

Rapid Development of a Patient-Preferred Nasal pMDI Device

Richard Brewer and Ashish Dasani

3M Drug Delivery Systems, Loughborough, Leicestershire, LE11 1EP.

Introduction

Pharmaceutical devices and products have historically taken many years from initial concept to realisation into a physical product. Modern advances in technologies and processes have enabled significant reduction in development lead times. 3M™ Drug Delivery Systems are working with some of the industry's leading suppliers to bring our new product technologies to a state of "design freeze" sooner, in order to meet increasingly aggressive product introduction demands.

More traditionally, R&D groups have had to rely heavily on the facilities and technologies provided by Computer Numeric Control (CNC) machining centers, and more recently from rapid prototyping (sintered plastic powders or resins) to validate their designs. The ability to reliably produce rapidly manufactured prototyping injection mould tooling has allowed for design concepts to be trialled in moulded plastics quickly and economically.

Additionally the use of Computed Tomography has now made inspection of parts and assemblies rapid, reliable and non destructive [1]. Using sophisticated software to produce chromatic evaluations (colour-coded deviation displays) has reduced cycle times further. As a comparison; a simple device design once took in excess of two months to trial through machined manufacturing techniques. Now the same design can now be moulded and inspected in weeks for only modest cost increases.

Reductions in lead time can reduce the overall cost of inhalation programs, therefore use of these technologies has enabled 3M Drug Delivery Systems to produce complex inhalation devices such as our Integrated Dose by Dose Counter, which has recently been commercialised. Following experiences in developing the dose counter, the use of these technology advances has been further optimised during the development of a new nasal pMDI device to satisfy the patient demand for improvements in the delivery of nasal medication.

Why a Nasal pMDI?

Nasal pMDIs were used to treat allergic rhinitis until the phase out of CFC propellants, when allergy treatments were not included in the essential use exemption afforded to pulmonary inhalers. Therefore in recent years the majority of allergy sufferers have had little alternative other than to use aqueous sprays to manage their symptoms. However, patient research has shown that aqueous sprays are an unpleasant experience, with formulations often running down the back of the throat, or dripping out of the nose. This can result in a nasty aftertaste or even a burning sensation, and potentially reducing the dose the patient receives [2].

The disagreeable experiences associated with aqueous sprays can be eliminated by offering allergic rhinitis medication in a pMDI which is delivered as a taste free non-drip spray. The switch to a pMDI can also offer significant benefits for pharmaceutical companies, providing fast line extensions for inhaled corticosteroid pMDIs and life cycle management for existing allergic rhinitis products. The pMDI is also differentiated compared to existing aqueous spray pumps which could provide market advantage for pipeline mono or combination allergy molecules.

Design Evolution

The processes of evolving a new product has not changed dramatically for decades, but the time required to complete each process is where real improvements have been made. As computing capabilities improve, more manual methods are replaced. It is often the human element which slows a procedure down. The diagrammatic representation of a product development flow map (figure 1) shows the computer aided sections in the dashed boxes.

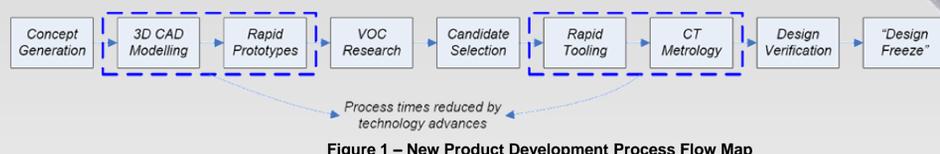


Figure 1 – New Product Development Process Flow Map

As allergic rhinitis products are often over-the-counter medications, the inclusion of patient preferences during the design phase was seen as a critical step. Therefore a number of initial concepts were designed and prototyped to test patient preferences incorporating key attributes such as a retained nose piece cover and the option to include a dose counter in a variety of designs. Rapid prototyping was used to produce samples of these concepts to test in the hands of allergy sufferers.



Figure 2 – Examples of Nasal pMDI Concepts

Following the patient research a preferred design concept was selected and the manufacture of the rapid tooling started. First moulded samples were produced and inspected in less than three weeks of data release. This is an impressive decrease from the eight to ten weeks it took with previous technology.

Physical Evaluation

One of the fastest growing technologies for component inspection is chromatic evaluation (colour-coded deviation display). This allows developers to assess components in seconds. The physical sample is subjected to an X-Ray Computed Tomography (CT) scan and then converted into a universal Computer Aided Design (CAD) file format. Computed Tomography can provide accuracies on small components of $\pm 0.01\text{mm}$. This scanned file is then overlaid with the native CAD component file. The software calculates the difference in surface location between the CAD and scanned files. The resultant image shows a colour gradient of how accurately the scanned part has been moulded. From this colour coded deviation display it is immediately obvious which features of the moulded sample have not been moulded in tolerance. Corrective work can then be completed on surfaces and areas whether they are dimensionally referenced on an engineering drawing or not. These can be presented as chromatic evaluations in an interactive self contained executable file that can allow any basic user to interact with the model and investigate every detail of their moulded product.

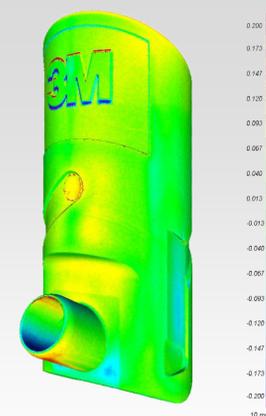


Figure 3 – Screenshot of 3M Nasal pMDI Device Chromatic Evaluation

Performance Evaluation

One of the significant advantages of prototype tooling is the ability to hold precise tolerances in critical parameters of the device. For actuators this is often exit orifice geometry, surface finish and material, all of which need to be accurate and repeatable to generate representative analytical data. Use of rapid tooling enables production of samples suitable for analytical evaluation within a relatively short period of time. These samples are representative of the final commercial manufacturing process and allow analytical evaluation to be conducted significantly earlier in the development cycle.

Data generated from Dose Content Uniformity (Ex-Actuator) testing performed using ten nasal actuators and Fluticasone Propionate suspension pMDI aerosol units are shown in Figure 4. Three doses were collected from each of the actuator/unit combinations. All ten combinations demonstrated excellent dose consistency, with all doses within $\pm 20\%$ of the mean and a low RSD value for the dataset.

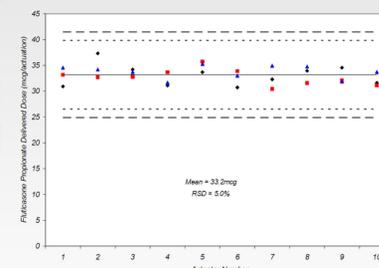


Figure 4 – Dose Content Uniformity (Ex-Actuator) Using Fluticasone Propionate HFA pMDI Aerosol Units.

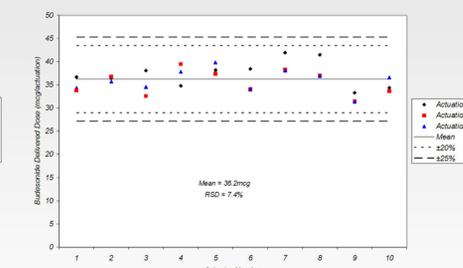


Figure 5 – Dose Content Uniformity (Ex-Actuator) Data Using Budesonide HFA pMDI Aerosol Units.

Data generated from Dose Content Uniformity (Ex-Actuator) testing performed using ten nasal actuators and Budesonide suspension pMDI aerosol units are shown in Figure 5. Again three doses were collected from each of the actuator/unit combinations. All ten combinations demonstrated excellent dose consistency, with all doses within $\pm 20\%$ of the mean and a low RSD value for the dataset.

Conclusion

During the development of the 3M Nasal pMDI actuator rapid prototyping has enabled fast generation of design concepts which were then used to assess patient preference. Use of modern rapid tooling capabilities enabled the findings from the patient research to be quickly incorporated into commercially representative samples. Suitability of these commercially representative samples was confirmed using techniques such as computed tomography. Consequently analytical evaluation could be conducted at the earliest opportunity to confirm the pharmaceutical performance.

Acknowledgements

Stewart Griffiths - 3M Drug Delivery Systems, Loughborough, Leicestershire LE11 1EP
Neale Griffiths - 3M Drug Delivery Systems, Loughborough, Leicestershire LE11 1EP

References

1. Stuart A. "The Role of X-Ray Computed Tomography as an Investigation Tool in Hardware Design" In Dalby R.N, Byron P.R. Eds: Proc. Respiratory Drug Delivery 2009, Davis Healthcare International Publishing, River Grove IL, Pp 213-216.
2. 3M proprietary patient research, December 2009

