USING DESIGN OF EXPERIMENTS (DOE) TO OPTIMISE INTERNAL LUBRICANT CONTENT IN INHALATION CAPSULES

Fernando Diez[1], Maria Teresa Gasso[2], Guillermo Ayala[3], Brian Jones[1,4], Juan Ramiro Aparicio[1], Rafael Martin Portugues[1]

[1] Qualicaps Europe S.A.U. 28108 Spain
[2] Departamento de Matemática Aplicada, Universidad Politécnica de Valencia.46022 Valencia. España
[3] Departamento de Estadística e Investigación Operativa, Universidad de Valencia, 46100 Burjassot. España
[4] The School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, CF10 3NB, UK

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INTRODUCTION

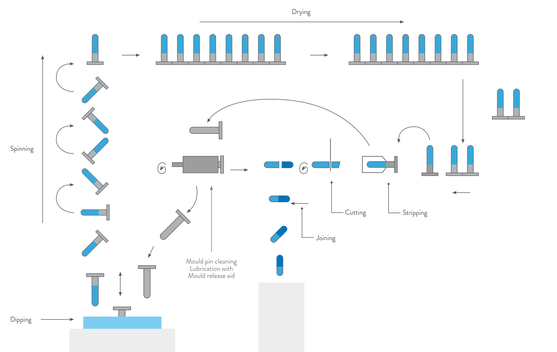
Pulmonary delivery is being investigated as a route for delivering active pharmaceutical ingredients that cannot be administered through the standard oral route, as well as offering an improved alternative to the parenteral route.

The use of hard capsules in DPIs to deliver formulations to the lung has been in use since 1970, and recently there has been an interest in returning from metered-dose systems to capsule-based systems because they are simple to formulate, cheap to manufacture and patient-friendly. The original inhalation grade hard capsules were made from gelatin, which becomes brittle when exposed to low humidities. Inhalation grade hypromellose (carragean gelling agent) has been developed in the last few years to overcome this problem and has also been shown to have better aerosolization properties. [1]

Hard capsules are made by a dipping process in which surface lubricant is an essential processing aid for removing dried capsule shells from the manufacturing pins. This lubricant has been shown to have an effect on powder retention in capsules that are used for inhalation of medicines. [2, 3, 4]

The goal of this work is, through the use of an ANCOVA model, to evaluate the interaction of three manufacturing process parameters in order to produce inhalation capsules with the required internal lubricant content.

Quali-V®-I capsules manufacturing process



METHODS

The experimental design consisted of 432 experiments based on a full factorial design of three variables, replicating the experiment for each condition. Software R was the tool used for all the statistical computing and graphics. Factors and levels are collected on Table 1. [5, 6, 7]

Table 1

Factor	Levels
Pump Flow	3
Pin Position	3
Manufacturing Time (from Shell Grease Replacement)	24

List of Factors and Levels in DoE

The internal lubricant was extracted from empty HPMC capsules (Quali-V®-I) using an extraction solvent. The fatty acids present in the resulting solution were derivatized using a methylating agent, each solution was analyzed using GCMS (gas chromatography mass spectroscopy), and the amount of methyl oleate was quantified as surrogate for internal lubricant. [8]

RESULTS AND DISCUSSION

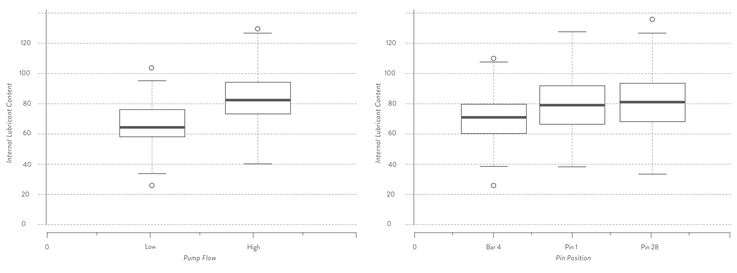
Three experimental factors have been controlled. The first two factors are categorical: the pump flow (units are cycle/s and the levels are low, medium and high) and the pin position (three different places in pin table). The third one is numerical and corresponds to the manufacturing time or time from the last shell grease replacement. The response variable is the internal lubricant content as ppm of methyl oleate.

In **Figures 1** and **2** the influence of each categorical factor is displayed

In order to predict the response, a general lineal model has been used with all interactions. A variable selection has been applied; the Akkaike information criterion (AIC) has been minimized using the AIC step function from the R package MASS (Modern Applied Statistics with S). The final lineal model obtained has no three order interaction, besides the interaction position/ time is negligible.

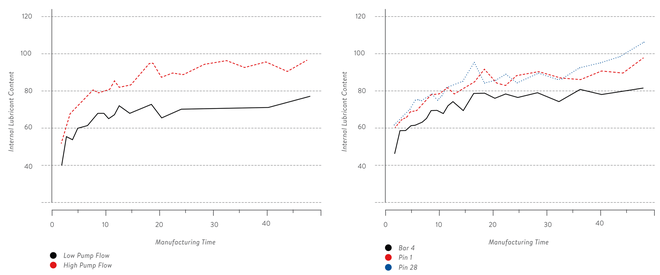
By therefore fixing pump flow and time, the inhalation capsule internal lubricant content can be predicted. In **Figure 3** the average value with the corresponding confidence interval is displayed for a medium pump flow.

Figure 1



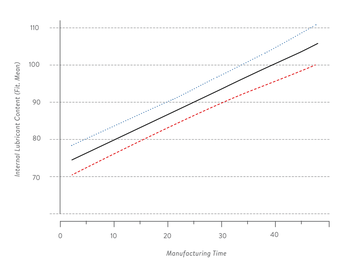
Box plot for pump flow (left side) and pin position (right side). In Y axis ppm methyl oleate.

Figure 2



Influence of the Manufacturing Time in the Internal Lubricant Content at different pump flow (left) and at different pin positions (right). The internal lubricant content units are ppm of methyl oleate.

Figure 3



Average value (black line) and confidence interval (dotted line) for medium pump flow. Values obtained from the model. X axis time in hours.

CONCLUSIONS

Inhalation capsules' internal lubricant content is a key factor in inhalation performance, since parameters as emitted dose, fine particle fraction and mass media aerodynamic diameter depend on this value. This factor is critical to control for an optimal capsule performance.

An analysis of covariance has been applied in order to study the influence of different experimental factors. The dependence of the internal lubricant with respect to the manufacturing time and its interaction with the other two categorical predictors has been shown.

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