How do Formulation and Process Parameters Impact Blend and Unit Dose Uniformity? Further Analysis of the Product Quality Research Institute Blend Uniformity Working Group Industry Survey

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ABSTRACT: Responses from the second Product Quality Research Institute (PQRI) Blend Uniformity Working Group (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 loading of the active pharmaceutical ingredient (API). 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 because of blend and tablet content uniformity concerns, the data for direct compression processes reported by the respondents to the PQRI survey suggest that such processes are being used routinely to manufacture solid dosage forms of acceptable quality even when the drug loading is quite low. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:982–986, 2013

Keywords: content uniformity; formulation; mixing; processing; powder technology; solid dosage form; granulation

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 findings 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] These also led to the development of recommendations for interpreting the results of such sample testing. Since that time, the sampling and analysis approaches described in the white papers 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 among 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 objectively 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.

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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 number	Blinded
API loading	Percentage
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, 1–3× 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

The goal of the work described in this manuscript was to reexamine 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 guidance to industry on practices that can enhance drug product quality.

MATERIALS AND 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 20,000 unique data points. Anonymous responses were received from nine companies, and data were reported for 76 unique products and over 800 lots.[a]

Initially, the raw data were pooled, sorted, and checked for errors. Any obviously incorrect data (e.g., 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, Massachusetts). More complex statistical analyses (such as partial least square analysis) were attempted using MatLab software (MathWorks, Natick, Massachusetts).

[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.

RESULTS AND 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 overinterpret the results. The data from the PQRI BUWG industry surveys are also more than 10 years old, so 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 and quality by design). 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 were obtained, and it is worth noting that a wide range of batch sizes from pilot scale (24 kg) to commercial scale (2400 kg) was represented.

The frequency of the 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

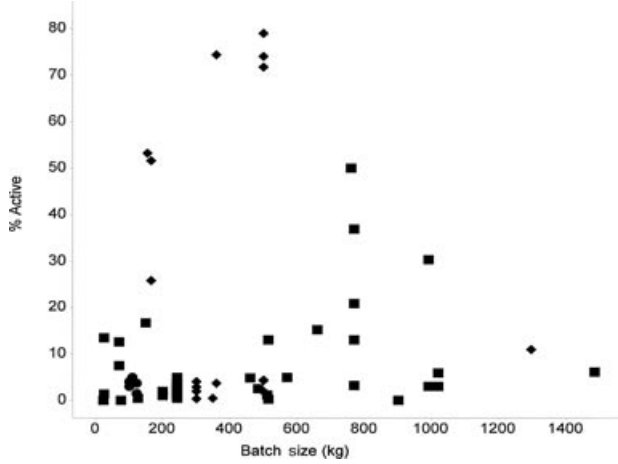

Figure 1. Relationship between percentage of API in the product and the batch size (squares, direct compression; circles, dry granulation; and diamonds, wet granulation).