Online Quality Control with Raman Spectroscopy in Pharmaceutical Tablet Manufacturing

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Abstract

Quality testing for tablet composition and uniformity at the manufacturing stage is critical to the pharmaceutical industry. However, current off-line, destructive, wet chemistry analysis incurs significant costs and long test times. This paper introduces a methodology to form a population batch size for quality control sampling in tablet manufacturing for an alternative online testing technology, Raman spectroscopy. An approach is presented to determine the minimum testing batch size for quality control sampling based on the desirable confidence level, margin of error, testing rate, and production rate. Experiments with both traditional wet chemistry analysis and Raman spectroscopy are conducted. The results demonstrate that the quality of Raman spectroscopy is comparable to that of wet chemistry analysis. The proposed quality sampling methodology reduces the queue time by orders of magnitude for typical tablet batches of one to four million tablets awaiting test results following the tablet compaction process. Furthermore, it increases the tablet sample size, which subsequently raises the confidence level.

Keywords: Pharmaceutical Quality Control, Sampling, Raman Spectroscopy

Introduction

Global pharmaceutical sales are a $466.3 billion industry (Yahoo! Finance 2004). The pharmaceutical industry is characterized by significant research and development activities, high capital investments, labor intensive processes, limited-time patent protection, and regulatory requirements (Knoop and Warden 1988; Yevich 1991; Papageorgiou, Rotstein, and Shah 2001; Viswanadham and Narahari 2001; Sarantopoulos, Altiok, and Elsayed 1995).

In the manufacturing phase, quality control is an important element. The U.S. Food and Drug Administration (FDA) is encouraging the development of new methods for process monitoring through its Process Analytical Technology (PAT) initiative (CDER 2004). The estimated improvements in pharmaceutical industry performance with PAT include increased quality and decreased cycle time through the use of online and at-line measurement methods that include near-infrared, infrared, and Raman techniques (Clegg and Hughes 2004).

Currently, tablets are tested in a destructive manner. Drug products must be destroyed in the process of dissolution testing for wet chemistry analysis. A sample of between 10 and 30 tablets is tested off-line from a population of one to four million tablets in a typical pharmaceutical manufacturing system (Williams et al. 2002; Romanach and Santos 2003). The random sample is taken from the end of tablet compaction processing. Tablet composition and uniformity are the main concerns in the test. Significant amounts of labor are involved in this process, from preparation of the apparatus to carrying out the experiments and generating reports on the results. The small sample size opens the possibility for false negative rejection of large batch populations (Sarantopoulos, Altiok, and Elsayed 1995; Niemczyk, Delgado-Lopez, and Allen 1998).

The main objective of this research is to analyze how the pharmaceutical industry should form a population batch size for quality control sampling in tablet manufacturing with the advent of an alternative, nondestructive testing technology, Raman spectroscopy (Skoog and Leary 1992). With advances in optics, affordable Raman spectroscopy is beginning to support the latest advances in drug research and development by permitting rapid identity testing of various test materials (Frank 1999; Taylor and Langkilde 2000). The most obvious cost saving feature of Raman technology is its ability to quickly analyze samples without laborious preparation.
Literature Review

Due to patent expiration, it is crucial for pharmaceutical companies with research and development investments to reduce the research and development time as well as the manufacturing time to maximize profit opportunities. Viswanadham and Narahari (2001) develop a fluctuation-smoothing scheduling policy to reduce drug development lead time and demonstrate a 14% improvement in discrete event simulation models. Further improvements may be realized when the processing times for testing procedures are reduced with vibrational spectroscopy (Jones-Bey 2004). Before discussing new technologies, current procedures are summarized.

Current Quality Control Methodology

Sarantopoulos, Altiok, and Elsayed (1995) point out that the growing necessity for experimental and stability testing of solid dosage forms during the development and manufacturing processes has created a significant workload in sample preparation. Sample preparation is required prior to dissolution testing, content uniformity testing, and moisture analysis in medicinal formulations. Stability testing of solid dosage forms requires a wet chemistry dissolution test in which the tablet must be dissolved in pure water for composition analysis. Next, the active ingredient composition is measured with high-performance liquid chromatography (HPLC) or ultraviolet (UV) light. Both purity and impurity profiles are typically evaluated with HPLC using statistical methods (Parra and Rodriguez-Loaiza 2003-04). Preparation of the apparatus, test performance, data interpretation, and analysis for a single batch test of 30 tablets may take up to 18 hours to complete.

Once stability testing is completed, the results are subject to a two-stage analysis, such as the international testing standard proposed by the Japanese Pharmacopoeia, JP Forum (Williams et al. 2002). In the first stage, a sample of 10 tablets from a batch of one to four million is removed from production, destroyed, and tested for active ingredient composition and uniformity. The value of the active ingredient composition represented by $\bar{X} + ks$ must fall within ±15% of the label claim, where $\bar{X}$, s, and k are the sample mean, standard deviation, and tolerance interval constant, respectively. For $k = 2.2$, no more than one tablet may lie outside the tolerance limit. In the second stage, the sample size is expanded to 30 tablets and $k$ is lowered to 1.9. In this stage, no more than one tablet can exceed the ±15% label claim and no tablet can lie outside ±25% (Williams et al. 2002). If the sample passes both stages, then a production batch of one to four million is labeled acceptable and ready to be released. Improved quality control at the end of the manufacturing line is needed, while online monitoring is the ultimate goal in batch process monitoring (Undey and Cinar 2002).

Alternative Quality Control Technologies

In this section, alternative technologies for improved quality control in pharmaceutical development and manufacturing are reviewed. These technologies require significantly less sample preparation.

One alternative, laser-induced breakdown spectroscopy (LIBS), is an at-line, destructive quality control technique of elemental analysis (St-Onge et al. 2002). LIBS does not require sample preparation and incurs a short 0.5 seconds analysis time. However, the laser radiation and shock wave effect may cause tablets to be fragmented, scattered, and expelled.

Similar to LIBS, near-infrared spectroscopy (NIRS) is a noncontact optical procedure (Wilson, Byron, and Sellors 1998). NIRS requires a significantly shorter sample preparation time than wet chemistry analysis; a sample may be intact or crushed to record the spectral data (Niemczyk, Delgado-Lopez, and Allen 1998; Ciurczak 1997; Blanco and Villar 2003; Andre 2003; Romanach and Santos 2003).

Compared to the previous at-line techniques, Raman spectroscopy has a higher resolution and is an online, real-time, nondestructive technique that can be used to detect the active ingredient in pharmaceutical tablets when the concentration is greater than 1% by weight (Taylor 2001). Raman technology does not require sample preparation for uncoated tablets or cleanup (Frank 1999; Jedvert, Josefson, and Langkilde 1998; Taylor 2001). Spectra read from Raman are typically acquired in less than one second even when penetrating a sample in a glass vial. Furthermore, because Raman is compatible with fiber optics, remote monitoring is possible (Lewis and Owen 2001). The ability of Raman to detect fundamental molecular vibrations produces sharp peaks in the spectra reading that often can be explicitly
assigned to chemical properties. Because the active ingredient is usually sufficiently different from other ingredients in an uncoated tablet, the peaks belonging to the active ingredient can be identified with Raman spectroscopy (Taylor 2001). Thus, it is simple to construct a Raman model to derive the quantitative composition of drug substances (Niemczyk, Delgado-Lopez, and Allen 1998; Taylor and Langkilde 2000; Taylor 2001).

Confidence level (CL) and test time are considered to compare quality control approaches. Current testing of a sample of 30 tablets to represent a population of one million tablets only provides a CL of 41.0%, if the margin of error around the active ingredient is ±5%. Furthermore, current testing incurs an approximately 18 hour testing time prior to accepting a production batch of tablets. Because the current testing delay of 18 hours is the activity with the longest processing time, it is a production bottleneck. Other nondestructive off-line or at-line tests are limited by the destructive nature of the tests and, in some cases, sample preparation and analysis time. Because Raman spectroscopy, on the other hand, provides nondestructive, online, real-time testing capability, it warrants investigation for inclusion in the quality control methodology for tablet manufacturing.

### Problem Statement

This research studies quality control in pharmaceutical development and manufacturing between the tablet compaction and tablet coating stages. Figure 1 illustrates the current and proposed tablet manufacturing processes, with the quality control sampling activities italicized (Sarantopoulos, Altiok, and Elsayed 1995). Currently, after compaction, the tablets queue until the destructive quality control tests are completed on a small sample. If the tests indicate good quality, the untested tablets pass to tablet coating. Otherwise, the batch is rejected and disposed.

Commonly, the average time to produce one tablet is 0.01 seconds (Sencorp 2004; Korsch 2004; Fette 2004; Manesty 2004). Raman spectroscopy, on the other hand, may take 0.25 seconds to read a high-resolution spectrum from a single tablet. Testing every individual tablet either requires a lower resolution, involves significant testing capacity for the production and testing rates, or creates a production bottleneck. Instead, testing a larger sample from a smaller population batch with Raman spectroscopy, rather than testing with HPLC or UV, would improve the CL. A batch is defined as a collection of tablets from which a sample will be drawn to decide on its conformance to the acceptance inspection. A batch includes tablets of the same type, size, raw material mixture, production condition, and time period. Currently, batch sizes vary depending on the manufacturer because they are frequently based on the hourly production rate. As batch size increases, rejected samples lead to larger disposal quantities. Thus, smaller batch sizes are preferred. Ideally, a quality control sampling procedure is needed for pharmaceutical manufacturing that tests...
more tablets at a rate less than or equal to the production rate.

This paper proposes to answer the questions:
• How do the constraints of Raman technology affect quality control sampling of tablet compaction?
• How can the pharmaceutical manufacturing company determine the optimal population batch size for quality control sampling following tablet compaction?

**Determining Feasible Testing Population Batch Size and Sample Size**

Choosing a population batch size (PBS) for tablet production affects the frequency of testing as well as the size of the batch accepted or rejected. Testing capacity and technology constrain the testing batch size. This faster testing rate offered by Raman spectroscopy provides an opportunity to dramatically increase the CL. Figure 1 also illustrates the proposed tablet manufacturing process. In Figure 1, the current process destroys the sample, while the proposed nondestructive sampling procedure using Raman spectroscopy directs a passing sample to coating and a rejected sample to disposal. In this section, a formula is derived to determine the minimum PBS for feasible testing. In accepting or rejecting a batch, a maximum number of defective tablets is also calculated.

Using the central limit theorem, the sampling distribution of the sample mean is approximately normal. With the notation defined at the end of this paper, the standard normal random variable for a given CL, \( z \), a margin of error, \( m \), and a sample proportion, \( u \), may be specified to calculate the sample size, \( SS \), for an infinite batch size as shown in Eq. (1) (Moore 2004).

\[
SS = \frac{z^2 \cdot u \cdot (1-u)}{m^2} \tag{1}
\]

If the batch size is finite, Eq. (2) determines the sample size, \( SS' \) (Montgomery and Runger 1999):

\[
SS' = \frac{SS}{1 + \frac{SS - 1}{PBS}} \tag{2}
\]

Statistically, as the finite population batch size increases, \( SS' \) approaches \( SS \). The time to test tablets in a sample of size \( SS' \) is expressed in Eq. (3) when the quality testing rate is \( q \).

\[
TTB = SS' \cdot q \tag{3}
\]

The relationship between the tablet production rate, \( t \), PBS, and the batch production rate, \( b \), is defined in Eq. (4).

\[
b = \frac{t}{PBS} \tag{4}
\]

To prevent a testing bottleneck, the testing time per batch, TTB, must be less than or equal to the production rate, as expressed in Eq. (5). This approach seeks to test nondestructively more products due to safety considerations, without long delays at the “tablet queue for QC information” in Figure 1.

\[
TTB \leq \frac{1}{b} \tag{5}
\]

To determine the optimal testing batch size, Eqs. (2), (3), and (4) are substituted into Eq. (5), which is solved for PBS to form Eq. (6). Optimal is defined as the smallest population batch size for which the testing time for a given CL and margin of error does not exceed the production rate.

\[
PBS \geq SS \cdot q \cdot t - SS + 1 \tag{6}
\]

Substituting Eq. (1) in Eq. (6) and simplifying results in Eq. (7):

\[
PBS \geq \left[ \frac{z^2 \cdot u \cdot (1-u)}{m^2} \right] \cdot \left( (q \cdot t) - 1 \right) + 1 \tag{7}
\]

For a small press machine used in the drug development stage, there are cases where the expression \( q \cdot t \) is less than 1. In this case, the PBS must be set equal to \( t \), the tablet production quantity per time period. Equation (7) then becomes a conditional function in Eq. (8).

\[
PBS = \begin{cases} 
= t & , t \leq \frac{1}{q} \\
\geq \left[ \frac{z^2 \cdot u \cdot (1-u)}{m^2} \right] \cdot \left( (q \cdot t) - 1 \right) + 1 & , t > \frac{1}{q}
\end{cases} \tag{8}
\]
Specifying the desirable CL, margin of error, testing rate, and production rate in Eq. (8) provides the minimum testing batch size. In the development stage, where smaller production is needed, the PBS will equal the tablet production rate, while in the manufacturing stage, where large production of tablets is needed, PBS will be calculated using Eq. (7).

**Computational Analysis**

*Table 1* compares the CL for the current maximum testing sample size, $SS' = 30$, and a proposed 99.9% CL with a specified margin of error for PBS equal to one million tablets using expression (1). Two levels for margin of error, ±5% and ±15%, are shown in accordance with those reported in St-Onge et al. (2002) and Williams et al. (2002), respectively.

Next, the minimum PBS for various tablet production rates is calculated using Eq. (8). *Table 2* specifies four different tablet production rates that are currently available from tablet press manufacturers as well as the rate in the Industrial and Physical Pharmacy Lab at Purdue University. In all cases in *Table 2*, the Raman quality testing rate, $q$, is 0.25 seconds per tablet. The batch production rate, $b$, illustrates the frequency of testing, while PBS represents the number of tablets rejected if a batch is rejected.

**Batch Acceptance or Rejection**

To accept a batch, the number of tablets outside the margin of error must be less than or equal to the established maximum, $c$, to maintain a minimum CL. The probability of acceptance, $Pa$, given by expression (9) represents the probability that a batch submitted with a certain fraction defective, $p$, will be accepted (Montgomery 1991). Given a minimum $Pa$ and $p$ from past observation, $c$ can be determined using Eq. (9).

$$Pa = P\{d \leq c\} = \sum_{d=0}^{c} \frac{SS'!}{d!(SS'-d)!} p^d (1-p)^{SS'-d} \quad (9)$$

**Experiment**

To validate the proposed formula, this paper compares the probability of type I error, $\alpha$, and type II error, $\beta$, between the current sample sizes to the proposed CL sample size at two levels of margin of error. Type I error, or the manufacturer’s risk, is the probability that the manufacturer rejects good tablets. Type II error, or the consumer’s risk, on the other hand, is the probability that the manufacturer fails to reject defective tablets.

*Table 3* presents the experimental design for tests in the Purdue Raman Spectroscopy Measurement Lab. Three parameters are varied: margin of error, testing technology, and CL for a PBS of 2,000 tablets. The first set, scenarios 1–3, use a margin of error of ±5%; the second set, scenarios 4–6, use a margin of error of ±15%. Scenarios 1 versus 3 and scenarios 4 versus 6 compare type I and II errors. Scenarios 1 versus 2 and scenarios 4 versus 5 validate the accuracy and compare the testing time between Raman spectroscopy and traditional wet chemistry analysis. These procedures are discussed next.

<table>
<thead>
<tr>
<th>$M$ (%)</th>
<th>$t$ (tablets/hour)</th>
<th>Tablet Press Mfr. Ref.</th>
<th>Minimum PBS (tablet)</th>
<th>$b$ (batches/hour)</th>
<th>$SS'$ (tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2,000</td>
<td>(Purdue 2004)</td>
<td>2,000</td>
<td>1</td>
<td>703</td>
</tr>
<tr>
<td>15</td>
<td>2,000</td>
<td>(Purdue 2004)</td>
<td>2,000</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>5</td>
<td>123,000</td>
<td>(Sencorp 2004)</td>
<td>8,167</td>
<td>15</td>
<td>957</td>
</tr>
<tr>
<td>15</td>
<td>123,000</td>
<td>(Sencorp 2004)</td>
<td>909</td>
<td>135</td>
<td>107</td>
</tr>
<tr>
<td>5</td>
<td>230,000</td>
<td>(Korsch 2004)</td>
<td>16,212</td>
<td>14</td>
<td>1,016</td>
</tr>
<tr>
<td>15</td>
<td>230,000</td>
<td>(Korsch 2004)</td>
<td>1,803</td>
<td>127</td>
<td>114</td>
</tr>
<tr>
<td>5</td>
<td>585,600</td>
<td>(Fette 2004)</td>
<td>42,950</td>
<td>13</td>
<td>1,057</td>
</tr>
<tr>
<td>15</td>
<td>585,600</td>
<td>(Fette 2004)</td>
<td>4,774</td>
<td>122</td>
<td>119</td>
</tr>
<tr>
<td>5</td>
<td>786,000</td>
<td>(Manesty 2004)</td>
<td>58,018</td>
<td>13</td>
<td>1,064</td>
</tr>
<tr>
<td>15</td>
<td>786,000</td>
<td>(Manesty 2004)</td>
<td>6,448</td>
<td>121</td>
<td>119</td>
</tr>
</tbody>
</table>
Raman Spectroscopy Testing Procedures

As noted in Table 3, scenarios 2, 3, 5, and 6 utilize Raman spectroscopy technology. Before starting the experiment, a spectra library was constructed. The Raman laser was calibrated for 75%, 85%, 90%, 95%, 100%, 105%, 110%, 115%, and 125% of active ingredient of 30 tablets in each range (SpectraCode 2004). The calibration tablets were measured while stationary with the rotating laser. Calibration tablets contained 121 mg or 24.89% by weight of acetaminophen. Ten tablets were manually aligned in three rows at a time on an aluminum sheet. The Raman laser probe was mounted vertically in a static position less than 0.5 mm above each tablet and set to a reading time of 0.2 seconds. Data was transferred in 0.05 seconds. The Raman laser operated while the aluminum sheet was manually moved with the aligned tablets. After the library calibration, the Raman laser was ready for tablet inspection for the experimental design in Table 3.

According to Table 3, 703 tablets were selected randomly from 2,000 tablets produced in the Industrial and Physical Pharmacy Lab at Purdue University. These tablets were carried to the Raman Spectroscopy Measurement Lab for analysis. It is important to analyze the tablets in the lab where the Raman calibration took place because different lighting in different labs could affect the results. The tablets were aligned 25 tablets per row for two rows on an aluminum foil sheet. Similar to the calibration procedures, the tablets were manually aligned and the foil sheet was moved manually under the mounted Raman gun to collect the spectra data. The test using Raman spectroscopy with manual tablet alignment required 25 minutes to test 703 tablets. The samples of 30 and 115 tablets were selected randomly from the 703 tablets for scenarios 1, 2, 4, 5, and 6 (Microsoft 2002).

Wet Chemistry Validation Procedures

The 30 random tablets were set aside and individually weighed and prepared for the wet chemistry validation in the Industrial and Physical Pharmacy Lab at Purdue University. Each tablet was dissolved in pure water in a 250 ml flask. Eight ml from this solution was filtered and then diluted into a different 250 ml flask to prepare the solutions for UV analysis (Harris 1999). Each tablet preparation required 15 minutes. After each UV analysis, the testing compartment had to be cleansed with distilled water and then acetone to remove any residue. The UV test for 30 tablets was completed in 90 minutes. To test 30 tablets using traditional, destructive wet chemistry testing required 10 hours, including apparatus preparation and cleaning. The results of both the Raman and wet chemistry experiments are given in the next section.

Experimental Results

First, the percent of active ingredient data collected for 30 tablets using Raman spectroscopy (RS) is compared with the data from wet chemistry analysis (WCA). Table 4 summarizes the experimental results

Table 4
Experimental Results for Active Ingredient Composition Tests

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Technology</th>
<th>Testing Time (hours)</th>
<th>Variable Testing Cost ($)</th>
<th>Mean (%)</th>
<th>Std Dev (%)</th>
<th>c (defective tablet threshold)</th>
<th>Stage 1 d (actual defective tablets)</th>
<th>Stage 2 Δ (actual defective tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>WCA</td>
<td>10</td>
<td>500</td>
<td>101.99</td>
<td>2.76</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>RS</td>
<td>0.018</td>
<td>—</td>
<td>100.07</td>
<td>4.12</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>RS</td>
<td>0.42</td>
<td>—</td>
<td>99.54</td>
<td>4.37</td>
<td>84</td>
<td>170</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>WCA</td>
<td>10</td>
<td>500</td>
<td>101.99</td>
<td>2.76</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>RS</td>
<td>0.018</td>
<td>—</td>
<td>100.07</td>
<td>4.12</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>RS</td>
<td>0.08</td>
<td>—</td>
<td>99.96</td>
<td>4.04</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
and specifies the defective tablet threshold, \( c \), and the actual number of defective tablets, \( d \) and \( \Delta \), in Stages 1 and 2, respectively. The data show that the sample mean for active ingredient composition by wet chemistry analysis is 1.99% higher than expected. Nevertheless, the result is still within an acceptable error range of ±5%. Contributing to the experimental variability were several factors that could contribute to potential water evaporation, such as unskilled personnel performing the wet chemistry analysis and that tablet testing was conducted on different days due to the long testing time requirements. Another factor that may have affected variability is that the tablets were stationary during calibration but moving during the experiments. Future tests are planned to check the sensitivity of the calibration to movement. The Raman spectroscopy results are only 0.07% from the expectation. This indicates that Raman spectroscopy requires less training, which can increase the speed of implementation while reducing personnel training cost.

Experiments were conducted using Raman spectroscopy with sample sizes of 30, 115, and 703 tablets. Figure 2 compares the percentage of active ingredient for the 30 tablets using wet chemistry and Raman spectroscopy. Like previous studies, the accuracy of Raman spectroscopy was comparable to that of wet chemistry analysis (Jedvert, Josefson, and Langkilde 1998).

Figure 3 indicates the frequency of active ingredient composition spread. 46.6%, 46.1%, and 48.2% of the tablets lie within the 100%±2.5% for the 30, 115, and 703 tablet samples respectively.

The mean and standard deviation for the traditional wet chemistry analysis and Raman spectroscopy are summarized in Table 4. The standard deviation for Raman spectroscopy can be lowered by increasing the calibration samples (Jedvert, Josefson, and Langkilde 1998; Taylor 2001).

Table 4 shows that testing 703 tablets using Raman spectroscopy was 24 times faster than testing 30 tablets using traditional wet chemistry analysis. The Raman spectroscopy testing time was significantly faster because it does not require sample prepara-
Table 4 also illustrates the economic implications of faster testing time under the assumption that one chemist incurs a burdened rate of $50/hour including benefits and overhead for wet chemistry analysis, while no additional testing expert labor is required for Raman spectroscopy. However, a capital expenditure of $100,000 for the Raman laser is required. Assuming a production rate of 786,000 tablets/hour (Manesty 2004) for five hours of tablet production per day and a chemist performing the quality control for 10 hours, the payback period is approximately 10 months. Additional savings may occur from improved testing with Raman, which may include less rejection of good tablets and lower liability.

Considering the amount of defective tablets in the batch, Table 4 summarizes the maximum number of defective tablets allowed in the testing sample, c, and the actual number of defective tablets, d. Values of c are acquired from expression (9) using a fraction defective level of \( p = 0.10 \).

Table 4 shows that for margin of error \( m = \pm 15\% \), \( d = 0 \); thus, the batch passes stage 1 testing. The Raman spectroscopy result agrees with the traditional wet chemistry analysis results to accept the batch. However, at a tighter margin of error, \( m = \pm 5\% \), Table 4 shows that for the 30 tablet sample tested using wet chemistry analysis, \( d \) is less than \( c \), which means to accept the batch in stage 1, but for the 703 tablet sample tested using Raman spectroscopy, \( d \) is greater than \( c \), which means to reject the batch. Hence, what would have been accepted using the current testing method is rejected using the proposed Raman technology. However, a smaller PBS of tablets is potentially rejected in practice.

Table 4 also illustrates stage 2 testing according to the Japanese Pharmacopoeia standard where zero tablets may lie outside the \( \pm 25\% \) margin of error range. Stage 2 is a safety check to prevent lethal doses. If a batch fails stage 1, it is rejected regardless of the results of the stage 2 test.

Next, probability of type I error, \( \alpha \), and type II error, \( \beta \), are compared. Type I error is controllable by setting the confidence interval (Montgomery and Runger 1999). This paper looks at two levels of margin of error, \( \pm 5\% \) and \( \pm 15\% \), which translates to confidence intervals of 95% and 85%, respectively. To find \( \beta \), Montgomery (1991) suggests:

\[
\beta = \Phi \left( z_{\alpha/2} - \frac{\delta \sqrt{SS'}}{\sigma} \right) - \Phi \left( -z_{\alpha/2} - \frac{\delta \sqrt{SS'}}{\sigma} \right) \quad (10)
\]

where \( \delta \) is the difference between the sample mean and the real mean and \( \sigma \) is the standard deviation. Theoretically, as \( SS' \) is increased, \( \beta \) tends to decrease when \( \alpha \) is held constant.

Table 5 summarizes the \( \beta \) calculation for different \( \alpha \) and \( SS' \). Holding \( \alpha \) constant at 15\%, increasing \( SS' \) from 30 to 115 results in \( \beta \) decreasing by 0.2\%. When holding \( \alpha \) constant at 5\%, increasing \( SS' \) from 30 to 703 results in \( \beta \) decreasing by 79.1\%. Table 5 demonstrates that as the confidence interval is improved to reduce \( \alpha \) errors, subsequent improvements in \( \beta \) errors may also occur with increased \( SS' \).

Conclusions

This paper investigates a new technology for quality control in the pharmaceutical industry. The current off-line, destructive quality control method of wet chemistry analysis is a bottleneck in manufacturing because it requires extensive sample preparation. Raman spectroscopy, on the other hand, is a nondestructive identification technique that requires no sample preparation.

This paper proposed a formula that determines the minimum population batch size such that the quality control stage is not a production bottleneck in the manufacturing line. This formula may be applied to either the development stage or the manufacturing stage.

Experiments using both the proposed Raman spectroscopy technology and traditional wet chemistry analysis were carried out. As the number of tablets tested is increased, \( SS' \), the probability of failing to reject defective tablets, decreases.

Table 4 summarizes the experiments with the traditional and proposed quality control methods for post tablet-compaction testing. For scenarios 1 and 3, with a tighter margin of error of 5\%, the Raman
spectroscopy results would reject the batch, where it would have been accepted if wet chemistry testing was used. On the other hand, for the 15% margin of error level, the Raman spectroscopy results agreed with the wet chemistry results to accept the batch. However, in practice, a smaller PBS is accepted or rejected with each test.

Using Raman spectroscopy as a quality control instrument in the pharmaceutical industry requires a capital investment and careful calibration (Jedvert, Josefson, and Langkilde 1998; Taylor 2001). Nonetheless, Raman spectroscopy dramatically reduces the time and labor costs to prepare, conduct, and analyze active ingredient composition of tablets while increasing the number of tablets tested and, hence, the confidence level.

Acknowledgments

The authors appreciate helpful discussions with Håkan Wikström, Lynne Taylor, Ed Grant, Mark Lawley, Saly Romero, Xiuli Qu, and Sudaratana Wongweragiat. This research was funded by an E-enterprise grant from Purdue University’s Discovery Park.

List of Symbols

$\Delta$ Number of defective tablets in stage 2 (tablets)
$
\delta$ Difference between sample mean and real mean
$\sigma$ Standard deviation

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