

NEBULISERS: TIME TO REINVENT THE WHEEL

In this article, John Pritchard, PhD, Director, PMO and Technology, Respirionics Respiratory Drug Delivery, discusses the history of the nebuliser, its fall in popularity with the advent of DPIs and pMDIs, and its current resurgence due to the success of the mesh nebuliser, continuing on to how changing the development paradigm to utilise nebuliser technology more effectively can have significant benefits.

NEBULISED DRUG DELIVERY

Over a century and a half ago, nebulisers were the first widely commercialised devices used for the delivery of medical aerosols to the lungs.¹ Over the intervening period the complexity and efficiency of designs based on the use of a jet of high-pressure air have steadily increased, and jet nebuliser technology has dominated the nebuliser market. However, it was not until the aerosol generation technique employed in nebulisers was successfully reinvented, with the arrival of mesh technology, that the efficiency and features of nebulisation devices began a leap forward in performance.

The popularity of the nebuliser as an aerosol delivery device has been linked with both developments in nebuliser design and other developments in the field of aerosol delivery. The invention of the portable dry powder inhaler (DPI) and pressurised metered dose inhaler (pMDI) in the mid-20th century led to a reduction in the popularity of the nebuliser. Today that decline has been reversed, with the number of doses of medication taken by nebuliser growing faster than either DPIs or pMDIs.² This resurgence in popularity is driven by a number of concurrent developments as well as the advantages that nebulised drug delivery provides over other forms of aerosol drug delivery (Figure 1).

The primary advantage that nebulisation has maintained over other aerosol delivery devices has been its universal applicability to all those requiring aerosol treatment, be they very young, very old, severely ill or coping with disability. Other types of aerosol delivery device require specific actions on the part of the user, in terms of the way the aerosol bolus is inhaled in a single breath, whereas nebulised aerosol delivery merely requires the patient to breathe naturally. This universal applicability has come at a cost in terms of the time required to receive a treatment, but

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the main disadvantage of nebulised therapy over other inhaler therapy has been its lack of portability. The invention of the mesh nebuliser addressed the portability issue, and recent enhancements in mesh nebuliser performance have more than halved the time required for a treatment.³

These developments, along with universal applicability, are opening the window of opportunity to apply the benefits of nebulised therapy past the traditional niche patient groups of cystic fibrosis and pulmonary hypertension into the wider arena of respiratory care. Chronic obstructive pulmonary disease (COPD) is predicted to become the third leading cause of death worldwide by 2030,⁴ and nebulised therapy is well placed to provide a key treatment option in the treatment of patients suffering from this disease.⁵ Patients with COPD are usually elderly and experience chronic detrimental alterations to their typical breathing patterns, which manifest as reduced peak inhalation flows (PIFs) and an extended exhalation phase. Consequently, they are an ideal patient group for consideration for treatment by nebulised therapy.



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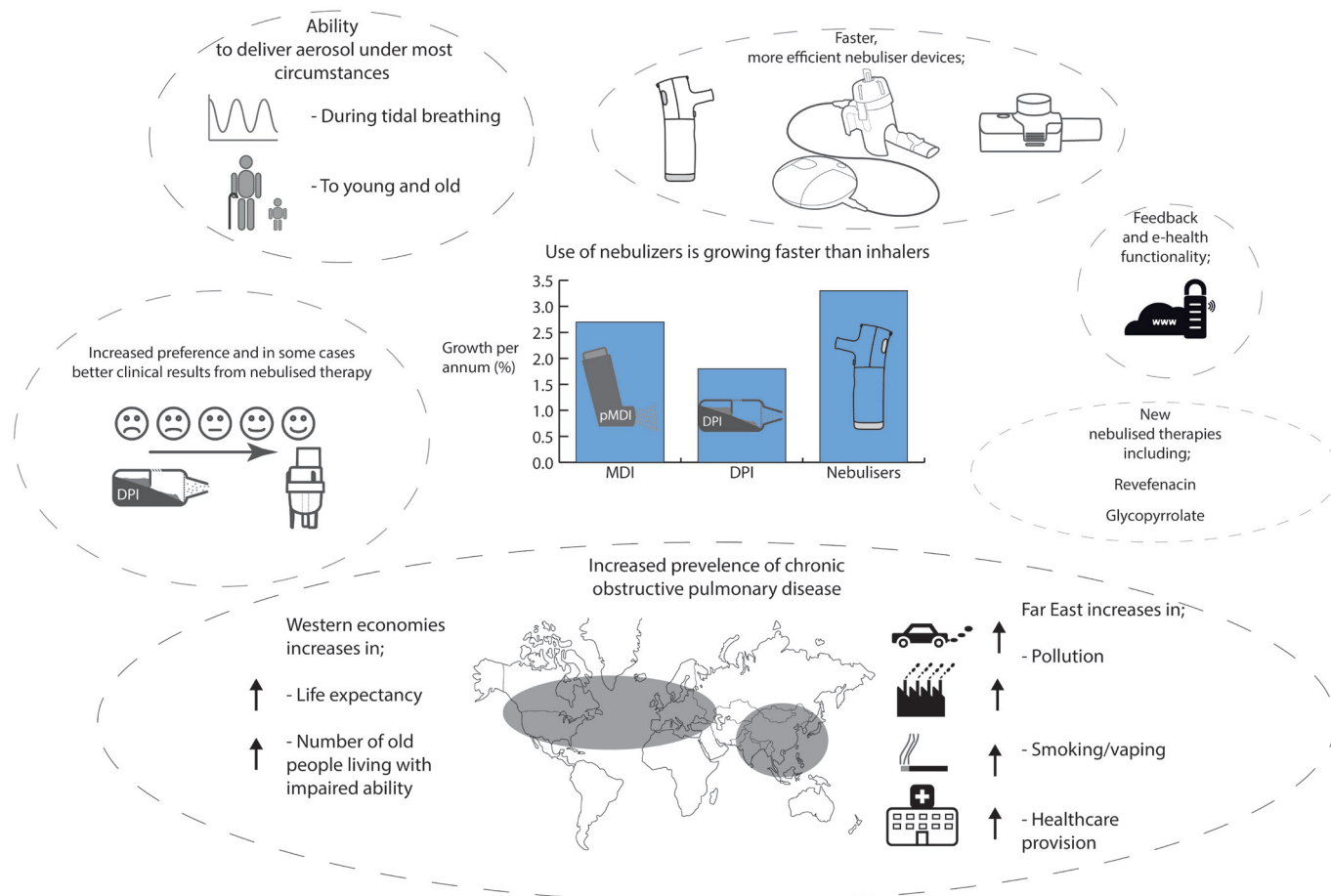


Figure 1: Contributing factors in the resurgent popularity of nebulised drug delivery.

In the US, around 50% of those discharged from hospital can currently be expected to be prescribed nebulised treatment. A recent study in patients admitted to hospital following an exacerbation of COPD raised an interesting difference between sub-groups using different aerosol devices. Patients with PIFs below 60 L/min who were exclusively prescribed a DPI upon discharge from hospital showed higher levels of all causes of COPD readmission compared with those exclusively prescribed a nebuliser upon discharge.⁶

Patient preference for nebulised therapy has long been known, but considering the properties of use of nebulised therapy compared with inhaler therapy as applied to patients with COPD, it is perhaps surprising that this type of clinical effect has not been noticed before. The answer may lie in the low level of commercial and academic interest in nebulised therapy in the years when nebulised therapy was limited to bulky, noisy devices that administered treatment over more than 10 minutes, compared with seconds for an inhaler. The advantages of these new mesh nebulisers for patients with COPD have now been recognised by commercial drug developers. The first drug for COPD, Lonhala (glycopyrrolate) from

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Sunovion Pharmaceuticals (Marlborough, MA, US), developed specifically for use with a mesh nebuliser (Magnair), from PARI Pharma (Gräfelfing, Germany), has now been approved by the US FDA, with others to follow.

USING A NEBULISER TO IMPROVE THE CHANCES OF SUCCESS WITH INHALED DRUG DEVELOPMENT

One commercially focused area in which nebulisation maintained a limited but persistent role during the 20th century was in the development of new drug entities.⁷ New drug development is a highly financially risky venture with high dropout rates and high manufacturing costs for

the small batches of novel drugs produced during early development. In these key early stages, the cost of small batch production can make the drugs as valuable as gold. Therefore quantities are kept as low as possible within the requirement to satisfy the quality and regulatory demands of the required testing programme.⁸

It was recognised that use of nebulised solution formulations in the early stages avoided the need for time-consuming and costly activities, such as:

- Particle size reduction processes
- Overcoming formulation issues with propellant/carrier
- The demonstration of end-of-shelf-life performance.

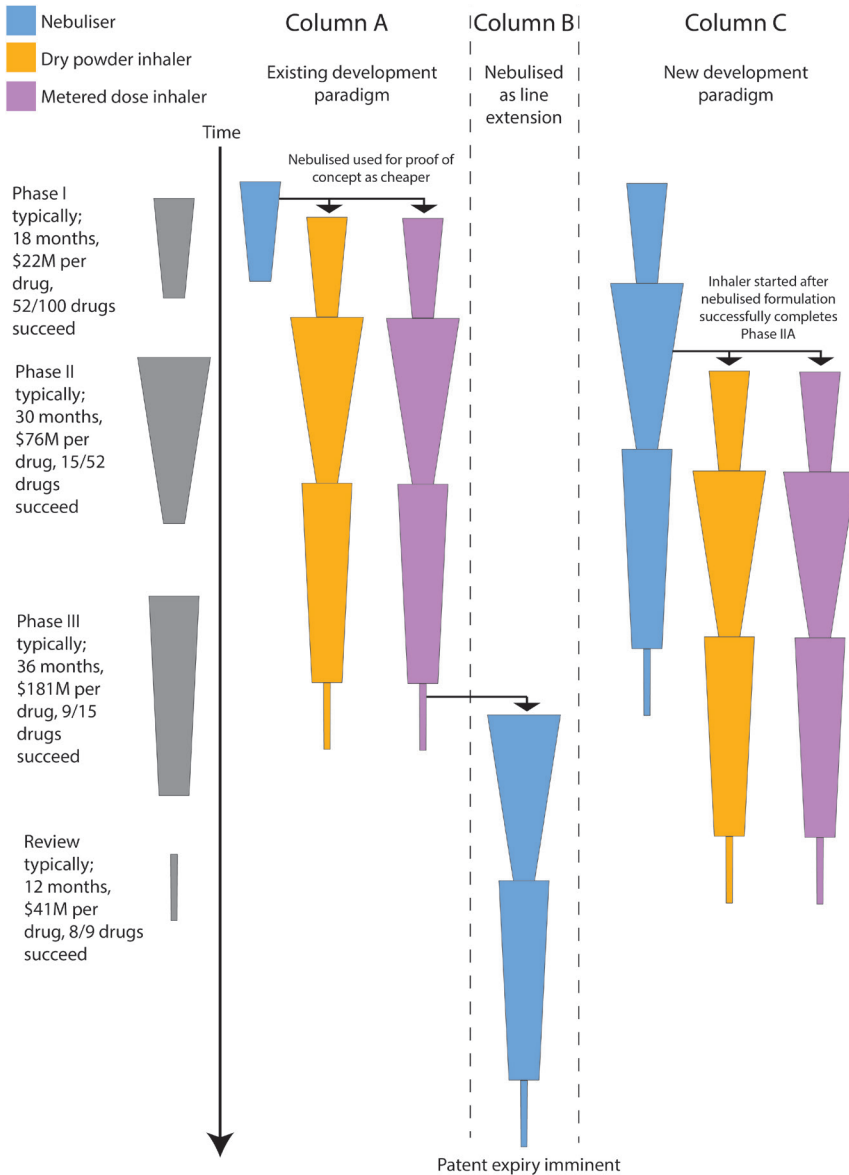


Figure 2: Drug development paradigms.

Additionally, delivery into tidal breathing and the ability to deliver a wide range of volumes of solution also simplified dose-ranging studies. The savings obtained by using nebulised formulations in the early development stages, during proof of viability, more than offset the additional time required to reset the development programme to the inhaler format required for the end commercial product for successful drug candidates (Figure 2, Column A).

Although the cost efficiency gains to the development programme as a whole were worthwhile, using the traditional development paradigm still led to waste of the initial nebulised development work. The arrival of portable, patient-friendly nebulisers that provide a much lower inter-device drug delivery variability increased the attractiveness of launching new drugs in a nebulised form. Thus the time had come to re-examine and possibly reinvent the established drug development paradigm. A financial model investigating the return on investment of the traditional development paradigm compared with two waste-limiting alternatives showed improvements for return on investment for both.⁹ Addition of a nebulised formulation as a line extension to the existing inhaler formulation (Figure 2, Column B) offered an increased return on investment, but by far the greatest returns were seen using an entirely new development paradigm that prioritised development of the nebulised formulation right through to commercial launch (Figure 2, Column C). The model showed that the advantages were present across a range of expected sales values and discount rates that allow for interest rate changes (Figure 3).^{8,9}

With a convincing alignment of so many factors falling into place in support of the development and commercialisation of a nebulised drug delivery format in the

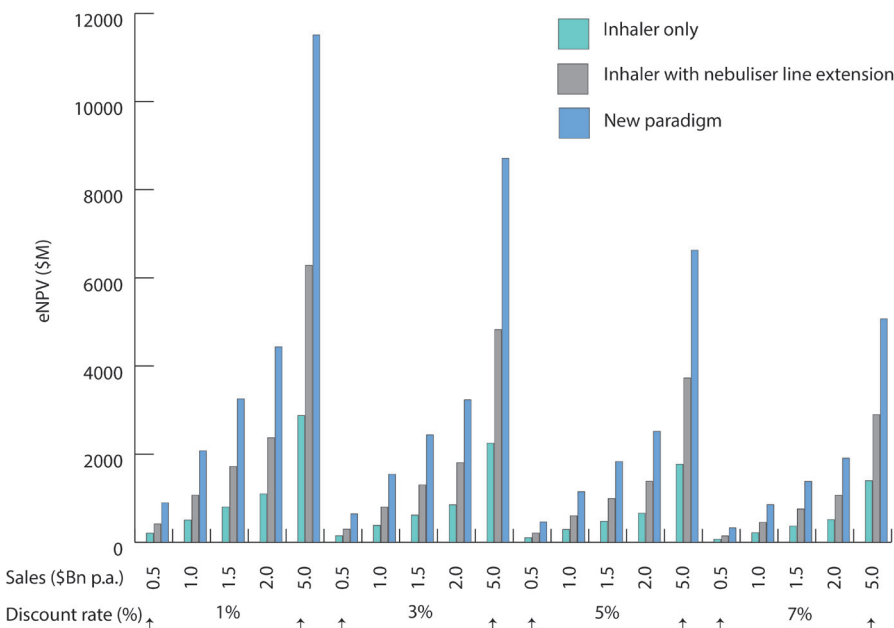


Figure 3: The expected net present value (eNPV) of three drug development paradigms.

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arena of modern-day aerosol drug delivery, the question for forward-looking drug developers changed from, “which drug delivery format should the drug be launched in?”, to “which nebulisation technology should the drug be launched in?”.

PICKING THE RIGHT NEBULISER

Reinvention does not mean that older designs no longer have appropriate applications. Traditional jet nebuliser technology still provides a cost effective delivery option for generic drugs with wide therapeutic indexes intended to reach as wide a treatment population as possible, and provides a simplified regulatory route to market. Jet nebulisation offers a range of options in terms of delivery efficiency (Figure 4), from conventional constant output jet nebulisers, through breath-enhanced jet nebulisers up to mechanically breath-actuated jet nebulisers, each with its own advantages and drawbacks for the treatment of different patient groups.¹⁰

However, the main potential for novel drug developments lies in mesh nebuliser designs that provide better drug delivery efficiency in a portable, silent, energy efficient, rapid aerosol delivery and user-friendly package. Modern drug development encompasses a broad range of drug molecules and macromolecules that may be more expensive to produce and require greater volumes of formulation to be delivered. The high delivery efficiency

of the mesh nebuliser, with as little as 0.1 mL of drug formulation left behind in the medication chamber at the end of the treatment,¹¹ provides the potential to minimise the volume contained in the drug nebuliser and increase the amount of packaged drug that is delivered to the patient.

The electronic platform that the mesh aerosol generator is built on also allows for the incorporation of other features and capabilities to improve both drug delivery and usability.¹² Feedback to the user in the form of automatic detection of the end of the treatment can provide users with added confidence that they have received a complete treatment without spending additional time breathing through the nebuliser after aerosol production has ceased. Breath activation can ensure that all of the intended dose of drug is delivered to the patient regardless of differences in the way that different patients breathe and it can minimise the amount of aerosol wasted to the environment. Breath activation can also be supplemented with additional feedback mechanisms to aid the patient in

breathing in a manner to achieve optimal aerosol delivery into the lungs.¹³

The increased number of feedback signals, from basic on/off and end of treatment, to a range encompassing guidance on the best flow rate and how long to inhale for, has resulted in the use of audible, visible and also tactile feedback signals to the user, to ease interpretation of the different signals.

Such guidance on the correct use of the nebuliser to optimise the efficiency of aerosolised drug delivery to the lungs is one of the key drivers of the expectation of better disease control via nebulised drug delivery in the future. However, the top end of the scale of devices for increasing drug delivery efficiency must deal with the issues surrounding adherence of the patient with the prescribed treatment regimen. The electronic basis of mesh nebulisers, with associated feedback mechanisms, allows the seamless integration of connectivity, electronic monitoring and internet-based patient management programmes that are designed to support the patient in their use of nebulised therapy in their daily lives.¹⁴

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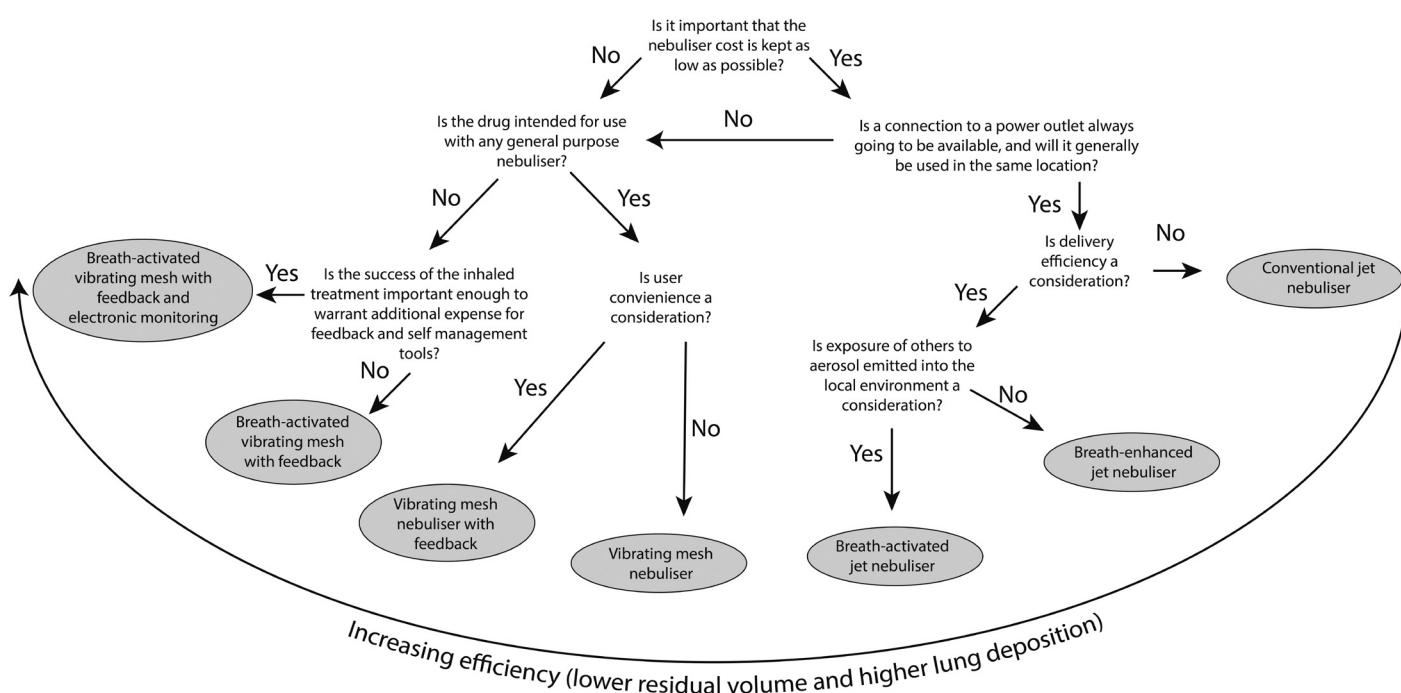


Figure 4: Some factors in selection of the appropriate nebuliser.

THE INCREASING WORLD OF MESH NEBULISERS

With all the advantages that mesh nebulisers have brought to nebulised drug delivery, their increased use has progressed through the early adoption phase and has begun to move into widescale acceptance. The number of clinical trials sponsored by pharmaceutical companies that use mesh nebulisers now outweighs the number that use jet nebulisers,¹⁵ and as more new drugs are trialled and approved using mesh nebulisers their share of the respiratory market will increase further.

Another driver for increased use of mesh nebulisers is reduced cost; as mesh technology has developed the cost of producing the aerosol generators has reduced, and will continue to do so as new materials and processes are used to create the meshes, which require thousands of holes made to fine engineering tolerances. At one end of the scale nickel palladium alloy mesh designs promise aerosol heads that could last as long as the nebuliser, while at the other end of the scale plastic meshes offer a solution that could be disposable on a weekly or even daily basis. As the costs of ownership decrease, the simpler, more basic models will increasingly take over from jet nebulisers while, at the other end of the scale, systems with advanced feedback may open new markets to nebulised therapy.

The latest advanced systems already include feedback systems to guide the user to achieve the optimal treatment, for example Respironic's own I-neb AAD System guides

the patient to an optimised inhalation and the Breelib from Vectura (Chippenham, UK) mesh nebuliser provides an illuminated mouthpiece that indicates when the patient is inhaling with the optimal flow rate. Both these devices can be connected to an e-health application to provide usage information to both patient and healthcare provider.¹³

With so many simultaneous developments in nebuliser performance and capability across the range of simple to advanced devices, the future of nebulised therapy in the treatment of respiratory diseases is looking stronger than ever.

CONCLUSIONS

Nebulised therapy has been used for the delivery of aerosols to the lungs for over 150 years, but lost favour due to drawbacks and the development of more convenient aerosol delivery systems. New developments in the field of nebulised therapy have prompted a resurgence in popularity, which is only just beginning. New drugs and novel, more sophisticated nebulisers will provide new opportunities to treat both the core user base of the very young, very old and very ill, as well as bringing the advantages of nebulised therapy to a wider range of respiratory patient groups.

ABOUT THE COMPANY

Respironics Respiratory Drug Delivery (UK) Ltd is a subsidiary of Royal Philips of the Netherlands. Royal Philips is

a leading health technology company focused on improving people's health and enabling better outcomes across the health continuum from healthy living and prevention, to diagnosis, treatment and home care. Philips leverages advanced technology and deep clinical and consumer insights to deliver integrated solutions. The company is a leader in diagnostic imaging, image-guided therapy, patient monitoring and health informatics, as well as in consumer health and home care.

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ABOUT THE AUTHOR

From January 2011 to September 2018, Dr John Pritchard was Director, PMO and Technology, for Philips Respironics Drug Delivery, with global accountability for the development of products for the treatment of respiratory diseases. He is now a private consultant specialising in strategic approaches to developing respiratory devices, drugs and digital health. At different stages in his career across three major pharmaceutical companies, he has been associated with the launch of 11 major products and at the Respiratory Drug Delivery (RDD) conference in April 2018, Dr Pritchard received the Charles G Thiel award for outstanding research and discovery in respiratory drug delivery. Dr Pritchard has published widely in the field, as well as having served as a board member on various scientific and industry bodies. He is currently a member of the UN Committee that makes recommendations on the essential uses of propellants.

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