Innovations in nebulized delivery

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Summary

In recent years, much of the focus of novel treatments for respiratory diseases has been in the development of inhalers containing new, longer-acting compounds in established drug classes, either alone or in combination. However, there remain patients who are unable to use such devices properly, who rely upon nebulized therapy, yet there have been few new drugs marketed in nebulized form in the last 30 years. This undoubtedly has had a negative impact on disease control.

A novel approach to development is to focus first on bringing the nebulized formulation to market, and only to start development of the inhaler once the new drug candidate has successfully demonstrated safety and efficacy. Not only does this mitigate the risks associated with developing an inhaler formulation only for the drug to fail in the clinic, it also studies drug outcomes in the most severe group of patients, in whom a positive effect should be easiest to demonstrate. This can reduce the commercial barriers to the introduction of new nebulized drugs, thereby ensuring such patients have access to the latest innovations in drug development.

Parallel device developments will ensure this market continues to grow at a faster rate than that of the overall inhaler market. Innovations such as small volume, breath activated mesh nebulizers are likely to see the gap narrow between the treatment times for inhaler and nebulizer use, whilst the added benefits of an electronic-based technology will lead to adoption of patient monitoring approaches in inherently more at-risk patient populations.

Introduction

In recent years, much of the focus of novel treatments for respiratory diseases has been in the development of inhalers containing new, longer-acting compounds in the classes of β-agonists, muscarinics and combinations, either together or with a corticosteroid [1]. Accompanying this has been the introduction of new dry power inhalers and/or engineered particle formulations. These are suitable for the vast majority of patients. Nonetheless, there remain classes of patient, notably the very young, very old and very sick, who are unable to use such devices properly. These patients rely upon nebulized therapy, a delivery system that has been in existence for over 150 years. Yet there have been very few new drugs marketed in nebulized form in the last 30 years. Despite this lack of new product introductions, nebulized treatments are still estimated to be growing faster than those delivered by inhalers (Figure 1 [2]). Globally, this may in part be due to increasing longevity in the general population. However, this is also being driven by increasing access to medicines in developing economies, to the extent that nebulized treatments are now the largest value segment in China [3].

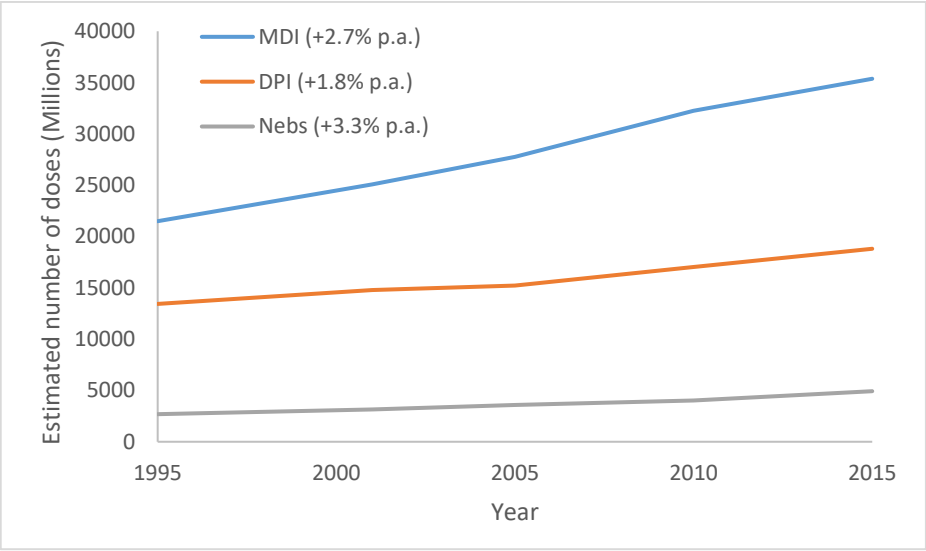

Figure 1 - Estimated global number of inhaled doses of medication by delivery system (adapted from [1]).

Nevertheless, patients on nebulized therapy are unable to access the latest drug developments. This undoubtedly has had a negative impact on disease control. Take for example, the case of a COPD patient who exacerbates and is hospitalized in the US. Upon discharge, 50% are prescribed a nebulized treatment [4], most commonly a combination of short-acting β-agonist and muscarinic drugs. Thus, their burden of disease can shift from taking treatment from an inhaler once or twice per day, to a series of 4 nebulized treatments, each lasting several minutes. It is well documented that increased treatment burden adversely affects adherence [5] and it has been estimated that a reduction in adherence of 20% leads to an increase in adverse events in COPD patients of over 10% [6]. It is not surprising, therefore, that once-daily nebulized bronchodilators have been described as a "compelling market opportunity" [4]. However, to date, this opportunity has been largely overlooked; this paper looks at key barriers to the introduction of new nebulized therapies and current initiatives to overcome them.

Changing the development paradigm

Pharmaceutical companies often begin inhalation drug developments with nebulizers in the early stages, to provide cheaper and faster drug development, but then switch to inhaler devices in later clinical trials to address the majority of patients. Typically it can take 10 to 12 years to launch the new drug onto the market. As a completely different delivery system and formulation, nebulized products will require fresh dose-ranging and pivotal Phase III studies, which will again take some 5 years or more to gain marketing approval. This means that there is little of the original drug patent life left by the time the nebulized formulation reaches the market. As a consequence, unless formulation patents can be obtained on the nebulized formulation, there is insufficient time left to recover the investment in developing this product before generic copies enter the market. Thus, by leaving nebulized development until late in the drug's life-cycle makes the development of a new drug in nebulized form commercially unattractive. In order to overcome this problem, one company (Mylan) has decided to go straight to market with a new long-acting muscarinic (LAMA) drug moiety in nebulized form [7], despite having previously successfully developed a different LAMA for use in inhalers [8].

Building on this, a novel approach to development is to focus first on bringing the nebulized formulation to market, and only to start development of the inhaler once the new drug candidate has successfully demonstrated safety and efficacy. Not only does this mitigate the costs associated with developing an inhaler formulation only for the drug to fail in the clinic, it also studies drug outcomes in the most severe group of patients, in whom a positive effect should be easiest to demonstrate. This has also been modelled from a financial perspective, calculating the expected Net Present Value (eNPV, the value in today's terms of cash flows expected from the project in the future, scaled down by the likelihood of success) under varying conditions of peak annual sales for the drug, and interest on the cash equivalent (Discount rate). This is shown in Figure 2 [9].

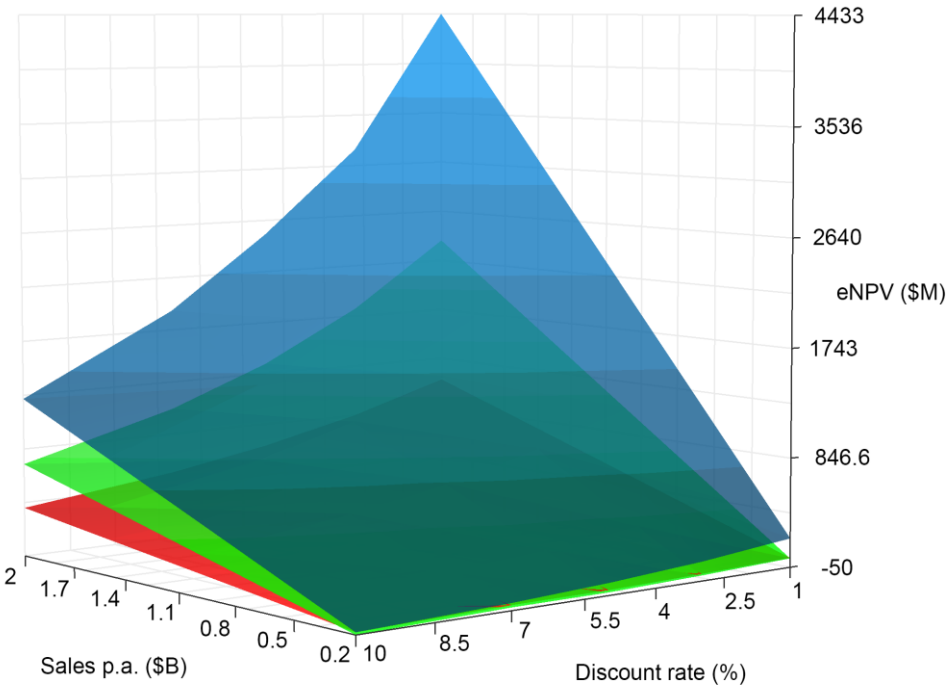

Figure 2 - Financial returns improve if developing a nebulized formulation before an inhaler (blue), rather than as life-cycle management (green) or an inhaler alone (red) (adapted from [9]).

It transpires that there is likely to be a much greater financial return than that from adopting a traditional approach to development of the inhaler first. Additionally, nebulized products can command a higher price per dose, and whilst device costs for nebulized products are higher as an initial outlay, they can be amortized over months or years of treatment, making them similar overall to those of a portable inhaler. Furthermore, the capital investment in device production is borne by the nebulizer manufacturer; it does not require an often lengthy development of a bespoke inhaler, and some nebulizers are available immediately with medical device market authorization. If this novel approach to development is adopted moving forward, then the commercial barriers to the introduction of nebulized drugs are significantly reduced, thereby ensuring patients requiring nebulized therapy have access to the latest innovations in drug development.

Improving the usability of nebulizers

Nebulizers are inherently relatively simple to use, in that the patient is only required to put the formulation into the device and then breathe through it using their natural tidal breathing pattern until delivery is complete. However, for jet nebulizers, there are drawbacks to the patient, including the noise of the compressor, lack of portability, treatment time and cleaning regimen. As a consequence, vibrating mesh nebulizers are gaining increasing popularity, as they address many of the above limitations [10]. As may be seen from Figure 3, they are capable of delivering a wide variety of formulations, so are suited to the delivery of most drugs. Indeed for drugs with low potency, nebulizers may be the only suitable delivery system. Mesh nebulizers are also assuming increasing use in a hospital setting, and with new developments such as mesh nebulizer systems for use in the emergency room (Aerogen Ultra™, Aerogen, Galway, Ireland), it is possible to have a single droplet generation system that can be bridged from in-line ventilator use right through to home use.

If new drugs are forthcoming, then using state-of-the-art nebulizers will become increasingly important, as regulatory authorities expect a new drug only to be promoted with nebulizers for which the developer has clinical experience. Increasingly, the drug market authorization will be as a specific drug-device combination product. New, breath-activated mesh nebulizers with low residual volumes, mean that the dose from 2.5 mL of a current nebulizer formulation can be delivered in as little as 0.25 mL. Indeed, there is a novel nebulizer in development for the delivery of inhaled insulin that is capable of delivering doses as low as 50 µL with residual volumes less than 20% [11]. Such small volumes reduce treatment times to one or two breaths. The diameter of the apertures in the mesh can also be controlled to sub-micron tolerances [12], enabling the droplet size to be optimized for a particular mechanism of action. High efficiency may be particularly important in the development of treatments involving macromolecules. Not only are such drugs expensive to manufacture, they are inherently less potent, thereby requiring doses beyond those for which conventional inhalers are capable of delivering, not to mention any additional excipients required to enhance cell penetration. Furthermore, large doses will drive the development of faster output nebulizers in order to maintain an acceptable treatment time. Due to their inherently efficient use of energy, mesh nebulizers are likely to lead the way. This might be through increased hole density, larger aperture plates, or higher vibration frequencies.

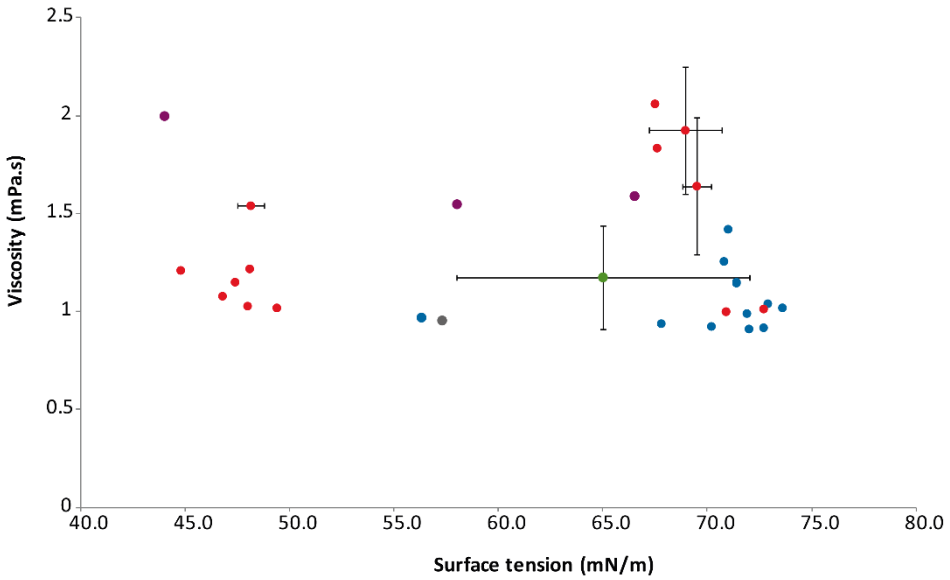

Figure 3 - Variation in physicochemical properties of formulations successfully delivered using a vibrating mesh nebulizer (reproduced with permission from Respiratory Drug Delivery 2014, Virginia Commonwealth University and RDD Online [13]). Small molecules (●), proteins/peptides (●), liposomes (●), suspensions (●), and surfactants (●). Bars represent a range of values measured over a range of concentrations.

Improving adherence to therapy

However good the device and drug, a therapy will be ineffective unless the patient is motivated to take their medication. Many factors influence this, so feedback from the device on correct operation can be important [14]. With

a breath-activated mesh nebulizer, it is possible to log when and how the device has been used and upload the information to a server [15]. This information is helpful in understanding the challenging nature of true adherence, and may be crucial to the development and assessment of interventions to promote adherence; it allows patient, physician or support personnel such as relatives to monitor, provide feedback or coach the patient to improve adherence and technique. In the future, monitoring symptoms and capturing the data in the same system may offer even greater benefits, both by ensuring there is optimum treatment and by providing positive feedback to the patient to encourage proper adherence and manage their disease.

Concluding remarks

Patients requiring nebulized therapy have not benefitted from the recent spate of new products launched in inhaler format for the treatment of asthma and COPD. This situation is changing, as companies begin to recognize this unmet need. Parallel developments in the device technology will ensure this market continues to grow at a faster rate than that of the overall inhaler market. Innovations in nebulized delivery are likely to see the gap narrow between the treatment times for inhaler and nebulizer use, whilst the added benefits of an electronic-based technology will lead to rapid adoption of patient monitoring approaches in what are inherently more at-risk patient populations.

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