Article:
Tobyn, M, Ferreira, AP, Lightfoot, J et al. (5 more authors) (2018) Multivariate analysis as a method to understand variability in a complex excipient, and its contribution to formulation performance. Pharmaceutical Development and Technology, 23 (10). pp. 1146-1155. ISSN 1083-7450

https://doi.org/10.1080/10837450.2018.1534862

Taylor & Francis
Taylor & Francis Group

Pharmaceutical Development and Technology

ISSN: 1083-7450 (Print) 1097-9867 (Online) Journal homepage: http://www.tandfonline.com/loi/iphd20

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To cite this article: Mike Tobyn, Ana Patricia Ferreira, Jane Lightfoot, Elaine B. Martin, Manish Ghimire, Charles Vesey, Andrea Kasuboski-Freeman & Ali Rajabi-Siahboomi (2018): Multivariate analysis as a method to understand variability in a complex excipient, and its contribution to formulation performance, Pharmaceutical Development and Technology, DOI: 10.1080/10837450.2018.1534862

To link to this article: https://doi.org/10.1080/10837450.2018.1534862

Multivariate analysis as a method to understand variability in a complex excipient, and its contribution to formulation performance

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Abstract

A key part of the Risk Assessment of excipients is to understand how raw material variability could (or does) contribute to differences in performance of the drug product. Here we demonstrate an approach which achieves the necessary understanding for a complex, functional, excipient.

Multivariate analysis (MVA) of the certificates of analysis of an ethylcellulose aqueous dispersion (Surelease) formulation revealed low overall variability of the properties of the systems. Review of the scores plot to highlight batches manufactured using the same ethylcellulose raw material in the formulation, indicated that these batches tend to be more closely related than other randomly selected batches. This variability could result in potential differences in the quality of drug product lots made from these batches.

Manufacture of a model drug product from Surelease batches coated using different lots of starting material revealed small differences in the release of a model drug, which could be detected by certain model dependent dissolution modelling techniques, but they were not observed when using model-independent techniques. This illustrates that the techniques are suitable for detecting and understanding excipient variability, but that, in this case, the product was still robust.

1. Introduction

From March 2016 it has been a requirement for Regulatory Filings for New Drug Products in Europe to have a documented "Risk Assessment" for excipients in the system (Anon 2015), covering both technical and business related risks. The form of that risk assessment is not agreed or specified, but there has been some progress in defining appropriate paths forward (IPEC 2015), and how such an approach can be reduced to practice (DeVos 2016). A key part of such assessment will be whether variation in the properties of the excipient will influence the robustness of the pharmaceutical product. This has spurred considerable interest in excipient variability as a topic of interest to companies and regulators (Thoorens et al. 2014; Dave et al. 2015; Narang 2015; Soh et al. 2015; Narang et al. 2016; Zarmpi et al. 2017).

Different approaches to assessing variability of excipients have been proposed and adopted. The use of QbD (Quality by Design) samples, generally differentiated by a univariate parameter, is a widely used technique (Moreton 2016). However there are potential shortcomings in this approach, including:

a) The "performance" of an excipient may not be definable within a single parameter. Indeed, this is the case for most functional excipients. If one considers that the performance of an excipient is defined both by the function for which it is included, but also how it interacts with other components of the formulation, and how the whole system might interact with analytical methods (e.g. PAT(Corredor 2016)) it may not be a single value on the CoA which defines the overall "performance" which can then be tested as a hypothesis or potential root cause.

b) The variability of commercial materials is generally much less than the limits of any specification. In order to achieve a model level of variability it is often necessary to change manufacturing parameters, for instance to manufacture in a pilot plant. This inevitably changes multiple factors, including the factor under examination but also related or unrelated parameters (for instance the impurity profile of the system) which may cloud the outcome of any conclusion looking at the apparently "independent" parameter under test;

Whilst a "random" selection of batches from a vendor may help confirm level of variability (Gamble et al. 2010), and give the user some confidence that their product is robust, it cannot be assumed that observed low variability is not a function of sampling (e.g. consecutive similar batches) or other cause, as the batches represent a small fraction of the general production. Such considerations may also apply to situations such as manufacture of Long Term Stability Studies (LTSS) batches, which are often manufactured using different (up to three) batches of components, including excipients. Three consecutive batches, although distinct, may not capture the entire range of variability of the materials and the potential impact on the system that differences could have on the drug product.

Multivariate analysis (MVA) methods are a suite of widely used statistical methods, which can be used to study data with more than one variable, and are suitable for studying variability and generating knowledge on a diverse range of systems. The wide suite of techniques can be applied for diverse purposes e.g. exploratory analysis, multivariate classification, multivariate regression, design of experiments (DoE) to name a few. Their application to pharmaceutical data sets was encouraged by the FDA's PAT guidance for industry (FDA 1997) and since then methods have been adopted by different areas of the pharmaceutical industry (Ferreira and Tobyn 2015; Tobyn et al. 2018). The methods are transparent and reproducible, and can be verified and, in some cases, validated for use in filings to support manufacturing and other decisions(Cook and Cai 2018).

The use of MVA to study the variability of excipients was initially proposed and developed by a team at Pfizer (Kushner 2013). The approach of examining the certificates of analysis for actual variation, taking into account all parameters, rather than a univariate approach, was shown to be of value. Such an approach requires that the supplier has in place the mechanisms to monitor and output this data, and can supply it to the users, usually in association with a confidentiality agreement. Kushner and his colleagues (Kushner et al. 2014) have further shown that a robust formulation could accommodate the variability of a key excipient in a process, using a model formulation.

More recently an excipient vendor used an MVA approach to look at the variability of one of their excipient products, namely microcrystalline cellulose (Thoorens et al. 2015). They were able to

quantify variability in their product, and noted that there may be differences attributable to manufacturing at two separate sites. However, they could not determine whether these differences were due to physical differences between the batches or analytical methodologies at the two manufacturing sites. As MVA does not distinguish the source of variation (e.g. analytical or material related) it is an important part of the process to examine the causes, effects, and potential solutions to variability after the data analysis has occurred, and what impact they will have on the drug product. The customer, once variability has been identified, then has to consider how it will impact their system specifically to make a reasoned Risk Assessment.

In other examples, .MVA techniques were used in various ways to assess the risk related to excipients, and their choice and performance (Hertrampf et al. 2015).

Ethylcellulose is one of the most commonly used water insoluble barrier membrane polymers for multiparticulates to achieve controlled drug release. Ethylcellulose may be dissolved in an organic solvent and applied by Wurster bottom spray technique to form a barrier membrane film coating on drug loaded pellets. Aqueous dispersions of ethylcellulose are often used to overcome environmental and economic challenges associated with organic systems. Surelease® is a fully formulated aqueous dispersion system containing ethylcellulose, plasticizers and stabilizers (Leng DE, Warner, G.L 1977; Leng DE, Mossbach, W., Sigelko, W.L, Sounders, F.L., Uirumaa, R.S, 1985) and is widely used in investigational and commercial controlled release dosage forms (Jagadeesh and Bala Ramesha Chary 2011; Paul et al. 2011; Vonica et al. 2011; Yin et al. 2011; Melegari et al. 2016; Afrasiabi Garekani et al. 2017; Kazlauske et al. 2017; Patil and Belsare 2017).

Surelease can be applied to drug or drug loaded substrate (beads, granules or pellets) to modulate drug release (Parikh et al. 1993b, 1993a; Rajabi-Siahboomi A, Mehta, R., Dias V., Tiwari, S 2017; Rajabi-Siahboomi A et al. 2017). The drug release is mainly by diffusion through the Surelease membrane and is directly controlled by film thickness and controlled diffusivity of the formulated ethylcellulose film. Simply increasing or decreasing the applied quantity of Surelease and the resulting film thickness modifies the rate of drug delivery (Tang et al. 2000). In recent years, particular attention has been made to understand impact of excipient variability on controlled release

dosage forms (Viridén, Abrahmsén-Alami, et al. 2011; Viridén, Wittgren, et al. 2011; Cao et al. 2013; Mohammadpour et al. 2016; Kubova et al. 2017). It has been demonstrated that release profiles of some controlled release formulations can be significantly affected by batch to batch variation in its excipients' properties, and that understanding the nature of these differences is key to development of a robust product.

It has been reported that the application of different grades of ethylcellulose in a formulation may influence performance of the dosage form (Garekani et al. 2017), but less is known about how it may contribute to variability in a formulated and controlled product such as Surelease, where the specifications of the material are controlled, and the raw material differences may be mitigated for by the formulation. The variability of the contribution of ethylcellulose to the performance of films applied from organic solvent systems has been recently examined (Mehta et al. 2016) . Using QbD approaches it has been demonstrated that, when appropriately formulated, the univariate parameters chosen as critical material attributes (using QbD samples) did not affect the performance of a well formulated system, indicating robustness to these parameters.

The primary aims of this study were:

a) To examine the feasibility of using MVA to distinguish between the contributory factors to variation in a complex, formulated, functional system. Although MVA has been used for simple (functional and non-functional) excipients its use in complex excipients has not been published;

b) To examine, if the contribution to variation could be elucidated, whether those factors could be used to understand the variability in performance in a formulated product, should it exist. Alternatively it was hoped to confirm whether the techniques could establish that the variability seen was not a contributor to variability in performance in a robust drug product.

2. Materials and Methods

2.1. Certificates of analysis

The certificates of analysis (CoA) for 431 batches of Surelease E-7-19040 were compiled for further examination, covering several years of production of this excipient. All numerical parameters

reported in the CoA were included in the exploratory analysis of variability in this material. As all batches were released and within specification any parameter noted as "Pass", or which was a limit test, was not further examined in this study. The parameters that were captured are given in Table 1. Those parameters included within the NF monograph (Aqueous Ethylcellulose Dispersion, Type B) driven by what was already included on the certificate of analysis and items considered to be indicators of identity, quality, and purity of the excipient. The data was generated according to the validated analytical methods at the time of the analysis of the batches, and the methods did not change during the course of the testing period.

In a further review of the results, information on the parent ethylcellulose batches which were used to produce batches of the ethylcellulose matrix was taken into account. This information was only considered for a subset of the batches from the data set described above. Four different parent batches of ethylcellulose were identified, each associated with multiple batches of Surelease. Table 2a shows the list of batches of Surelease that were manufactured from a particular batch of ethylcellulose, and Table 2b shows the manufacturing parameters.

2.2. Exploratory analysis of CoA data with PCA

The data set described above was analysed using principal component analysis (PCA) (Esbensen and Geladi 2010; Ferreira and Tobyn 2015) to explore relationships between batches and variables. PCA is a mathematical procedure that transforms a large set of variables into a lower dimensional set of new variables designated as principal components (Esbensen and Geladi 2010; Geladi and Grahn 2018). This technique can be used to study relationships in the data (both between samples and between variables) and to identify features/patterns/clusters in a data set. The philosophy behind this method is that, in any data set, it is likely that the key information is contained in some dominating sources of variability while other sources of variability (e.g. noise in the measurements, correlated measurements) do not contribute with additional relevant information. As most systems are multidimensional in nature, only rarely will all the latent information in a given data set be

contained in a single measurement – most of the time, that information will have a contribution from several of the original measurements. The purpose of PCA is to express this latent information contained in the data set using a lower number of variables. Each of these new variables, called principal components (PC), is a linear combination of the original variables. The first principal component to be extracted is that which captures the highest amount of variability in the dataset and each subsequent component to be obtained is that which captures the highest amount of the residual variance (i.e. after previous components have been extracted). By applying PCA, irrelevant variation due to redundancy and noise is removed and the projection of the data into a lower number of variables enables the use of simpler graphical representations thus improving interpretability of the information contained in the data. The analysis was performed using the software package SIMCA (MKS Data Analytics Solutions, version 13.0).

2.3. Manufacture and testing of formulated systems

2.3.1. Materials and Methods for dissolution testing

The Surelease grade used was E-7-19040. This fully formulated dispersion consists of ethylcellulose, ammonium hydroxide, medium chain triglyceride, oleic acid and water. The method of Surelease manufacture is detailed in U.S Patents 4,123,403 and 4,502,888 (Leng DE, Warner, G.L 1977; Leng DE, Mossbach, W., Sigelko, W.L, Sounders, F.L., Uirumaa, R.S, 1985). In summary, ethylcellulose is blended with plasticizer, then extruded and melted. The molten environment plasticized ethylcellulose is then directly emulsified in ammoniated water in a high shear mixing device under pressure. Ammonium oleate is formed in-situ to stabilize and form the dispersion of plasticized ethylcellulose particles.

Chlorpheniramine maleate (CPM) loaded sugar spheres (Suglets® , 850-1000 microns (Tayade et al. 2016)) were used in this study, to represent a model formulation. CPM is frequently used a model drug in controlled release systems, and formulations can be sensitive to raw material changes (Mustafa et al. 2014; Zhang 2016). CPM beads were coated with each batch of Surelease using an Aeromatic Strea-1 (Niro, USA) fluid bed equipment with a Wurster assembly. Immediately

following the Surelease coating, an additional clear coating of a Hypromellose based Opadry® was applied to further protect the beads and prevent sticking post coating. Table 2b gives specifics of coating process conditions.

Dissolution testing was carried out by placing 1g beads in basket of USP apparatus I dissolution unit (VanKel, VK 7000) in USP purified water. Drug release was measured at 262 nm using UV-Visible spectrophotometer (Agilent, 11-1300).

2.4 Comparison of dissolution profiles: model-independent and model-dependent approaches

The comparison of dissolution profiles has been performed in a qualitative manner since the adoption of dissolution testing by the industry. While qualitative assessment of similarity is useful, regulatory requirements have led to the development of more objective and quantitative methods to compare dissolution profiles (FDA 1997; Polli et al. 1997). The approaches developed can be model-independent or model-dependent.

2.4.1 Model-independent approach

A model independent approach using a difference factor (f1) and a similarity factor (f2) was used as described in the FDA guidance (FDA 1997) to determine similarity of dissolution profiles. The difference factor is a measure of the relative error between two dissolution curves and is calculated using Equation 1, where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t the dissolution value of the test batch at time t.

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R_t - T_t|\right] / \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100$$

Equation 1

The similarity factor is a measure of the similarity between the two curves and is calculated using Equation 2.

$$f_2 = 50 \times log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\right\} \times 100$$

Equation 2

Two dissolution curves are considered to be similar if f1 is not greater than 15 and f2 is not lower than 50 (FDA 1997).

2.4.2 Model-dependent approach

In the model-dependent approach, the dissolution profiles are fitted to a model. Several models are well established for this purpose (Polli et al. 1997; Costa and Sousa Lobo 2001). Here in this study, the Weibull model (Equation 3) was used.

$$Q = 100\,(1 - e^{-(t/\tau)^{\beta}})$$

Equation 3

In this equation, τ is the Weibull model scale factor corresponding to the apparent rate constant and β is the Weibull model shape factor, which characterises the shape of the curve. (Sathe et

al. 1996) The Weibull model parameter estimates were obtained using a non-linear regression method (MATLAB, MathWorks). Values for beta and tau were compared using One Way analysis of variance, followed by Tukey's test, using Minitab (Minitab V17, Minitab Corporation).

3. Results and discussion

The initial results of the PCA on the CoA data for the 431 Surelease batches are shown in Figure 1. The scores plot (Figure 1a) displays a summary of the relationships between batches. There are no evident groups or clusters in this plot, and no outliers were identified, and this result is consistent with the variability in the data set arising merely from "common cause variation" rather than any systematic variation. While the first two components explain around 45% of the total variance in the data, the variance predicted by internal validation is negligible (4%) suggesting the variability present is mostly natural variation, which is consistent with this observation. An explanation of this variance of the data is held to be appropriate for exploratory models, but may not be sufficient when building a predictive model. The results indicate overall low variability in the data, which may be expected as none of the systems was generated with variability in mind. .

The loadings plot (Figure 1b) indicates which parameters contribute the most to observed variability. In this case the reported percentage of ethylcellulose, MCT: ethylcellulose ratio and oleic acid: ethylcellulose ratio are the variables that dominate the first two principal components, see Figure 1b.

It is not possible to ascertain from these results alone what is the cause for the variation observed in the reported results. The causes may include batch to batch variation, but also analytical variation and, potentially, sample variation.

Figure 2 shows the scores plot highlighting batches of Surelease made from different batches of ethylcellulose. Materials manufactured from different lots of starting material show some tendency to cluster together. This provides some evidence that batches related in this way have more similar properties than would be accounted for by common cause variability. These relationships could be

driven by the material properties of the ethylcellulose used or could be related to measurements made on the incoming lot of polymer material.

In addition, for the subset of materials studied, a separation by input material lot is observed along the second principal component, as the Surelease lots manufactured using ethylcellulose lot B project predominantly on the upper half of the scores plot while those manufactured using the remaining input lots appear in the lower half of the scores plot. Further analysis (Figure 3) was performed to assess what parameters drive this observation. The scores contribution plots was inspected to identify which parameters drive the separation between the two groups of lots highlighted in Figure 3a. The highest contribution is from percentage of ethylcellulose and the ethylcellulose: MCT ratios, as is shown Figure 3b.

Having identified groupings which may be linked to raw material lots with specific properties the next stage of the work was to identify if these groupings could be seen to influence the performance of a formulation made from these batches, specifically the dissolution characteristics.

The dissolution of the different batches of Surelease in the CPM model system is shown in Figure 4. No differences in the extent or rate of dissolution can be seen from the batches, indicating that, despite some differences in the properties of the Surelease batches there was no differences in the dissolution performance of drug product formulated with these batches. These data show that the natural variability of the system, whether related to ethylcellulose batch or other variability, did not cause any variability in the key performance characteristic of controlled-release systems in the formulated system.

The data were subjected to the model independent approach to compare dissolution profiles as described in the FDA guidelines(FDA 1997). The f1 and f2 parameters are summarised in Table 3, using Lot A as the reference batch of ethylcellulose. However it should be noted that any other reference batch choice would have led to the same conclusions. The results obtained meet the acceptance criteria for similarity of dissolution performance, even for batches identified as having distinct properties.

The model dependent approach was used to analyse the data further. Table 4 shows the Weibull model fitting results for each Surelease® batch and Table 5 shows the descriptive statistics for each input ethylcellulose lot. A graphical representation of the data included in Table 5 is provided in Figure 5 detailing the mean and confidence intervals for the Weibul model parameters obtained for each input ethylcellulose lot.

Analysis of the data (mean and confidence interval) generated by Weibull modelling did not reveal any significant differences in the beta values between batches manufactured from different parent lots of ethylcellulose. There was a significant difference in the tau values between the batches manufactured using from Lot C and those manufactured using the remaining lots. A small, but significant, difference between one parameter (in this case tau) but not the other is not indicative of large differences in dissolution behaviour between the systems, which confirms the model independent approach. It can be seen from Figure 4 that the difference in Tau is driven by a small (3% overall, 64% vs 61% at 700 minutes) difference in extent of release, but the rate at which it gets there is proportionally similar.

It is known that model dependent approaches can identify differences between dissolution curves that model independent approaches cannot distinguish (Mercuri et al. 2017; Paixão et al. 2017), and the two approaches can be complementary. The differences seen here are not large by any of the techniques.

It can thus be seen that MVA techniques, combined with dissolution modelling, can help elucidate the impact of starting materials on observed variability of complex excipients on performance. If a batch of ethylcellulose was used which had significantly different properties it would have been found via this approach, and if this made a difference to formulation performance it would have been detected. An absence of such an effect demonstrates the value of controlling input material properties.

This work relates to the performance of a formulation of a low dose, soluble drug. The methodology is suitable to examine other types of drugs, with differing solubility and drug loading, but the outcomes with respect to robustness may be different.

In this case for a model formulation, the differences observed were not large. This is similar to the findings from previous work, which could detect differences between materials via MVA techniques but confirmed that, in a formulation, these differences did not have a corresponding impact on the variability in the drug product quality (Kushner et al. 2014).

4. Conclusions

This work demonstrated that MVA of CoA's is a viable option for a complex excipient. It has previously been demonstrated that this is feasible for simple, or non-functional, excipients, but its use in examining a complex, functional, excipient has not previously been demonstrated.

It is also important to note that the technique can pick up a variation in properties which are composite, and reliant on, subtle changes in a number of parameters (which may or may not be correlated), which would not always be picked up by single component trending.

Sources of variability can be determined, and this analysis could, if extended, identify if the causes of variability were batch related or were a feature of the analytical methods used. Identifying such variability is key to understanding the risk that the excipient might pose to the formulation system.

It was found that the lot of ethylcellulose used to manufacture Surelease batches was a significant contributor to the variability in the certificates of analysis.

This type of analysis can be part of an overall approach towards elucidating possible risks, to the product from excipient and can thus be a starting point to mitigating those risks. Further confirmation that this level of variability does not contribute to final product variability could be a significant contributor to understanding product robustness. In the case of this formulation the observation that a robust formulation could accommodate small levels of variability was demonstrated, in line with previous observations.

The final part of such an assessment would be the ongoing monitoring of excipient properties to ensure that the characteristics of the excipient are not changing, from that which was initially assessed. This challenge can be met by putting in place mechanisms between vendors and customers to monitor the ongoing properties of the excipient, throughout the life of the drug product. Such mechanisms are used in the food industry, and others, but have not yet been introduced to the pharmaceutical industry.

It is important to note that the techniques here allow the customer to choose lots which represent the real level of variability in their chosen excipient over time. In conjunction with analysis (e.g. by QbD batches to assess robustness) an appropriate design space could be developed for an excipient. This could obviate the need for restrictive specification.

5. Acknowledgements

We are grateful for advice from Dr. Daniel McNamara on interpreting Weibull dissolution data.

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Table 1: Composition of a Surelease formulation

C of A Parameter	**Functionality in Surelease**
% Ethylcellulose	Polymer
Medium Chain Triglycerides (MCT) (%)	Plasticizer
MCT to Ethylcellulose ratio	Plasticizer to Polymer ratio
% Oleic Acid	Plasticizer / Stabilizer
Oleic acid to ethylcellulose ratio	Plasticizer / stabilizer to Polymer ratio
pH	pH of Dispersion
% solids	Dispersion solids content in %
Viscosity (cps)	Dispersion viscosity

Table 2a: Individual batches of Surelease manufactured from specific parent lots of ethylcellulose

Ethylcellulose lots	Surelease batches
Lot A	7 Batches manufactured
Lot B	8 Batches manufactured
Lot C	6 Batches manufactured
Lot D	8 Batches manufactured

Table 2b. Surelease Coating Process Conditions:

Surelease Coating Parameters	
CPM Bead Charge (Kg)	0.5
Spray Rate (g min^{-1})	18
Spray Nozzle (mm)	0.8
Partition Height (mm)	10
Theoretical Weight Gain (%)	10
Dispersion Solid Content (%)	15
Product temperature (°C)	45
Inlet Air Volume (m^3 $hour^{-1}$)	100
Atomizing Air Pressure(bar)	1.0

Top Coat (Opadry) Application Process Parameters	
Inlet Air Temperature (°C)	0
Spray Rate (g min^{-1})	.0
Atomization Air Pressure (bar)	.5
Inlet Air Volume ($m^3 hr^{-1}$)	00
Weight Gain (%)	.5
Solids Content (%)	.0

Table 3: Model independent approach - Difference (f1) and similarity (f2) factors for dissolution curves of drug product batches manufactured using Surelease manufactured using different batches of raw material. Raw material batch A was used as the "reference" batch

Ref = Lot A		
Surelease Batches	f1 (difference factor)	f2 (similarity factor)
Lot B	1.70	96.49
Lot C	6.98	77.74
Lot D	2.04	95.13
Acceptable Range for Similarity	0 - 15	50-100

Table 4 – Weibull model parameters obtained for each Surelease® batch

Run	Ethylcellulose Lot No.	β	τ	R2	RMSE
Lot 356	Lot A	0.934	669.2	0.982	3.14
Lot 357		0.910	710.8	0.983	2.91
Lot 358		0.942	698.2	0.984	2.90
Lot 359		0.924	676.6	0.985	2.81
Lot 360		0.923	693.6	0.984	2.84
Lot 361		0.951	688.3	0.983	2.99
Lot 362		0.933	662.9	0.981	3.23
Lot 392	Lot B	0.933	674.5	0.983	3.03
Lot 393		0.931	688.2	0.983	2.96
Lot 394		0.940	671.6	0.981	3.21
Lot 395		0.956	670.4	0.979	3.34
Lot 396		0.907	639.8	0.982	3.19
Lot 397		0.920	668.6	0.980	3.22
Lot 398		0.902	673.8	0.983	3.00
Lot 399		0.878	708.4	0.981	3.02
Lot 415	Lot C	0.870	640.5	0.977	3.55
Lot 416		0.890	620.6	0.977	3.57
Lot 417		0.955	666.0	0.976	3.62
Lot 418		0.971	561.2	0.980	3.64
Lot 419		0.971	607.0	0.976	3.81
Lot 420		0.971	606.9	0.977	3.73
Lot 421	Lot D	0.938	676.2	0.980	3.21
Lot 422		0.938	665.3	0.977	3.50
Lot 423		0.949	693.9	0.976	3.53
Lot 424		0.944	666.9	0.978	3.42
Lot 425		0.936	672.6	0.975	3.65
Lot 426		0.929	660.3	0.978	3.44
Lot 427		0.942	669.0	0.976	3.61
Lot 428		0.920	655.9	0.976	3.60

Table 5 – Weibull model parameters obtained: summary statistics for each ethylcellulose lot

Ethylcellulose Lot No.	β			τ		
	Mean	**Standard deviation**	**%RSD**	**Mean**	**Standard deviation**	**%RSD**
Lot A	0.931	0.013	1.431	685.6	17.0	2.5
Lot B	0.921	0.025	2.690	674.4	19.3	2.9
Lot C	0.938	0.046	4.879	617.0	35.5	5.7
Lot D	0.937	0.009	0.949	670.0	11.6	1.7

Figure Legends

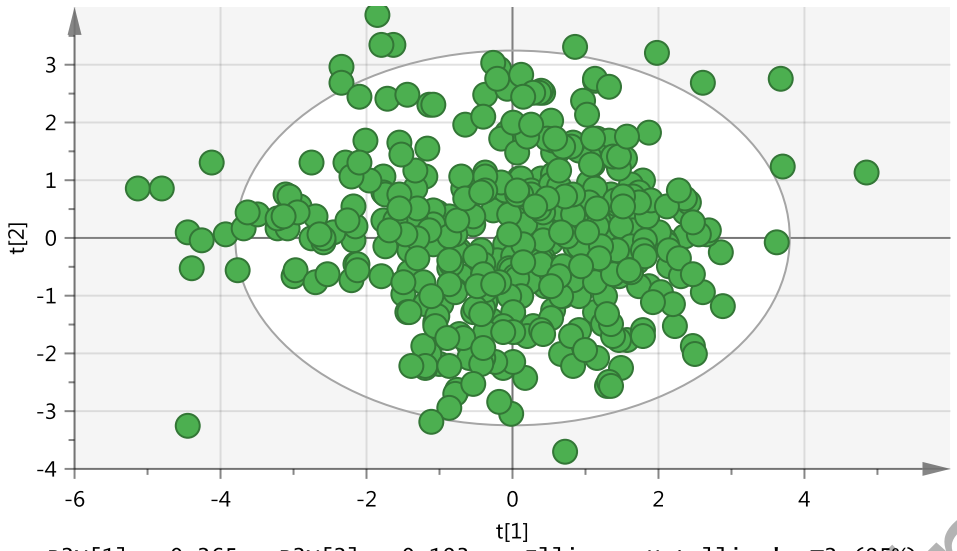
Figure 1: Scores plot (a) and Loadings Plot (b) from PCA of certificates of analysis from Surelease

Figure 2: Scores plots for PCA for different lots of ethylcellulose associated with Surelease batches: (a) all lots in data set shown; (b) showing only lots under study for their input material. The plots are colored by the input material lot number.

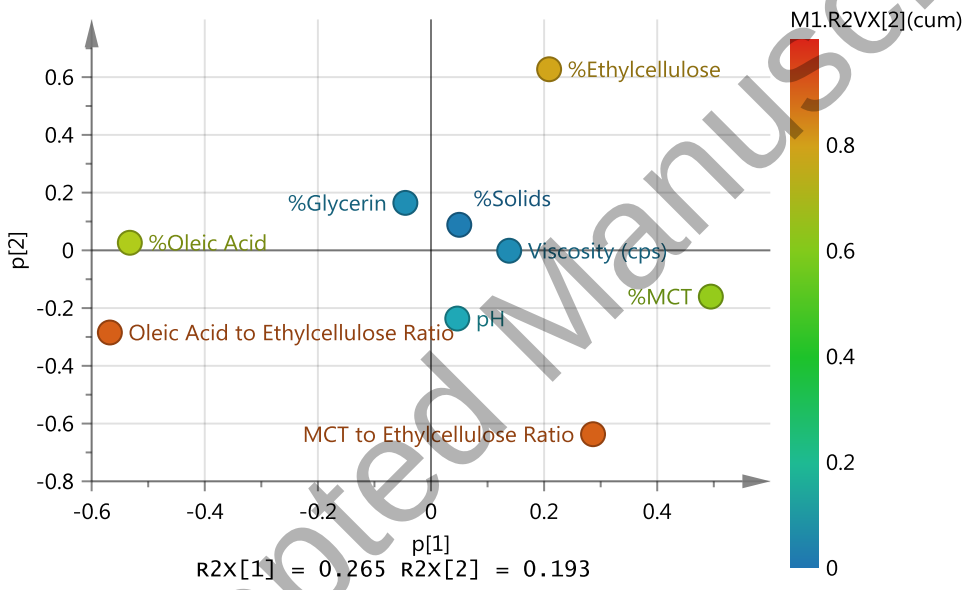
Figure 3: Contribution plot analysis (a) groupings observed; (b) scores contribution plot

Figure 4: Mean dissolution curves of batches of drug product made from Surelease systems manufactured from specific lots of ethylcellulose. The error bars represent the 95% confidence interval for the mean.

Figure 5 – Weibull model parameters obtained for each ethylcellulose lot: a) β (beta), b) τ (tau)



R2X[1] = 0.265 R2X[2] = 0.193 Ellipse: Hotelling's T2 (95%)



R2X[1] = 0.265 R2X[2] = 0.193