THE INTRODUCTION OF PROCESS ANALYTICAL TECHNOLOGY, USING NEAR INFRARED ANALYSIS, TO A PHARMACEUTICAL BLENDING PROCESS

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ABSTRACT
This study investigates the use of a laboratory scale blender fitted with a near infrared probe to monitor lubricant uniformity in a granule blend. A software method was developed to monitor the change in absorbance at significant wavelengths for the granule and lubricant (magnesium stearate) as the blend proceeded in real-time. The standard deviation of the absorbance was plotted as a function of time to monitor the change in the blend. With near infrared spectra, when a process is complete, the spectra will not change, therefore the standard deviation will be small [6]. To verify this, the blend was sampled using a standard sampling method and analyzed with an atomic absorption method for magnesium stearate to ascertain the distribution in the blend. Blends sampled at the predetermined time intervals were well blended when the standard deviation of the absorbance was low and poorly blended when the standard deviation of the absorbance was high, thus verifying the near infrared prediction on the state of the blend in terms of lubricant uniformity.

Key Words: Process analytical technology (PAT), near infrared, blend uniformity, magnesium stearate and granule.

INTRODUCTION
Process analytical technologies are systems for the analysis and control of manufacturing processes to assure acceptable end-product quality [11]. This is achieved by timely measurements of critical parameters and performance attributes of raw material and in-process...
material and processes [11]. The desired goal of process analytical technology (PAT) is to
design and develop processes that can consistently ensure a predefined quality at the end of the
manufacturing process [1]. To “build quality” into a product requires the manufacturing
process to be monitored and controlled as opposed to only testing the product at the end of the
manufacturing process to assure quality [1].

The blending of solids is a critical step in the production of many pharmaceutical products [4,
7]. Traditional methods for blend uniformity determination involve sampling of the blend
using a sample thief and laboratory analysis of the samples using chemical methods [2]. In
addition, blend uniformity in the “traditional sense” focuses on the distribution of the active
pharmaceutical ingredient in the blend as opposed to distribution of the excipients in the blend,
which can influence the desired performance of the pharmaceutical product [2].

Magnesium stearate is a commonly used tablet lubricant that forms a film of low shear strength
around the granule thereby reducing the friction at the die wall during tablet ejection [8].
Blending for longer durations than is necessary could result in the incorporation of magnesium
stearate intra-granularly, which can influence the bioavailability by decreasing the dissolution
rate of the product, due to the hydrophobic nature of magnesium stearate [9]. In addition, over-
mixing could lead to the physical destruction of the granule leading to poor compression
profiles [9]. The common problems associated with poor lubrication are binding where tablets
have vertically scratched edges, lack smoothness or gloss and are often fractured at the top
edges; sticking where tablet faces appear dull; filming which is the early stages of sticking;
picking which represents the advanced stages of sticking and capping and lamination which is
normally associated with poor bonding and can also be a result of a system that is over
lubricated [5].

Due to the competitive nature of the pharmaceutical industry and the continuous emphasis on
quality from the regulatory authorities, pharmaceutical manufactures require a system to
monitor all materials in a blend with little or no sample preparation and the ability to “build”
quality into the product and predict end-points in real-time. PAT offers these advantages and
near infrared (NIR) spectroscopy is one such tool that is commonly employed [3].

The majority of active pharmaceutical ingredients and excipients absorb NIR radiation,
therefore NIR has the ability to provide information of all the components in the blend and is
non-invasive, speedy and requires no sample preparation [2]. In this study, NIR spectroscopy was used for the on-line monitoring of magnesium stearate in a granule blend.

EXPERIMENTAL

Materials
Magnesium stearate (EP 5.02) from approved suppliers to the pharmaceutical manufacturer was used as the lubricant. A proprietary granule was chosen to mix with the magnesium stearate.

Equipment
The study utilized a laboratory scale blender fitted with a NIR probe, operated by equipment specific software programmes. During the intermediate bulk container (IBC) inversion, the NIR probe measured the NIR spectrum of the material in the IBC. Therefore, every rotation captured a NIR spectrum.

Method

Obtaining fingerprint spectrum
The pure spectrum was obtained by placing approximately 50 g of each material on the Corona head and measuring the NIR spectrum. The NIR spectra of four random samples of magnesium stearate and six random samples of the granule were measured and the mean spectrum of each material was calculated to obtain a fingerprint spectrum. The fingerprint spectrum of magnesium stearate and the granule were superimposed.

The significant wavelengths for blend monitoring for the materials were obtained by examining the spectra in the second derivative. The software was used to highlight the peaks on the spectra (as seen in Figure 1). Preliminary blends were conducted using the wavelengths obtained from the software. The criteria used to choose the most suitable wavelengths was that the standard deviation of the absorbance at the wavelength representing the magnesium stearate and the granule should increase when the magnesium stearate was added to the blend and level off after a period of time. Following the preliminary blends using the wavelengths isolated by the software, 1213 nm was chosen to represent magnesium stearate and 1591 nm was chosen to represent the granule as highlighted in Figure 1.
Figure 1: Spectra of granule and magnesium stearate superimposed showing significant wavelengths

Following the determination of the significant wavelengths for blend monitoring, a method was created on the software to interpret the spectral data in terms of the rate of change in the blend. The second derivative was used for spectral pre-processing and the results were evaluated at the wavelengths of significance. The software was set to evaluate the standard deviation of the absorbance at the wavelengths of significance in a “moving block of eight” as outlined below.

Figure 2 shows a schematic of the variance calculation. Spectra are added to the block until eight spectra obtained (seen in block 1). Then for every spectrum that moves out of the block, one spectrum is added to the block (seen in block 2 and block 3). As the spectral difference decreases so too does the moving block difference. The standard deviation is calculated over the block and plotted over time to monitor the rate of change in the blend. With NIR spectra, once a process is complete, the spectra will not change, therefore the standard deviation will be small [6].

Figure 2: Moving block of eight variance calculation (adapted [6])
Spectral data from blends
During blending, spectral data were collected by the NIR probe during every rotation of the IBC. The IBC was set to rotate at 10 rotations per minute (rpm). The data were mathematically treated with the algorithms available on the software created during the method development. The blend was monitored by the standard deviation versus time plot that was generated. To confirm the prediction of end-point using NIR, the blends were sampled using a sample thief when the NIR spectrum showed no more change with respect to time at the wavelengths of significance (when a plateau level was reached) and at selected time intervals.

In order to determine the time intervals at which to sample, preliminary blends were conducted. A series of blends were run for approximately 20 minutes each. The standard deviation was plotted as a function of time and examined to identify three time intervals in the blend to predict three states namely before end-point, end-point and after end-point. The first time interval chosen was when the standard deviation had not levelled out and was high (depicting before end-point). The second time interval chosen was when the standard deviation was lower than the first time interval (depicting end-point) and the third time interval chosen was when the standard deviation maintained a low value for a longer period of time (depicting after end-point). Following these preliminary experiments the times for sampling as stated below were obtained.

The intervals for sampling of the granule blend were 1 minute and 30 seconds (before end-point), 6 minutes (at end-point) and 17 minutes (after end-point). The blends were carried out in triplicate at the predetermined time intervals. Five point samples were taken from the blender according to a sampling plan and were analysed using an atomic absorption (AA) spectroscopic method for magnesium stearate to ascertain the distribution of the magnesium stearate in the blend. One sample per point was taken due to the decreased capacity of the blender.

The standard deviation that predicted a uniform blend was obtained from the blends conducted to the selected time intervals. A further six blends were run and stopped when the standard deviation that predicted a uniform blend at the selected wavelengths was reached.
Blend preparation
Granule (3 kg) was loaded into the IBC. The IBC was rotated for 8 rotations. Thereafter the blender was stopped and 22.18 g of magnesium stearate was added to the granule. Care was taken to ensure that the magnesium stearate was evenly spread over the top of the granule. The IBC was then closed and blended for the predetermined time intervals. The blend was then sampled using a sample thief and the stated sampling plan.

Limits for AA results
A unit dose sample is 102.2 mg of which 0.75 mg is magnesium stearate. The United States Pharmacopoeial limit of content uniformity was used to calculate the acceptable limits for magnesium stearate [10]. The criteria for a uniform blend was a magnesium stearate assay of 0.6375 mg – 0.8625 mg and the relative standard deviation (RSD) less than or equal to 6.0 %.

RESULTS AND DISCUSSION
As the wavelength of significance for magnesium stearate was shown to be 1213 nm, the change in absorbance at this wavelength is presented. The standard deviation versus the number of rotations at the magnesium stearate wavelength for blends conducted for 1 minute and 30 seconds depicting before end-point can be seen in Figure 3.

![Figure 3](image_url)

**Figure 3**: Standard deviation vs. number of rotations (before end-point) [** Standard deviation at the end of the blend]

An increase in the standard deviation was noted when magnesium stearate was added to the blend. At the end of the blend duration, the standard deviation was above $3 \times 10^{-6}$. The AA results revealed a non-uniform distribution of magnesium stearate.
Figure 4 reflects the blends carried out for 6 minutes, depicting end-point.

Figure 4: Standard deviation vs. number of rotations (end-point) [* Leveling out of the standard deviation, ** Standard deviation at the end of the blend]

A levelling out of the standard deviation could be seen at the 28th rotation. The standard deviation at the magnesium stearate wavelength was less than $3 \times 10^{-6}$ at the end of the blend duration and the AA results revealed uniform distribution of magnesium stearate in the blend.

Figure 5 represents the blends conducted for 17 minutes depicting after end-point.

Figure 5: Standard deviation vs. number of rotations (after end-point) [* Leveling out of the standard deviation, ** Standard deviation at the end of the blend]
A leveling out of the standard deviation was noted at the 28th rotation. At the end of the blend duration, the standard deviation at the magnesium stearate wavelength was less than $3 \times 10^{-6}$. The AA results revealed uniform distribution of magnesium stearate in the blend.

Table 1 shows a summary of the relationship between the standard deviation and the uniformity of the blend for blends conducted to predetermined time intervals.

**Table 1:** Relationship between standard deviation and AA results of the blends.

<table>
<thead>
<tr>
<th>Blend duration</th>
<th>Standard deviation</th>
<th>AA Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before end-point (1 min 30 sec)</td>
<td>$&gt; 3 \times 10^{-6}$</td>
<td>Non-uniform</td>
</tr>
<tr>
<td>End-point (6 min)</td>
<td>$&lt; 3 \times 10^{-6}$</td>
<td>Uniform blend</td>
</tr>
<tr>
<td>After end-point (17 min)</td>
<td>$&lt; 3 \times 10^{-6}$</td>
<td>Uniform blend</td>
</tr>
</tbody>
</table>

The distribution of the magnesium stearate in the blends for 17 minutes and 6 minutes show a relationship, in that both sets of blends are uniform and the standard deviation of the absorbance was below $3 \times 10^{-6}$. It was noted that a decrease in blend time of 11 minutes still resulted in a uniform blend. The blends for 1 minute and 30 seconds had a higher standard deviation (greater than $3 \times 10^{-6}$) and the AA results revealed an uneven distribution of magnesium stearate.

Based on the blends conducted above, the criteria selected to predict a uniform blend in “real-time” was a standard deviation value below $3 \times 10^{-6}$ at 1213 nm (wavelength for magnesium stearate) at four consecutive data points. Figure 6 shows the standard deviation versus number of rotations for six blends conducted to an end-point as predicted by NIR and Table 2 shows the AA results.
Figure 6: Blends conducted to end-point as predicted by NIR

Table 2: AA results for magnesium stearate per 102.2 mg sample mass (values shown in red represent out of specification results)

<table>
<thead>
<tr>
<th>End-point</th>
<th>Blend 1</th>
<th>Blend 2</th>
<th>Blend 3</th>
<th>Blend 4</th>
<th>Blend 5</th>
<th>Blend 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>Blend Time</td>
<td>3 min 18 sec</td>
<td>2 min 23 sec</td>
<td>2 min 10 sec</td>
<td>2 min 27 sec</td>
<td>3 min 9 sec</td>
</tr>
<tr>
<td>Point 1</td>
<td>0.678 mg</td>
<td>0.781 mg</td>
<td>0.686 mg</td>
<td>0.655 mg</td>
<td>0.697 mg</td>
<td>0.630 mg</td>
</tr>
<tr>
<td>Point 2</td>
<td>0.701 mg</td>
<td>0.680 mg</td>
<td>0.706 mg</td>
<td>0.726 mg</td>
<td>0.675 mg</td>
<td>0.655 mg</td>
</tr>
<tr>
<td>Point 3</td>
<td>0.684 mg</td>
<td>0.743 mg</td>
<td>0.706 mg</td>
<td>0.744 mg</td>
<td>0.718 mg</td>
<td>0.649 mg</td>
</tr>
<tr>
<td>Point 4</td>
<td>0.717 mg</td>
<td>0.744 mg</td>
<td>0.697 mg</td>
<td>0.682 mg</td>
<td>0.710 mg</td>
<td>0.627 mg</td>
</tr>
<tr>
<td>Point 5</td>
<td>0.694 mg</td>
<td>0.715 mg</td>
<td>0.736 mg</td>
<td>0.706 mg</td>
<td>0.701 mg</td>
<td>0.687 mg</td>
</tr>
<tr>
<td>Mean</td>
<td>0.695 mg</td>
<td>0.732 mg</td>
<td>0.706 mg</td>
<td>0.703 mg</td>
<td>0.700 mg</td>
<td>0.650 mg</td>
</tr>
<tr>
<td>RSD</td>
<td>2.24 %</td>
<td>5.17 %</td>
<td>2.62 %</td>
<td>5.00 %</td>
<td>2.34 %</td>
<td>3.71 %</td>
</tr>
</tbody>
</table>

The results show that all blends were uniform with the exception of blend 6 where the amount of magnesium stearate was marginally out of specification. Blend 6 also represents the shortest blend duration. It was noted that the standard deviation at the 1591 nm (wavelength for granule monitoring) wavelength at the end of the blend was the highest for blend 6.

At present, the blend duration for this granule is set at 10 minutes, which was determined by standard validation techniques. With NIR, blend durations range from 2 min 10 sec to 3 min...
18 sec. It was noted that the time durations are significantly lower than the standard blend durations.

CONCLUSION
A relationship exists between the uniformity of the blend and the standard deviation of the absorbance at the significant wavelength. Blends were found to be poorly blended when the standard deviation of the absorbance was high and well blended when the standard deviation of the absorbance was low. It is evident that more information regarding the uniformity of the blend could be obtained from the 1591 nm wavelength to aid an accurate prediction of end-point using NIR. The standard deviation value selected should be on a product-by-product basis and optimised in conjunction with standard blend uniformity methods.

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REFERENCES


