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Ensuring Pharmaceutical Product Success through Excipient QbD Efforts

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SUMMARY

It is essential to understand excipients' critical material attributes. A QbD strategy that includes historical data analysis and experimental work has been used in functional excipients such as Hypromellose (HPMC) to develop this understanding. The use of multivariate analysis helped to identify excipient variability and the support it could provide to improve the final product robustness.

INTRODUCTION

To understand drug product variability formulator must understand and overcome API (active pharmaceutical ingredient), process, and excipient variabilities (Ferreira et al., 2018). Excipient variability plays an important role in determining overall pharmaceutical product variability. Examining and controlling the excipient impact, upfront, saves enormous time and prevents challenges in developing robust formulations. Excipient variability can be understood and introduced into the product design in many ways, from simple analysis like trend data and Quality by Design samples to complex, multi-year data analysis through MVA (multivariate analysis) or principal component analysis (PCA). These analyses can be used by formulators to understand critical excipient attributes that may contribute to product variability, and also by excipient manufacturers to improve manufacturing control and reduce variability. The work presented here will provide insight on how an excipient manufacturer like IFF can use QbD (Quality by Design) efforts to understand and avoid extreme variability in its excipient products, and best supporting pharmaceutical product formulators.

MATERIALS AND METHODS

Tablet Formulation: The tablet formulation is given in Table 1. Multiple formulations were made with the HPMC K4M hydroxy propoyl (HP) content varying from 6 to 12. The dissolution was performed in 0.1% SLS in 900 mL water at 37°C using 50 rpm paddle speed all tablets (n=6) were placed in hanging baskets.

Multivariate analysis: All raw data for HPMC K4M was obtained from LIMS. The raw data was cleaned, and multivariate analysis was performed by SIMCA.

Table 1. Indapamide formulation varying of HP 6-12.

Ingredient	Quantity (%wt)
Indapamide	2.5
HPMC K4M (HP 6-12)	40
Lactose	40
MCC PH102	16.5
Magnesium stearate	0.5
Talc	0.5

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RESULTS AND DISCUSSION

Tablet Formulation: Understanding the critical material attributes (CMA) of an excipient is an important step in QbD analysis. Figure 1 shows the dissolution profiles of an indapamide formulation using HPMC K4M of varying HP substitution levels. It can be observed that within the HP range 6-8% the dissolution profile differs very little. However, as the HP substitution increased above 8% a step-change in performance was observed and a faster indapamide release profile could be achieved. This indicates that the control of critical material parameters for excipients is of paramount importance in drug product development and should be considered by the formulation scientist as part of their QbD strategy.

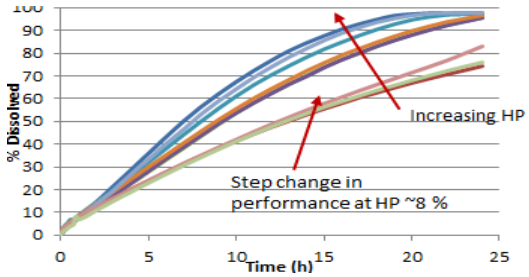

Figure 1: Indapamide release from HPMC K4M varying HP substitution.

Multivariate analysis: Multivariate analysis is used for problem-solving and display (classification, relationships, control charts) by analyzing more than 2 variables at once. The PCA score plot for METHOCEL® HPMC K4M is shown in Figure 2. The data show an even distribution of the PC space, with no patterns observed, and less than 5% of batches are outside of the 95% control ellipse. This type of data can be used by excipient manufacturers to capture and control material variability. PCA graphs can also be used to understand the realm of variability that formulators have experienced based on lots they have used. For example, in Figure 3, 6 batches (randomly selected to represent what a customer may have received) were analyzed against 8 years of production data. All 6 batches are evenly distributed in the PCA space. There are two batches that appear outside the 95% confidence interval in PC3 vs PC4 analysis due to an attribute that is low in value but within spec. Despite PCA's apparent outliers, all batches showed similar release behaviour during dissolution (data not shown), demonstrating the robustness of the formulation against a range of normal manufacturing variability. This kind of data modelling can help to identify critical material attributes and define a QbD design space during formulation development.

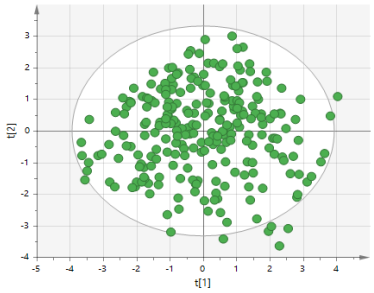

Figure 2: PCA score plot for METHOCEL™ K4M

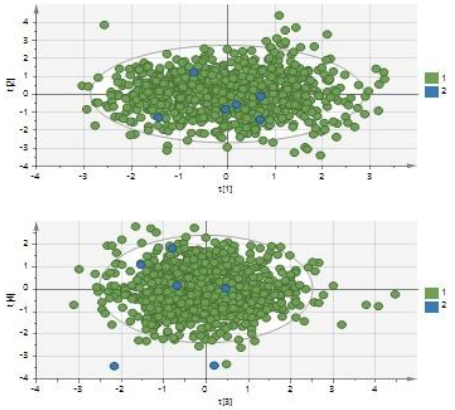

Figure 3. PCA score plot with 6 highlighted batches

CONCLUSIONS

Understanding excipients' critical material attributes are imperative to ensure robust drug products in the market capable of withstanding small variability during the production cycle. A QbD strategy that includes historical data analysis and experimental work – both by the excipient manufacturer and pharmaceutical formulators - will support an understanding of this potential variability and could lead to improvements in product robustness.

REFERENCES

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