Statistical tools and control of internal lubricant content of inhalation grade HPMC capsules during manufacture

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Abstract

The internal lubricant content (ILC) of inhalation grade HPMC capsules is a key factor to ensure good powder release when the patient inhales a medicine from a dry powder inhaler (DPI). Powder release from capsules has been shown to be influenced by the ILC. The characteristics used to measure this are the emitted dose, fine particle fraction and mass median aerodynamic diameter. In addition the ILC level is critical for capsule shell manufacture because it is an essential part of the process that cannot work without it. A design of experiments has been applied to the manufacture of inhalation capsules with the required ILC. A full factorial model was used to identify the controlling factors and from this a linear model has been proposed to improve control of the process.

Keywords: HPMC capsules, internal lubricant, aerosolization, dry powder inhaler (DPI), Linear models.

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1. Introduction

Hard capsules are manufactured in a continuous process on large automatic machines, see Figure 1. They are formed on stainless steel mould pins mounted in-line onto metal strips (bars). There are different sets of bars to make the caps and bodies of each size of capsule. Groups of bars are dipped in to a temperature controlled container, called a dip pan, containing a warm aqueous solution of the polymer, either gelatin or hypromellose (HPMC). Films are formed on the mould pins most commonly by a gelation process that relies on the temperature difference between the cold pin and the hot solution. This is an inherent property of gelatin solutions and HPMC solutions are formulated to gel by the addition of a network former such as carrageenan and potassium chloride as a promoter [1]. The bars are raised out of the dip-pan and are rotated end over end to improve the film distribution on the pins as they are transferred from the lower level of the machine to the upper one. At this point the films have set and are no longer mobile. Groups of bars are moved by hydraulic pushers through a series of drying kilns, which use large volumes of controlled humidity and temperature to dry the films. At the end of the upper level the bars are transferred to the lower level and are moved back to the front-end of the machine. When the pins emerged from the kilns they are dried to a level of >16.0%, which is just above the upper level of the standard moisture content specification. These dried films adhere strongly to the pins. The next part of the process is to strip them from the pins using metal jaws. The ILC is a critical factor enabling this to occur without capsule damage. If insufficient is used the capsule shells will split during removal. Pairs of bars, one cap and one body are selected from each side of the machine and enter into the automatic section. The lubricant is a propriety mixture pharmaceutical grade excipients and is different for each capsule manufacturer and their compositions are registered in the companies Drug Master File. Lubricant is loaded into a pump, the flow rate from which can be adjusted using a pressure valve. The lubricant is applied to a circular foam roller that transfers a sufficient quantity to the pins as they pass underneath. The pin bars are moved towards the centre of the machine and the pins are inserted into rotating circular tubes lined with a felt pad. These clean the pins and spread the lubricant evenly over their surface. These pads are changed at regular intervals to avoid a build-up and saturation with the lubricant [2, 1, 3, 4, 5].

Several papers have described the influence of ILC on aerosolization [6, 7].

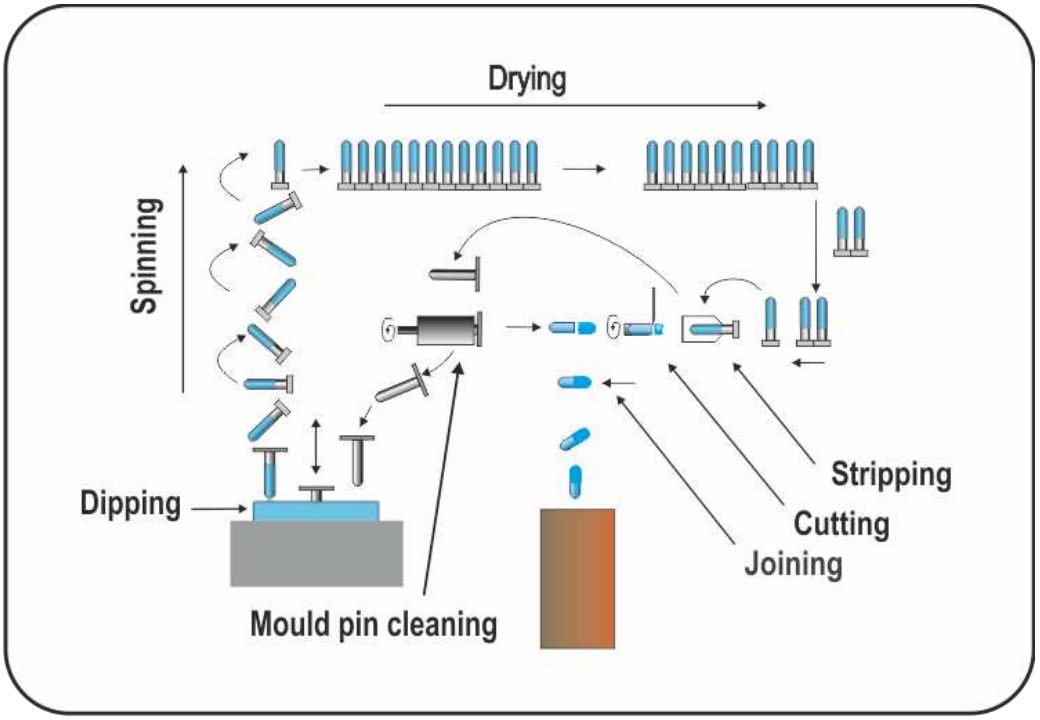


Figure 1: Capsules manufacturing (From Qualicaps Europe).

The reference [7] showed that there is an optimum ILC range to obtain good powder release from capsules as measured by their emitted dose and fine particle fraction [7]. They suggested that the effect could be related to the roughness of capsule internal surface.

The goal of this work was to propose a statistical model that could be used to control the internal lubricant content of capsules within the required limits during the manufacturing process.

2. Materials and methods

2.1. Materials

HPMC inhalation grade capsules were manufactured by Qualicaps Europe (Spain, Madrid). Capsule pin lubricant was manufactured with pharmaceutical grade materials using the formulation registered in the USA drug master file, N14765 (Qualicaps Europe S.A.U.) Internal lubricant concentration was

evaluated by determining methyl oleate (MO), which was taken as a marker for the lubricant content.

2.2. Methods

2.2.1. Determination of the ILC content of capsules

Samples of 11 capsules were weighed in a glass vial. Five ml of Hexane: chloroform, 60:40 (v/v) extraction solvent containing 10mg/l of the internal standard were added to the samples. The vial was sonicated during one hour in an ultrasonic bath; then 100l of the extract was transferred into a 2ml vial for derivatizasion using 50l of Trimethyl sulfonium hydroxide(TMSH). The resulting methyl esters were analyzed by Gas chromatography-mass spectrometry (GCMS). The MO was identified by GCMS and quantified using an internal calibration method using six points in the 0.5-20mg/kg concentration range. One microliter of the derivatized MO was injected in the splitless mode in the GCMS [8].

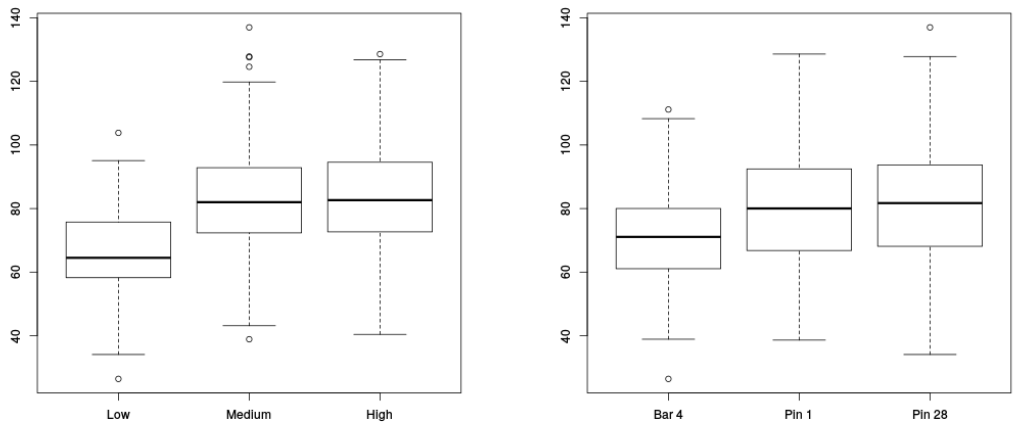
2.2.2. Relationship between ILC and machine factors

The internal lubricant content was studied as a function of different factors in the production process; previously selected by people experienced in capsule manufacturing. The three factors considered to be important were: ILC application pump-flow rate, pin position on a bar in the dipping pan where capsule are formed and the time interval from the last change of the ILC application shells. This resulted in three levels for pump-flow (low, medium and high), for pin position (Bar 4, Pin 1-2-3 and Pin 28-29-30) and time from the change of application shells. Replicate samples were taken for each condition that resulted in 432 samples. In order to predict the response, a general lineal model has been used with all interactions [9]. A variable selection has been applied. The Akaike information criterion (AIC) has been minimized using the stepAIC function from the R package [10]. The final lineal model obtained has no three order interaction, besides the interaction position/ time is negligible.

3. Results

3.1. Comparing means and variances

Figure 2 shows boxplots comparing the ILC values for pump-flow rates A) and pin position (B). A similar behaviour judged by medians and interquartile ranges was seen for medium and high pump-flow rates but not



(A) (B)

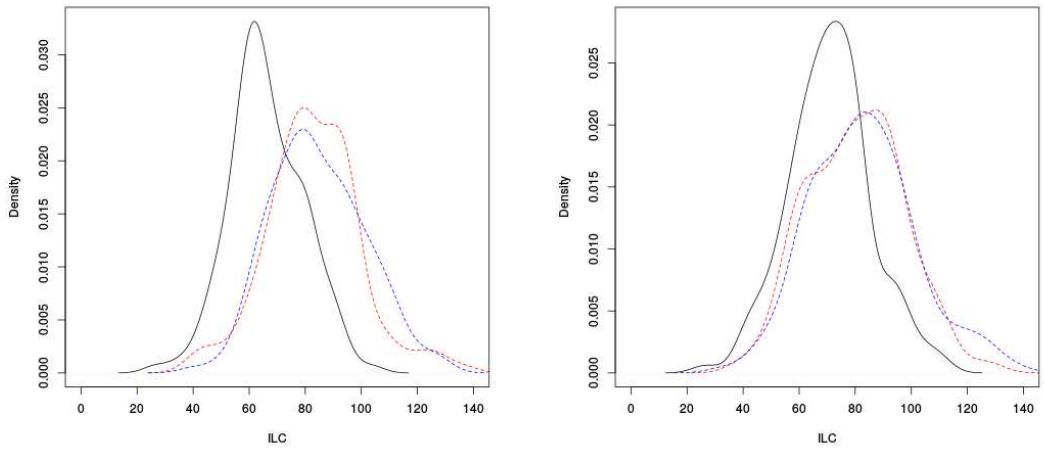
Figure 2: Shows the effect on ILC of variations in pump-flow and pin position. Box-plot A, the effect of different pump-flow rates and Boxplot B, the effect of different pin positions.

for low pump-flow. The pin position showed no clear difference between the pin 1 and 28 showing that is not a significant variable and not an important factor in capsule manufacture. Table 1 shows the ILC by pin position and pump-flow.

Table 1: Statistical summaries for ILC by taking into account Position and pump-flow.

		Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
Position	Bar 4	26.42	61.08	71.08	70.88	79.95	111.20
	Pin 1	38.61	67.03	80.03	80.31	92.46	128.60
	Pin 28	34.08	68.31	81.71	82.63	93.62	137.00
Pump-flow	Low	26.42	58.30	64.50	66.27	75.68	103.80
	Medium	38.89	72.53	82.00	82.93	92.80	137.00
	High	40.42	72.76	82.65	84.62	94.42	128.60

Figure 3 shows the three kernel density estimators corresponding to the response for the different pump-flows and pin positions. The kernel estimators for pin positions 1 and 28 are very similar and different from the estimated density for Bar 4. A similar comment applies to the pump-flow where at a low rate the density is clearly different from the medium and high



(a) (b)

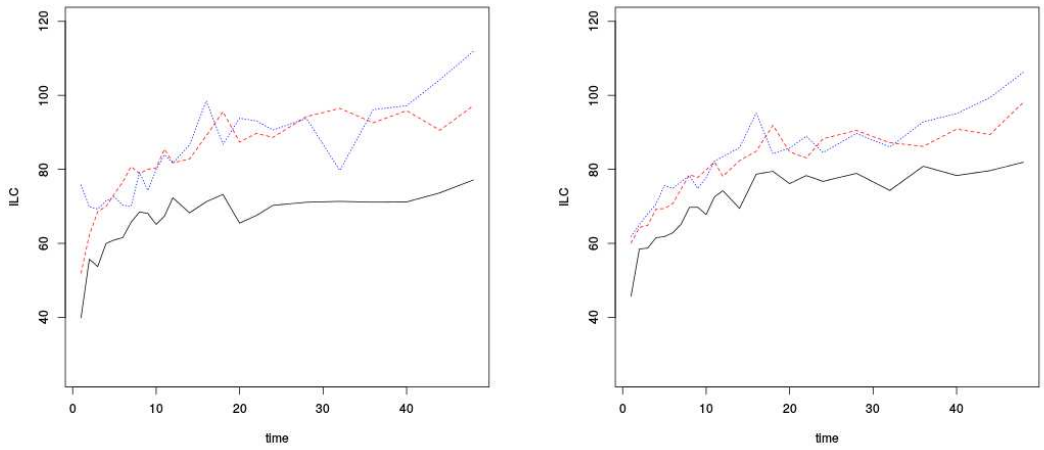
Figure 3: Shows the effect on the ILC of pump-flow rates and pin-position on the density. Graph A shows the effect of pump-flow rate; key low (black line), medium (red line) and high (blue line). Graph B the effect of pin position; key, Bar 4 (black, line), Pin 1 (red line) and Pin 28 (blue line).

rates.

Figure 4 shows the observed means for ILC taken at different times from the change of application shells, at different pump-flow rates (A) and different pin positions (B). The curves are similar for both plots. Those for the medium and high pump-flow rates are similar while for low pump-flow the values are lower. The curves for pin positions 1 and 28 are clearly higher than the curve for bar 4.

A comparison was made of the mean values for each pair of pump-flow rates and each pair of pin positions. The null hypothesis of a common mean for each pair of pump-flows has been tested using a t-test and the results are shown in Table 2.

Some descriptives are displayed in the four first columns: the difference of means (first); lower and upper 95% confidence limits (second and third) and the p-value observed (fourth). A simple evaluation of the p-values in the fourth column shows that the difference between the means for medium and high pump-flows is not significant ($p = 0.39$). However, the pairs of means low-medium and low-high are significant different with very low p-values (p



(a) (b)

Figure 4: Shows the effect time of pump-flow rates and pin positions on ILC. A: Graph of mean values at the different pump-flow rates: low (black line), medium (red line) and high (blue line). B: Graph of mean values at different positions on the pin bar: Bar 4 (black line), Pin 1 (red line) and Pin 28 (blue line).

<0.00001 in both cases). Figure 3 shows that the lower pump-flow is clearly different from the two other levels.

The equality of the variances have been tested for using an F-test. The results are shown in Table 2. The medium and high pump-flow rates have the same variance ($p = 0.98$). However, there is a significant difference between the variances for low and medium pump-flow rates (respectively low and high). The kernel estimators for medium and high flow rates are very similar, for both means and variances, and are clearly different from the low pump-flow. The means for the different pin positions were compared using a t-test. There was no significant difference between the means for Pin 1 and Pin 28 ($p = 0.2726$) but the mean of Bar 4 was significantly different from the other two groups.

3.2. Model

In order to evaluate the influence of the three experimental factors (pump-flow, position and time) to the response variable (ILC) a general lineal model has been fitted [9]. We have evaluated a full design with the main effects and

Table 2: Mean and variance comparisons. First, second and three rows correspond to the comparisons pump-flows low-medium , medium-high and low-high respectively. Last three rows correspond to different positions: Bar 4- Pin 1, Pin 1-Pin 28, and Bar 4-Pin 28, respectively. The first columns display the diference of means (Dif.), the 95 % confidence interval (95% CI), the t-test p-value (p_1). The last four columns of the table correspond to the comparations of variances: ratio of variances (ratio) the 95 % confidence interval of the ratio (95% CI) and the F-test p-value (p_2).

		Dif.	95% CI	p_1	Ratio	95% CI	p_2
Pump-flow	low-medium	-16.66	[-20.14,-13.18]	0.00	0.61	[0.44,0.85]	0.00
	medium-high	-1.69	[-5.56,2.17]	0.39	1.00	[0.72,1.40]	0.98
	low-high	-18.35	[-21.83,-14.88]	0.00	0.62	[0.45,0.86]	0.00
Position	Bar4-Pi1	-9.43	[-13.12,-5.73]	0.00	0.74	[0.53,1.03]	0.07
	Pi1-Pi28	-2.32	[-6.47, 1.83]	0.27	0.84	[0.60,1.17]	0.29
	Bar4-Pi28	-11.75	[-15.64,-7.85]	0.00	0.62	[0.45,0.86]	0.00

second and third order interactions. Beginning from this model, a variable selection has been applied minimizing the Akaike information criterium (AIC) using the stepAIC function from the R package MASS [10]. The final lineal model obtained has no significant three order interaction, besides the interaction position/time is not significant. In short:

$$ILC = pumpf\ low + position + time + (pumpf\ low * time) + (pumpf\ low * position)$$

i.e. main effects plus the two interaction terms. The estimated coefficients appear in Table 3 with the p-values corresponding to the null hypotheses of a null value. Table 4 displays the p-values obtained when each interaction is removed from our model. Note that the p-value corresponding to the interaction between pump-flow and position is much lower than the corresponding to interaction pump-flow and time. So the interaction pump-flow and position is clearly more significant than the interaction pump-flow and time.

The proposed model can be used to predict the mean ILC. Figure 5 displays the estimated means and their confidence regions. The plot has been produced using the R package [11]. For instance, left figure considers the time and the different values of pump-flow. Note that the observed value of the factor position is replaced by the observed proportion of each category. Generally, for a given plot, the non-considered predictor is replaced by its

Table 3: Coefficients estimates for the model fitted and the p-values testing a null coefficient.

	Estimate	Pr(>|t|)
(Intercept)	56.772	0.000
pumpflowMedium	3.826	0.201
pumpflowHigh	6.545	0.029
time	0.401	0.000
positionPin 1	3.833	0.111
positionPin 28	3.633	0.131
pumpflowMedium:time	0.270	0.008
pumpflowHigh:time	0.355	0.001
pumpflowMedium:positionPin 1	9.226	0.007
pumpflowHigh:positionPin 1	7.557	0.027
pumpflowMedium:positionPin 28	15.110	0.000
pumpflowHigh:positionPin 28	9.230	0.007

Table 4: Evaluation of the remaining two order interactions.

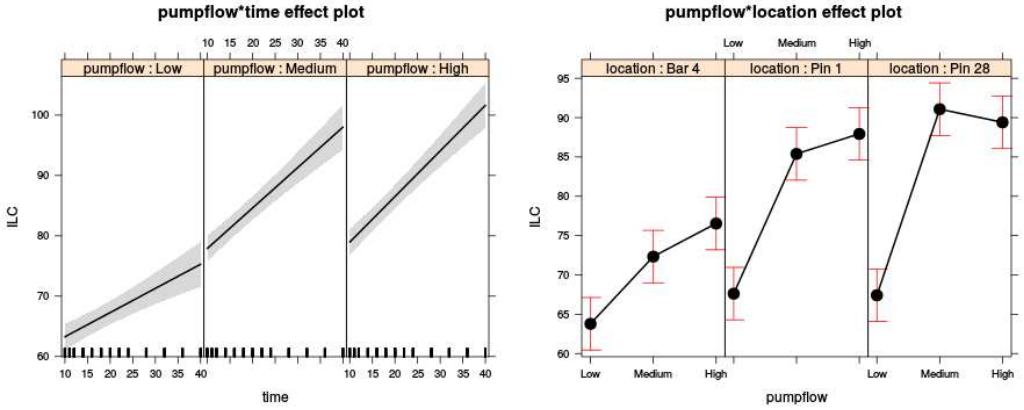
Term	pump-flow * position	pump-flow *time
p-value	0.0003744	0.001423

mean value (for a numerical predictor) or the observed proportion (for a categorical predictor).

4. Conclusion

For inhalation grade capsules the quantity of internal lubricant on the inside surface of the shells is a significant factor in their performance. The key powder aerosolization factors, emitted does, fine particle fraction and mass medium aerodynamic diameter, are influenced by this factor. An experiment was designed and realized to measure the effect of three machines factors; ILC application pump-flow rate, pin position on a bar in the dipping pan and the time interval from the time of change of the application shells. An analysis of covariance has been applied to the results and a lineal model derived for the process. This identified the machine settings to control the capsule manufacturing process and produce capsules with correct ILC level.

Figure 5: Estimated mean response with the confidence regions



Acknowledgements

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