

Optimising Dry Powder Inhaler Design for Children – A Multi-Disciplinary Investigation

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Summary

Dry powder inhalers (DPIs) currently on the market have been designed primarily for a target population of adult patients.

In this paper, we describe some preliminary work that illustrates how a combination of user research and flow analysis (CFD) can be utilised to inform the development of inhalers suitable for paediatric use. In research, with children, we observed significant variations in inhalation profile and also in the ability to interpret instructions. The CFD work shows variations in deposition due to variations in physiology and inhalation profile.

We conclude that the availability of new inhalation technologies that can reduce constraints on patients, together with appropriate human factors research and design analysis (such as CFD), the industry can develop more optimised paediatric inhalers for the paediatric market.

Introduction

Dry powder inhalers (DPIs) currently on the market have been designed primarily for a target population of adult patients despite the prevalence of asthma in children.

Studies have been carried out on the use of DPIs by children – in particular to assess their usability and how this affects delivery and device performance, although much of the work relates to studies conducted with devices already marketed rather than to support actual device development. Furthermore, owing to ethical concerns regarding the inhalation of radio-labelled particles by children, very few studies have been conducted which explore drug deposition patterns in children's lungs, even though it is widely accepted that particle deposition in the upper airways is affected by the device design and inhalation profile.

The design of current DPI devices may thus have not have taken fully into account:

- differences in inhalation profile and inspiratory flow rates between adults and children – and between children of different ages
- differences in lung morphology as a function of age
- the specific needs of children of different ages and their abilities to learn and maintain over time the necessary inhalation technique

In this paper, we describe some preliminary work that illustrates how a combination of user research and flow analysis (CFD) can be utilised to inform the development of inhalers suitable for paediatric use.

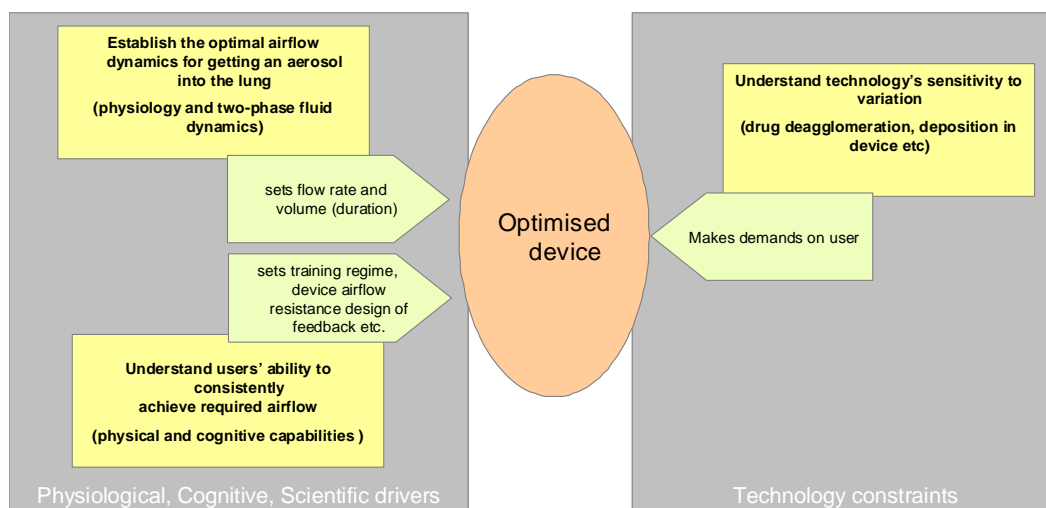


Figure 1: Factors Affecting Development of an Optimised Inhalation Device

Background

Figure 1 shows how human factors and device technology affect the development of an optimised device. In developing an “optimised” inhaler the following drivers and constraints need to be considered.

1. **Establish the optimal airflow dynamics for getting an aerosol into the lung.** For adults, *deposition* of drug in the throat due to impaction increases with flow rate and for flows >60l/min can be in excess of 60% [1]. Furthermore, variations in lung physiology between subjects may be a significant cause of variability in lung deposition [2]. For children, the relatively larger size of the tongue and the smaller size of the oral-pharyngeal airway are likely to increase deposition for a given volume flow rate as has been observed in clinical studies [3]. This work by Anhoj et al showed similar plasma concentrations between adults and children for the same inhaled dose, as a result of “auto-scaling” of dose due to differences in physiology and inhalation technique. However, ideal dosage needs to take into account both safety and efficacy [4] and thus should consider where all the inhaled drug is deposited in the patient. An “ideal” inhalation profile for a child may not be the same as that for an adult.
2. **Understand users’ ability to consistently achieve the required airflow.** As the inhalation profile is important in ensuring effective and repeatable drug delivery to the lung, it is important to understand inter- and intra-subject variations that are seen during usage and also how these can be maintained through appropriate training and user feedback. A number of paediatric studies have been reported which have investigated the ability of children to achieve appropriate inhalation profiles [5] and their ability to retain these over time [6]. The majority of published studies have been for devices that are already on the market, at which point there is no opportunity to optimise the design for inhalation profiles that are more easily trained and retained.
3. **Establish the variability of the drug deagglomeration technology.** Most currently marketed devices are not “ideal” from a patient perspective and consistent delivery can be challenging to achieve because of the demands placed on patients. In particular, devices generally utilise aerosolisation engines that require the patient’s inspiratory flow to deagglomerate the drug which means their ability to generate fine particles tends to be flow dependant [7] and many devices require relatively high flow rates to ensure effective aerosol production which can be hard for children to achieve [8]. However, with the advent of active devices [8] and advanced formulations [9] that allow for effective drug deagglomeration at low flow rates, there is greater potential to target a flow rate that optimises the flow of drug from a device to the appropriate region of the lung (see 1 above).

The majority of *in vitro* inhaler testing reported in the literature use systems such as Anderson Cascade Impactors and Next Generation Impactors in order to investigate the use and *in vivo* performance of “real devices”. Hence, such studies show variations in fine particle fraction that arise from a combination of the above drivers and constraints. In developing new devices, experiments also need to be conducted to investigate the influence each of these factors individually has on overall performance.

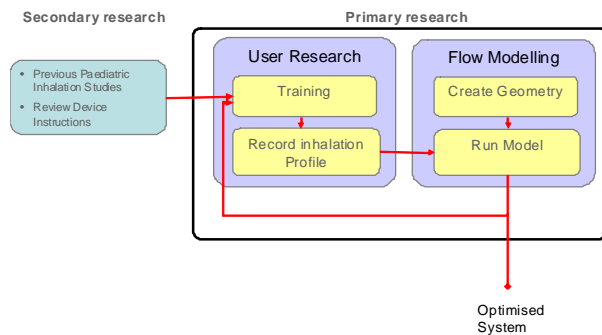


Figure 2: User Research: Methodology

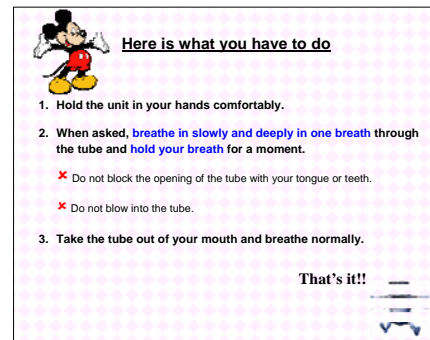


Figure 3: User Instructions

Overview of the Current Study

The intention of this study was to explore the range of inhalation profiles that children (age range 5-10) would achieve following simple instruction and then, using CFD analysis, to see if these variations would lead to significant changes in throat deposition. The study approach is shown in Figure 2. The CFD analysis is described in detail elsewhere [10]

User Research: Methodology

The aim of this pilot study was to explore the range of flow profiles that children would produce following simple instruction. It was not the intention of the study to draw quantitative conclusions from the research: rather the work was intended to demonstrate the feasibility of incorporating small scale user studies into the early stages of a device development programme in order to gain insights that can inform the development process. Although the study used healthy volunteers as this allowed easier recruitment and reduced ethical concerns, once piloted, the work could easily be extended to include patients.

For this study we used two flow resistances (2.8mm and 5mm diameter apertures each of which was inserted in line with the spirometer) in order to give a flow resistance range that would encourage low flow rates so as to reduce throat impaction.

Thirteen healthy child subjects aged between five and ten were recruited for this study. The moderator provided them with the instructions (see Figure 3) and they were asked to inhale through a mouthpiece (single use disposable cardboard tube) attached to a spirometer with a given flow resistance. Their inhalation profile was recorded on a computer attached to the rig. Each child was asked to record their inhalation three times for each of the two resistances. The collected data was then processed in Excel.

Results and Discussion

Some of the inhalation profiles obtained in the study for the 2 flow restrictors used are shown in Figure 4. As can be seen from the data, significant variations in profile were observed. From this data “typical” profiles were selected for use in the CFD modelling as described elsewhere [10]

All the children aged 8 and above could read the instructions and perform the inhalation exercise, whereas those under 8 could not. Of the 5 younger children, 4 were able to perform the exercise after training was given by the researcher. These findings do not appear to be inconsistent with other reported studies such as those by Iqbal et al [5] and Kamps et al [6]. However given differences in approach, choice of subject and size of study, detailed comparison is not appropriate.

There is some evidence of a trend with increased age towards lower and longer profiles (see Figure 3b). However, it is difficult to determine how the older children interpreted the instructions. Their profiles may depend both on this interpretation and physiological properties such as lung size.

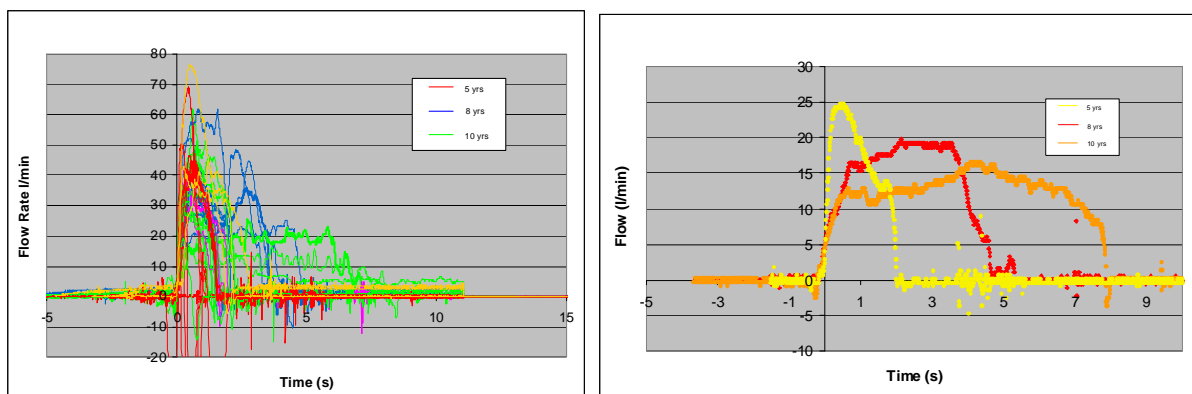


Figure 4: Inhalation profiles by age of subject:
a) Ø5mm all data

b) Ø2.8mm profiles selected for modelling

Conclusions

In this paper we have argued that with developments in device technology, it is now possible to optimise the delivery of inhaled drugs based upon the given constraints of patient physiology and cognition rather than on attempting to address the deficiencies of device technology. Device developers need to work closely with physicians in order to gain insights as to how best to design inhalers that can work in the real world rather than relying on physicians to address shortcomings after devices have been launched.

References

- [1] Ta-Chun Lin, Breyse, P.N., Laube, B.L., and Swift, D.L., 2001, Mouthpiece Diameter Affects Deposition Efficiency in Cast Models of the Human Oral Airways, *J of Aero. Med.* 14(3) pp335-41
- [2] Borgström L., Olsson B, Thorsson L., 2006, Degree of Throat Deposition Can Explain the Variability in Lung Deposition of Inhaled Drugs, *Journal Of Aerosol Medicine*, Volume 19, Number 4,
- [3] Anhøj J, Thorsson L, And Bisgaard H, 2000, Lung Deposition of Inhaled Drugs Increases with Age, *Am J Respir Crit Care Med* Vol 162. pp 1819–1822
- [4] Amirav I. and Newhouse M., Lung Deposition Of Inhaled Drugs Increases With Age?, *Am. J. Respir. Crit. Care Med.*, Volume 163, Number 5, April 2001, 1279-1279
- [5] Iqbal S.M., Ritson S., Buck H., Ellis S., Everard M., 2003, Majority of Children Aged 3 Years and Above Can Reliably Inhale Through the Clickhaler, *Pediatric Pulmonology* 36:63–68
- [6] Kamps A W.A., van Ewijk B, Roorda R.J. and Brand P L.P., 2000, Poor inhalation technique, even after inhalation instructions, in children with asthma, *Pediatric Pulmonology*, vol 29 no 1, pp39-42
- [7] Palander A.; Mattila T.; Karhu M.; Muttonen E. 2000, In vitro Comparison of Three Salbutamol-Containing Multidose Dry Powder Inhalers: Buventol Easyhaler, Inspieryl Turbuhaler® and Ventoline Diskus, *Clin Drug Inv*, vol 20, 1, pp. 25-33
- [8] Harper N.J., Gray, S., De Groot, J., Parker, J.M., Sadzadeh, N., Schuler, C., Schumacher, J.D., Seshadri, S., Smith, A.E., Steeno, G.S., Stevenson, C.L., Taniere, R., Wang, M., Bennett, D.B., 2007, The Design and Performance Of The Exubera® Pulmonary Insulin Delivery System, *Diabetes Technology & Therapeutics*, Volume 9, Supplement 1,
- [9] DeLong M, Wright J, Dawson M, Meyer T, Sommerer K, Dunbar C: 2005, Dose delivery characteristics of the AIR pulmonary delivery system over a range of inspiratory flow rates. *J Aerosol Med*;18:452–459.
- [10] Underwood R, Dufour F, Davies G, Pocock A, Gupta S, 2008 Using Computer Modelling to Investigate the Effect of Inhaler Design, and Patient Variation in the Deposition of Particles in the Upper Airway of Paediatric Patients, submitted to DDL19