

Developing Analytical Methodology and Test Apparatus to Study Drug Deposition in the Throat

Matthew Potts¹, Ben Myatt¹, Sam Apoola² & Peter Healey¹

¹Kindeva Drug Delivery Limited, Charnwood Campus, 10 Bakewell Road, Loughborough, LE11 5RB, United Kingdom

²School of Mechanical Engineering, Leeds University, Woodhouse Lane, Leeds, LS2 9JT, United Kingdom

Summary

Drug deposition in the mouth/throat is a common problem with many respirable medicines. To aid the development of products which reduce this deposition, suitable analytical methodology must be developed. Knowing more about where the drug is impacted within the mouth/throat can allow for greater insight into the causes of the deposition and what changes to the product may have the greatest impact on reducing this deposition. A split anatomical throat was designed, manufactured and then incorporated into analytical methodology developed to determine regional throat deposition and the fine particle mass/fraction (FPM/FPF). The methodology was developed utilising a Fast Screening Impactor (FSI) to achieve rapid screening of device prototypes and novel formulations.

Key Message

We developed novel anatomical throat apparatus and analytical methodology to accurately determine regional oropharyngeal drug deposition of inhaled respiratory medicines, enabling rapid screening of device prototypes and novel formulations. The drug deposition data is comparable to that generated using a standard OPC anatomical throat and Next Generation Impactor testing setup.

Introduction

Drug deposition in the throat is a common problem with many respirable medicines. One of the most significant disadvantages of the pMDI is inherently high oropharyngeal (mouth/throat) deposition, greater than 70% in some marketed products^[6]. A significant mass of active pharmaceutical ingredient is deposited in the oropharyngeal cavity *in-vivo* which does not lead to patient therapeutic effect. Understanding where the drug deposits within the mouth and throat can lead to insights into the causes of this deposition and therefore inform any developed solutions to address this. This leads to more efficient medicines and devices, in turn driving improved patient outcomes and reducing costs for manufacturers, customers and patients.

Analytical measurements using compendial techniques to determine pharma performance of an inhalation product utilise the USP-IP (United States Pharmacopeial Induction Port) as an interface between the test product and the cascade impactor apparatus. Recently, anatomically relevant throat models have become more commonly used during *in-vitro* cascade impaction measurements^[1] because they more accurately represent the *in-vivo* geometry of the human throat, that the drug droplets/particles produced by a device must navigate through prior to entry to cascade impaction particle sizing equipment. Correlation of *in-vitro* lab data to *in-vivo* lung deposition data generated in a clinical setting has been shown to be much higher when using anatomically relevant throat models compared to the USP-IP^{[2][3]}.

The objective of this work was to develop test apparatus and analytical methodology which could be used to assess the regional drug deposition within the mouth and throat, and if possible, couple this with existing *in-vitro* cascade impaction measurements.

1. Developing the Testing Apparatus

To accurately understand where inhaled drug is deposited in the mouth/throat, the internal geometry of the equipment used is critical. Based on the work of the Oropharyngeal Consortium (OPC) ^[4] an anatomical throat, manufactured by Emmace Consulting, (Lund, Sweden), is commercially available to the inhalation community to use when performing *in-vitro* cascade impaction measurements. The medium OPC throat design was taken as the base geometry for design of a mouth/throat geometry which could be split into sections for regional assay. The geometry was split into four regions of interest: the tongue, oral cavity, oropharynx and laryngopharynx, indicated in Figure 1.

The outline of the tongue was approximated using a curved geometry along the region where the tongue and wall of mouth meet, as a vertical cutting plane. The oral cavity was taken as the remainder of the geometry above the tongue from the front of the cavity to a vertical plane intersecting the tip of the uvula. The oropharynx was taken as the region behind the uvula and above a horizontal plane intersecting the tip of the epiglottis with the laryngopharynx the remaining region below.

Figure 1 – Sectioning the Regions of the Mouth/Throat

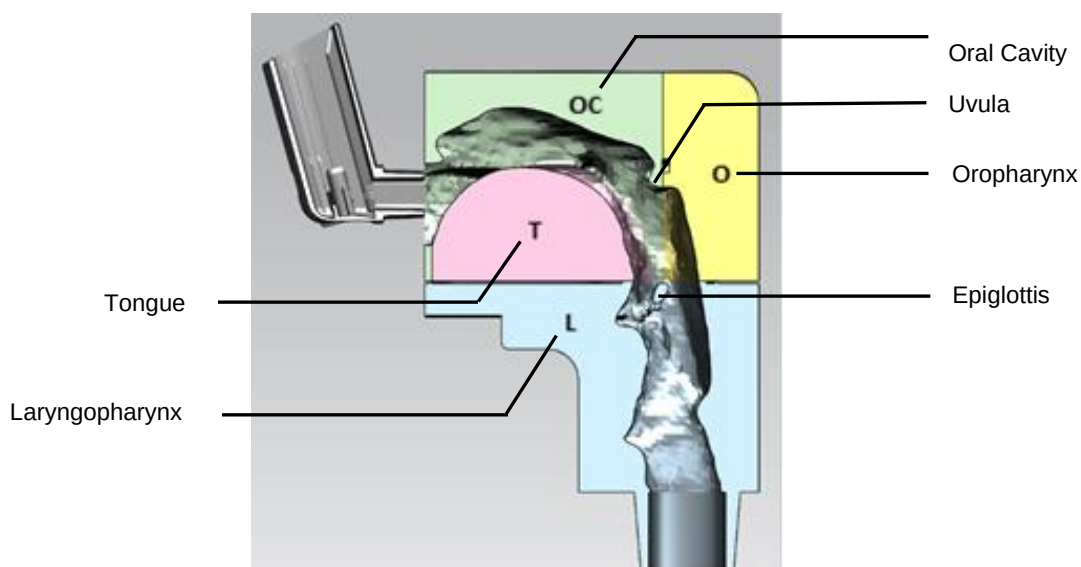


Figure 1: Cross-sectional view of KDD split anatomical throat showing location of pMDI during testing. OC = oral cavity, T = tongue, L=laryngopharynx, O = oropharynx

The four components of the Kindeva Drug Delivery (KDD) split anatomical throat were additively manufactured by Emmace Consulting, (Lund, Sweden) using the same material and manufacturing processed as the standard, commercially available OPC anatomical throats. Gas tight sealing of the individual sections was achieved using a gasket (orange component in Figure 2), a seal fitted in the groove in the yellow oropharynx component, and a nitrile sleeve placed over the assembled throat.



Figure 2 - KDD split anatomical throat exploded view

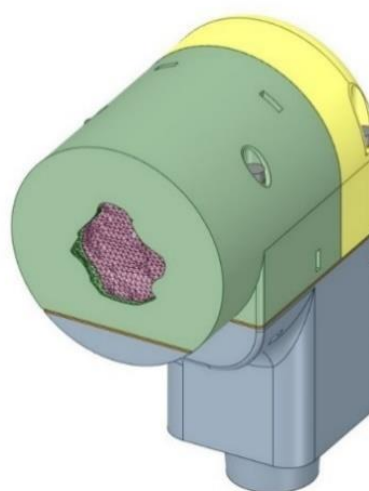


Figure 3 - KDD split anatomical throat assembled view

2. Analytical Methodology

Testing Apparatus

The KDD split anatomical throat was coupled to a Fast Screening Impactor (FSI) operating at 30L/min and containing a 30L/min 5-micron pre-separator insert (Copley Scientific Limited, Nottingham, UK) to determine regional mouth/throat deposition and the fine particle fraction/mass of the delivered drug. The KDD split anatomical throat can also be coupled to a full NGI apparatus if a more extensive analysis of the respirable fraction is required. Sample analysis was performed using a UV Spectrophotometer or, when required for reasons of specificity, HPLC analysis. For each sample analysis methodology (UV & LC) specificity was assessed with respect to the gasket and rubber seal materials.

Comparison to OPC Throat coupled with NGI Apparatus

A pMDI containing 5mcg/act Tiotropium was tested (n=5) using the KDD split anatomical throat coupled to the FSI. The same product was also tested using a medium anatomical OPC throat coupled to a NGI. The flow rate through both devices was set to 30L/min and the pMDI plumes fired horizontally.

Each component part of the KDD split anatomical throat was assayed, using a suitable diluent to recover the deposited drug. The determination of Tiotropium drug deposition was performed using a chromatographic system (HP1100 series, Agilent Technologies) equipped with a binary pump, autosampler and a variable wavelength detector.

3. Results and Discussion

Comparison of KDD split anatomical throat coupled to FSI with medium OPC throat coupled with NGI

The deposition of drug in the medium OPC throat and in each section/region of the KDD split anatomical throat can be seen in Figure 4. Although there is an observed small reduction in total drug recovered from KDD split anatomical throat, it is still comparable to that recovered from the medium OPC throat and provides valuable insight into the deposition sites within the throat. The increased variability, observed between test replicates, in the total throat drug deposition for the KDD split anatomical throat, when compared to the standard medium OPC throat, (5.3% vs 1.2%) is not unexpected due to the increased sample recovery complexity and potential for cumulative error.

Figure 4 – Comparison of Device and Throat Drug Deposition

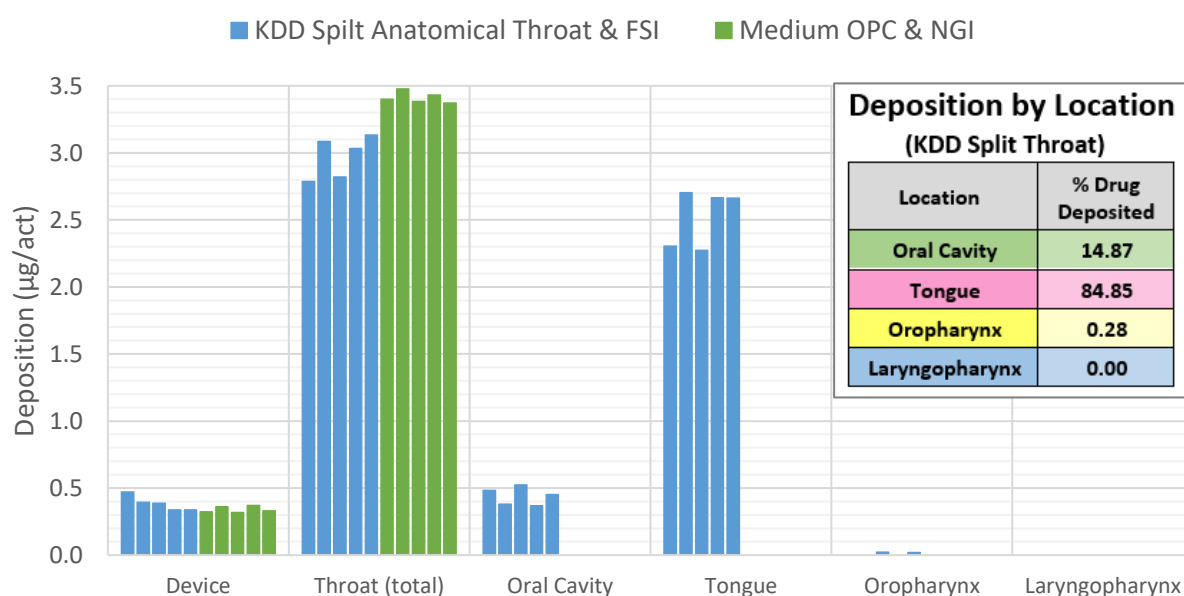


Figure 4: Comparison of drug deposition on the device and throat between the KDD split anatomical throat (coupled with FSI) and the medium OPC throat (coupled with NGI).

Identifying that 85% of the total drug deposition in the throat was located on the Tongue, and that virtually all the drug was deposited in the upper throat, informed further product development activities. The high drug deposition in the mouth/throat agrees with previously published work concerning oropharyngeal drug deposition of aerosolised particles^{[5][6]}. However, this technique is undoubtedly faster and less costly, and with the advantage of higher throughput, when compared to gamma scintigraphy for quantifying mouth/throat deposition.

The percentage mass balance (%MB), Fine Particle Mass (FPM) and Fine Particle Fraction (FPF) values for the two systems are shown in Figure 4. These values are broadly similar, with the slightly lower mass balance observed for the KDD split anatomical throat system within acceptable pharmacopeial limits. Therefore, the KDD split anatomical throat is acceptable for use as an indicative fast screening tool. It is possible that further improvements such as rinse methodology, surface coatings and component sealing of the KDD split anatomical throat system could reduce the test variability in line with the medium OPC throat system.

Figure 5 – Comparison of Mass Balance, FPM and FPF

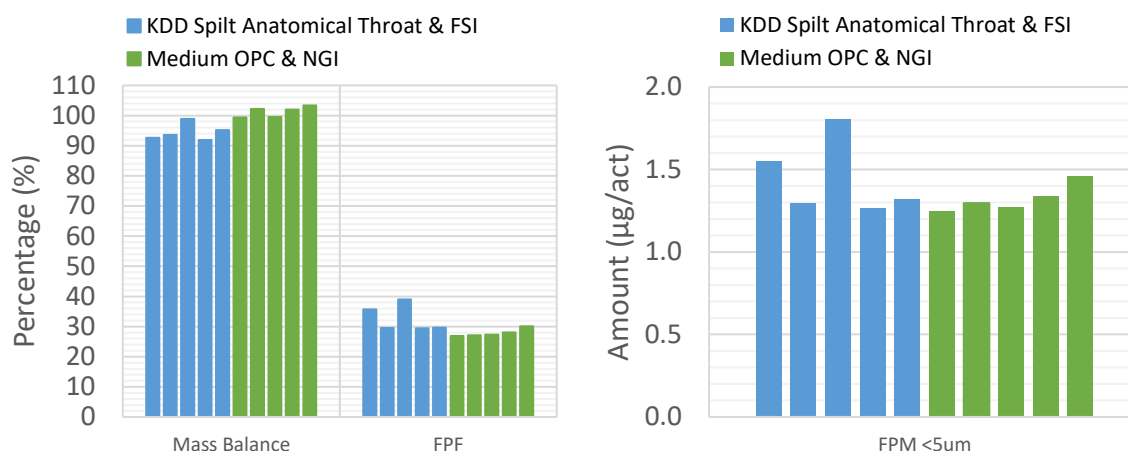


Figure 4: Comparison of mass balance and FPF between the KDD split anatomical throat (coupled with FSI) and the medium OPC throat (coupled with NGI).

Rapid Screening

The use of a FSI coupled with the KDD split anatomical throat, proved an efficient way of generating information on FPF and the location of drug deposited on the throat. The number of samples to recover and analyse was reduced from twelve (full NGI) to eight (FSI), with subsequent testing reduced to only five samples (valve and actuator recovery eliminated and pre-separator recovery, where insignificant, was eliminated). This saved time during the HPLC analysis and data analysis (reduced sample numbers), and even accounting for the assembly/disassembly of the KDD split throat, saved time during the drug recovery steps. Solvent usage in the laboratory was reduced, and in some cases, testing times could be reduced still further by using UV analysis instead of HPLC.

4. Conclusions

Regional breakdown of throat deposition offers additional real data and insight into drug deposition location post pMDI mouthpiece, enabling informed product design modification decisions. Coupling the KDD split anatomical throat with the FSI enables an innovative, fast and efficient methodology for assessing product design changes. The reduction in testing time from using the fast screening methodology is significant and enables a quicker turnaround from new prototype or formulation to *in-vitro* product performance data. The data produced using the KDD split anatomical throat with FSI showed good agreement with full Anatomical Throat / NGI testing, with respect to predicted Pharma performance (FPF, FPM etc), indicating it is a useful product development analytical tool, particularly in the rapid development of next generation, high efficiency inhalation products.

We found, for the product tested, that tongue deposition was most significant in the mouth/throat region and can be a hugely significant factor for some pMDI products. Developing products that minimise throat, and specifically tongue, deposition could lead to much more efficient products, reducing costs, and improving the patient experience.

References

- [1] Samantha Holmes, Alex Slowey: *A comparison of Different Anatomical Throats vs The USP Throat*. Drug Delivery to the Lungs (DDL2017), 2017.
- [2] Stephen P. Newman, Hak-Kim Chan: *In vitro-in vivo correlations (IVIVCs) of deposition for drugs given by oral inhalation*. Advanced Drug Delivery Reviews, 167 (2020), 135-147
- [3] Xiangyin Wei, Michael Hindle, Anubhav Kaviratna, Bao K. Huynh, Renishkumar R. Delvadia, Dennis Sandell and Peter R. Byron: *In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth–Throat Models and In Vitro—In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler*. Journal of Aerosol Medicine and Pulmonary Drug Delivery, Volume 31, Number 6, 2018
- [4] Patricia K.P. Burnell, Lars Asking, Lars Borgström, Steve C. Nichols, Bo Olsson, David Prime, Ian Shrubbs: *Studies of the Human Oropharyngeal Airspaces Using Magnetic Resonance Imaging IV—The Oropharyngeal Retention Effect for Four Inhalation Delivery Systems*, Journal of Aerosol Medicine Vol. 20, No. 3, 2007.
- [5] Stephen P Newman, Demetri Pavia, Folke Moren, Noirin F Sheahan, Stewart W Clarke: *Deposition of pressurised aerosols in the human respiratory tract*. Thorax, 36(1), pp. 52-55, 1981.
- [6] Y.S. Cheng, C.S. Fu, D. Yazzie, Y. Zhou: *Respiratory deposition patterns of salbutamol pMDI with CFC and HFA-134a formulations in a human airway replica*, Journal of Aerosol Medicine Vol. 14, No. 2, 2001