pMDI Uniformity of Delivered Dose Method Development using an Automated Dose Collection Apparatus

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Introduction

The methodology for uniformity of delivered dose (UoDD) or dose content uniformity (DCU) is a Critical Quality Attribute (CQA) of Orally Inhaled and Nasal Drug Products (OINDP).

The UoDD and DCU methodology is sensitive to user-operation variability associated with the shaking and actuation process of pressurised metered dose inhalers (pMDIs) [1]. The analytical method therefore requires control of these parameters for the priming, dose collection and waste actuations.

During the development of the analytical methodology, the priming and dose collection actuations are typically performed by an analyst, with automation being used only for the waste actuations that are performed between the stages of container life where the dose collection actuations are performed. The aim of this study is to understand if automation can be extended to the dose collection actuations, using the Vertus from Novi Systems Ltd [2], and also the priming actuations.

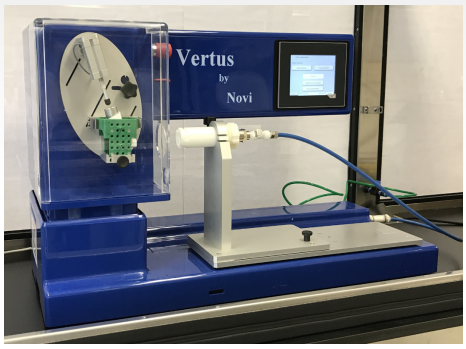

Figure 1. Vertus by Novi Systems Ltd Configured with Unit Spray Collection Apparatus

Method

Samples were prepared, from suspension pMDI's, using Unit Spray Collection Apparatus (USCA), in accordance with Ph.Eur and USP guidelines [3, 4]. All priming and test actuations were performed in ambient conditions, with a minimum of 30 seconds between actuations, by the Vertus. An MDI FD-10 instrument (InnovaSystems, New Jersey, USA) was used to automate the waste actuations between the stages of container life. All doses collected in USCA tubes were recovered with a known volume of the appropriate diluent. In accordance with ICH guidelines [5], UV Spectrophotometer methodology was validated for specificity, linearity and sample stability. HPLC-UV (High Performance Liquid Chromatography – Ultra Violet detection) methodology was fully validated. Three experiments were performed as outlined below and in Table 1.

Experiment	SoL / EoL	No. of Actuations	Formulation Type	Analysis Method
1	SoL & EoL	1	Creaming, Sedimenting	UV
2	SoL	2	Sedimenting	HPLC
3	SoL & EoL	1 or 2	Creaming, Sedimenting	HPLC or UV

Table 1. Experiments performed

Experiment 1. Shake/fire/hold parameter screening - Automated

The first experiment focused on understanding the effect of three shake/fire variables via design of experiments (DoEs) - shake vigour, post shake delay and actuation hold time. Certain parameters were not assessed for effect on DCU (e.g. actuation force). However, the force profile was appropriately optimised prior to final testing to ensure on target shot weight. The peak firing force setting was chosen to imitate an average analyst.

Experiment 2. Sensitivity analysis of shake delay - comparison of Manual and Automated

A sensitivity analysis was conducted on the post shake delay parameter for both the Vertus and manual collection.

Experiment 3. Feasibility for routine UoDD/DCU testing of 3 pMDI products - Automated

Assessments of three different suspension products, including creaming and sedimenting formulations, with 3M and competitor hardware, were performed with appropriate shake/fire parameter settings on the Vertus.

Results and Discussion

Experiment 1. From a theoretical perspective, suspension pMDI's should be tested by use of a shake with sufficient vigour (Shake - HIGH) and then actuated immediately following the shake (Shake delay - LOW). The depression of the valve should also be minimised so that re-sampling of the homogenised formulation (Hold time LOW) can occur. The data shown in Figure 2 are normalised versus these ideal parameters. The data demonstrate the expected trends, i.e decreased shake vigour, increased post shake delay and increased hold will all lead to more drug in the valve sampling region for a sedimenting formulation. These trends are reversed for a creaming formulation.

Results and Discussion Continued

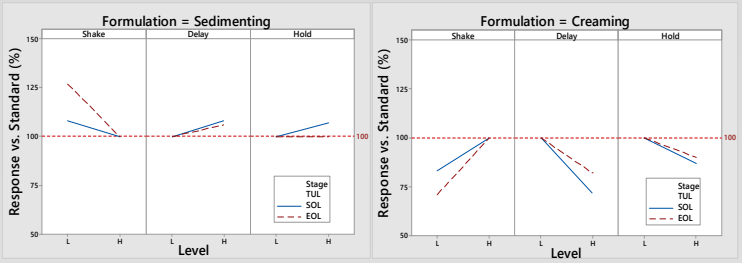

Figure 2. Effect of shake/fire parameters for sedimenting (LHS) and creaming (RHS) formulations at SOL / EOL (n = 18 doses per formulation).

Experiment 2. Data in Figure 3 show that the Vertus collection doses demonstrate the expected trend of increasing dose with increased post shake delay time (increased sedimentation). This is not clear from the manual data. This demonstrates the advantage of using automation for such experiments – they are less subject to sources of variability linked to user operation.

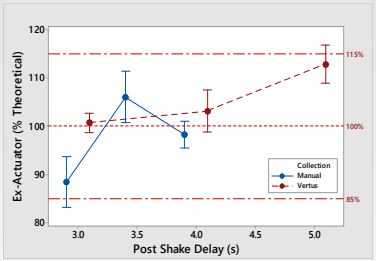

Figure 3. Sensitivity Analysis Plot; 95% CI for the Mean (n = 9 doses per shake delay)

Experiment 3. The data in Figure 4 demonstrate the feasibility of using the Vertus for testing of multiple suspension pMDI's. Average data are all within 5% of the theoretical ex-actuator dose (e.g. label claim). Relative Standard Deviation data are also all below 5%. The outcome was independent of formulation type and hardware.

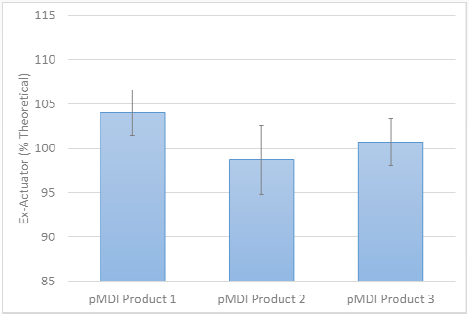

Figure 4. Plot of Feasibility for Routine Analysis (n = 4 doses, 15 doses, 9 doses; for products 1, 2 & 3 respectively)

Conclusions

The data demonstrate that an automated dose collection apparatus (Vertus from Novi Systems Ltd.) can be used to understand user-operation variability associated with the pMDI shaking and actuation process.

The DoE approach is a useful tool for early phase product development. The product understanding helps the design of a more robust product and it provides an opportunity to develop a more robust analytical testing method

It is shown that it is advantageous to use automation for such experiments; they are less subject to sources of variability linked to user operation which may be useful for optimisation studies during method development. Finally, it was demonstrated that the Vertus can be used for routine product analysis – The data for three different suspension products were very accurate and precise in terms of theoretical ex-actuator dose.

References

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