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Emerging trends in inhaled drug delivery

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ABSTRACT

Ideally, inhaled therapy is driven by the needs of specific disease management. Lung biology interfaces with inhaler performance to allow optimal delivery of therapeutic agent for disease treatment. Inhalation aerosol products consist of the therapeutic agent, formulation, and device. The manufacturing specifications on each of the components, and their combination, allow accurate and reproducible control of measures of quality and in-vitro performance. These product variables in combination with patient variables, including co-ordination skill during inhaler use, intrinsic lung biology, disease and consequent pulmonary function, contribute to drug safety and efficacy outcomes. Due to the complexity of pulmonary drug delivery, predicting biological outcomes from first principles has been challenging. Ongoing research appears to offer new insights that may allow accurate prediction of drug behavior in the lungs. Disruptive innovations were characteristic of research and development in inhaled drug delivery at the end of the last century. Although there were relatively few new inhaled products launched in the first decade of the new millennium it was evident that the earlier years of exploration resulted in maturation of commercially successful technologies. A significant increase in new and generic products has occurred in the last decade and technical, regulatory and disease management trends are emerging. Some of these developments can trace their origins to earlier periods of creativity in the field while others are a reflection of advances in other areas of basic and computer, sciences and engineering. Select biological and technical advances are highlighted with reflections on the potential to impact future clinical and regulatory considerations.

Contents

1. Introduction

High quality, pharmacologically mechanistic targeted Inhaled therapy has become the primary strategy for pulmonary disease management over the last seventy years. These modern therapies can, in many cases, trace their origins to the earliest records of anecdotal use of inhaled natural products in India and China [1]. The last decade has been characterized by the innovative technologies of the previous quarter century maturing into commercial products or being fine-tuned to meet development, quality, safety or efficacy needs. As this evolution of inhaled medicines has occurred the opportunity space has been filled leaving little to explore in the context of conventional pulmonary disease targets. A disruptive technological approach will likely come from the demands of as yet unmet medical need. In this regard, rare and infectious lung diseases are receiving considerable attention and the field of systemic drug targeting through pulmonary drug delivery remains in its infancy.

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Fig. 1 summarizes the requirements of matching the therapeutic agent to the desired treatment outcome while considering the overall host system barriers (deposition and clearance mechanisms) and target (receptor or pathogen) biology guiding selection or development of a suitable drug delivery technology. The therapy, biology and technology each introduce complex variables that must be taken into account to optimize efficacy and safety. The nature of the therapeutic agent (small molecule, nucleic acid or other biological) imposes specific limits on formulation and device based on stability and performance considerations. Specialized formulation technologies may be required to modulate the physico-chemical behavior and biological disposition of the therapeutic agent. Device technology is generally adopted to accompany the formulation which is dictated by the needs of the drug properties (i.e. solubility, crystallinity, stability) and to support delivery to the lungs. Elements of the lung physiology that are involved in the pharmacokinetics of disposition, such as local dissolution, clearance mechanisms (absorption, mucociliary and cell mediated transport), metabolism or sequestration (transporters) need to be considered on a drug by drug basis [2].

There is increasing interest in less common diseases such as pulmonary arterial hypertension, idiopathic pulmonary fibrosis and acute lung injury as targets for novel therapeutic strategies [3–5]. Consequently, innovations may be anticipated in the treatment of these diseases, Moreover, the ongoing COVID-19 pandemic raises questions of the role that protecting lung integrity during an overwhelming immune response might play in reducing mortality [6,7]. Understanding response to infection and the role of co-morbidities may give greater insight into the role of the pulmonary immune system in both protection from, and exacerbation of lung damage. This will have significant implication for future efforts in vaccine and immunomodulator delivery [8].

The intent of this review is not to describe comprehensively inhaled dosage forms. Thorough reviews of this nature, some of which are referenced below, are available in the literature. Indeed, the author has recently co-edited two volumes on this topic [9,10]. The perspective taken below is to highlight key developments and speculate on directions that may drive future advances in inhaled drug delivery. This approach is intended to complement the existing literature.

2. Inhaler design and function

Inhaler design has seen little change in the last decade but some features have resulted in improvements that offer new opportunities for disease treatment.

The most significant improvement in nebulizer technology was the development of vibrating mesh systems [11]. The most prominent of these are the eFlow (Pari) and iNeb (Philips) [12,13]. While the technologies themselves were developed over several decades the applications seem to be increasing the range from very small (individual micrograms, Treprostinil, Iloprost) to large (hundreds of milligrams, Tobramycin) doses of drug delivered [14,15]. In addition, a unique opportunity has been explored of evaporating vibrating mesh nebulizer output to create an aerosol that can be introduced through a nasal cannula. This aerosol increases peripheral lung deposition though the use of excipients that are subject to hygroscopic growth [16].

Dry powder inhaler technology has three major components, the formulation, the metering system and the aerosol dispersion features [17]. All commercially available inhalers are actuated passively in response to the patients' inspiratory flow. Regulatory approval and commercialization of Advair®/Seretide® (GlaxoSmithKline) was one of the most significant developments at the beginning of the millennium [18,19]. The combination salmeterol xinafoate/fluticasone dipropionate product was the first dry powder product for maintenance therapy of asthma, notably containing a long-acting β_2-agonist, unlike earlier combination products. Subsequently, this product was also approved for the treatment of Chronic obstructive pulmonary disease. The complexity of the drug-lactose blend and Diskus® inhaler was challenging to manufacture and in the interval since approval has proven difficult to

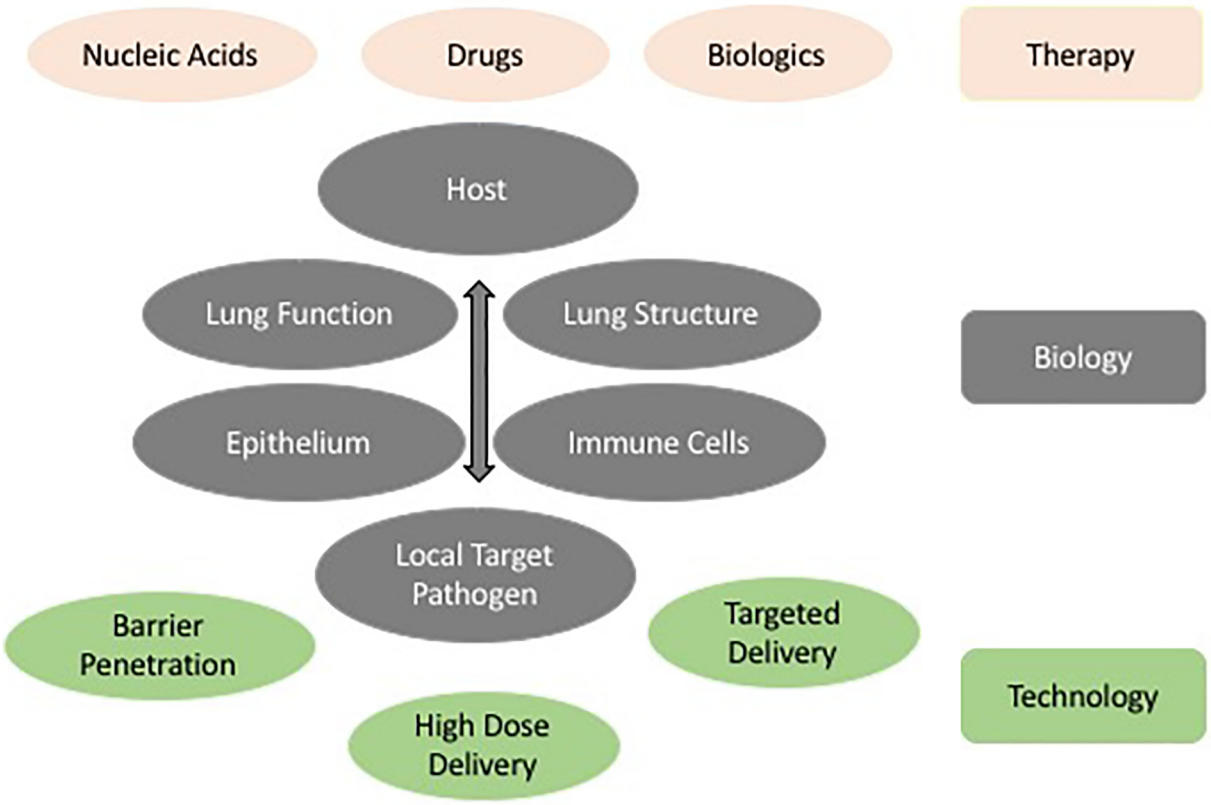

Fig. 1. Considerations of therapy and technological challenge to be overcome to address the biology associated with disease.

reproduce rapidly as a generic product [20]. Despite these challenges Mylan received US FDA approval for its generic salmeterol xinafoate/fluticasone dipropionate in 2019. The combination of two drugs in a single powder was both an exciting new therapeutic development and a formidable test of quality and performance controls. In this context, one of the most significant advances of the last decade was the approval of Ellipta® devices that are capable of delivering two drugs independently from two separate blister strips, thereby avoiding the arduous task of ensuring combination drug stability and optimizing performance of two drugs from a single formulation [21,22]. Fig. 2a depicts schematically the Ellipta in the configuration used in the Breo product (vilanterol trifenetate/fluticasone furoate). The illustration shows the separate indexing systems for the lidding and base components of the blister strips arranged to bring the dosing blisters to the mouthpiece mechanism and concurrently opened to allow for concurrent dosing.

As will be discussed in the next section the difficulty of dispersing micronized dry powders has been recognized since modern DPIs were developed in the 1960s and 1970s [1,23]. Often tortuous paths and baffles have been inserted in DPIs to help de-agglomerate drug but historically this was not possible without the presence of lactose in the formulation [24]. The challenge has been to generate sufficient energy on the inspiratory flow of the patient to disperse micronized particles alone. The use of a cyclone classifier as part of a passive inhaler design has allowed a device driven approach to disperse micronized particles [25]. This has opened the possibility for relatively high dose delivery of antimicrobials, as required for the treatment of infectious diseases. Fig. 2b show the Cyclops™ device [25]. The powder is drawn from a metering blister built into the device through a cyclone classifier such that only respirable particle can pass into the airstream to the patient. This is a simple disposable inhaler, approximately the size of a credit card, resulting in ease of storage and transport of bulk product and offering a discreet form factor for patient convenience.

Metered dose inhaler technology has undergone incremental developments with regard to new actuator orifice inserts and dimensions, and, particularly during the propellant transition from chlorofluorocarbons (CFC) to hydrofluoroalkanes (HFA), elastomers, O-rings and seals that were compatible with the new propellant [26]. These are important to the products they serve but they do not change the overall operating principles of the device. Perhaps the most substantial new developments in pMDI technology are the addition of counters and exploration of electronic patient data recording systems that may ultimately lead to major steps forward in personalized medicine [27].

It should be noted that as the vigorous debate on climate change and global warming agents begins to focus on limiting their use another transition may be required from existing HFA propellants to alternatives with lower global warming potential. If history repeats itself this will support another period of innovation.

3. Formulation

The preparation of formulations for inhalation is constrained by the device employed for drug delivery. Nebulizers and soft mist sprays employ solutions or suspensions in an aqueous medium. Dry powders inhalers contain formulations of solid drug with excipients that enhance performance. Metered dose inhalers employ solutions or suspensions in a non-aqueous medium.

Nebulizer solutions and suspensions use limited formulation additives. However, recently the use of liposomes to aid in drug preparation and delivery and to aid in targeting of macrophages has advanced formulation options [28,29]. The use of ethanol in the solutions delivered from the Respimat™ soft mist inhaler, e.g. tiotropium (Spiriva®, Boehringer Ingelheim) enhances the solubilization properties of the medium and facilitates a hand held aqueous based system with accurate and reproducible performance in delivering very low doses (<10 μg) on a single breath analogous to a metered dose inhaler [30,31].

Dry powder inhaler products began their modern development with a characteristic respirable drug particle blend in lactose that allowed delivery of small drug doses (≤1 mg) from large total powder masses (≤25 mg) [24]. These lactose blends were employed due to the large forces of interaction that typified micronized powders and prevented their accurate metering and reproducible dispersion [32]. Many highly successful products have been manufactured that conform to this general description. A breakthrough occurred in the late 1990s when it was observed that low density particles prepared by spray drying exhibited low forces of interaction and were easily dispersible [33]. Since these particles could be manufactured with the presence of small quantities of excipient it was possible to deliver large drug doses. Fig. 3a illustrates the low density, collapsed hollow sphere appearance of the early low-density particles [34,35]. Fig. 3b shows the whiffle ball appearance of Pulmosphere™ tobramycin in the TOBI® Podhaler® product (Novartis) [36]. This low-density morphology allows the delivery of 112 mg of drug (4 capsules, 28 mg/capsule) increasing the previous limit on dry powder drug delivery by 2 orders of magnitude. However,

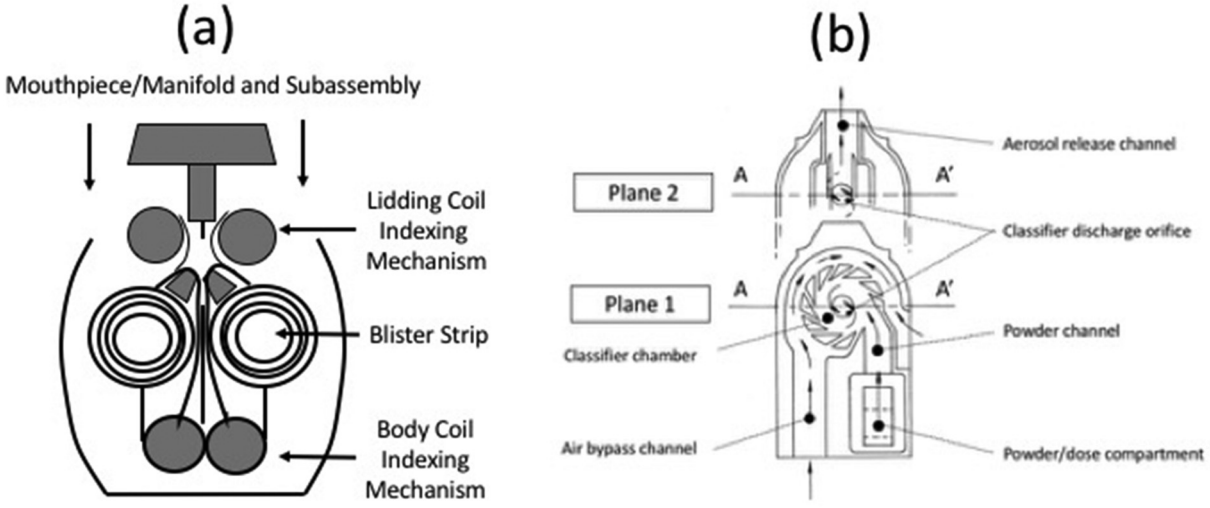

Fig. 2. Illustrations, not to scale, of (a) Ellipta® dual blister strip mechanism to allow independent drug delivery in combination products and (b) Cyclops® micronized drug particle high dose delivery device* showing the cyclone classifier dispersion mechanism. *Courtesy of Dr. Anne de Boer.

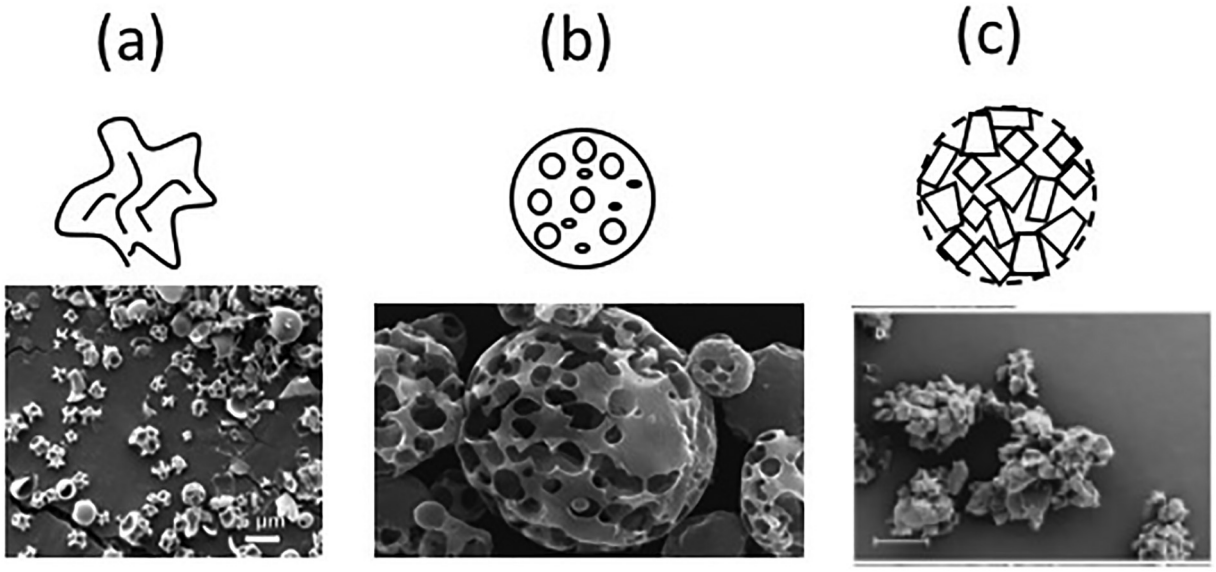

Fig. 3. (a) Collapsed hollow sphere spray dried; (b) Whiffle ball spray dried; and (c) micronized agglomerate particle morphologies.

a formulation conundrum was exposed with this major advance in dry powder drug delivery. In order to deliver a large mass of low-density powder, large volumes are required. Hence the need for 4 capsules in the tobramycin product. This may be acceptable for certain severe disorders but increasing the number of actuations/breaths required to deliver the dose increases the possibility of lack of patient adherence to the therapy. Recently, it was observed that micronized particles may be prepared in a manner that forms aggregates that mimic low density particles and may, therefore, exhibit reduced interparticulate forces sufficient to allow their dispersion [37].This represents a compromise between low volume and low density that allows for accurate and reproducible dispersion in a minimum number of actuations/breaths that would pose less of a challenge to patient adherence. Fig. 3c shows a stable aggregate of micronized particles of clofazimine with sufficient interstitial space to provide the agglomerate low-density performance and ease of dispersion characteristics.

The infectious disease drivers of innovation in high dose drug delivery are evident from the application of tobramycin to treat *Pseudomonas aeruginosa* infection in cystic fibrosis and clofazimine to treat non-tuberculous mycobacteria infection in populations with compromised lung function.

Metered dose inhalers have had a standard composition for decades, namely canister, propellant formulation, valve and actuator [23]. There have been advances in each of these most significantly the shift from chlorofluorocarbon propellants to hydrofluoroalkanes [38]. The latter required considerable reformulation efforts but the transition is now complete. The new HFA formulations have lower velocities and smaller droplets that maximize lung deposition while minimizing oropharyngeal deposition [39]. As the reformulation effort was occurring it became evident that the excipient options were even more limited than had been the case with CFCs. In a recent development, knowledge gained from dry powder formulation has been transferred to metered dose inhalers. The addition of low-density lipid particles to HFA as a dispersant for micronized drug has allowed for a range of new metered dose inhaler products to come to market [40]. The environmental concern over ozone depletion that was the cause of the CFC to HFA transition has been superseded by concern over global warming potential [41,42]. Unfortunately, HFAs have significant global warming potential. As a consequence, the search for new propellants is underway that will extend the future of metered dose inhalers in the event of new environmental regulation on global warming [42].

4. Diseases therapy

Fig. 4 depicts two important characteristics of disease management using inhalers. On the x- axis the dose that has been delivered from different inhalers, depicted on the left, and the number of breaths required to inhale the dose of drug, shown on the right. While there are differences in the performance of these inhalers with respect to aerodynamic particle size distribution, the parameter governing lung delivery, for the purposes of this discussion it is sufficient to assume that all deliver respirable aerosols (<5 μm) [43]. Nebulizers have long been known to be capable delivering large doses, >100 mg. The introduction of vibrating mesh nebulizers allowed for much shorter delivery times on large doses (5–7 min) and much lower therapeutic doses than historically possible on individual breaths as is the case in the treatment of pulmonary arterial hypertension with treprostinil and iloprost. Dry powder inhalers were limited initially by the need for lactose excipient to facilitate the dispersion of micronized drug. However, the advent of low-density and other engineered particles extended the dose to >100 mg while increasing the number of breaths/actuations required to deliver the dose. The range of pMDI dosing has remained fairly constant over several decades. Broadening the range of accurate and reproducible dosing is a significant achievement of the last decade.

Fig. 5a depicts schematically the anatomical representation of an alveolus and its blood supply. Fig. 5b shows a transverse section through this alveolus depicting the proximity of the capillary blood supply to the alveolus and the presence of lumenal alveolar macrophages. These images are frequently depicted as textbook representations. However, Fig. 5b also points out that the milieu in which these anatomical features exist also contains interstitium and lymphatics, shown as the shaded region. As a consequence, the usual discussion of disposition of drug in and from the lungs would benefit from an additional level of scrutiny that is rarely considered, disposition within lung tissue not simply from the airways to the vasculature. A number of disease states that might be treated with aerosols are not associated with airways.

Potent drugs that are given in low doses and penetrate readily though the lung mucosa to the blood supply may be suitable for treating diseases that require systemic delivery. The most recent development in inhaled insulin to treat diabetes is Afrezza® (MannKind). This product employs a dry powder formulation including a unique carrier particle composed of the excipient fumaryl diketopiperazine [44]. Additionally, loxapine, an antipsychotic for the treatment of schizophrenia, has been delivered from an evaporation condensation device, Staccato®,

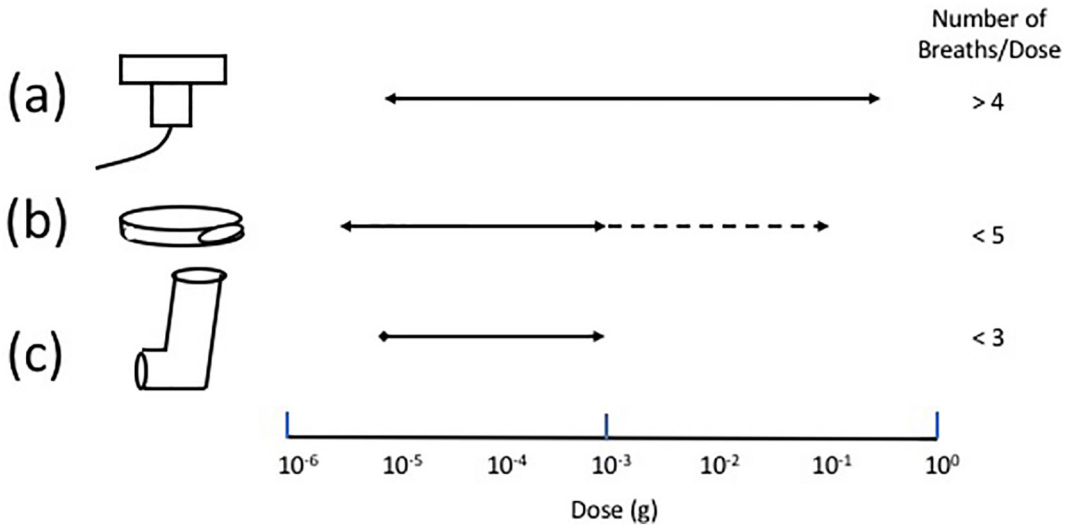

Fig. 4. Illustration of the dosing range of each of the major therapeutic categories of (a) nebulizer; (b) dry powder inhaler and (c) pressurized metered dose inhaler and the limit on actuations/breaths to deliver the dose. Dotted line represents increase in dose range accomplished by particle engineering.

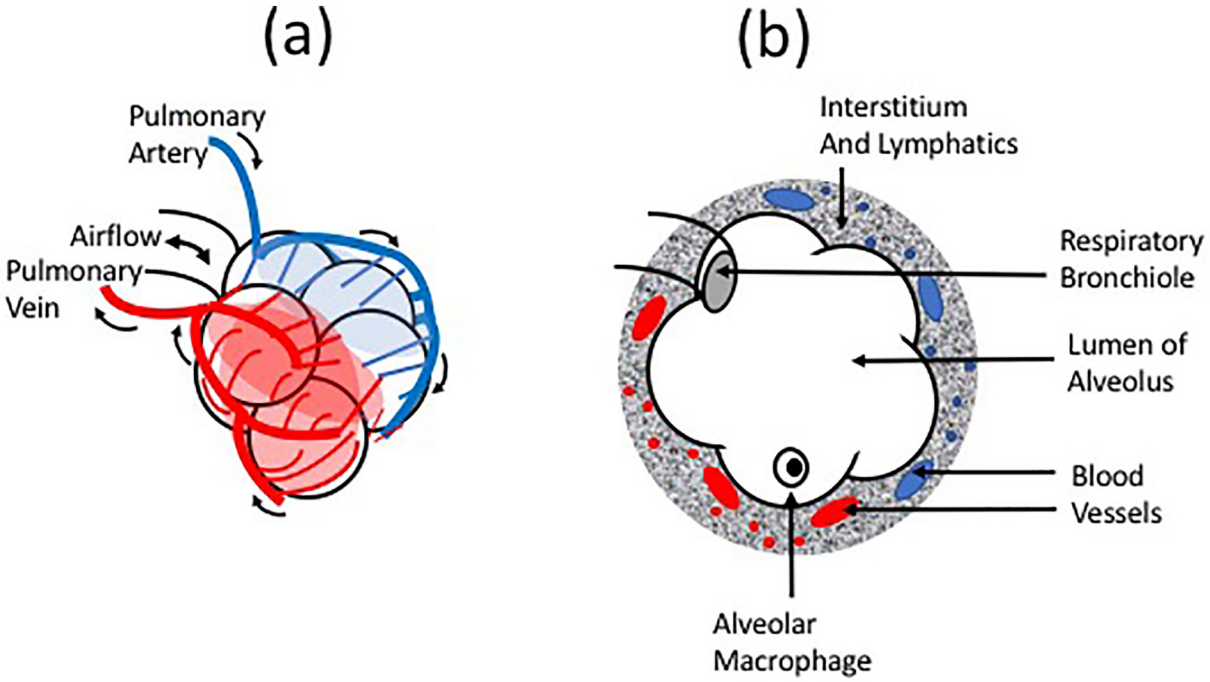

Fig. 5. Terminal bronchiole and alveolus illustrating (a) three-dimensional anatomy and (b) transverse section.

in the Adasuve® product (Alexa) [45,46]. The delivery of systemically acting agents continues to be a promising area of opportunity for future aerosol products.

Recent interest in pulmonary arterial hypertension and idiopathic pulmonary fibrosis focuses attention on the transport of drug at the cellular level in the regions of the lungs between airway and blood vessel lumens [3,4]. Residence time of drug at therapeutic concentrations is crucial to the effectiveness of drugs to target the local manifestations of these diseases. When placed in the context of the illustration in Fig. 5 consideration of techniques of maintaining locally efficacious drug concentrations outside the airways may offer new opportunities for innovation.

Pulmonary infectious diseases have long presented an opportunity for inhaled drug therapy. Non-tuberculous mycobacteria, primarily caused by *Mycobacterium avium complex* and *Mycobacterium abscessus*, lung infections are found in immunocompromised and otherwise functionally compromised lungs. It is particularly serious in cystic fibrosis patients and a portion of the elderly population identified in Lady Windermere Syndrome [47–49]. The disease manifests as extracellular biofilms associated with bronchiectasis and intracellular disease in lung macrophages [50]. The recent approval of Arykace® (liposomal amikacin) for the treatment of non-tuberculous mycobacteria represents a thoughtful approach to matching device, formulation to the needs of the disease. The liposomes are taken up by infected macrophages and penetrate biofilms sufficiently to treat the infection and improve lung function [51]. Clofazimine offers a unique potential to intervene in this disease as the drug spontaneously targets macrophages and local delivery as an aerosol obviates systemic side effects

arising from other routes of administration [52]. Development of new therapies for NTM treatment capitalizes on the decades of research into development of inhaled therapy for tuberculosis [53].

This brief review of example disease targets and their therapy illustrates the range of dosing that is required and can now be achieved from very low, single microgram, to high, several hundred mg, doses that support efficacious concentrations of drugs at different sites in the lungs not simply the airways.

5. Regulatory advances

As changes to aerosol products have occurred new guidance from regulatory agencies was necessary to accommodate the needs of industry. In the last ten years many new guidances to industry on generic products have been issued [54]. The initial challenge was replacement HFA products for the existing CFC products with the first albuterol product being approved in 2003 [55]. Subsequently, complex combination products such as the salmeterol xinafoate/fluticasone dipropionate (Advair®) took longer to consider with the guidance appearing in 2013 [56]. Perhaps the most significant event of the last decade was the first revision to the draft guidance (1998) on chemistry manufacturing and controls relating to testing of dry powder and metered dose inhaler products in 2013 [57,58]. Also, the weight of evidence approach advocated by the Food and Drug Administration gives applicants insight into expectations that can be pursued in formal discussions at various stages of development.

The demand for an approach to bioequivalence has been a driver of industry activities over the last ten years [60]. Two consensus meetings can be noted in this context. The first occurred in 2006 and framed the issues surrounding pharmaceutical and bio-equivalence [61]. More recently, a workshop considered the foundations of an inhaled Biopharmaceutical Classification System (iBCS) that might be used, as was the original oral BCS is, to guide product development and illuminate regulatory review [62]. These events facilitated discussion of standard methods to assure quality and safety in the context of product performance but they also encompassed efforts to develop predictive approaches that would conform to the philosophy of quality by design. This will continue to be a focus for inhaled drug product development and regulation.

6. Illustrations of potential disruptive change

New observations in biology may emerge from the evolution of thought over decades of scientific endeavor or from sudden disruptive events that expose new challenges and illuminate underlying mechanisms. Two examples can be given, recognizing that many more may be in the literature to illustrate this point.

It has recently been observed that the fibroblast cytoskeleton may play a role in asthma. This has implications for the function of muscle function in conducting airways. Protein tyrosine phosphorylation has been reported to regulate actin polymerization in smooth muscle contractile stimulation. Consequently, the role of protein/threonine phosphorylation in modulating actin dynamics has been investigated with a specific focus of Ste20-like kinase (SLK), a serine/threonine protein kinase that plays a role in apoptosis, cell cycle, proliferation and migration [63]. The major finding of this study was that SLK mediates actin cytoskeleton reorganization and may facilitate force transmission between contractile units and the extracellular matrix. Since bronchoconstriction as a response to airway hyper-reactivity is mediated by muscle tone in asthma this may offer a new target for bronchodilatation.

The recent observation that caspase, an important protein in defending from bacterial infection, may become overactive and provoke a damaging inflammatory reaction has implications for allergic asthma therapy [64]. Caspase-11 causes cell death which results in the release of cell contents and is a key driver of inflammation in asthma. Caspase-4, the human equivalent of Caspase-11 has never been implicated in asthma so it is a promising possible target for new drugs to treat this disease.

The recent COVID-19 pandemic caused by the SARS-CoV2 virus has one significant and alarming clinical outcome, the rapid progression in susceptible individuals to bilateral interstitial pneumonia [6,7]. Major effort has been expended in preventing deterioration of lung function including, in the extreme, the use of ventilators to support gaseous exchange [65]. However, since understanding of the pathogenesis of disease is increasing, it is evident that being able to ensure the patency of the lungs is a key to survival. The historical precedents of zanamivir (Relenza, GSK) and ribavirin to treat influenza and respiratory syncytial virus indicate that lung delivery of therapeutics has merit for respiratory viral infections [66–68]. However, to prevent the manifestations of disease seen in COVID-19 early intervention with agents that prevent viral uptake and/or replication and can target affected areas of the lung in therapeutic concentrations is desirable. Examples would include aerosol delivery of antibodies, antisense oligonucleotides or antivirals, such as remdesivir [69,70]. In addition, the observation that in countries where Bacille Calmette Guerin (BCG, attenuated *Mycobacterium bovis*) immunization for tuberculosis is conducted the population has a lower incidence of COVID-19 mortality raises the potential for a directed vaccine strategy [71]. Further research is required to address some of the inconsistencies in this initial observation. However, if evidence based on rigorous interrogation of the data supports any protective effect conferred by BCG, it should be noted that mycobacterial antigens delivered as aerosols induce a systemic and lung mucosal immune response. [72–74]. Moreover, work continues on the pharmaceutical properties of inhaled BCG vaccine [75] and a recombinant viral vector approach is also under development for Antigen 85A, a mycobacterial secreted subunit protein [76].

Raising these speculative opportunities for potential clinical intervention simply highlights new biological challenges posed by our evolving understanding of the pathophysiology of disease. The disease biology will drive both new therapeutic agent development and the technological needs to address them. As the potential disease applications for aerosol therapy expand innovation will necessarily follow.

7. Conclusion

There has been continuous development of novel inhaled medicines for decades. The last ten years has seen a maturation of technologies and some novel excursions to expand the application of inhalation technology to more effectively treat pulmonary diseases. There have been developments in each of the major categories of inhaler that have enabled a wider range of doses and improved the accuracy and precision of dosing from which it can be inferred that quality has improved. The safe and efficacious new products improve management of pulmonary diseases for which aerosols have long been used, such as asthma and more recently chronic obstructive lung disease. In addition, the expanded range of dosing allows for the treatment of emerging infectious diseases and local rare and systemic diseases. The growth and variety of new regulatory submissions has led to many new guidance documents being issued and new product approvals. If there is likely to be disruptive change in inhaled design it will be in the adoption of electronics and the use of data collection systems that support patient adherence and inform clinicians/manufacturers facilitating effective dosing and disease maintenance. There do not appear to be obvious limits to the future of inhaled therapy as new underlying causes are observed and diseases appear. The identification of clear new challenges will drive disruptive change. Perhaps the latest pandemic will inform the biology of the lung, open up new possible targets and drive new technology.

References

[1] M. Sanders, in: H.D.C. Smyth, A.J. Hickey (Eds.), Pulmonary Drug Delivery: An Historical Overview in Controlled Pulmonary Drug Delivery, Springer, New York, NY 2011, pp. 51–73.

[2] N.P. Mortensen, A.J. Hickey, Targeting inhaled therapy beyond the lungs, Respiration 88 (2014) 353–364.
[3] G. Simonneau, M.A. Gatzoulis, I. Adatia, D. Celermajer, C. Denton, A. Ghofrani, M.A. Gomez Sanchez, R.K. Kumar, M. Landzberg, R.F. Machado, H. Olschewski, I.M. Robbins, R. Souza, Updated clinical classification of pulmonary hypertension, J. Am. Coll. Cardiol. 62 (suppl) (2013) D34–D41.
[4] T.E. King Jr., A. Pardo, M. Selman, Idiopathic pulmonary fibrosis, Lancet 378 (2011) 1949–1961.
[5] E.R. johnson, M.A. Matthay, Acute lung injury: epidemiology, pathogenesis and treatment, J. Aerosol. Med. Pulm. Drug Deliv. 23 (2010) 243–252.
[6] C.-C. Lai, T.-P. Shih, W.-C. Ko, H.-J. Tang, P.-R. Hsueh, Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenge, Int. J. Antimicrob. Agents 55 (2020), 105924.
[7] H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, Y. Fan, C. Zheng, Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect. Dis. 40 (2020) 425–434.
[8] M. Heilfritzsch, R. Scherlieβ, Mucosal immunization via the respiratory tract, Pharmaceutics 11 (2019) 375.
[9] A.J. Hickey, S.R. da Rocha, Pharmaceutical Inhalation Aerosol Technology, Third edition CRC Press, Boca Raton, New York, NY, 2019.
[10] A.J. Hickey, H.M. Mansour, Inhalation Aerosols, Physical and Biological Basis for Therapy, Third edition CRC Press, Boca Raton, New York, NY, 2019.
[11] J.N. Pritchard, R.H.M. Hatley, J. Denyer, D. von Hollen, Mesh nebulizers have become the first choice for new nebulized pharmaceutical drug developments, Ther. Deliv. 9 (2018) 121–136.
[12] W. Lenney, F. Edenborough, P. Kho, J.M. Kovarik, Lung deposition of inhaled Tobramycin with eFlow/LC Plus nebulizer in healthy and cystic fibrosis patients, J. Cyst. Fibros. 10 (2011) 9–14.
[13] D. Hubert, S. Leroy, R. Nove-Josserand, M. Murris-Espin, L. Mely, S. Dominique, B. Delaisi, P. Kho, J.M. Kovarik, Pharmacokinetics and safety of tobramycin administered by the Pari eFlow® rapid nebulizer in cystic fibrosis, J. Cyst. Fibros. 8 (2009) 332–337.
[14] T. Gessler, W. Seeger, T. Schmehl, The potential for inhaled treprostinil in the treatement of pulmonary arterial hypertension, Ther. Adv. Respir. Dis. 5 (2011) 195–206.
[15] H. Ochewski, Inhaled iloprost for the treatment of pulmonary hypertenstion, Eur. Respir. Rev. 18 (2009) 29–34.
[16] P.W. Longest, R.L. Walenga, Y.-J. Son, M. Hindle, High-efficiency generation and delivery of aerosols through a nasal cannula during non-invasive ventilation, J. Aerosol Med. Pulm. Drug Deliv. 26 (2013) 266–279.
[17] A.H. de Boer, P. Hagedoorn, M. Hoppentocht, F. Buttini, F. Grasmeijer, H.W. Frijlink, Dry powder inhalation: past present and future, Expert Opin. Drug Deliv. 14 (2017) 499–512.
[18] H. Chrystyn, The Diskus™: a review of its positioning among dry powder inhaler devices, Int. J. Clin. Pract. 61 (2007) 1022–1036.
[19] H.S. Nelson, Advair combination treatment with fluticasone propionate/salmeterol in the treatment of asthma, J. Allergy Clin. Immunol. 107 (2001) 397–416.
[20] E. Burmeister Getz, K.J. Carroll, J. Mielke, L.Z. Benet, B. Jones, Between batch pharmacokinetic variability inflates type I error rate in conventional bioequivalence trials: a raondomized Advair Diskus clinical trial, Clin. Pharm. Ther. 101 (2016) 331–349.
[21] A.C. Grant, R. Walker, M. Hamilton, K. Garrill, The Ellipta® dry powder inhaler: design, functionaility, in vitro dosing performance and critical task compliance by patients and caregivers, J. Aerosol. Med. Pulm. Drug Deliv. 28 (2015) 474–485.
[22] K. Athanasiou, L. Silvestro, S.R. Savu, Assessment of the bioequivalence of two DPIs containing fluticasone and salmeterol, in patients with controlled or partly controlled asthma, Eur. Respir. J. 48 (2016) PA618.
[23] S.W. Stein, C. Thiel, The history of therapeutic aerosols: a chronological review, J. Aerosol Med. Pulm. Drug Deliv. 30 (2017) 20–41.
[24] M.J. Telko, A.J. Hickey, Dry powder inhaler formulation, Respir. Care 50 (2005) 1209–1227.
[25] M. Hoppentocht, O.W. Akkerman, P. Hagedoorn, H.W. Frijlink, A.H. de Boer, The Cyclops for pulmonary delivery of aminoglycosides; a new member of the Twincer family, Eur. J. Pharm. Biopharm. 90 (2015) 8–15.
[26] P.B. Myrdal, P. Sheth, S.W. Stein, Advances in metered dose inhaler technology: formulation development, AAPS PharmSciTech 15 (2014) 434–455.
[27] S.W. Stein, P. Sheth, P.D. Hodson, P.B. Myrdal, Advances in metered dose inhaler technology: hardware development, AAPS PharmSciTech 15 (2014) 326–338.
[28] J. Zhang, F. Leifer, S. Rose, et al., Amikacin liposome inhalation suspension (ALIS) penetrates non-tuberculous mycobacterial biofilms and enhances amikacin uptake into macrophages, Front. Microbiol. 9 (2018) 915.
[29] D. Cipolla, J. Blanchard, I. Gonda, Development of liposomal ciprofloxacin to treat lung infections, Pharmaceutics. 8 (2016) 6, https://doi.org/10.3390/pharmaceutics8010006.
[30] T. Iwanaga, Y. Tohda, S. Nakamura, Y. Suga, The Respimat® softmist inhaler: implications of drug delivery characteristics for patients, Clin. Drug Invest. 39 (2019) 1021–1030.
[31] S. Leiner, D. Cipolla, J. Eicher, W. de Kruijf, H. Wachtel, in: A.J. Hickey, S.R.P. da Rocha (Eds.), Soft Mist Inhalers in Pharmaceutical Inhalation Aerosol Technology, Third editionCRC Press, Boca Raton, FL 2019, pp. 493–507.
[32] A.J. Hickey, Fundamentals of dry powder inhaler technology, in: H.G. Merkus, G.M.H. Meesters, W. Oostra (Eds.), Particles and Nanoparticles in Pharmaceutical Products, Springer, New York, NY 2018, pp. 213–232.
[33] D.A. Edwards, J. Hanes, G. Caponetti, J. Hrkach, A. Ben-Jebria, M.L. Eskew, J. Mintzes, D. Deaver, N. Lotan, R. Langer, Large porous particles for pulmonary drug delivery, Science 276 (1997) 1868–1871.
[34] T.M. Crowder, J.A. Rosati, J.D. Schroeter, A.J. Hickey, T. Martonen, Fundamental effects of particle morphology on lung delivery: predictions of Stokes' law and the particular relevance to dry powder inhaler formulation and development, Pharm. Res. 19 (2002) 239–245.
[35] A.J. Hickey, D.A. Edwards, Density and shape factor terms in Stokes' equation for aerodynamic behavior of aerosols, J. Pharm. Sci. 107 (2018) 794–796.
[36] D.E. Geller, J. Weers, S. Heuerding, Development of an inhaled dry powder formulation of tobramycin using Pulmonsphere™ technology, J. Aerosol. Med. Pulm Drug Deliv. 24 (2011) 175–182.
[37] A.D. Brunaugh, S.U. Jan, S. Ferrati, H.D. Smyth, Excipient-free pulmonary delivery and macrophage targeting of clofazimine via air jet micronization, Mol. Pharm. 14 (2017) 4019–4031.
[38] K.J. Macdonald, G.P. Martin, Transition to CFC free metered dose inhalers – into the new millennium, Int. J. Pharm. 201 (2000) 89–107.
[39] N. Roche, P.N.R. Dekhuijzen, The evolution of pressurized metered dose inhalers, J. Aerol. Med. Pulm. Drug Deliv. 29 (2016) 311–327.
[40] G.T. Ferguson, A.J. Hickey, S. Dwivedi, Co-suspension delivery technology in pressurized metered dose inhalers for multi-drug dosing in the treatment of respiratory diseases, Respir. Med. 134 (2018) 16–23.
[41] H. Kumar Jeswani, A. Azapagic, Environmental impacts of healthcare and pharmaceutical products: influence of produc design and consumer behavior, J. Clean. Prod. 253 (2020), 119860.
[42] S. Panigone, F. Sandri, R. Ferri, A. Volpato, E. Nudo, G. Nicolini, Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment, BMJ Open Respir. Res. 7 (2020) https://doi.org/10.1136/bmjresp-2020-000571 (2020).PMC7173981.
[43] A.J. Hickey, Preclinical and Clinical Considerations in "Inhaled Pharmaceutical Product Development Perspectives", Elsevier, New York, NY, 2016 53–71.
[44] R. Angelo, K. Rousseau, M. Grant, A. Leone-Bay, P. Richardson, Technosphere® insulin: defining the role of Technosphere particles at the cellular level, J. Diabetes Sci. Technol. 3 (2009) 545–554.
[45] J. Valdes, T. Shipley, J.A. Rey, Loxapine inhalation powder (Adasuve), Pharm. Ther. 39 (2014) 621–623(628).
[46] K. Dhe, D.J. Myers, M. Glazer, T. Schmidt, C. Devereaux, K. Simis, P.D. Noymer, M. He, C. Choosakul, Q. Chen, J.V. Cassella, In vitro aerosol characterization of staccato® loxapine, Int. J. Pharm. 403 (2011) 101–108.
[47] D.H. Ballard, C.H. Previgliano, Lady Windermere syndrome, Am J Med Sci 351 (2016) e7.
[48] B. Banaschewski, T. Hofmann, Inhaled antibiotics for mycobacterial lung disease, Pharmaceutics 11 (2019) 7(pii: E352).
[49] T.P. Kennedy, D.J. Weber, Non-tuberculous mycobacteria an underappreciated cause of geriatric lung disease, Am. J. Respir. Crit. Care Med. 149 (1994) 1654–1658.
[50] S. Faria, I. joao, L. Jordao, General overview on non-tuberculous mycobacteria, biofilms and human infection, J. Pathog. 2015 (2015), 809014.
[51] C. Kelly, C. Jefferies, S.A. Cryan, Targeting liposomal drug delivery to monocytes and macrophages, J. Drug Deliv. (2011) http://doi.org/10.115/2011/727241 (Article ID 727241).
[52] B. Banaschewski, D. Verma, L.J. Pennings, M. Zimmerman, Q. Ye, J. Gadawa, V. Dartois, D. Ordway, J. van Ingen, S. Ufer, K. Stapleton, T. Hofmann, Clorazimine inhalation suspension for the aerosol treatment of pulmonary non-tuberculous mycobacterial infections, J. Cyst. Fibros. 18 (2019) 714–720.
[53] A.J. Hickey, A. Misra, P.B. Fourie, Drug Delivery Systems for Tuberculosis Prevention and Treatment, John Wiley and Sons, New York, NY, 2016.
[54] A.J. Hickey, Regulatory Strategy in "Inhaled Pharmaceutical Product Development Perspectives", Elsevier, New York, NY, 2018 73–84.
[55] US Food and Drug Administration, Albuterol Sulfate Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf 2016.
[56] US Food and Drug Administration, Guidance, Fluticasone Dipropionate and Salmeterol Xinafoate Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf 2013.
[57] US Food and Drug Administration, Metered Dose Inhaler and Dry Powder Inhaler Guidance, http://www/fda.gov/downloads/Drugs/GuidanceComplianceRegulatroyInformation/Guidances/UCM70573.pdf 1998.
[58] US Food and Drug Administration, Metered Dose Inhaler and Dry Powder Inhaler Guidance, 2018 (Revision 1 April 2018).
[60] G. Apiou-Sbirlea, S. Newman, J. Fleming, R. Seikmeier, S. Ehrmann, G. Scheuch, G. Hochhaus, A.J. Hickey, Bioequivalence of inhaled drugs: fundamentals, challenges and perspectives, Ther. Deliv. J. 4 (2013) 343–367.
[61] W.P. Adams, R.C. Ahrens, M.L. Chen, D. Christopher, B.A. Chowdhury, D.P. Conner, R. Dalby, K. Fitzgerald, L. Hendeles, A.J. Hickey, G. Hochhaus, B.L. Laube, P. Lucas, S.L. Lee, S. Lyapustina, B. Li, D. O'Connor, N. Parikh, D.A. Parkins, P. Peri, G.R. Pitcairn, M. Riebe, P. Roy, T. Shah, G.J. Singh, S.S. Sharp, J.D. Suman, M. Weda, J. Woodcock, L. Yu, Demonstrating bioequivalence of locally acting orally inhaled drug products (OIPs): workshop summary report, J. Aerosol Med. Pulm. Drug Deliv. 23 (2010) 1–29.
[62] J.E. Hastedt, P. Backman, A.R. Clark, W.H. Doub, A.J. Hickey, G. Hochhaus, P.J. Kuehl, C. Lehr, P. Mauser, J. McConville, R. Niven, M. Sakagimi, J.G. Weers, Scope and relevance of a pulmonary biopharmaceutical classification system AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD, AAPS Open 2 (2016) 1), 1–20.
[63] Y. Wang, R. Wang, D.D. Tang, Ste20-like kinase-mediated control of actin polymerization is a new mechanism for thin filament associated regulation of airway smooth muscle contraction, Am. J. Respir. Cell Mol. Biol. 62 (2020) 645–656, https://doi.org/10.1165/rcmb.2019-0310OC.
[64] Z. Zaslona, E. Flis, M. Wilk, R.G. carroll, E.M. Palsso-McDermott, M.M. Hughes, C. Diskin, K. Banahan, D.G. Ryan, A. Hooftman, A. Misliak, J. Kearney, G. Lochnit, W.

Bertrams, T. Greulich, B. Schmeck, O.J. McElvaney, K.H.G. Mills, E.C. Lavelle, M. Wygrecka, E.M. Creagh, L.A.J. O'Neill, Nature Communications, vol. 11, 2020 https://doi.org/10.1038/s41167-020-14945-2.

[65] N. Arulkumaran, D. Brealey, D. Howell, M. Singer, Use of non-invasive ventilation for patients with COVID-19: a cause for concern? Lancet Respir. Med. (2020) https://doi.org/10.1016/S2213-2600(20)30181-8.

[66] A.W. Peng, S. Milleri, D.S. Stein, Direct measurement of the anti-influenza agent zanamivir in the respiratory tract following inhalation, Antimcrob. Agents Chemother. 44 (2000) 1974–1976.

[67] L. Li, R. Avery, M. Budev, S. Mossad, L. Danziger-Isakov, Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation, J. Heart Lung Transplant. (8) (2012) 839–844.

[68] E.F. Dumont, A.J. Oliver, C. Ioaniou, J. Billiard, J. Dennison, et al., A novel inhaled dry powder formulation of ribavirin allows for efficient lung delivery in healthy participants and those with chronic obstructive pulmonary disease in phase I study, Antimicrob. Agents Chemother. 64 (2020)(e002267-19).

[69] W. Olszewska, P. Openshaw, Emerging drugs for respiratory syncytial virus infection, Expert Opin. Emerg Drugs 14 (2009) 207–217.

[70] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, Compassionate use of remdesivir for patients with severe COVID-19, New Engl. J. Med. (2020) https://doi.org/10.1056/NEJMoa2007016.

[71] M. Gursel, I. Gursel, Is global BCG vaccination coverage relevant to the progression of SARS-CoV2 pandemic? Med. Hypothesis (2020) https://doi.org/10.1016/j.mehy.2020.109707.

[72] L. Garcia-Contreras, Y.L. Wong, P. Muttil, D. Padilla, J. Sadoff, J. Derousse, W.A. Germishuizen, S. Goonesekera, K. Elbert, B.R. Bloom, R. Miller, P.B. Fourie, A. Hickey, D. Edwards, Immunization by a bacterial aerosol, Proc. Natl. Acad. Sci. 105 (2008) 4656–4660.

[73] D. Lu, L. Garcia-Contreras, P. Muttil, D. Padilla, D. Xu, J. Liu, M. Braunstein, D.N. McMurray, A.J. Hickey, Pulmonary immunization using antigen 85-B polymeric microparticles to boost tuberculosis immunity, AAPS J. 12 (2010) 338–347.

[74] D. Lu, A.J. Hickey, Pulmonary vaccine delivery, Expert Rev. Vaccines 6 (2007) 213–226.

[75] D.N. Price, N.K. Kunda, R. Ellis, P. Muttil, Design and optimization of a temperature stable dry powder BCG vaccine, Pharm. Res. 37 (2020) https://doi.org/10.1007/s11095-019-2739-8.

[76] Z.R. Manjaly Thomas, I. Satti, J.L. Marshall, S.A. Harris, R. Lopez Ramon, A. Hamidi, A. Minhinnick, M. Riste, L. Stockdale, A.M. Lawrie, S. Vermaak, M. Wilkie, H. Bettinson, H. McShane, Alternate aerosol and systemic immunization with a recombinant viral vector for tuberculosis MVA85A: a phase I randomized controlled trial, PLoS Med. 16 (4) (2019) e1002790.