Further analysis of the PQRI BUWG industry survey: How do formulation and process parameters impact blend and unit dose uniformity?

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Summary

Responses from the second PQRI BUWG survey of industry have been reanalyzed to identify potential links between formulation and processing variables and the measured uniformity of blends and unit dosage forms. As expected, the variability of the blend potency and tablet potency data increased with a decrease in the API loading. There was also an inverse relationship between the nominal strength of the unit dose and the blend uniformity data. The data from the PQRI industry survey do NOT support the commonly held viewpoint that granulation processes are necessary to create and sustain tablet and capsule formulations with a high degree of API uniformity. There was no correlation between the blend or tablet potency variability and the type of process used to manufacture the product. Although it is commonly believed that direct compression processes should be avoided for low API loading formulations due to blend and tablet content uniformity concerns, the data for direct compression processes reported by the respondents to the PQRI survey suggests that such processes are being used routinely to manufacture solid dosage forms of acceptable quality even when the low drug loading is quite low.

Introduction

Between 2000 and 2003 the Blend Uniformity Working Group (BUWG) of the Product Quality Research Institute (PQRI) surveyed pharmaceutical companies on two occasions to better understand the practices used for blend sampling [1] and to clarify the relationships (if any) between blend potency test results and dosage unit potency [2]. The results of these surveys resulted in a proposed guidance for industry regarding in-process sampling protocols for powder blends and solid dosage units (tablets and capsules) [3]. They also lead to the development of recommendations for interpreting the results of such sample testing. Since that time the sampling and analysis approaches described in the whitepapers published by the BUWG have become the *de-facto* standard for formulation and manufacturing scientists throughout the industry.

The second BUWG survey of industry solicited responses relating to the formulation composition (drug loading and dose) and type of manufacturing process used to manufacture solid dosage forms, but these responses were not included in the original analysis [2]. Conventional wisdom amongst pharmaceutical formulators is that granulation processes are useful for enhancing the uniformity of dosage units, especially in low dose products. However, to the authors' knowledge there has never been an in-depth retrospective analysis of manufacturing data to establish whether this widely held conviction is correct. In theory, the results of the BUWG anonymous survey should provide an opportunity to assess the impact of the drug loading, dose, and the choice of processing method on both the blend uniformity and the dose uniformity of the final dosage form.

The objective of the work described in this manuscript was to re-examine the responses from the second PQRI BUWG survey of industry to identify any potential links between formulation and processing variables and the measured uniformity of blends and unit dosage forms. This

analysis should increase the industry's understanding of how formulation and processing factors can impact the content uniformity of solid dosage forms, consistent with PQRI's mission of providing objective guidance to industry on practices that can enhance drug product quality.

Materials & methods

Raw data from the BUWG survey of industry were received in blinded form from PQRI. Details of the survey methodology used to obtain the data can be found elsewhere [2]. The responses solicited during the survey are shown in Table 1. The raw data comprised nine spreadsheets containing over twenty thousand unique data points. Anonymous responses were received from nine companies, and data were reported for seventy-six unique products and over eight-hundred lots[a].

Initially, the raw data were pooled, sorted and checked for errors. Any obviously incorrect data (for example, API loadings of more than 100%) were omitted from further analysis. Potential correlations between the various survey responses were then explored using SpotFire software (TIBCO Software Inc., Somerville, MA, USA). More complex statistical analyses (such as partial least square (PLS) analysis) were attempted using MatLab software (MathWorks, Natick, MA, USA).

Results & discussion

The amount of data collated from the cross industry PQRI BUWG survey is unprecedented and it is certainly worthy of further examination. However, the data are not as perfect as would be desired (missing data, obviously incorrect values, *etc*), so it is important not to over-interpret the results. The data from the PQRI BUWG industry surveys are also more than ten years old, so

[a] Some data were received by PQRI after the original deadline for the survey, and thus not all of the results included here were considered in the original PQRI BUWG reports.

any trends that are uncovered reflect the practices of the 20th century and cannot provide any insights into more recent development and manufacturing practices (such as process analytical technologies (PAT) and quality-by-design (QbD)). However, the data can provide useful information about longstanding formulation design and process development practices.

The pooled data exhibit some notable trends. The vast majority (~90%) of the formulations were to be compressed as tablets rather than being filled into capsules. As shown in Figure 1, the API loading in the solid dosage formulations was generally much less than 20% by weight and in many cases (~60%) was less than 10% by weight. This low percentage of API in the formulations and products covered by the survey could influence the trends that emerge from the data as it is further analyzed. Figure 1 shows the range of batch sizes for which the data was obtained, and, it is worth noting that a wide range of batch sizes from pilot scale (24kg) to commercial scale (2400kg) was represented.

The frequency of use of different manufacturing methods by the responding companies is represented in Figure 2. The most commonly used manufacturing methods were direct compression and wet granulation. Of the nine responding companies, six used direct compression processes, six used wet granulation and only two used dry granulation. No company reported data for all three processing techniques, but just over half of companies (5 out of 9) used more than one approach. Four companies reported only one type of data, suggesting that they make a single manufacturing pathway work irrespective of the API properties that are presented. More detailed analysis of the individual batch data showed that there was a bias in the survey data towards direct compression (67% of batches) and wet granulation (32% of batches). Data for products manufactured by dry granulation represented only 1% of the pooled batch data, and it was clustered in a narrow range of API contents

(between 1 and 5 %) and batch sizes (100 to 123 kg). These trends should be taken into consideration as the data from the survey are further analyzed.

From Figure 3 it is readily apparent that all three manufacturing pathways are used for formulations with moderate (2 – 10%) API loadings. For the very lowest API loadings (<1%), direct compression and wet granulation are both used extensively. Direct compression was used for up to 50% API loading and wet granulation was exclusively used for the formulations with the very highest drug loadings. This is presumably to impart good flow and compaction properties to the formulations which contain limited amounts of excipients. These trends seem to reflect the commonly help beliefs about the strengths and weaknesses of each possible method for manufacturing solid oral dosage forms. However, whilst Figures 2 and 3 show the trends in manufacturing process selection, they do not give any insights into the reasons for those choices. This topic will be the subject of the following analysis and discussion.

To further understand the trends in the survey data, it is necessary to examine the relationships between well accepted measures of product quality, such as blend uniformity and tablet potency variation, and the reported manufacturing data. The first relationships examined were those between the most common measures of product quality (such as blend uniformity and dosage form content uniformity) and the company identity and batch size. It was found that there was no correlation between the identity of the company or the batch size and the various measures of product quality (data not shown).

Next, the pooled data from all nine companies were examined to determine if there was any relationship between the API loading and the various measures of product quality. Figure 4 shows that the variability of the blend potency data from any given batch (“blend RSD”) tends to increase with a decrease in the API loading. A similar trend is apparent when the stratified

tablet sample potency variation data are plotted in an analogous manner (plot not shown). This is consistent with conventional wisdom regarding the challenges of making and sustaining a uniform blend for a formulation that contains a low percentage of API [4]. Notably, Figure 5 shows that there is also a relationship between the nominal strength of the unit dose and the blend uniformity data. Presumably, this is a direct result of the strong dependence of the API loading on the nominal strength of the unit dose (that is, lower doses are usually associated with lower API loadings, and *vice versa*).

It is a widely held belief that granulation processes can be necessary to create and sustain tablet and capsule formulations with a high degree of API uniformity. This is believed to be especially true when the API loading in the formulation is very low (say, <1%). The data from the PQRI industry survey do NOT support this commonly held viewpoint. As illustrated in Figure 6 there was no correlation between the mean blend potency variability and the type of process used to manufacture the product. When only the formulations containing between 1 and 5% API were considered, again there was no consistent trend between the mean uniformity of the blend and the type of process used (Table 2). This trend is also seen in the mean stratified tablet uniformity data (Figure 7 & Table 2), although the dry-granulation data is notable for a single outlying data point. Interestingly, although it is commonly believed that direct compression processes should be avoided for low API loading formulations due to blend and tablet content uniformity concerns, the data for direct compression processes reported by the respondents to the PQRI survey suggests that such processes are being used routinely to manufacture solid dosage forms of acceptable quality even when the low drug loading is quite low. In fact, data for direct compression processes were the most widely reported in the PQRI survey and the blend uniformity variation was always less than 10%. The largest variation in blend potency data was found for the wet granulated products, but this could be because these products were the most challenging to manufacture because of poor API physical properties or

high API loadings. Without API property data for these products or more details of the manufacturing processes (such as whether the blends were made by high or low shear mixing) it is impossible to be sure of the underlying cause of the observed trends.

As a final method of analysis, multivariate regression techniques were used to scrutinize the data. Unfortunately these analyses were unsuccessful because the data for the different manufacturing methods were not evenly distributed and several parameters (such as batch size) were not fully independent variables. However, it was possible to confirm that the method of manufacture had a negligible contribution to blend and dosage uniformity differences.

Conclusions

The responses from the second PQRI BUWG survey of industry have been reanalyzed to identify any potential links between formulation and processing variables and the measured uniformity of blends and unit dosage forms. As expected, the variability of the blend potency and tablet potency data increased with a decrease in the API loading. There was also an inverse relationship between the nominal strength of the unit dose and the blend uniformity data. This is probably a direct result of the strong dependence of the API loading on the nominal strength of the unit dose. The data from the PQRI industry survey do NOT support the commonly held viewpoint that granulation processes are necessary to create and sustain tablet and capsule formulations with a high degree of API uniformity.. There was no correlation between the blend or tablet potency variability and the type of process used to manufacture the product. Although it is commonly believed that direct compression processes should be avoided for low API loading formulations due to blend and tablet content uniformity concerns, the data for direct compression processes reported by the respondents to the PQRI survey suggests that such processes are being used routinely to manufacture solid dosage forms of acceptable quality even when the low drug loading is quite low. The re-analysis of the PQRI

BUWG industry survey increases the industry's understanding of how formulation and processing factors can impact the content uniformity of solid dosage forms, consistent with PQRI's mission of providing objective guidance to industry on practices that can enhance drug product quality. It also shows the value of analyzing blinded manufacturing data for a large number of products and companies. Additional work aimed at creating cross-industry data sets that can provide additional insights into formulation and manufacturing best-practices would be of significant value to regulators, industry scientists, and academic researchers.

Acknowledgements

The Board of Directors of the Product Quality Research Institute (PQRI) is thanked for providing blinded access to the Blend Uniformity Working Group (BUWG) survey results.

References

1. Boehm, G., Report on the industry blend uniformity practices survey. Pharmaceutical Technology, 2001, August, p.20-26.
2. Boehm, G., et al., Results of statistical analysis of blend and dosage unit content uniformity data obtained from the Product Quality Reasearch Institute blend uniformity working group data-mining effort. PDA Journal of Pharmaceutical Science and Technology, 2004, 58(2): p.62-74.
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Table 1: Formulation and process parameters collected in the BUWG survey of industry

Parameter	**Description / units**
Company	Blinded
Product	Blinded
Lot No	Blinded
API Loading	Percent
Batch Size	Kilograms
Method of Manufacture	Direct compression / Dry granulation / Wet granulation
Dosage Form	Tablet / Capsule
Dose	Milligrams
Blend Sample Location	Top, middle, bottom, *etc*
Target Blend sample size	X – Y mg, 1-3x unit dose, *etc*
Blend Potency Result	Percentage of theory
Stratified Tablet Sample Location	Percentage of batch
Stratified Tablet Result	Percentage of theory
Dosage Form Weight	Milligrams
Composite Assay Value	Percentage of Label Claim

Table 2: Mean blend and tablet potency variability data for batches manufactured using different methods

API loading (%)	Manufacturing method	# of batches	Blend potency variability ('blend RSD', %)	Stratified tablet potency variability ('tablet RSD', %)
All	Direct compression	693	3.6	2.9
	Dry granulation	19	3.5	4.6
	Wet granulation	97	5.3	2.6
1-5%	Direct compression	375	3.6	2.5
	Dry granulation	19	3.5	4.6
	Wet granulation	30	3.1	2.5

Figure 1: Relationship between percentage of API in the product and the batch size (squares = direct compression, circles = dry granulation, diamonds = wet granulation)

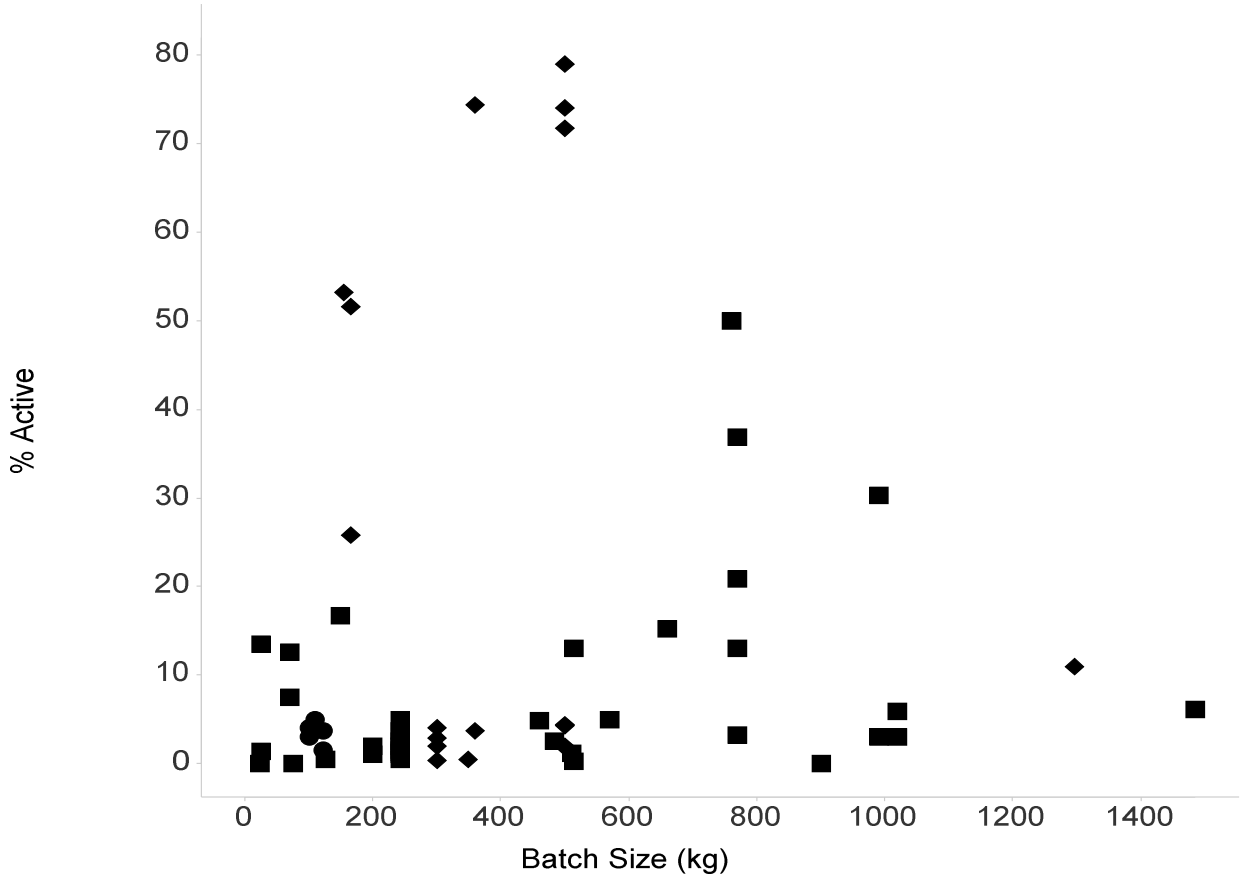

Figure 2: Manufacturing methods used by each company responding to the survey

(WG = wet granulation, DG = dry granulation, DC = direct compression)

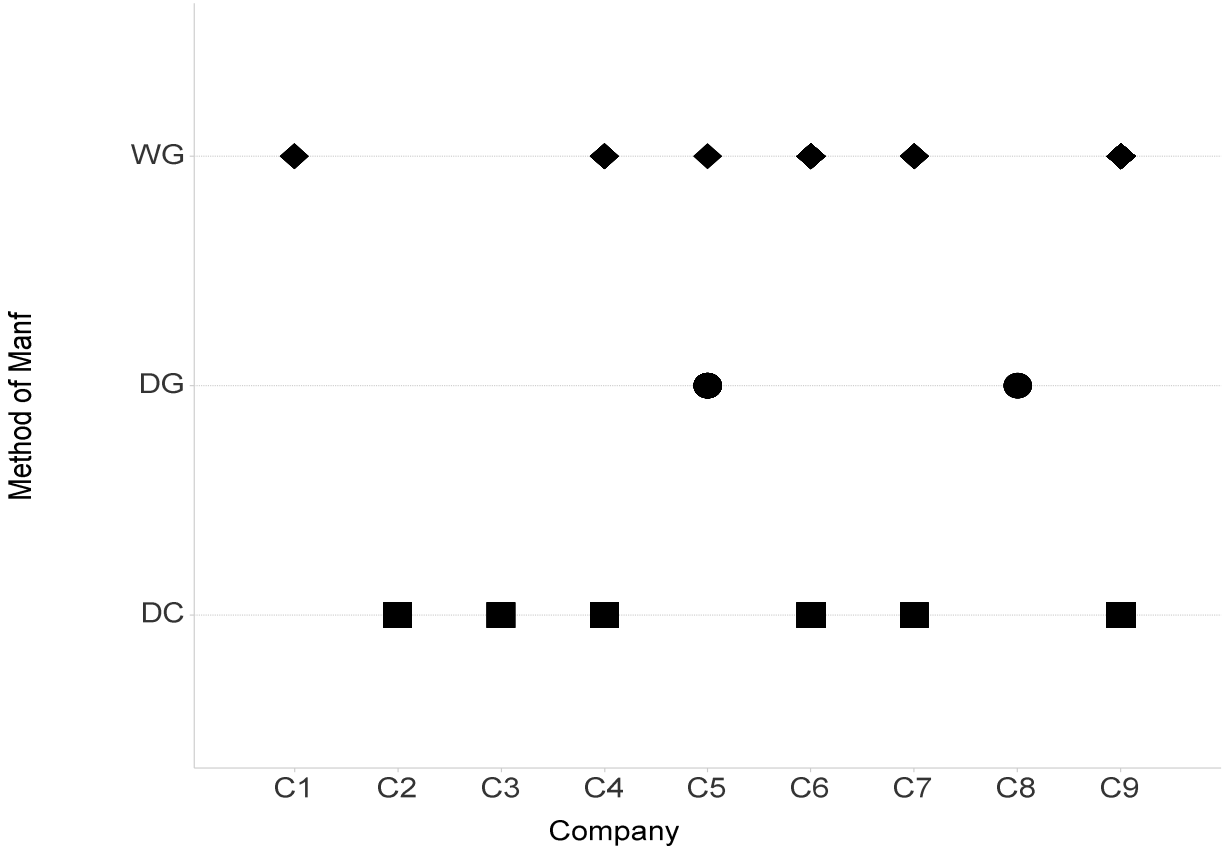

Figure 3: Percentage API distribution for each manufacturing method

(WG = wet granulation, DG = dry granulation, DC = direct compression)

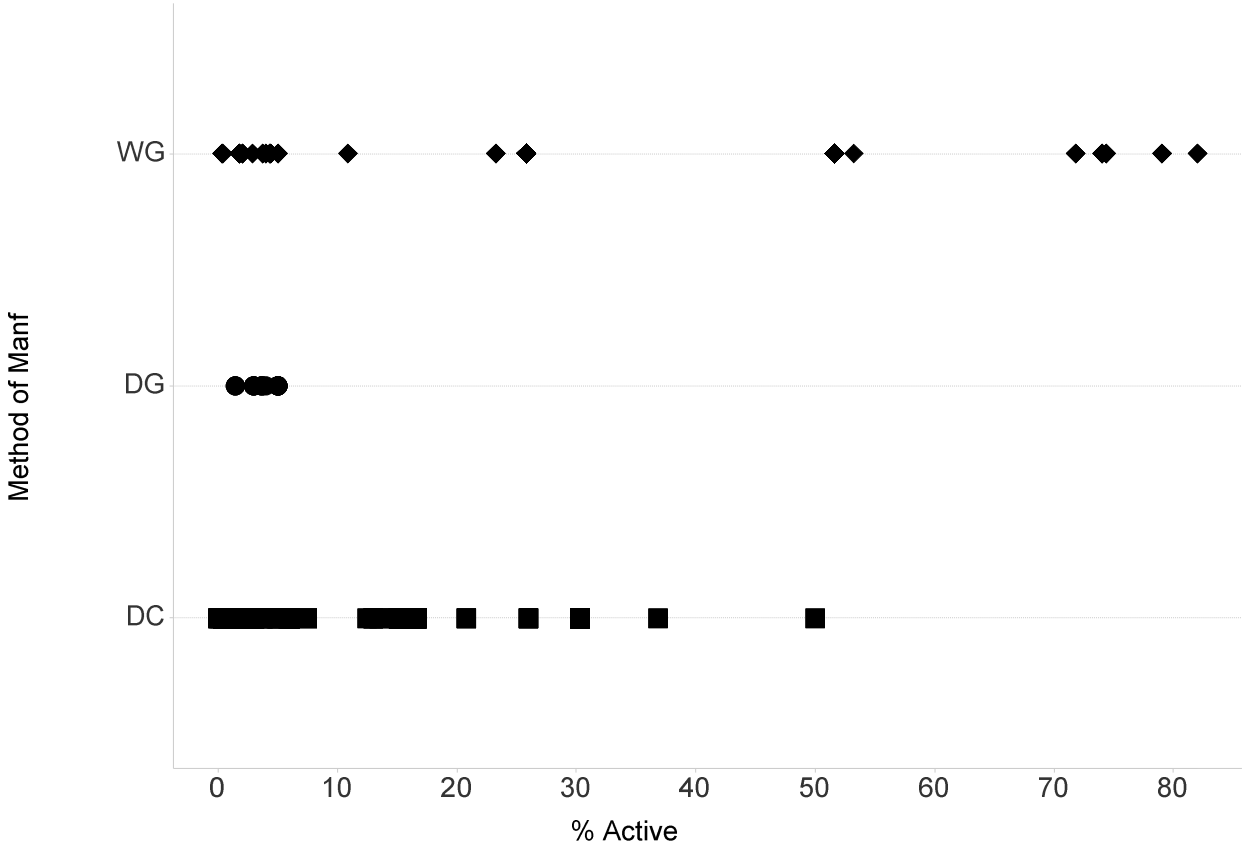

Figure 4: Relationship between percentage API and blend sample variability

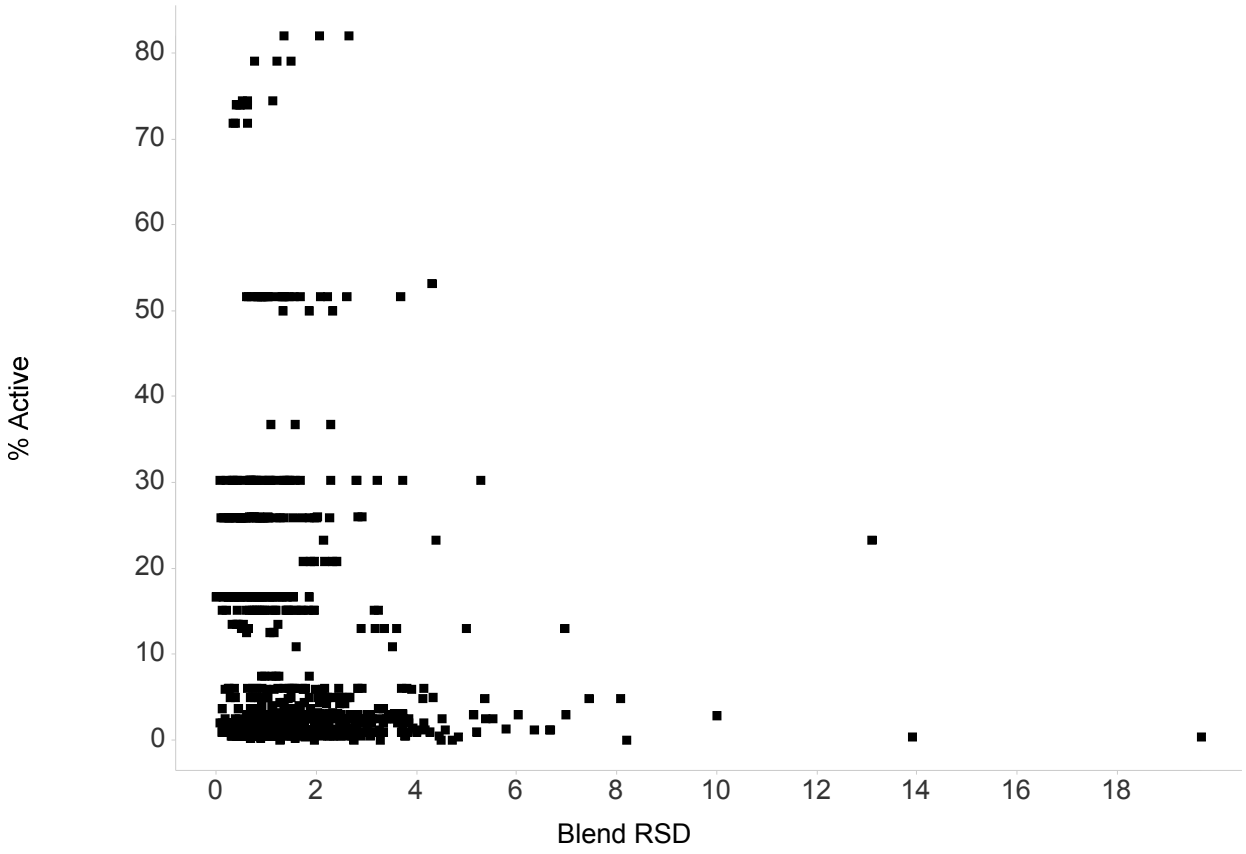

Figure 5: Relationship between dose strength and blend sample variability

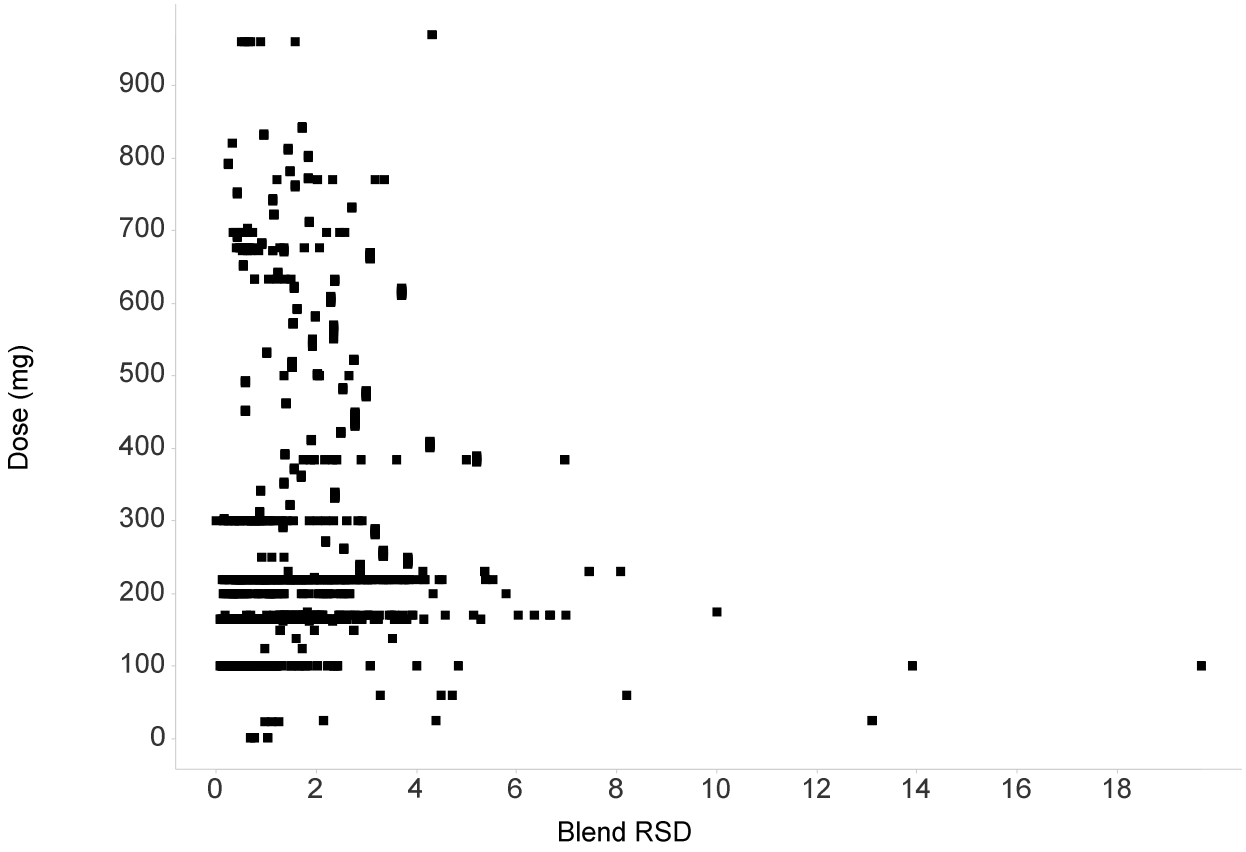

Figure 6: Blend sample variability distribution for each method of manufacturing

(WG = wet granulation, DG = dry granulation, DC = direct compression)

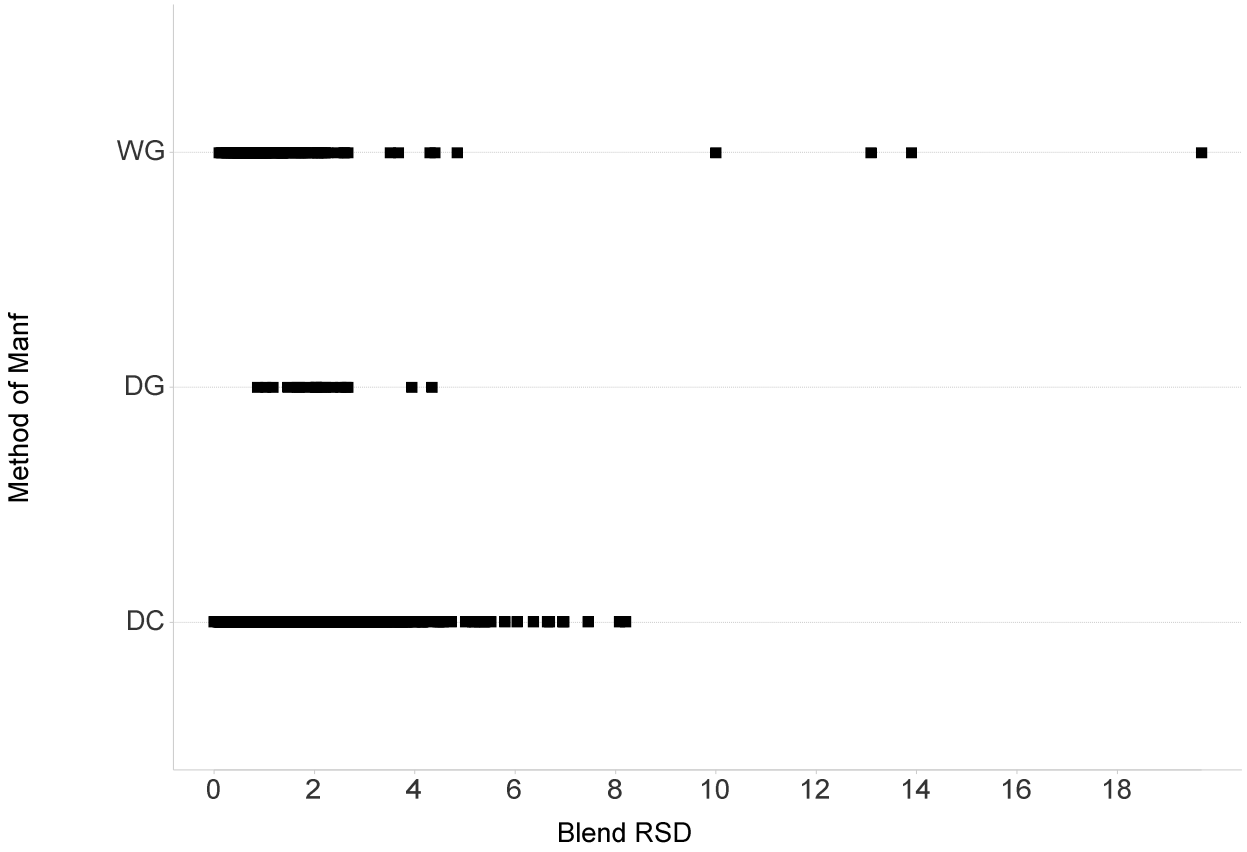

Figure 7: Stratified tablet sample variability distribution for each manufacturing method (WG = wet granulation, DG = dry granulation, DC = direct compression)