# Matching delivery device to a patient's condition: Use of lung deposition modelling to optimise delivery in idiopathic pulmonary fibrosis

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## Summary

As companies consider the development of new products directed towards specific patient groups e.g. paediatrics, or towards niche diseases or specific disease severities, the question of which is the most appropriate inhalation drug delivery system, is arising more frequently. Where a range of delivery platforms (dry powder inhaler (DPI), pressurised metered dose inhaler, (pMDI) or nebuliser) is available for selection, it is possible to use representative performance data to conduct a series of deposition modelling experiments using lung computed tomography (CT) scans from real patients to allow for deposition comparisons that could provide a more scientific rationale for device selection.

In this study, representative aerosols delivered by several inhaler systems were administered *in silico* to five pairs of lungs, scanned from patients with a range of idiopathic pulmonary fibrosis (IPF) disease severity. The results of these modelling experiments demonstrated that significantly improved lung (particularly small airways), deposition is achievable with certain smart nebuliser systems as a consequence of their long-slow-deep, breath-activated inhalation, when compared with standard jet nebulisation. The DPI device and formulation studied herein provided a more even deposition throughout all lung regions across a range of different inhalation flow rates.

Whilst computational experiments are based upon a series of assumptions, they can provide guidance in selecting an appropriate inhalation drug delivery platform for a given disease, severity of disease or patient group.

## Background

A broad range inhalation drug delivery systems have been developed over the years and are now in routine use, primarily for the treatment of respiratory disease [1]. The primary classes are DPIs, pMDIs and nebulisers. Within each of these classes there is a bewildering range of designs and performances reflecting the incorporation of different features and technologies. Furthermore, there is a plethora of designs resulting from the fact that companies active in the field have their own ideas of what constitutes an “easy to use” device or an attractive design. When selecting a device for a new indication, the choice is often limited because the originator company typically only has a single delivery platform and formulation technology at its disposal and so there is, no choice to be made, irrespective of whether this is actually the best delivery device for the targeted disease.

As interest in the treatment of a broader range of respiratory diseases increases, it has become evident that the “one size fits all” approach is no longer suitable either for different disease severities and/or different patient groups (paediatrics, the elderly, etc.). There is therefore a need to give more careful consideration to the most appropriate delivery platform to satisfy the needs of a particular target patient population.

## Methodology

In this study, the authors conducted a computational fluid dynamics (CFD) deposition modelling evaluation using representative data derived from a range of delivery device technologies in an effort to determine what might be the most appropriate delivery platform to use in the treatment of patients with IPF. CFD has been used in a variety of settings typically to optimise the design of inhaler geometries [2] but also to estimate lung deposition [3].

IPF is a chronic, fibrosing interstitial pneumonia of unknown cause that occurs primarily in older adults. The disease is characterised by variable degrees of inflammation and scarring and is associated with a histological or radiological pattern of usual interstitial pneumonia (UIP). IPF is the most common form of idiopathic interstitial pneumonia, having the worst prognosis with only three to five years median survival [4].

In order to conduct the evaluation, the authors first created an equivalent data set using real performance data gathered across a range of formulation types used in conjunction with the devices to be studied. The data were then normalised so that all devices were filled with, and had the potential to deliver, the same dose. The delivery devices used in the evaluation were the lever operated multi-dose inhaler (LOMI™) DPI, the AKITA® JET breath-activated jet nebuliser system, the FOX® breath-activated hand held mesh nebuliser system plus a standard continuously producing jet nebuliser. The LOMI™ DPI was additionally evaluated using two different inhalation flow profiles. A pMDI was not included in the evaluation because of the higher dose under consideration. The representative data used in the evaluation are summarised in Table 1 below.

**Table 1: Summary of inhaler performance data used in the comparative deposition modelling study**

| Device | DD [%] | FPF [%] | MMAD [µm] | GSD | Start Time | End Time |
|---|---|---|---|---|---|---|
| LOMI™ slow | 84.0 | 45.9 | 2.9 | 1.9 | t=0 | t=0.35s |
| LOMI™ fast | 89.0 | 61.0 | 2.3 | 1.9 | t=0 | t=0.35s |
| FOX® | 89.0 | 68.0 | 4.0 | 1.7 | t=0 | min(4, max(tinsp/2, tinsp-1)) |
| AKITA® JET | 50.0 | 52.0 | 4.7 | 1.9 | t=0 | min(5, max(tinsp/2, tinsp-1)) |
| Standard Jet Nebuliser | 48.0 | 55.0 | 5.0 | 1.9 | t=0 | t=tend |

Deposition modelling was conducted in collaboration with FLUIDDA™. The representative performance data (Table1) were applied to 5 pairs of lung CT images taken from IPF patients with differing disease severity. Two different upper airways models were also used in the evaluation (high volume and low volume). The different inhalation manoeuvres used to apply the representative aerosols to the CT derived lung models are summarised in Figure 1.

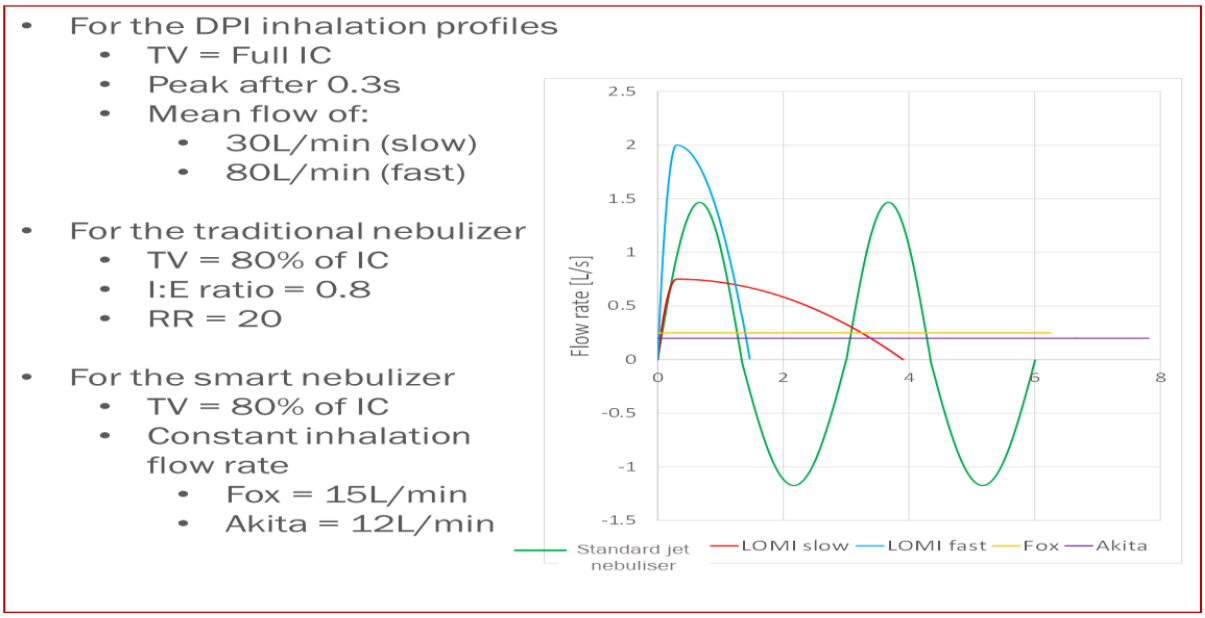


**Figure 1: Inhalation manoeuvres applied, reflecting how the patients would use the devices as a consequence of their features and/or patient instructions**

**Results and Discussion**

Representative aerosols from each of the delivery systems were applied to the IPF lung models using the specified inhalation manoeuvres so that lung deposition could be evaluated. Predictably, more than 50% of the aerosol delivered by the standard jet nebuliser was not inhaled because it continued to be delivered even when the patient was exhaling. Similarly, it was not surprising that the LOMI™ device with the higher inhalation flow rate gave the highest overall extrathoracic deposition as a consequence of the high speed with which the aerosol emerged from the device, resulting in higher mouth/throat deposition.

More surprising were the modelled whole lung deposition data (Figure 2). These showed high lung deposition for AKITA® JET, primarily as a consequence of the breath-actuated long-slow-deep inhalation imposed by the FAVORITE™ (Flow And VOlume Regulated Inhalation TEchnology), system which is employed by this device. The lung deposition achieved via FOX® (also employing FAVORITE™), was next highest but not as high as for the AKITA® JET even though FOX® gives a higher measured % Fine Particle Fraction (%FPF). This is probably as a consequence of the slightly higher nominal flow for the FOX® when compared with AKITA® JET (15 l/min FOX® versus 12 l/min AKITA®).

The lung deposition data from the LOMI™ DPI achieved with the two different inhalation manoeuvres were also noteworthy. Surprisingly, the modelled lung depositions achieved were broadly similar even though there was an observable flow rate dependency in the standard testing data with a higher %FPF for the LOMI™ evaluated at 80 l/min using the Next Generation Impactor (NGI) when compared with the data obtained from NGI testing at 30 l/min (see Table 1). It was postulated that even though there was a higher %FPF at 80 l/min compared with the data obtained at 30 l/min, that this was offset by higher throat deposition at the higher flow that does not occur to the same extent at the lower. As a result, there was broadly equivalent modelled lung deposition at the different flow rates.

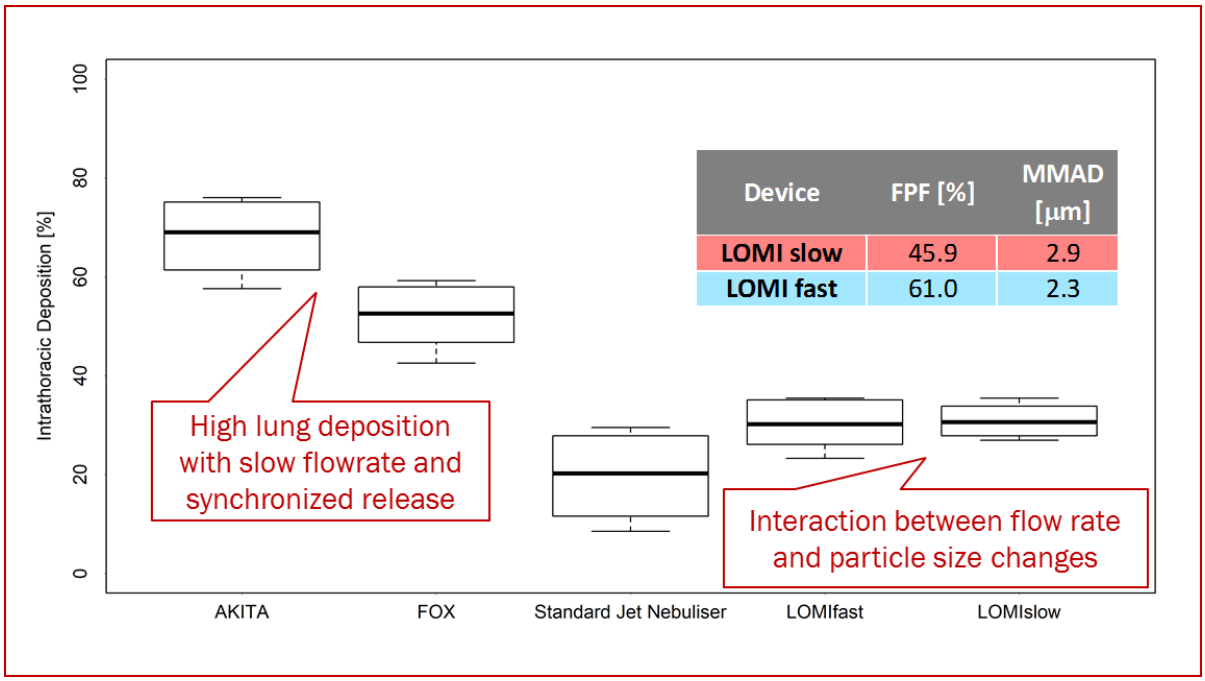


**Figure 2: Intrathoracic deposition data for each delivery platform (% of delivered dose)**

The modelled data also indicated that a fairly consistent proportion of the delivered aerosol was deposited in the central airways (15-25%) across all the device platforms. However, the smart nebuliser technologies were significantly more effective at targeting the peripheral airways than the standard nebuliser or the DPI (Figure 3).

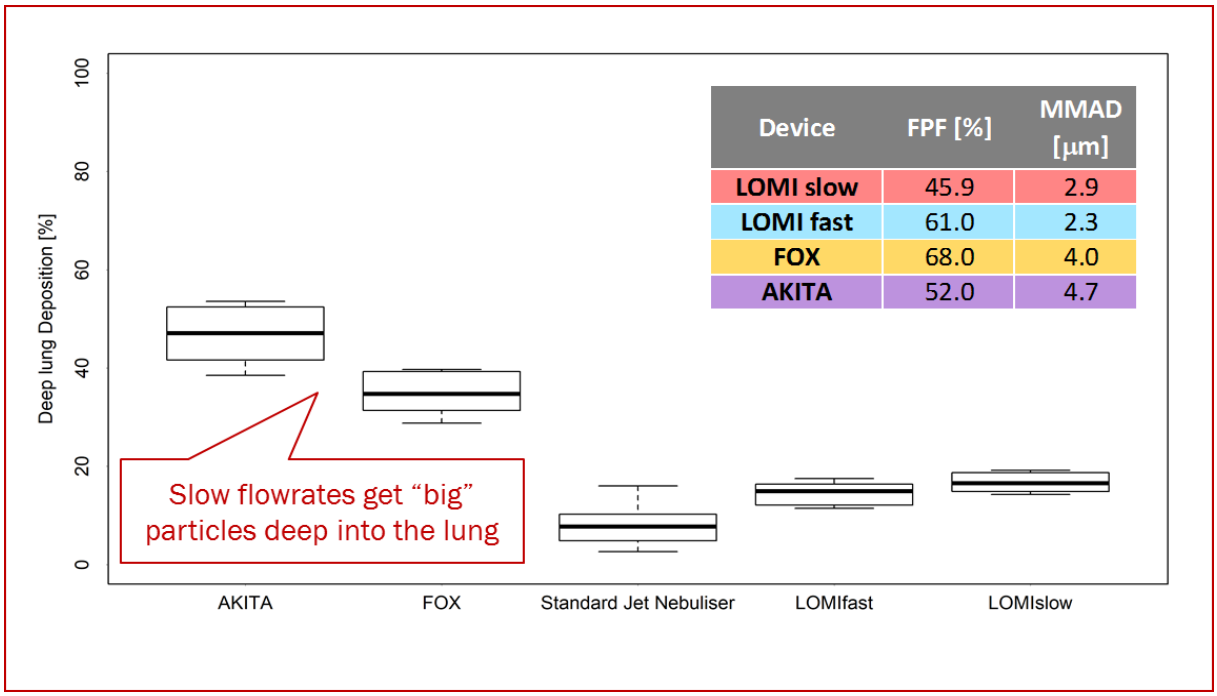


**Figure 3: Deep lung deposition (% of delivered dose)**

Furthermore, the Central to Peripheral (C:P) ratios for all of the delivery platforms demonstrated that the smart nebulisers with their characteristic long-slow-deep inhalation were particularly effective at targeting the deep lung, whereas the standard jet nebuliser strongly favoured the central airways. The DPI provided a relatively even distribution between the central and peripheral regions regardless of the inhaled flow rate.

Comparison of data obtained using the narrower versus normal upper airways geometries, indicated there was typically a 10-15% reduction in lung deposition for the nebuliser devices, whereas the DPI appeared to exhibit only a 5-10% reduction in overall lung deposition. Similarly, both the AKITA® JET and the FOX® demonstrated a reduction in deep lung deposition in switching to the narrower upper airways geometry.

**Conclusions**

A computational lung deposition modelling study was undertaken, within which representative aerosols delivered *via* a range of inhalation drug delivery systems were delivered *in silico* to the lungs of IPF patients with varying disease severity. Inhalation manoeuvres specific to the individual devices being studied were employed. The modelled data clearly indicate the potential benefits of controlling inhalation flow and volume alongside the aerodynamic particle size distribution. The data showed that higher lung deposition was possible at lower flow rates for aerosols producing larger droplets/particles.

The importance of the relationship between particle size and inhalation flow rate has long been known [5-7] but was particularly well demonstrated in this data set. Of particular note was the potential for the smart nebuliser systems (AKITA® JET and FOX®) to be very effective at targeting the peripheral airways whereas the LOMI™ DPI was effective at more general delivery across the lungs. For LOMI™, it was interesting to note that the modelled data showed less of a difference in lung deposition at the two different inhaled flow rates than might have been expected based purely on the %FPF data.

As the developers of new medicines strive to improve the efficacy of their products and as interest in speciality diseases increases, it becomes imperative to try to select the delivery device and formulation combination that will give the best outcome for the selected patient group and/or disease. Reliance purely on traditional cascade impactor testing data in an effort to differentiate, may not give an accurate picture of the best option. The kind of deposition modelling data presented herein may be able to provide a better means to differentiate between systems because it makes of use of lung models from patients and uses more realistic inhalation manoeuvres to apply the aerosol to the lungs. The lung deposition performance achievable for a particular delivery platform applied in a particular disease setting (IPF in this case), may not be the only consideration in the selection process but improved knowledge of how the device and formulation may influence the site of deposition, set against awareness of the disease and the mode of action of the intended therapeutic is potentially hugely advantageous compared with opting for the only platform available and hoping that it is going to be sufficiently effective in the clinic and beyond.

**References**

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