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Research Article

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Actuator Performance Comparison by an Integrated Multivariate Approach

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Abstract

During the development of a new Pressurized Metered Dose Inhalers (pMDI) one of the key aspect is to achieve the right performances of the emitted aerosol. Among all variables that can impact the performances, the configuration of the actuator largely affects the atomization process and, as a consequence, the pMDI performances.

In order to understand the effect of actuator orifice diameter and actuator sump volume on the final performance, a Face Centered Design has been applied. For each experiment fifteen responses were measured, using a Unit Spray Collector Apparatus (USCA) for the Delivered/Metered Dose and a Next Generation Impactor (NGI) for the Aerodynamic Particle Size Distribution tests.

A Principal Component Analysis showed that the NGI responses can be used to demonstrate how the two variables affect the performance of the actuators, while the USCA responses are useless for this purpose.

The effect of orifice diameter and sump volume on Fine Particle Mass, Fine Particle Fraction and Mass Median Aerodynamic Diameter, three relevant Aerodynamic Particle Size Distribution responses, were then quantitatively evaluated by Multiple Linear Regression.

Keywords: Actuator; Multivariate; Experimental design; Aerodynamic performance; Prediction; Model

Introduction

Pressurized Metered Dose Inhalers (pMDIs) are the most popular choice for inhalers and make up almost 85% of the total inhaled drug market for the treatment of asthma [1]. The medication contained in a pMDI is delivered to the patient through an actuator that atomizes the spray.

The pMDI efficiency depends on its structural configuration and is determined by evaluating the atomization process by means of performance tests, allowing measuring the amount of the medication reaching the small peripheral airways of the lungs.

Different variables can impact the aerodynamic performances of the emitted aerosol and different responses are obtained during performance characterizations. Mainly, the performance tests consist in measuring the Delivered Dose (DD), the Fine Particle Mass (FPM), the Mass Median Aerodynamic Diameter (MMAD) and the Fine Particle Fraction (FPF) provided by the product, together with the Aerodynamic Particle Size Distribution (APSD).

The OD being the diameter of the cylindrical channel that allows the spray to exit and the SV being the volume of a small expansion chamber located under the valve stem where the atomization process begins (Figure 1).

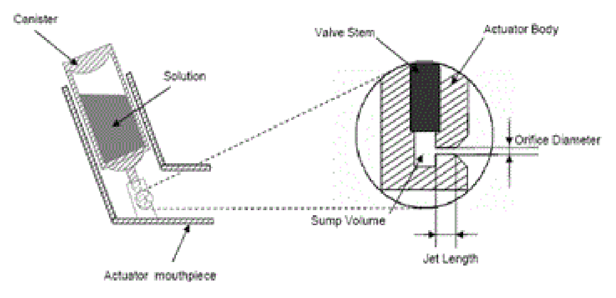

Figure 1: Internal actuator geometry.

The performances of the different actuators are usually compared by applying univariate statistical tests (F-test, t-test, ANOVA, etc.) to the different responses, each of them being treated separately. Aim of this work was to evaluate the impact of the two actuator variables orifice diameter (OD) and the sump volume (SV) on the aerodynamic performances responses applying a multivariate approach to extract the maximum amount of information with a reasonable experimental effort.

In this work both the setting of the different actuators and the elaboration of the responses were performed by using a multivariate approach (Design of Experiments followed by Principal Component Analysis).

An ethanolic pMDI formulation provided by Chiesi was evaluated.

The multivariate analysis of the responses obtained by the designed experiments also allowed to understand the correlations among the responses and the amount of information brought by each of the two sets of results (USCA and NGI). The actuator variables were set according to a Face Centered Design with one center point [2,3]. The experimental matrix and the experimental plan are reported in Table 1 and graphically visualized in Figure 2. It has to be noticed that, for practical reasons related to the construction of the actuators, the three levels are not equally spaced. Therefore, the central level has been coded accordingly (-0.20 for OD and -0.07 for SV).

Since a relatively high experimental variability was expected, for each of the nine experiments three independent replicates were carried out. The performance tests chosen were the Delivered/Metered Dose and APSD tests. They were carried out by assaying the deposition on USCA at 28.3 L min^{-1} and NGI at 60 L min^{-1} respectively, with the analytical measurements performed by validated HPLC/UV methods.

The following fifteen responses were obtained (in brackets the coding used in the plots): 1) Fine Particle Mass (FPM); 2) Fine Particle Fraction (FPF); 3) NGI Actuator deposition (NAct); 4) Induction Port deposition (IP); 5-12) NGI Cups and MOC depositions (C1, C2, …, C7, MOC) ; 13) Mass Median Aerodynamic Diameter (MMAD); 14) USCA Actuator deposition (UAct); 15) USCA Delivered Dose (DD).

Exp. number	Experimental Matrix		Experimental Plan	
	OD	SV	OD	SV
1	-1	-1	0.22	6.07
2	1	-1	0.42	6.07
3	-1	1	0.22	19.66
4	1	1	0.42	19.66
5	-1	-0.07	0.22	12.37
6	1	-0.07	0.42	12.37
7	-0.20	-1	0.30	6.07
8	-0.20	1	0.30	19.66
9	-0.20	-0.07	0.30	12.37

Table 1: Experimental Matrix and Experimental Plan

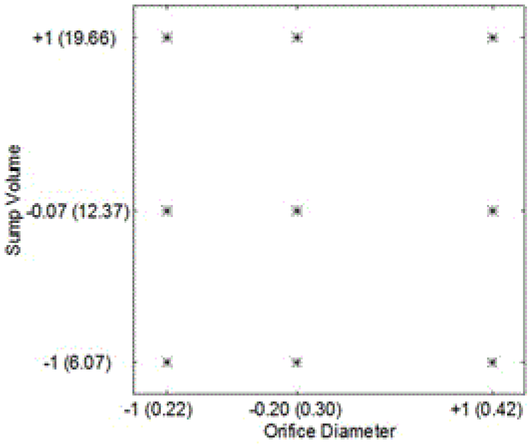

Figure 2: The experimental domain

Materials and Methods

The APSD was carried out using an NGI impactor (Copley Scientific, Colwick Nottingham, United Kingdom) at 60 L min^{-1}. The amount of the Active Pharmaceutical Ingredient (API) found at each location of the NGI impactor was determined using reverse phase HPLC with external standard quantitation. A gradient elution with purified water and acetonitrile (Scharlau Chemie, S.A, ES), both acidified by phosphoric acid (Sigma-Aldrich Chemie GmbH), was used. The chromatographic separation was achieved using an Atlantis d C18 column, 150 mm × 3.9 mm, 3 µm particle size (Waters Corporation, Milford, MA, USA), thermostated at 45°C. The UV detection was performed at a wavelength of 258 nm while the injection flow rate and injection volume were set at 1.5 mL min^{-1} and 30 µL respectively.

The Delivered/Metered Dose Test was carried out using a USCA tube (3M, MN, USA) at 28.3 L min^{-1}. The amount of the API found in the USCA analyses was determined using reverse phase HPLC with external standard quantitation.

A gradient elution with purified water and acetonitrile (Scharlau Chemie, S.A, ES), both acidified by phosphoric acid (Sigma-Aldrich Chemie GmbH), was used.

The chromatographic separation was achieved by the Atlantis d C18 column, 50 mm × 4.6 mm, 5 µm particle size (Waters Corporation, Milford, MA, USA), at 45°C.

The UV detection was performed at 258 nm while the injection flow rate and injection volume were set at 1.5 mL min^{-1} and 30 µL respectively.

The data analysis was performed by using an R-based chemometric software developed by the Italian Group of Chemometrics (Italian Chemical Society, Division of Analytical Chemistry), freely downloadable from http://gruppochemiometria.it/gruppo-lavoro-r-in-chemiometria.html

Results

A Principal Component Analysis (PCA) [4,5] has been performed on the data table made by 27 rows (the 9 experiments of the design, each run in triplicate) and 15 columns (the 15 responses). The data were autoscaled. The two significant components explained 76% of the total variance (59% and 17%, respectively).

Figure 3 shows the loading plot, from which it is possible to understand the correlations among the responses and their relative weight. A group of responses has positive loading on the first component. This group, made by the depositions on the higher NGI cups (C3-C7) and on MOC, plus FPM and FPF, is negatively correlated to IP (having negative loading on the first component). This confirms that the higher the deposition at the Induction Port the lower the deposition at the higher cups, the FPM and the FPF. Moreover, it suggests that the classical univariate approach by which different actuators are characterised by taking into account each single response is not correct, because all these responses are strictly correlated.

When looking at the second component, another group of three positively correlated responses can be detected. They are MMAD and the deposition at the lower cups (C1 and C2), that are inversely correlated to NAct. They are also orthogonal (i.e., uncorrelated) to the responses previously described as having high loadings on the first component.

Finally, it has to be noticed that the two responses obtained by USCA (UAct and DD), having very low loadings on both components, bring a very little amount of information. Therefore, it can be concluded that this test can be considered useless for characterizing the actuators.

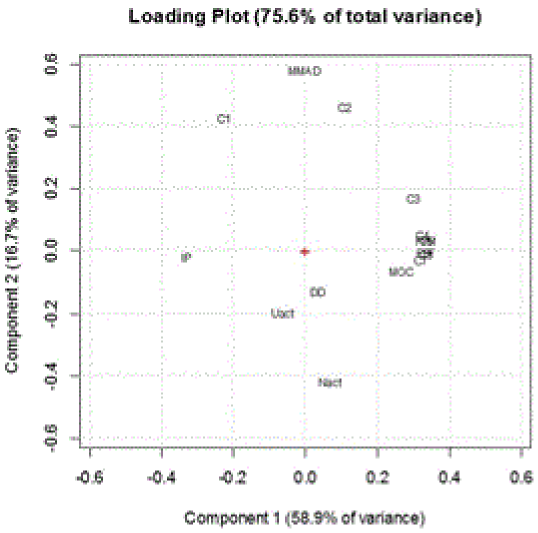

Figure 3: Loading plot on the plane component 1–component 2.

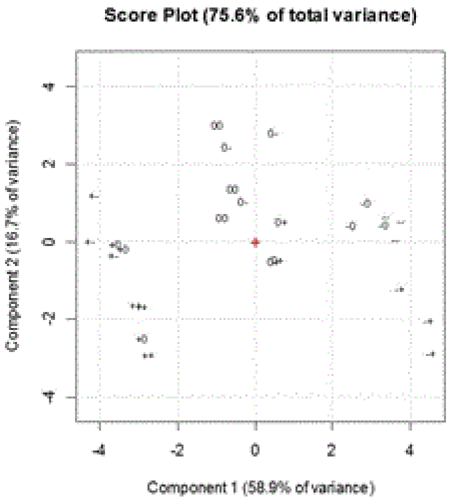

Figure 4: Score plot on the plane component 1–component 2.

Figure 4 shows the score plot, in which each experiment is coded according to the corresponding levels of the two variables (first character for OD, second character for SV).

A simple visual analysis shows that OD has a linear effect on the first component: all the experiments at low level have positive scores, while all the experiments at the central level have scores around zero and all the experiments at high level have negative scores. This means that an increase of OD causes a decrease of FPM and FPF and also a decrease of the depositions on the higher NGI cups (C3-C7) and on MOC, together with an increase of IP.

When taking into account the second component, a quadratic behaviour of OD can be detected, with the experiments at the central level having the highest scores; it can therefore be concluded that an intermediate level of OD leads to the highest values of MMAD, C1 and C2 and to the lowest values of Nact.

About SV, its increase produces a decrease of the scores on the second component, which means greater values of NAct and smaller values of MMAD, C1 and C2.

A small effect can be seen also on the first component, with higher values of SV leading to slightly higher scores on the first component, i.e., a small increase of FPM, FPF and of the depositions on the higher NGI cups (C3-C7) and on MOC, and a small decrease of IP.

It is anyway very clear that the effect of OD on the global performance of the actuator is much larger than the effect of SV.

In order to have a quantitative model, the scores on the two significant components are considered as response.

For the score on the first component, the following model is obtained:

Y = -1.26 - 3.49 OD (***) + 0.43 SV (***) + 0.10 OD*SV + 0.94 OD2 (***) + 0.59 SV2 (**)

(* = $p<0.05$, ** = $p < 0.01$, *** = $p < 0.001$)

The coefficient of the linear term of OD is by far the most relevant one, with the negative sign indicating that an increase of OD produces a decrease of the scores on the first component, and therefore a decrease of FPM and FPF and also a decrease of the depositions on the higher NGI cups (C3-C7) and on MOC, together with an increase of IP.

The model for the score on the second component is:

Y = 1.63 - 0.28 OD - 1.18 SV (***) + 0.03 OD*SV + 1.85 OD2 (***) - 0.63 SV2

Since the quadratic term of OD is the most relevant term, a better interpretation can be obtained by looking at the response surface shown in Figure 5.

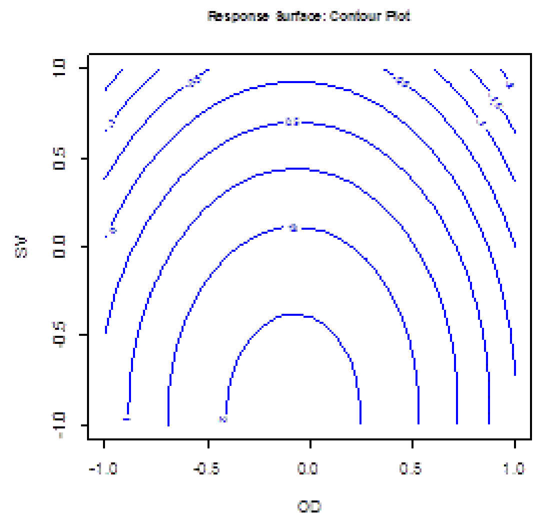

Figure 5: Response surface for the score on the second component.

It can be seen that the highest scores on the second component (and therefore the highest values for MMAD, C1 and C2 and the lowest values for NAct) are obtained at intermediate values of OD and at low values of SV.

It is interesting to notice that the mathematical models provide the same information that had been obtained by a simple visual analysis of the score plot.

The models obtained by taking as response the score on the principal components are very useful because they allow a general understanding of the phenomenon, but they have the limitation that the predicted values do not give any direct information about the single responses.

Therefore, it is also useful to compute the models for each response separately (only those for FPM, FPF, MMAD and will be shown).

For FPM the model is the following:

FPM = 0.34 - 0.20 OD (***) + 0.01 SV (*) + 0.00 OD*SV + 0.07 OD2 (***) + 0.02 SV2 (**)

while for FPF we have:

FPF = 38.7 - 22.9 OD (***) + 3.1 SV (***) - 0.1 OD*SV + 7.5 OD2 (***) + 2.7 SV2 (*)

It can be seen that these two models are very similar, both in what concerns the significant terms and their relative magnitudes. They are also very similar to the model obtained when taking as response the score on the first component. This is quite logical, since FPM and FPF are very much correlated and have a very high loading on the first component (see Figure 3).

For MMAD the following model is obtained:

MMAD = 1.24 - 0.01 OD - 0.06 SV (***) - 0.02 OD*SV - 0.08 OD2 (**) - 0.01 SV2

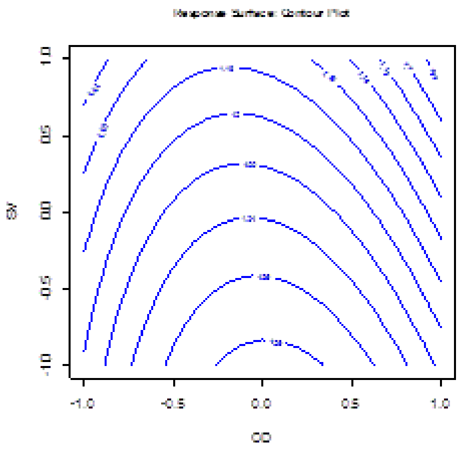

Figure 6: Response surface for MMAD

From the response surface it can be seen that the highest values are obtained at intermediate values of OD and at low values of SV. Thanks to response surfaces like the one above, clearly the formulator can easily chose the right variables combination to achieve the requested performances in the whole explored domain.

In this case the model and the response surface are very similar to what has been obtained when taking the score on the second component as response. Again, this is quite logical since MMAD has a large loading on the second component.

The main difference is that, since the principal components have less noise than the original variables, the R^2A for this model is 0.52, while the R^2A for the model computed on the scores of the second component was 0.71.

Therefore, it can be said that the models computed on the single responses are more directly interpretable (especially in what concerns the predicted values), but less precise than the models computed on the components.

Conclusion

The application of an experimental design and a proper multivariate treatment of the 15 responses obtained by each experiment allowed demonstrating that the NGI tests can differentiate pMDI actuators in which OD and SV have been varied, while the same result cannot be obtained with the USCA responses.

In particular, it has been demonstrated that the variation of OD has a large effect on the actuator performance, while the variation of SV affects it only marginally. Models to predict FPM, FPF and MMAD in the explored domain were established and reported.

The paper also showed that the best results can be obtained by an "integrated" multivariate approach, in which experimental design and multivariate treatment of the responses are used at the same time.

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References

1. Agertoft L, Pedersen S (1994) Influence of spacer device on drug delivery to young children with asthma. Arch Dis Child 71: 217-220 .
2. Lundstedt T, Seifert E, Abramo L, Thelin B, Nystrom A, et al. (1998) Experimental design and optimization. Chemometrics and Intelligent Laboratory Systems 42: 3-40.
3. Box GEP, Hunter WG, Hunter JS (1978) Statistics for experimenters, Wiley, New York.
4. Daffertshofer A, Lamoth CJC, Meijer OG, Beek P (2004) PCA in studying coordination and variability: a tutorial. Clinical Biomechanics 19: 415-428.
5. Nollet L, Toldrá F (2007) Advances in Food Diagnostics. Blackwell Publishing.