From Laboratory to Manufacturing: Understanding the Variability of a Granulated Product Between Different Scales, Production Sites and Testing Facilities Using JMP®

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Summary

Variations between scales going from laboratory to production can be difficult and daunting to assess. Having complex, underlying processes to manufacture the product is a greatly complicating factor and hence makes it even more complicated for the scientists to understand whether the difference is real or not.

Having a comparatively large dataset on one Syngenta range product allowed us to explore whether production site, analytical site, testing person or equipment used at the development site made any difference to the product. Via visual data exploration and using some basic statistical tools, we concluded that we had a stable product where 96.7%+ of our product comes out with excellent results. Furthermore, we were able to see that these were independent of production site, equipment used or testing facility; however the testing person may have a greater influence.

Briefly exploring modelling, we have found that using modelling techniques may greatly add value to a development project where there is limited opportunity to have repeat batches.

Background

Figure 1: A spray granulation process

One of the technologies Syngenta uses to deliver a safe and effective formulation of its active ingredients to its customers is a WG. This is a water dispersible granule, defined as “A formulation consisting of granules to be applied after disintegration and dispersion in water”. One of the technologies used is spray granulation, by which a porous raspberry like structure is formed. This process has a lot of variables: from the composition of the formulation, the pre-milling and milling processes to the granulation process which takes place in a granulator.

An example is a“top spray granulator”, as seen in figure one, which is a tower through which hot air flows from the bottom up whilst a water based slurry is sprayed from the top down.

This process has multiple variables. In broad terms they can be divided into the physical structure of the granulator, nozzle configuration, granulator settings and environmental influences. Table 1 gives a selection of factors impacting on the spray process.

In Syngenta, an array of different equipment is available for development and production of spray agglomerated WG with sizes range between a few 100g batch process to several tons a day in continuous production. Between these different scales, there is a lot of anecdotal evidence of the translation of settings between different scales; however we have previously not understood what impact this may have on the final product. Furthermore, there are many perceptions as to the quality of the product and the testing from different facilities.

Table 1: Table of various process parameters

Granulator Structure	Nozzle configuration	Settings	Environmental Influences
Size	Nozzle diameter	Air flow volumes	Humiditiy of air [#]
Geometry	Nozzle material	Temperature	
Nozzle Height	Nozzle air flow	Retention time in tower [‡]	
Air volume	Nozzle pressure of atomisation	Pumping speed of slurry	
Continuous or batch process			

[#] Can be controlled on some equipment

[‡] Level of control can greatly differ between batch and continuous processes

In an effort to further our understanding of the variability of the product, data has been gathered for a Syngenta commercial product. Data concerning batches produced in development and production were available from one development site and two production sites. These batches were analysed at four analytical laboratories.

Some of the questions we wanted this dataset to answer were:

1. What is the overall variability of the product?
2. Are there quality differences between the different equipment used in development?
3. Does the suspensibility of the product differ between the different sites?
4. Are the results of the suspensibility independent of the analytical site and the person testing (if known)?
5. Can we say anything about the accuracy of the testing method?
6. Can we model the data to use it for future development projects?

Obtaining data and data treatment

Data of the different batches from different sites was obtained from different analytical laboratories. As data was spread between different sites, formats, people and systems, we are certain that all not all batch data was able to be obtained in the 169 individual observations in the dataset. Whilst the data set from the development site is complete to the best of our knowledge, lots of data for the production sites is missing. The results of the data should be seen under this concession. The power of the analysis may be greatly enhanced by including these.

Besides included data on manufacturing sites, analytical sites, the dataset also included various testing that is usually done to analyse the batch quality. For the purpose of this paper, we are focusing on the measurement of suspensibility. This is a testing method that allows the assessment of how well solid particles remain dispersed through a water column over time. (MT 168 (W Dobrat, A Marjtijn, 1994)) It is often one of the most important measures of the performance of a WG.

All data was accumulated into one data table in JMP 12[1]. However, all other measures that were performed and recorded are also included in the dataset. Some analytical data, namely wet sieve residues and dispersibility proved difficult to handle. Both methods measure the amount of oversized material left on sieves of different sizes; however the measurement is not particularly sensitive when only trace amount of material is left in the sieves. A common statement if this occurs is to write for example “>0” or “<0.01”, leaving us with some data that required tidying up. For this, we used a “if else” function as shown below. At the same time, it was necessary to change the type of data by applying the Num() function.

```
Num(
  If(
    Dispersibility (2%, 1 min) 100um == "<0.01", "0.01",
    else(),
      If(
        Dispersibility (2%, 1 min) 100um == ">0", "0.01",
        else(),
          If(
            Dispersibility (2%, 1 min) 100um == "<0.1", "0.01",
            else(), Dispersibility (2%, 1 min) 100um
          )
      )
  )
)
```

[1] Work started in JMP 11. The main analysis was done in JMP 12.

What is the overall variability of the product?

Firstly, we used a bubble plot to explore the evolution of data through time. For this, we plotted suspensibility vs production site coloured in by analytical site. As dates were available, an animation was created to show the development through time

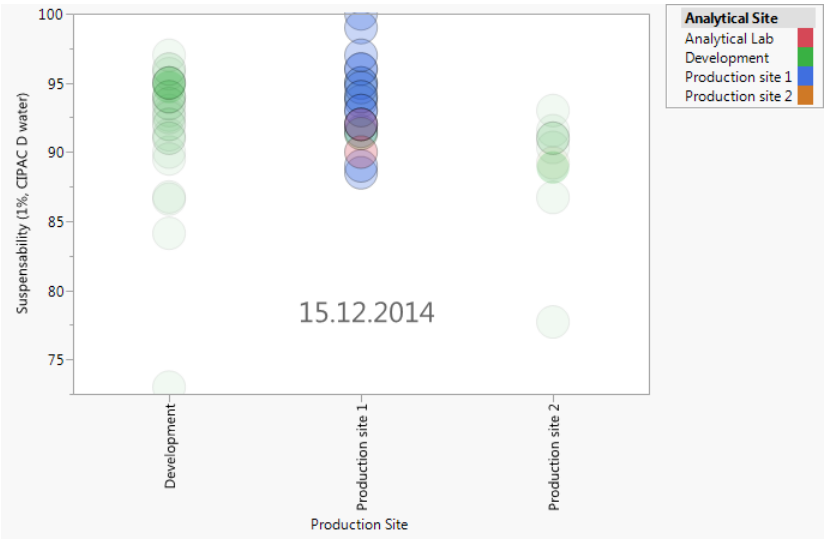


Figure 2: Snapshot of data of the bubble plot with time point 15.12.2014

By visualisation, it was possible to see that first few batches produced at a site seemed to perform worse in the test than later batches. This is a response we expect when we establishing a new product. As we learn about how the operations affect the product, we are able to produce our product to a higher quality.

Overall values of suspensibility were obtained using the “table” function.

	Suspensability (1%, CIPAC D water)
N	168
Mean	90.870238095
Std Dev	5.0979690628
Min	72
Max	100

Using the normal distribution, we can assume that 96.7% of our data is within two standard deviations – the lower end starting at around 80%. This is a good result for us, confirming that this is indeed a good quality product that we can reliably produce to a high standard.

Is there quality differences between the different equipment used in development?

Another question we wanted enquire our dataset about was whether we could see any significant differences between the different equipment that were used in the development site. As before, we looked at some of the basic statistics with JMP.

	Suspensability (1%, CIPAC D water)				
Equipment (if produced at Development Site)	N	Mean	Std Dev	Min	Max
Large Development	18	93.444444444	1.8856180832	90	96
Medium Development	5	89	9.0277350426	73	94
Small development	51	91.078431373	5.3882952304	78	97

We wanted to see whether these differences were actually significantUsing a “fit model” function with “standard least squares” and “effect leverage” set up, the following scaled estimates were obtained.

Scaled Estimates

Nominal factors expanded to all levels

Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	91.174292	0.889679	102.48	<.0001*
Equipment (if produced at Development Site)[Large Development]	2.2701525	1.127367	2.01	0.0478*
Equipment (if produced at Development Site)[Medium Development]	-2.174292	1.586654	-1.37	0.1749
Equipment (if produced at Development Site)[Small development]	-0.095861	0.980172	-0.10	0.9224

The result tells us that there seems to be some positive impact when we are using the largest equipment, but there does not appear to be a significant impact when using the small or medium scale equipment.

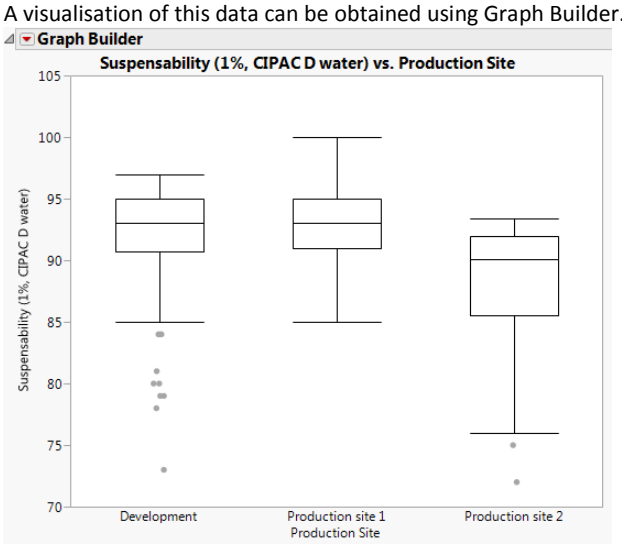
The reasons for this result may be multi-fold: first trials are usually done on this equipment and we have yet to find the ideal setting for producing the product. In line with the first point, once we have learned how to best spray it, the smaller equipment is often used to develop an understanding how the product responds to more extreme conditions. Another reason for these results may be that production and controlling quality can be made easier on larger equipment as this may not be as sensitive to minor changes in the system compared to the small scales.

Does the suspensibility of the product differ between the different sites?

Using the "Tabulate" function, we had a look the summary statistics (mean, standard deviation, minimum, maximum and number of observations) for each production site as well as for each analytical site.

		Production Site		
		Development	Production site 1	Production site 2
Suspensability (1%, CIPAC D water)	N	74	44	50
	Mean	91.513513514	92.840909091	88.184
	Std Dev	5.1637388049	3.1911445918	5.3328921586
	Min	73	85	72
	Max	97	100	93.4

A visualisation of this data can be obtained using Graph Builder.



From this primary data and having a look at various models, we could not find any conclusive evidence that the quality of the product is dependent on the manufacturing site.

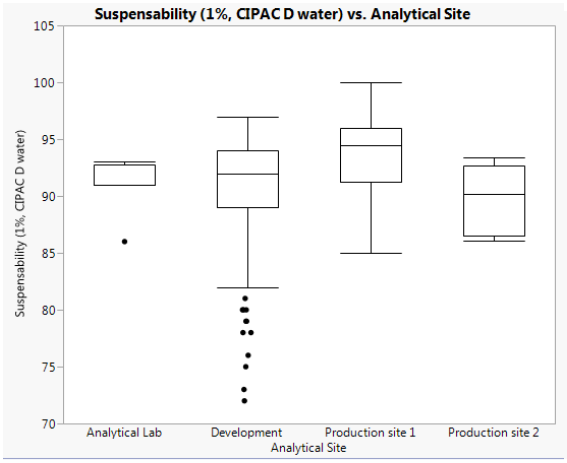
Are the suspensibility results independent of the analytical site and the person testing (if known)?

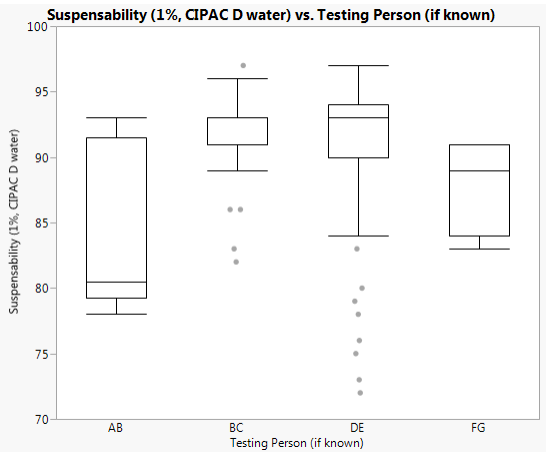
Using the "Tabulate" function, we had a look the summary statistics (mean, standard deviation, minimum, maximum and number of observations) for each production site as well as for each analytical site; as well as for testing person

		Analytical Site			
		Analytical Lab	Development	Production site 1	Production site 2
Suspensability (1%, CIPAC D water)	N	8	125	28	7
	Mean	91	90.288	93.678571429	89.885714286
	Std Dev	2.2038926601	5.4503861953	3.3670909681	2.7793455893
	Min	86	72	85	86.1
	Max	93	97	100	93.4

	Suspensability (1%, CIPAC D water)			
	Testing Person (if known)			
	AB	BC	DE	FG
N	8	29	77	11
Mean	84.125	91.517241379	90.792207792	88
Std Dev	6.3569422119	3.4498518566	5.7909586115	3.0659419434
Min	78	82	72	83
Max	93	97	97	91
Range	15	15	25	8

A visualisation of this data can be obtained using Graph Builder.





As there are many parameters that can be analysed (production site, analytical site, testing person and equipment at development site), we wanted to see which parameters actually had an influence on the formulation. For this, we used the "fit model" function using "standard least squares" and "effect leverage" as parameters for analysis. Using a 95% confidence interval, the only significant effect remaining was the testing person (summary of effects below).

Effect Summary

Source	LogWorth	PValue
Testing Person (if known)	4.462	0.00003
Equipment (if produced at Development Site)	0.742	0.18108
Production Site	.	.
Analytical Site	.	.

Despite this data indicating that the person who does the analysis of the product may make the biggest difference, there may be a confounding variable undermining the data: not all of the four analysts tested the same batches. Conclusive evidence would be needed in the form of a designed experiment where different analysts test the same batches using the same method to prove or disprove this theory.

Can we learn anything about the accuracy of the testing method between different sites?

	Suspensability (1%, CIPAC D water)				
Batch Number	N	Mean	Std Dev	Min	Max
DE4IP040	2	91	0	91	91
EP4J001EL	2	94.5	2.1213203436	93	96
EP4J002EL	2	94	2.8284271247	92	96
EP4J003EL	3	94	1.7320508076	93	96
EP4J004EL	3	93.666666667	1.1547005384	93	95
EP4J005EL	2	92.5	2.1213203436	91	94
EP4J027EL	2	88	2.8284271247	86	90
IP4K1872	3	91	0	91	91
IP4K1875	3	91	0	91	91
IP4K1883	2	88.5	2.1213203436	87	90
IP4K1884	3	84.033333333	1.7897858345	83	86.1
IP4K1885	3	85.5	1.3228756555	84	86.5
IP4K1886	2	88.7	6.6468037432	84	93.4
IP4K1887	3	89.9	2.4758836806	88	92.7
IP4K1888	3	91.1	0.8544003745	90.3	92
IP4L1939	2	90	1.4142135624	89	91
IP4L1960	2	91.5	2.1213203436	90	93
IP5A1501	2	91	0	91	91

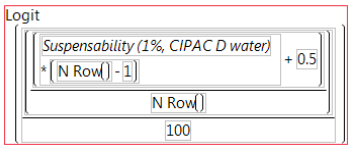
Leading on from the previous question, some repeat testing was carried out, although not in a well-controlled manner as is suggested before. In the dataset, we have a number of batches that were tested more than once, usually by two or more analytical sites. For this, we created a subset of data that only contained batches for which we had two or more observations. Looking at a summary table of basic statistics, we can see that the standard deviation for these usually does not exceed 3 units; however there is a notable exception: Batch number IP4K1886 shows a standard deviation of over 6.

Person to person variation is another aspect of testing method variability that should be looked into. In this case there is only one repeat available where one person has measured the same batch twice: DE4IP040. Although no variation is seen in this test, a designed experiment would be needed to confirm this observation.

Despite not perusing this item further, this gives some confidence in the test results between different analytical sites.

Can we model the data to use it for future development projects?

For ongoing and future development projects, we were interested to explore whether we would be able to model the data. This would allow adding value to projects based on the limited amount of repeat batches that can be done during a typical development of a water dispersible granule. The data we gather from these tests are non – symmetrically distributed and furthermore any values cannot pass 100%. Therefore, the choosing the appropriate method was important. For this reason, we started looking into transforming the data using a logit functions with an underlying beta regression.
Based on the formula



Using subsequent data tranformation and transformation back to a predicted percentage via a logist function, we found that we could start to model the data based on various parameters, such as production site. As this is a new tool for scientists to use in development, this data modelling will have to be applied and tested on a development project in order to assess its usefulness and applicability in real life.

Conclusion

For us, it was interesting to look at existing data in one of our spray granulated products as this is something we have not done before. Variations we were concerned about such as production site or analytical site did not come out as relevant factors in regards to the product suspensability. For us, this provides a great leap in knowledge about this process and its variability.
Although the power of the analysis could be greater if more data were available, this analysis was a valuable learning experience – especially with regards to the last point discussed: the modelling. The last area can really add benefit to future projects by using historical data. Future projects are required to help validate our concept; however if it works, this would be an exciting tool available to the development of future products.

Bibliography

W Dobrat, A Marjtijn. (1994). *CIPAC Handbook Volume F.* Collaborative International Pesticides Analytical Council Ltd.