Formulation concepts for small-volume nebulizers: Challenges and opportunities

The critical role of formulation science in the development of tomorrow's miniaturized devices for liquid inhalation

Stefan Ulvenlund, PhD and Ola Nerbrink, PhD
CR Competence AB, Respiron Consulting AB and Medicon Valley Inhalation Consortium

Introduction

Nebulization represents a well-established concept for pulmonary administration of aqueous formulations of pharmaceutical drugs. It is particularly useful when patient coordination and breathing pattern are problematic, for instance, when treating elderly or seriously ill patients with weak or impaired lung function.[1-4] For children, nebulization is often a valuable supplement to metered dose inhalers (MDIs) equipped with spacers.

The key disadvantage of conventional nebulization is the need for relatively complex and bulky devices. Jet nebulizers, for example, consist of a compressor and a nebulizer unit that are often large and require cleaning on a daily basis.[5] Furthermore, conventional nebulizers operate with fill volumes in the ml range, which often results in long treatment times.[6-7]

In order to achieve a true step-change in the way nebulization is applied, next-generation nebulizers need to be designed in such a way that they (1) are inconspicuous during patient use, (2) allow for the patient to conveniently carry the device in everyday life, (3) administer the dose in a shorter time, and (4) preferably do so with only one or two inhalations. When these requirements are fulfilled, the user-friendliness of nebulizers is comparable to that of dry powder inhalers (DPIs) and pressurized metered dose inhalers (pMDIs). However, these requirements also translate as a dramatic and technically challenging miniaturization of the device, compared to conventional technology. For obvious reasons, miniaturization of the nebulizer, in turn, means that the administered volumes will be small compared to conventional nebulizers. The relative decrease is actually quite dramatic. A conventional nebulizer operates using milliliter quantities for a single administration over a period of minutes, whereas a miniaturized device will rather administer a volume that is counted in tens of microliters over a much shorter duration. Device miniaturization thus represents a decrease of the administered volume by roughly two orders of magnitude. Unless the drug to administer is extremely potent, the key formulation challenge is therefore to identify concepts that allow for a high enough drug load, without adversely affecting device performance.

The Respimat Soft Mist Inhaler from Boeringer-Ingelheim is a small, handheld nebulization device. Designed to deliver about 10-20 µl of aqueous liquid per actuation, it is currently marketed in both Europe and the US under the product names Spiriva and Striverdi. A number of additional devices are in development that target delivery of small volumes of aqueous formulations.[8-9] Although technical concepts required for design and successful commercialization of miniaturized devices are clearly accessible, substantial challenges in formulation and delivery technology remain. As alluded to, the formulation challenge is particularly true for drugs with low to medium potency, including steroids. In this paper, we therefore briefly review these challenges and also identify opportunities for successful co-development of formulations and devices for next-generation nebulization.

General aspects of formulations

In conventional aqueous nebulization, the drug is formulated either as a solution or as a suspension of micronized drug. The choice between the two is trivially dictated by the drug solubility at the relevant pH (normally 4-5) and the drug load. Solutions and suspensions are equally relevant for miniaturized nebulizers, notwithstanding the fact that, if a suspension, it should not be composed of particles of size and concentration likely to interfere with the nebulization process. The need for higher drug load (which translates as higher concentration) often requires substantial adjustment of conventional technology. However, there are also unconventional concepts, such as microemulsions, that may be relevant for miniaturised nebulizers.

In all essence, what we need is a high enough drug load, in a formulation that does not adversely affect device performance. Fulfilling these partly counteracting requirements is a non-trivial task. The performance (droplet/particle size, flow rate, etc.) of any given nebulizer is directly dependent on physical characteristics of the formulation, primarily viscosity and surface tension, plus API particle size for suspensions. The formulation, therefore, needs to be carefully tailored to the device and the drug, and it is highly unlikely that a "one size fits all" formulation concept for miniaturized devices will ever prove possible to develop. This situation is very similar to the case of DPIs, where the interplay between formulation and device is such that it is basically meaningless to separate the two when evaluating concept performance.

Formulation concepts

Solutions

As previously described, Boeringer-Ingelheim's Respimat administers the Spiriva formulation, which contains tiotropium bromide as the active ingredient. The extremely high potency of tiotropium makes it possible to formulate a solution, in spite of the small volume administered. For less potent drugs, a higher aqueous solubility is obviously required if a solution is to be formulated. For acidic or basic drugs with acid dissociation constants in the relevant range, solubility may be optimized by rational selection of pH. Here, the small volume administered actually provides an opportunity, in the sense that it allows for selection of pH conditions that would be unacceptable for conventional nebulization, due to reasons of irritancy. In other words, the pH window applicable to small-volume nebulization is potentially wider than for conventional nebulization (although still subject to regulatory review and approval). The same holds true for other key formulation parameters, such as the concentration of excipients. A particularly pertinent example is provided by excipients that can be used to enhance solubility, namely co-solvents and cyclodextrins. Since such excipients can act as potent irritants on the sensitive mucosa in the respiratory tract, decreasing volumes potentially represent a way to increase concentration without inducing adverse effects. In this context, it is interesting to note that the sulphobutylether derivative of cyclodextrin (marketed under the brand name Captisol) has been shown to efficiently solubilize the poorly-soluble corticosteroid budesonide, and that this solution has been shown to be superior to a conventional suspension when nebulized.[10] We may thus conclude that there are new items in the formulation toolbox that may prove very helpful in the quest to reach the high concentrations required for small-volume nebulization.

Still, high concentrations of drug or excipients also influence the physical properties of the formulation, which is sometimes overlooked. Thus, at high concentrations, the surface activity of the constituents is a critical attribute when assessing the performance of the formulation in a given nebulizer. Similarly, high concentrations may affect viscosity in such a way that nebulizer performance is impacted. Regardless of these considerations, the thermodynamic stability and conceptual simplicity of solutions often make them the first-hand choice for miniaturized nebulizers.

Suspensions

In a suspension, the drug is present in the form of solid particles suspended in an aqueous vehicle. As is the case for all types of formulations intended for pulmonary administration, a necessary requirement is that the drug particles must have a size in the respirable range, i.e.,having an aerodynamic diameter < 5 μm. In conventional nebulization of suspensions, micronized drug is therefore used. However, for small-volume nebulizers, even smaller particles may be required. This is due to the fact that the physical properties of concentrated suspensions of nanoparticles ("nanosuspensions") tend to be more favorable for nebulization than those of concentrated suspensions of micronized material. Indeed, nanosuspensions as concentrated as 20% (w/v) have proved possible to nebulize, with excellent results.[11] At these high concentrations, a small-volume device (delivering 20 μl of a 20% nanosuspension, for example) actually compares quite favorably with conventional nebulization (delivering 2 ml of a 0.1% micronized suspension) in terms of administered amount of drug! In addition, reducing the particle size may also have profound and positive effects on the pharmacokinetics after inhalation. For nanosuspensions of budesonide, the time of onset has been shown to be halved and C_{max} to be doubled, as compared to a conventional micronized formulation.[12] These benefits are probably a combined effect of higher dissolution rate, improved lung deposition and increased retention. However when considering nanosuspensions, there should be recognition, on a drug by drug basis, of the need to understand the influence on local lung delivery, systemic absorption and toxicity.

The main inherent drawback of suspensions is their thermodynamic instability, which potentially manifests itself as an increase of particle size over time ("Ostwald ripening") and a tendency for particle flocculation (loose aggregation into larger clusters). In addition, proper dispersion of the drug particles typically requires addition of a wetting agent. For inhalation, this wetting agent is normally the non-ionic ethoxylated surfactant polysorbate 80. Surfactants are irritants on mucosa and the concentration consequently needs to be kept low. It is therefore an inherent disadvantage of nanosuspensions that they require higher amounts of surfactant than does micronized material. This is a direct effect of the increase of specific area with decreasing particle size. However, the smaller volume again partly counteracts the problems of increasing the concentration, and it is well-established that physically stable nanosuspensions are possible to formulate with therapeutically relevant concentrations of surfactant.[13]

All in all, nanosuspensions represent a very valuable formulation concept for miniaturized nebulizers. Very

recent publications show that their characteristics can be rationally optimized for use in these particular devices.[14]

Novel formulation concepts

Solutions and suspensions represent mature (even ancient!) formulation concepts, but successful development and implementation of miniaturized nebulizers may also call for more innovative solutions (no pun intended). A particularly interesting opportunity is provided by microemulsions, i.e., thermodynamically stable mixtures of oil, surfactant and water. The relevance of this type of systems for drug delivery is well-established.[15] However, to the best of our knowledge, they have never been applied within the field of pulmonary-administered pharmaceutics. Their capacity to solubilize both water-soluble and oil-soluble compounds should be of particular interest for combination products.

Microemulsions are isotropic and potentially could be designed to have a viscosity suitable for nebulization. Consequently, there are no obvious "showstoppers" from the viewpoint of physical properties. However, successful development would require excipients that are currently not approved for inhalation, which represents a substantial hurdle. Indeed, the anorectic assortment of excipients approved for inhalation and the reluctance to approve new ones is, in our opinion, the single largest inhibitor for the development of new formulation platforms for inhalation.

Conclusions

Changing from larger and bulkier conventional nebulizer systems to smaller and miniaturized, handheld devices could represent a clear advantage from a patient point of view. Mainly, the advantages come from the portability and the time to administer the drug to the patient, the latter often being seconds instead of minutes. Less or no cleaning is needed for a miniaturized device while the time to set up a conventional system for use can be considerably longer.

On the down side is the need for administering a dose to the patient in a relatively small volume. The drug needs to be potent enough to be able to be dissolved or formulated in 10 to 50 µl without changing the viscosity or surface tension in a way that affects delivery characteristics such as aerosolization time or droplet size distribution in a negative manner. A further significant potential drawback of miniaturized devices is their technical complexity and the resultant impact on cost, robustness and regulatory aspects.

A number of potential formulation approaches have been proposed in line with the requirements of these miniaturized nebulizer systems.

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Stefan Ulvenlund, PhD is co-owner of CR Competence AB, Chemical Centre, PO Box 124, 221 00, Lund, Sweden, Tel: +46 707 52 14 34, stefan@crcom.se. Website: www.crcom.se. Ola Nerbrink, PhD is owner of Respiron Consulting AB, Medicon Village, Building 403, 223 81, Lund, Sweden, Tel: +46 76 16 02 70, info@respironconsulting.com. Website: www.respironconsulting.com. Both authors are affiliated with the Medicon Valley Inhalation Consortium, MVIC AB, Building 301, Medicon Village, 223 81 Lund, Sweden. Website: www.mvic.se.