone dipropionate, budesonide, flunisolide and triamcinolinone acetonide which are available in dosage forms for nebulizers, and DPI, MDI, and SMI formats and some are available as combination products containing a steroid and a beta-agonist.

Anticholinergics
Another class of compounds with therapeutic effect in asthma and COPD are the anticholinergic alkaloids which have been used in herbal remedies for the treatment of respiratory disorders for centuries [4]. Naturally occurring anticholinergic alkaloids, such as atropine and scopolamine, given orally led to side effects [4]. New anticholinergic agents such as ipratropium bromide were therefore developed for administration via the inhalation route. These compounds have limited absorption from mucosal surfaces and thus require inhalation delivery to target the muscarinic receptors in the airways. A further benefit of inhaled therapy is that systemic drug concentrations are minimized due to their poor absorption from the lung. Anticholinergics are currently available in the nebulizer, MDI, DPI and SMI formats and some are combination products containing an anticholinergic and a beta-agonist.

Topical lung treatment: pulmonary arterial hypertension (PAH)
Pulmonary hypertension is characterized by an increase in arterial pressure and vascular resistance in the pulmonary circulation and without treatment PAH patients have a median survival of three years from diagnosis [16]. Continuous prostacyclin infusion improves exercise capacity and survival in PAH patients but prostacyclin is unstable with a half-life of 2–3 min in the blood stream. A prostacyclin analog, iloprost, was developed solely for inhalation treatment [16] as the site of action is in the pulmonary circulation. Longer-acting prostacyclin analogs including treprostinil were approved via intravenous (IV) and subcutaneous infusion (Remodulin® United Therapeutics). However, IV administration of this drug lacks pulmonary selectivity leading to systemic side effects (e.g. hypotension, nausea, vomiting, jaw pain, headache, among others) and ventilation-perfusion mismatch. Treprostinil was subsequently repositioned in an aqueous formulation via nebulizer dosed four times daily (Tyvaso®, United Medical). Because the prostacyclin analogs are potent, liposomal formulations have been conceived to reduce the frequency of inhalation administration to once-daily [16].

Topical lung treatment: infections
Severe respiratory infections are a major cause of morbidity and mortality in patients with chronic lung diseases (7). Two systemic antibiotics are now FDA approved for the management of respiratory infections with *Pseudomonas aeruginosa* (PA) in cystic fibrosis; they have been repositioned as inhaled therapeutics to provide higher drug concentrations in the lung, the site of the infections, while minimizing overall body exposure to reduce the incidence and severity of systemic side-effects: tobramycin (TOBI® Novartis) which was formulated in a high concentration aqueous solution for twice-a-day nebulizer delivery, and lyophilized aztreonam (Cayston® Gilead), which is dosed three times daily using a mesh nebulizer. Several other inhaled antibiotics are in development including a dry powder formulation of tobramycin in the NDA stage of development. Inhaled antibiotics can also be reformulated into liposomes which combine properties to target the bacteria in biofilm, and a sustained release profile to enable less frequent (i.e. once-daily) administration for added patient convenience [7]. Three nebulized liposomal antibiotic formulations are in late stage clinical development: amikacin (Arikace® Insmed) and ciprofloxacin (Lipoquin™ and Pulmaquin™, Aradigm) [7].

The four marketed injectable amphotericin B antifungal products, while not approved specifically for inhalation, have been reported to be nebulized without reformulation to treat or prevent fungal infections in the lung [7]. The liposomal product (Ambisome®, Gilead) appears to be the better tolerated of the four. The main drawback for all of these formulations appears to be the long nebulization times to achieve an adequate lung dose.

Topical lung treatment: preventing lung rejection
Systemic therapy with cyclosporine (Cys), an anti-fibrotic and immunosuppressive drug, to prevent bronchiolitis obliterans (BO) in lung transplant patients is limited by side effects and moderate efficacy. Nebulized Cys allows higher concentrations...
of Cys to reach the lung allograft, reduce the incidence of BO and confer a survival advantage [17]. However, the propylene glycol used to solubilize Cys was reported to be irritating [18]. Minimizing the irritation provided the motivation to develop a better-tolerated, lyophilized, liposomal Cys formulation which is delivered by mesh nebulizer and is in late stage clinical development [18].

**Topical lung treatment: lung cancer**

The idea of minimizing the toxicity at unwanted sites and maximizing the therapeutic effect at the site of action is particularly relevant to the treatment of cancers in the respiratory tract. However, there are formidable challenges to develop an inhaled cytotoxic formulation to treat lung cancer and none have entered late stage efficacy trials. Existing formulations of chemotherapeutics have been nebulized with improved survival demonstrated in animals [19]. A liposomal cisplatin formulation, with the potential to improve local tolerability and increase the drug concentration at the site of the tumors, has been evaluated in early human clinical studies [20].

**Systemic treatments via the inhalation route**

In the past two decades, significant investment has been devoted to overcoming the technical hurdles associated with inhalation of proteins and peptides to treat systemic diseases. The fuel driving these innovations was the market perception that a non-invasive inhalation product would be superior to injections, the ‘crude’ insertion of metal shafts into the body to inject proteins into subcutaneous tissue. The charge was to develop technologies able to efficiently, reproducibly and conveniently deliver protein therapeutics to the peripheral lung, where conventional wisdom stated that effective absorption into the blood stream would more easily occur across the thin, 0.2 µm alveolar epithelium. Exubera®, inhaled insulin, from Inhal, was the first such product actually to be approved, although it turned out to be a commercial failure for a variety of reasons. Other very interesting inhalation technologies were developed in pursuit of systemic delivery via the lung, for example, low density porous particles with larger geometric size allowed for simpler and less expensive DPI device technologies [21]. A new class of soft mist inhalers were developed, including the AERx System with its nearly monodisperse particle size distribution and breath control features practically eliminating deposition in the oropharyngeal region and thus resulting in intra-subject variability equivalent or superior to subcutaneous injection [12,22]. More recently a condensation aerosol inhalation system has demonstrated the capability to deliver fine aerosols for rapid systemic uptake of small lipophilic molecules [23].

The barriers to, and mechanisms for, systemic absorption of proteins from the lung have been reviewed [10,24,25] as well as the clean safety record of inhaled proteins [26]. Small peptides, unless they are sensitive to degradation by proteases attached to the plasma membranes of cells (which can be overcome, e.g. by blocking the ends of their exposed amino acid chains), are more rapidly absorbed from the lung than the larger proteins, with bioavailabilities in the range of 20–50% of that for subcutaneous injection [24]. Proteins up to about 50 kDa are systemically absorbed in animals following intratracheal (IT) administration (15–40% bioavailability), although the bioavailability in humans for inhaled growth hormone [27] and alpha interferon [14] is only 3–10% suggesting species differences or overestimation by IT instillation. Many other biologics have been evaluated for repositioning via the inhalation route including erythropoietin, PYY, oxyntomodulin, PTH, GLP-1 and beta interferon and in most cases development was terminated for ‘business reasons’ rather than for safety or efficacy concerns.

It is also important to point out that classical bioavailability comparisons in terms of dose-corrected comparisons of areas under the plasma curve for the drug or biologic in question may be misleading, especially for biologics. For example, in the case of alpha interferon given by inhalation, the pharmacodynamic response (in this case measured as a desirable immune response) was comparable to that observed for subcutaneous injection, despite much lower ‘bioavailability’ for the inhalation route [14].

While the enthusiasm for developing inhaled biologics has waned, these new delivery technologies are enabling the repositioning of small molecule central nervous system (CNS) drugs via inhalation with rapid pharmacokinetics [23]. The two most advanced inhaled CNS programs are under NDA review. An intravenous drug, dihydroergotamine, has been reformulated as the mesylate salt in a modified, breath-activated MDI device (Tempo®) to treat migraine; this inhaled product, Levadex® (MAP Pharma), provides a convenient, non-invasive alternative to IV administration with a comparable PK profile, and demonstrated superior pain relief over placebo [28]. Loxapine, a dopamine blocker, has also been repositioned using a condensation aerosol inhaler (Staccato®: loxapine, Alexza) to treat agitation associated with bipolar disorder and schizophrenia [29]. The Staccato® technology has also been utilized to deliver alprazolam in Phase 2 trials to treat anxiety, and earlier stage trials of zaleplon for insomnia and fentanyl for analgesia. The AERx® System demonstrated rapid pain relief for inhaled morphine [12] and a reduction in craving for cigarettes with inhaled nicotine [30].

**Lung anatomy and considerations for selecting the region of delivery**

For orally inhaled drugs, the human respiratory tract is conventionally divided into three regions: extrathoracic (mouth,
oropharynx and larynx), central airways (the conducting or tracheobronchial airways) and the alveolar or peripheral lung, where gas exchange takes place. The conducting airways can be further subdivided into the large and small airways (less than 2 mm diameter). For all repositioned drugs, it is desirable to avoid deposition in the oropharyngeal region as that reduces the amount of drug reaching the central and peripheral airways. To treat lung disease, the site of action is either the location of the disease itself (e.g. the lung region that is infected) or the location of the cells expressing the specific receptors of interest. For example, to treat asthma or COPD, beta-adrenergic and muscarinic receptors are located on smooth muscle and so these drugs should be delivered to the small and large airways, whereas the glucocorticoid receptors are widely distributed throughout the lung and on inflammatory cells so it makes sense to deliver steroids throughout the lung.

Systemic delivery of small lipophilic drugs is typically very rapid (seconds to minutes) and is relatively insensitive to site of deposition within the lung although more peripheral deposition is generally preferred because it is highly vascularized and there is a thin cell barrier between the airways and blood circulation [10]. The lung periphery – the alveolar region – also represents a huge surface area that has been often described in a healthy adult as being comparable to a ‘tennis court’. This logic applies to small hydrophilic drugs as well, although absorption may be slower, on the order of minutes to tens of minutes [10]. Generally, for systemic uptake of proteins and peptides, delivery to the alveolar regions is thought to be necessary for meaningful bioavailability, but bioavailability decreases with increasing protein size and for antibodies may be negligible in the absence of active transport mechanisms [10]. While no delivery technology can exclusively target the central or peripheral airways, it is important to select an inhalation system (device and formulation combination) which is biased towards the specific region of interest. When evaluating whether a class of drugs may be amenable to repositioning via the inhalation route, characteristics of the drug and disease state do come into consideration, but for the majority of opportunities a technology solution is readily available (Table 3).

The lung has evolved to prevent the accumulation of foreign particles and rapidly eliminates them through mucociliary clearance in the central airways and scavenging by alveolar macrophages. These alternative pathways of elimination of the drugs from the lung that compete with absorption into the systemic circulation should also be considered for the design of specific inhalation products, and in particular for design of the optimum regional deposition in the target patient population. The regional deposition of particles and droplets depends on their size, shape, density and velocity. Particle size may also evolve during the transit through the respiratory tract due to condensation and evaporation phenomena [31]. Regional deposition also depends on the timing of the introduction of the aerosol within the breathing cycle: for most efficient delivery into the ‘deep lung’ – the alveolar region – the aerosol should be introduced into the early part of the inspiration cycle.

### Key issues in the choice of formulation and delivery technologies

For the early inhalers, oropharyngeal deposition was the key cause of poor efficiency and high variability in deposited dose in the airways. The deposition in the oral cavity is due to impaction which increases with particle size and velocity. Efficient and precise lung delivery therefore requires good control over these parameters. Effective dry powder inhalers (DPIs) design the particle size, shape and density appropriately. The velocity of the particle is affected by the ejection from the device as well as by the inspiratory flow rate. To avoid oropharyngeal deposition, it is therefore necessary to have small particles (typically aerodynamic diameters <3–5 μm) and low intrinsic velocity (i.e. the inhaler is not generating high velocity particles). The inspiratory flow rate by the patient can be controlled through appropriate device engineering; for example, the maximum inspiratory flow rate can be controlled by a critical orifice, or the device can provide feedback to the patients to guide them into the correct breathing rate [12,32]. Breath-actuated devices

<table>
<thead>
<tr>
<th>Drug parameter</th>
<th>Impact on repositioning by inhalation route</th>
</tr>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Dose to the lung per administration &lt;50 mg, preferably &lt;10 mg DPIs and nebulizers have the capability to deliver higher doses</td>
</tr>
<tr>
<td><strong>Lipophilicity (log P)</strong></td>
<td>Soluble and lipophilic drugs are typically rapidly and completely absorbed in minutes Small MW hydrophilic drugs are absorbed in minutes to tens of minutes</td>
</tr>
<tr>
<td><strong>Molecular weight (MW)</strong></td>
<td>Topical applications: molecular weight is not a consideration For systemic effect, bioavailability is reduced with increasing MW. For proteins &gt;20 kDa, typically &lt;10% bioavailability</td>
</tr>
<tr>
<td><strong>Drug solubility</strong></td>
<td>May limit the choice of delivery technology; for example, if cannot formulate at a high enough concentration Very poor solubility could reduce drug action if clearance mechanisms exceed dissolution rate in the lung</td>
</tr>
<tr>
<td><strong>Airway safety and tolerability</strong></td>
<td>Drugs with known pulmonary toxicity should be avoided</td>
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assure that the drug is delivered at the beginning of inspiration. More sophisticated electronic devices can place the ‘bolus’ of the drug into a specified part of the inhaled volume to achieve targeted deposition [32]. Of course, the pathophysiology of the lung has a profound impact on inhalation delivery. Partial obstruction of the airways causes turbulent flow that can increase the deposition in the vicinity of that region. Smaller particles are less sensitive to this phenomenon.

Because there are several different categories of inhalation delivery systems, each with their inherent performance characteristics and formulation requirements [32], selection and development of both the device and formulation in parallel must be carefully considered to achieve the therapeutic objectives for the target population of patients.

Inhalation devices fall broadly into five categories: nebulizers have been in use from the mid-1800s [http://www.inhalatorium.com/], MDIs entered the market in 1956 (epinephrine and isoproterenol MDIs, Riker Laboratories), DPIs were first marketed in the early 1970s, soft mist inhalers (SMIs) became options in the last decade, and the evaporation-condensation aerosol devices are currently in late-stage development.

**Nebulizers**

Nebulizers are systems that disperse liquid formulations using compressed air or piezoelectric vibrations. These are often off-the-shelf systems approved by the regulatory agencies. An inhaled nebulizer formulation is probably the easiest to develop as the drug can simply be dissolved or dispersed in water. To avoid airway irritation, the solution should be isotonic as both hypertonic and hypotonic solutions are known to cause bronchoconstriction [13]. Buffers can be used to control pH but consideration should be made to avoid low pH and polycarboxylic acids such as citrate and succinate as they have the potential to cause cough and bronchoconstriction [13]. If the drug has poor aqueous solubility, solubilizing agents including surfactants can be considered or alternatively, a micron or even nanosized suspension of the drug can be nebulized as was done for budesonide [33]. The solutions or suspensions for nebulizers are usually packaged in single-dose disposable containers (e.g. glass vials or blow-fill-seal (BFS) ampoules) to preserve sterility without the use of potentially toxic preservatives that would be probably required for repeated use of multi-dose aqueous formulation containers.

Apart from the relative ease of development, nebulizer delivery can be used by almost any type of patient as only tidal breathing is required. Indeed, even ventilated patients can receive nebulized drugs. The primary disadvantage of nebulizers are the length of time it takes to use them (typically at least several minutes to set up, inhale and clean), and their size and weight may limit portability.

**Metered dose inhalers**

These are at present the most common drug inhalation devices. Most formulations today use hydrofluoroalkane propellants (e.g. HFA-134a and HFA-227). There are a wide variety of excipients available for these formulations, including co-solvents such as ethanol, propylene glycol, suspension stabilizers such as oleic acid, lecithin and sorbitan trioleate. The choice of excipients must be optimized with respect to the properties of the drug and the propellant solvency and, of course, safety. MDI formulations are typically used with high potency drugs as the practical upper limit on delivered dose is dictated by the metered volume of the propellant (~50 µL).

The advantages of MDIs are very low unit dose cost (a typical MDI will contain at least 100 doses), excellent portability and total isolation of the drug from the external environment aiding preservation of stability and purity. Developing physically and chemically stable formulations that are compatible with HFAs may be challenging. Add-on devices that synchronize the inspiration with the aerosol generation, slow down the aerosol cloud emanating from the device and control the inspiratory flow rate may be required for efficient and repeatable lung delivery [34].

**Dry powder inhalers**

The early DPIs (e.g. Spinhaler® and Rotahaler®) contained micronized drug blended with coarse lactose carrier particles to improve powder flow and dispersibility and were packaged in hard gelatin capsules. These were followed by reservoir devices containing bulk powder metered by the device (e.g. Turbuhaler®) or multiple pre-metered hermetically enclosed individual doses of powder (such as the Diskhaler). DPIs require sophisticated powder formulations to achieve good aerosol performance. Adhesive forces that hinder emptying of the powder from the device need to be minimized; intraparticle cohesive forces also need to be minimized to achieve good powder dispersibility. To that end, powder fluidization and dispersibility have been improved by reducing the cohesive force of particles (e.g. increasing physical size while reducing density, or increasing porosity and rugosity) and using new blending technologies that mix the active ingredient with functional carrier particles. Reduction of the surface energy with hydrophobic excipients has been proposed (e.g. the use of fine lactose and hydrophobic force control agents such as magnesium stearate, leucine or phospholipids) but the use of new excipients may require additional toxicology testing. Processing, too, can improve the powder quality: several innovative powder processing technologies have been applied including spray-drying, spray freeze-drying, wet milling, foam-drying, supercritical fluid precipitation, solution atomization crystallization (SAX), high gravity controlled crystallization, and confined impinging jet precipitation [11,35]. Of all of the delivery devices, DPIs can deliver the highest mass of drug per puff, up to the tens
of mgs if the ‘neat’ drug can be used or if the amount of excipients can be minimized while maintaining good powder stability and dispersibility. DPI systems that use the energy from the patient’s breathing to disperse the powder (‘passive inhalers’) need to be designed carefully to match the patient’s ability (inspiratory flow rate and inspired volume) to get adequate powder delivery into the desired areas of the respiratory tract. ‘Active DPIs’ were also developed in which the energy for powder dispersion is supplied from batteries or from compressed air generated by the patient’s manual action prior to the device actuation but none are currently marketed.

**Soft-mist inhalers**

While traditional nebulizers deliver aqueous formulations (typically 2–5 mL) during tidal inhalation over several minutes, soft mist inhalers typically deliver a bolus of drug in just one or a small number of inhalations similar to MDI and DPI products, using ~10–100 μL of the liquid formulation per inhalation. Thus, the SMI formulations are similar to those used for nebulized products. Higher drug concentrations may be necessary as the inhaled volumes are much lower than from nebulizers; for poorly soluble drugs, judicious choice of buffer salts, pH, cosolvents [12] and solubilizing agents including phospholipids [7], cyclodextrins or surfactants can be utilized, provided that the safety of such excipients has been established. Alternatively, fine suspensions, including nanosuspensions, can be used. For multi-use reservoir products, the addition of a preservative may be required, but finding a safe and tolerable preservative may be challenging. The advantages of SMI technology are the ease of formulation as solutions or suspensions, small device size, sterile nature of the product, adjustable droplet size and velocity of droplets controlled by the inspiratory flow rate [32].

**Evaporation-condensation aerosol devices**

Evaporation-condensation was probably the first inhalation method for ‘drugs’ in the form of various smokes. A pharmaceutical evaporation-condensation aerosol device is in late stage clinical development [23]. The drug for this particular device must be amenable to deposition in a layer of thin, solid film on a heating element which can vaporize the drug which condenses into small droplets or solid particles. Typically this is accomplished by dissolving the drug in a solvent or mixture of solvents (e.g. ethanol, acetone, chloroform, hexane, or methanol) and spray coating the solution onto a metal substrate. The advantage of this technology appears to be small device size, particle velocity determined by the inspiratory flow rate and good aerosol particle size. For drugs which exist as unstable liquids at ambient conditions, alternative strategies to form thin films include complexation with metal halides as was done for nicotine [36] or formation of a stable prodrug as was done for dronabinol.

**Conclusions**

The inhalation route maximizes the delivered dose to the respiratory tract while minimizing the dose delivered to the rest of the body where it may serve no useful purpose and has the potential to cause side effects. Inhalation delivery is therefore more often superior for the treatment of respiratory diseases than other routes of administration. In addition to the obvious benefits for the patients in terms of improved efficacy and reduced systemic toxicity (and often improved convenience, especially over parenteral administration), there is a broad selection of formulations and inhalers to provide market differentiation or intellectual property protection. Rapid, non-invasive delivery via the lung for systemically acting drugs whose benefits are amplified with increased speed of action (e.g. pain management) is an attractive option for repositioning.

The entry of biosimilars is likely to catalyze increased competition and renewed interest in product differentiation. Studies continue to indicate that patients prefer inhalation to injections. A safe and elegant inhaled protein or peptide product has the potential to significantly improve patients’ acceptance and compliance over injections, and thus dominate the market and provide delivery-related patent protection. There are many inhalation technologies with a variety of capabilities that are now available for the repositioning of small molecules as well as macromolecular drugs. The development of formulations with even greater bioavailability and reduced COGs using novel excipients to increase transcytosis can be envisioned. Many excipients can increase the inhaled bioavailability of peptides, by up to 7-fold, and some appear to have no acute toxicity at low concentrations [37], but their safety and tolerability need to be verified in longer term studies.

Molecular engineering of proteins is also a viable strategy to address convenience if not COGs concerns; pegylated proteins could require less frequent inhalations. Co-opting existing active transport mechanisms, such as the Fc receptor, increased the bioavailability of EpoFc monomer over erythropoietin alone from 15 to 35%, [38], but the main advantages are a novel intellectual property position and a prolonged circulating half-life.

Unconventional strategies such as utilizing alveolar macrophages to take up nanoparticles and deliver proteins systemically require innovations to prevent degradation in the macrophages. Respiratory maneuvers such as a slow deep inhalation have been shown to increase the bioavailability of insulin [29] but exercise before or after inhalation had no effect. Although lung hyperinflation of a 30 kDa protein in anaesthetized monkeys resulted in 100% bioavailability, a tenfold increase over bolus inhalation in humans (Aradigm, unpublished data), it is unclear yet how to leverage that benefit in humans.

Are improvements in bioavailability really necessary? Safe, effective and patient-preferred inhaled products competitive
with existing injectable products can be developed now, utilizing existing technology, and are not dependent upon improvements in systemic bioavailability. Therapeutic benefits may not require high 'bioavailability' (for example, the benefit of improved compliance with non-invasive delivery may outweigh the higher cost per dose in the overall healthcare economic value proposition). Importantly, the costs of goods' considerations are likely to become more favorable with the entry of biosimilars.

Companies that do not possess expertise in inhalation delivery may be able to develop repurposed drugs given by inhalation through collaborative partnerships with organizations that have in-house expertise and often intellectual property that would afford the repurposed drug proprietary protection [32,39]. In fact, the 1990s witnessed the foundation of several new companies with proprietary technologies that focused on inhalation delivery of repurposed drugs and biologics through partnerships with well established pharmaceutical companies. While some of these companies have now abandoned their inhalation platforms or changed their business models, others continue to expand their inhalation technology capabilities and seek partnerships for these.

References
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