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OPORTUNITIES FOR PROCESS CONTROL AND QUALITY ASSURANCE USING ON-LINE NIR ANALYSIS TO A CONTINUOUS WET GRANULATION TABLETING LINE

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Abstract
This paper investigates the application of on-line near infra-red measurements as a means to measure blend uniformity in a continuous tableting line. Underlying all the monitoring and control methods is the ability to measure key tablet properties on-line at a rate suitable for control purposes. The use of NIR to determine any deviations in blend uniformity is demonstrated by interpreting the relevant spectral signature allowing quantitative information to be acquired for process monitoring and quality assurance. In addition to demonstrating the functionality of the NIR probe, the practical issues arising in the application are discussed.

The composition of the blend was measured using an NIR probe over a range of concentrations and the results were calculated comparing sub unit dose scale of scrutiny of small populations. This was compared with predicted product quality for whole tablets over the whole production period. This technique has demonstrated how data collected online can be used to successfully predict the quality of the whole production run for the purposes of real time product quality assurance.

Keywords

Near-infra Red spectroscopy, Tabletting, Process Analytical Technology, Quality Control, Pharmaceutics

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1. Introduction

Over the last decade Process Analytical Technology (PAT) has become increasingly important in the pharmaceutical industry as it attempts to satisfy regulatory requirements and exploit advances in process design and technological capability. The aim of advanced process monitoring and control techniques when coupled with real-time data analysis is to drive processes towards more efficient, economic and robust operation. PAT can be used to monitor material characteristics or quality end-point. This enables the generation of control loops for improvement of end-product quality based on the manipulation of input parameters, whether this is automated or through operator actions.

Traditionally, batch process monitoring in the pharmaceutical industry has relied on taking samples during batch progression and at the end-of-batch for periodic off-line laboratory analysis. This approach is regarded as providing the necessary level of quality assurance for product release, but it also results in large material and operating redundancy. The technology to move to on-line measurement exists and is attractive, with the potential for much higher sampling frequencies, but its adoption has been slow. While the regulators have moved to accept PAT, to overcome the industry inertia to rapid on-line process analysis, PAT process monitoring techniques must demonstrate a suitable measurement accuracy and reliability that can produce quality assurance concomitant with industry requirements. A prime industrial driver is to demonstrate the capability and effectiveness of on-line techniques for assuring quality, with real time release (RTR) of the product being the sought after operating policy [1]. A balance arises between the introduction of novel and powerful measurement methods and the requirement to ensure consistent, repeatable with a (statistical) confidence in process outputs that are comparable to more traditional validated procedures.

In a drive to increase operational efficiency and flexibility, the pharmaceutical industry is moving from batch to continuous processing [2]. However, the move to continuous processing causes online monitoring to become a necessity as product quality will vary with time. As with batch processing, continuous processing still requires the definition of a releasable entity in order to define a quantity of product which can be released or rejected based upon quality assurance criteria. With the development of instrumentation that is able to produce large quantities of high quality data quickly, the releasable entity size can be reduced. Reduction in this size allows for a significant reduction in risk of having to discard large quantities of out of specification material.

With the addition of the time variable in continuous pharmaceutical processing, the need for a change in mind set away from end of batch quality assurance is needed. It is necessary for any process disturbances or drifts to be detected and suitable action taken before out of specification material is produced. Real time process control becomes more attractive during continuous production but requires both accurate and timely measurements to be made. PAT gives the ability for both of these allowing for a greater opportunity to implement real time process control in continuous pharmaceutical manufacturing. This view is echoed by Yu and Kopcha [3] who state from the FDA perspective ‘continuous manufacturing and advanced PAT are necessary to broadly advance toward six sigma manufacturing quality’.

2. Continuous Pharmaceutical Tablet Manufacturing

Pharmaceutical manufacturing is historically performed batch-wise in discrete unit operations. Batch based primary pharmaceutical manufacturing has been the subject of intense research in terms of batch process control and automation [4]. Nevertheless, the lack of flexibility in batch processing in response to industry growth and a move within the industry to minimize the size of new manufacturing plants have given impetus for moving towards continuous processing in primary and secondary

manufacturing. From a broad business perspective there are hurdles to be overcome as discussed by Buchholz [5] when considering the overall whole process.

Leuenberger [6] demonstrated the advantages of continuous manufacturing in a pharmaceutical granulation process. Leuenberger stated that the principal arguments for continuous operation are the ease of scale-up of unit operations and the theoretical possibility of uninterrupted, continuous manufacturing allowing for much greater operational efficiency and flexibility in the plant.

Vervaet and Remon [7] presented a number of technologies for moving the granulation process from batch to continuous, including fluid-bed agglomeration, spray drying and extrusion. However, Plumb [8] presented the foremost argument for a change of mind-set in the pharmaceutical industry based on the FDA's nascent recognition that continuous processing does have a place in modern pharmaceutical manufacture. This is reflected by changes in the regulatory and business environments. Plumb argued that, with the advent of PAT principles, there was a great opportunity for engineers to examine the possibilities for driving a step change in pharmaceutical manufacturing philosophy, whilst continuing to conform to GMP and GAMP. A review by Fonteyne et al [9], in addition to commenting on the limited number of applications of PAT to continuous pharmaceutical processes, observed that probe positioning can be problematic and probe fouling can be an issue. They further observed that the challenge of acting on the information from the probe for control purposes needs to be addressed. This is discussed further by Hattori and Otsuka [10] who consider the integrated control system / PAT challenge.

2.1 On-line process measurement

Control methods and approaches require the ability to measure process state, whether it is at the intermediate stages or the final product quality. Spectroscopy is a popular technology which fits into the FDA's PAT framework. There are a number of different types of spectroscopy, Mid-Infrared (MIR), Near-Infrared (NIR) and Raman just to name a few. One of the major advantages with using one of these methods is that rapid online non-destructive measurements can be taken. Both MIR and NIR use the absorption of electromagnetic radiation to bring the molecules to a higher vibrational state. The molecular vibrations can occur in two ways, stretching and bending. Bending is defined as the change in bond angle and stretching is defined as the change in the inter-atomic distance along the plane of the bond [11]. In this application the greater path length associated with NIR offers distinct operational advantages.

Spectroscopy is not a new technology with it traditionally being used in an offline analytical setting, though it has found many uses as an inline monitoring approach in many industries including batch fermentations. Menezes et al [12] describes several case studies that typify such application in upstream and product recovery. Considering formulation related applications, work by Roggo et al [13] and subsequently De Beer et al [11] reviews the applications of NIR for monitoring pharmaceutical production processes highlighting applications of NIR in blending, granulation, fluidised bed drying/granulators and freeze drying. Others have also used NIR to characterise in-line blending performance [14-16].

The online determination of tablet quality has been considered by several authors. A number of quality measures are associated with tablets, one being dissolution rate. Pawar et al [17] applied NIR to determine the dissolution rate by relating principal components from the spectra to curve fit coefficients predicting the dissolution profile. While applied for a range of line operating parameters and API concentration variations, more general applicability remains to be demonstrated for different APIs and formulations. More typical of tablet quality assessment is the prediction of API concentration of the tablet. Fonteyne et al [9] provides a review of a number of applications of Process Analytical

Technology for API assessment in continuous pharmaceutical processing with focus on blending, spray drying, roller compaction, twin-screw granulation and compression. The review raises a number of common challenges experienced related to the ability to match calibration and operational conditions and implementation details that can cause significant long term operational difficulties related to sample presentation and fouling. They conclude by questioning the decision to utilise NIR as the method of first choice suggesting other techniques may be more suited. Work by Jarvinen et al [18] and Vargas et al [19] demonstrated the ability of NIR to provide in-line concentration in a tableting line. Wahl et al [20] went further and considered not only the capability of the NIR measurement but also addressed concerns around blend uniformity (as discussed below). Casian et al [21] followed these approaches but also addressed the concerns of Fonteyne et al by comparing Raman and NIR based measurement approaches finding comparable performance on the specific examples they considered. Recent work by Li et al [22] demonstrated the capability of Raman spectroscopy and concluded that it is 'a useful alternative to NIR'.

Whether NIR or Raman spectroscopy is used, spectral processing is a necessity to remove any spectral baseline shifts due to changing sample presentation or any other external influence which may cause increased variation and therefore increased modelling errors. The main reasons for spectral processing are :

- To process the data to keep the chemometric information while removing undesirable physical attribute effects.
- To remove any outliers which are not representative of the process conditions.

There are a number of well documented processing techniques which can be used to remove baseline shifts from the data. Some of the fairly common processing techniques are Standard Normal Variate (SNV), Multiplicative Scatter Correction, Baseline Correction and Savitzky-Golay Derivatives. Chen and Morris [23] highlight the different pre-processing techniques when a specific problem is encountered, such as temperature based spectral variation or variation because of the physical differences in samples.

Physical factors also can have a significant effect on accuracy of NIR spectroscopy [24], including the changing particle size distribution of the powders/granules, with the SNV spectral treatment being especially effective.

Calibration of the probe can be performed using a variety of methods, but predominately known calibration samples are manufactured and then used to calibrate the probe using a multivariate technique such as partial least squares. Though when using this method on the pharmaceutical production line, where the sample is in a granular form, the huge particle size distribution difference between the granular production samples and the powder based ideal lab samples will likely cause a large calibration error. Instead another method is used whereby the samples with which to build a calibration model are samples taken from the running production line.

NIR instruments work by shining a spot of light onto the sample. When using an NIR instrument it is possible to estimate the mass of sample that is being measured. The sample mass can be estimated based upon the spot size, which is the circular projection of the area being measured, the penetration of the light into the granule and bulk density of the granule in question.

When calculating the sample mass measured from an NIR instrument it is also important to understand the impact of measurement frequency. In general, when using an NIR instrument in the setup described in this paper, the measurement frequency will be much higher than the velocity of the powder flowing

past the probe itself. This will lead to large amount of re-sampling of the same material, and therefore a large volume of replicate data collection.

2.2 Content Uniformity

Content Uniformity is the measure of how much active ingredient is in a number of unit dose size samples. Content uniformity, unlike blend uniformity however is used on the final dosage form. There are also a number of regulatory requirements set out which must be met and which vary depending on the regulatory board which set them. For example, the US pharmacopeia states the following requirements must be met before releasing any product:

- After testing 10 tablets, not more than one can be outside the range of 85% to 115% of the target concentration and there must be a relative standard deviation (RSD) of less than 6%.
- If either of the above conditions are not met then a further 20 tablets must be tested, if only one is outside the 85% to 115% limits but within 75% to 125% of the target concentration and the relative standard deviation (RSD) of the total 30 tablets is within 7.8% then the requirements are met.

However, it should be noted that different regulatory bodies have differing content uniformity requirements [25].

2.3 Blend uniformity

Blend uniformity is the measure of homogeneity within a blend of different powders. Blend uniformity testing is recommended for dosage forms where content uniformity testing is also a requirement.

Traditionally blend uniformity is a measure of the homogeneity of a batch blend. Representative samples are taken from different positions in the blend, and then spatial homogeneity can be proven. It is difficult to specify the number of samples required as this will be dependent on the specific process, but 6-10 different locations are recommended with three samples at each location. The samples should be equivalent to the unit dose which is produced in further manufacturing steps. The FDA recommends the following acceptance criteria for blend uniformity:

- The mean assay is between 90% - 110% of target
- The relative standard deviation is not more than 5%

It can be noted that the blend uniformity requirements are more stringent than those specified by the content uniformity. This is to allow for any potential de-mixing which may occur in subsequent processing steps.

Continuous manufacturing requires blend homogeneity both spatially and with time. Currently the regulatory bodies haven't stated the blend uniformity requirements in continuous pharmaceutical manufacturing and therefore the above limits will be used in this study.

2.4 Challenge Addressed

Fundamental questions surrounding the scale of scrutiny arise in the application of PAT to assess tablet quality in continuous processing. Fundamentally from a patient perspective they are concerned about a single tablet concentration and the variation in concentration that could arise. Confidence to them relates to the mean and variation in API remaining within validated bounds. To move towards this

confidence, this paper firstly considers the offline predictive capability of the NIR probe when used to predict the active concentration levels compared to an offline standard measurement technique. In undertaking this comparison, it is necessary to address spectral data processing approaches. If predictive capability is proven, the next stage is to demonstrate the online performance of the NIR based prediction. Three aspects have been addressed. Firstly, blend uniformity is considered by looking at variation arising within individual dryer compartment cells through considering each sample of the NIR probe. Here high variation would be indicative of poor blend uniformity. Secondly, cell to cell variation is important to understand and mean and variance of NIR predictions per cell are compared to do so. Finally, the scale of scrutiny variation is considered from a single NIR measurement considering far less than a tablet dose to unit tablet dose. While intra-tablet variation maybe measured, it is the tablet dose scale of scrutiny that is indicative of patient delivery. In the cases addressed the use of a continuous tablet line subject to designed experiments is required and this is described in the first instance.

3 Material and Methods

3.1 Process Overview

The equipment used in this research study was the GEA Consigma Continuous Tableting line [26]. This consists of a number of intensified processing steps taking the raw powders through to finished tablets. A flow diagram of the process is given in Figure 1.

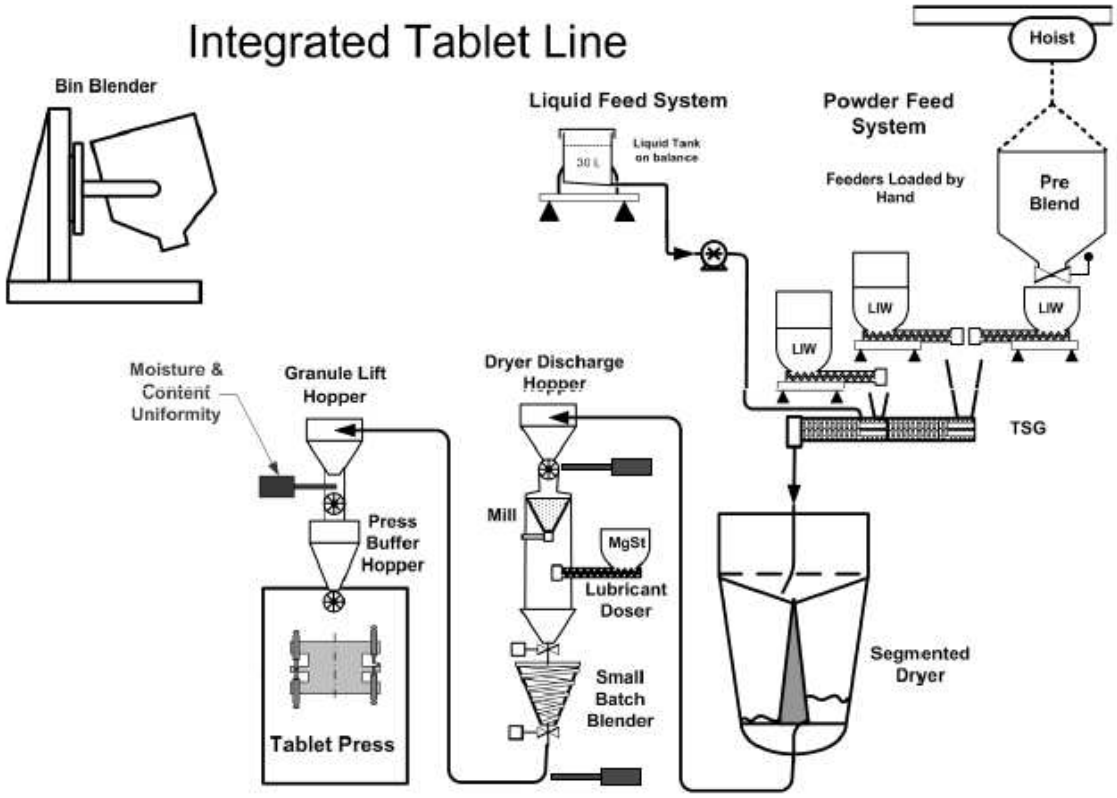

Figure 1 – GEA Consigma Continuous Tableting Line

The process starts with a number of different powders that are fed using loss in weight screw feeders. Some of the powders may already be pre-blended using a tumble blender. For this work two screw

feeders were used, one feeder was used to dose the pre-blended placebo formulation, and the second to dose the saccharin that acted as an exemplar of an active pharmaceutical ingredient (API). However, powders have poor flow properties so the powder mixtures need to be granulated to the desired particle size distribution. The granulator is a twin screw granulator (TSG), which has an average residence time of 3 to 4 seconds.

The wet granule is then transferred directly into the dryer that is a segmented fluidised bed dryer. Each segment acts as a small individual dryer, while every cell is subjected to the same inlet air. The act of using the segmented fluidised bed dryer splits the powder into smaller plugs which are given a tracking number as they pass through the rest of the system. These plugs are also referred to as cells.

After drying, milling is undertaken to get a smooth size distribution of the particles and to remove any large particles which may have survived the drying process. The samples taken to determine the blend uniformity were from this position prior to the blender. The blender is a small batch blender, where lubrication is added via a lubrication dowser.

The lubrication used is magnesium stearate and is necessary for successful tablet compaction. Finally, the tablets are pressed in the tablet press and this is the point that the composition of the tablets needs to be correct. The NIR instrument is placed above the press in the buffer hopper and is the two window version of the GEA diffuse reflectance lighthouse probe.

3.2 Experimental protocol

The experimental tests are designed to analyze the blend uniformity of the process using sodium saccharin as a marker. The sodium saccharin was dosed as a percentage of the GEA standard placebo. Importantly the sodium saccharin was dosed using a second screw feeder and is therefore independent of the flow rate of the rest of the formulation. The sodium saccharin was run at different concentrations, with the final aim of building a calibration model for the online NIR probe that could be used to measure the blend uniformity of a test dataset. Two experimental tests were developed in order to quantify the blend uniformity of the process under nominal conditions. The formulation was the GEA standard placebo with a varying percentage of sodium saccharin 100 mesh added.

Table 1: Formulation

Formulation	**Mass Fraction (% w/w)**
Lactose 200M	72
Corn Starch	24
PVP	4
Sodium Saccharin	Varies

The process was run under its nominal conditions except due to the sensitivity of sodium saccharin to water, the liquid addition rate (LAR) needed to be varied with the saccharin addition in order to maintain the granule quality.

Table 2: Granulation Operating Parameters

Run	**Mass Flow Rate**	**Speed**	**Liquid Addition Rate**	**Jacket Temp**
#	(kg/hr)	(rpm)	(%)	(°C)
1	25	700	varies	25

The tests undertaken were as follows:

Table 3: Experimental Plan for Run 1

Condition	Placebo Mass Flow Rate	Saccharin Mass Flow Rate	Cell Number
#	kg/hr	kg/hr	#
1	22.50	2.5	F1C1 - F2C5
2	20	5	F3C1 – F4C5
3	17.5	7.5	F5C1 – F6C5

Table 4: Experimental Plan for Run 2

Condition	Placebo Mass Flow Rate	Saccharin Mass Flow Rate	Cell Number
#	kg/hr	kg/hr	#
1	22.50	2.5	F1C1 - F2C5
2	20	5	F3C1 – F4C5
3	17.5	7.5	F5C1 – F6C5
4	23.75	1.25	F8C1 – F9C5
5	23.12	1.88	F10C1 – F11C6

Here the cell number refers to compartmental drier cell and is a means of tracking product down the line.

3.3 UV analysis

UV analysis of the blend samples was carried out using a J&M Tidas II spectrometer with a scan range of 0-300 nm, an integration time of 300ms and 100 readings taken. The following method was used:

- 250mg of sample granule was weighed out and then dissolved in 250ml DI water, followed by filtration of non-soluble formulation components. This was repeated in triplicate
- The blank was assessed using DI water in glass cuvette
- The measurement was then taken using glass cuvette with given solution. If absorption was outside the 0-1AU range then further dilution was performed. Each measurement in the spectrometer was carried out in triplicate.

3.4 NIR measurements

The GEA lighthouse probe as stated before is a diffuse reflectance probe that contains a self-cleaning and calibration system. This means that it can remove the effects of fouling on the windows and using its calibration medium can regularly check that the windows have not become contaminated. Finally, the probe can be installed and used as an online as a monitoring tool and a diagram of this can be seen in Figure 2.

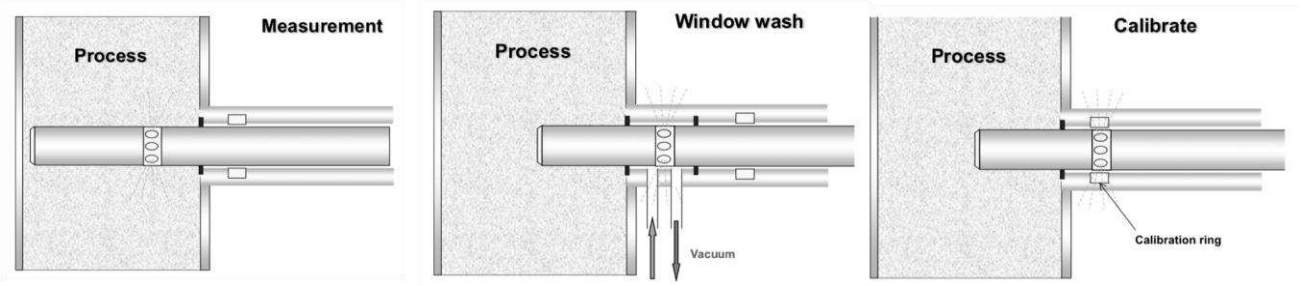

Figure 2 – The GEA lighthouse probe has three stages of operation. It takes a number of measurements, before retracting and gleaning itself, finally it uses its internal calibration medium to calibrate itself

3.5 Data analysis and Model Building

Data analysis was carried out using Matlab 7.10.0 (R2010a) and the Eigenvector Research PLS toolbox 6.7.1.

4. Results and discussion

4.1 Data pre-processing

With most process data it is typical to apply some simple pre-processing technique, such as scaling, prior to chemometric application. Particularly important is that spectral data generally have wavenumber regions that contain no information related to the properties of interest. These regions may be associated with noise artefacts related to the measurement device or areas unrelated to any physical or chemical property of interest. It is particularly important in chemometric analysis and model development to focus on the optimum wavenumber range and exclude those regions that contain no relevant information.

Pre-processing requirements can be judged by observing the raw NIR spectrum. The raw spectra after non-valid readings were removed where the probe is not submersed in powder, were plotted and can be seen in Figure 3. Here the results for multiple time samples are shown. It is clear that such information is difficult to interpret in the raw form and a range of data pre-processing and information compression techniques are required. In order to pre-process the data, a Standard Normal Variate (SNV) transformation was applied to the raw spectrum and this can be seen in Figure 4. The SNV technique removes slope variation by individual wavelength samples. Here wavelength selection based on physical insight has been adopted but in more complex instances a variety of wavelength selection techniques are available [27, 28].

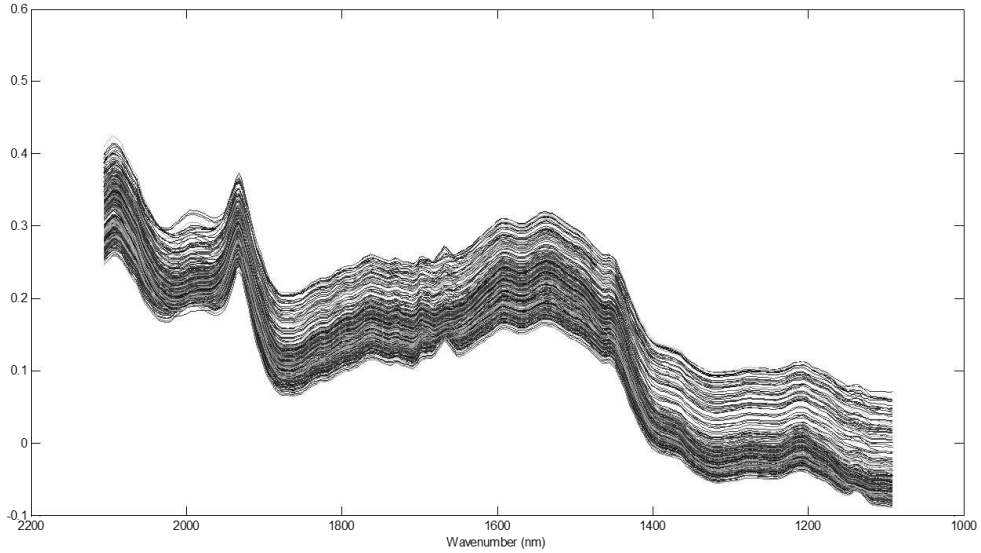

Figure 3: Raw NIR spectrum after non-valid reading removal for run 2

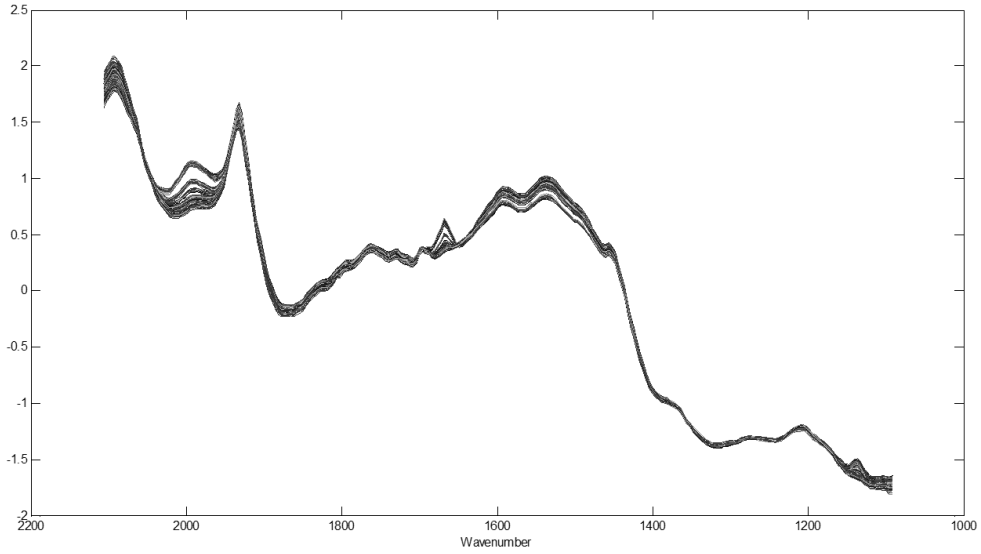

Figure 4 - NIR spectrum after Standard Normal Variate (SNV) Pre-processing for run 2

4.1.1 Principal Component Analysis for Process Monitoring

Using Principal Component Analysis it is possible to analyze whether the variation caused by changing the Sodium Saccharin concentration can be seen from the variation in the NIR absorbance spectrum. PCA was then applied to each run and the results can be seen from the loadings plot from principal component 2 in Figures 5 and 6.

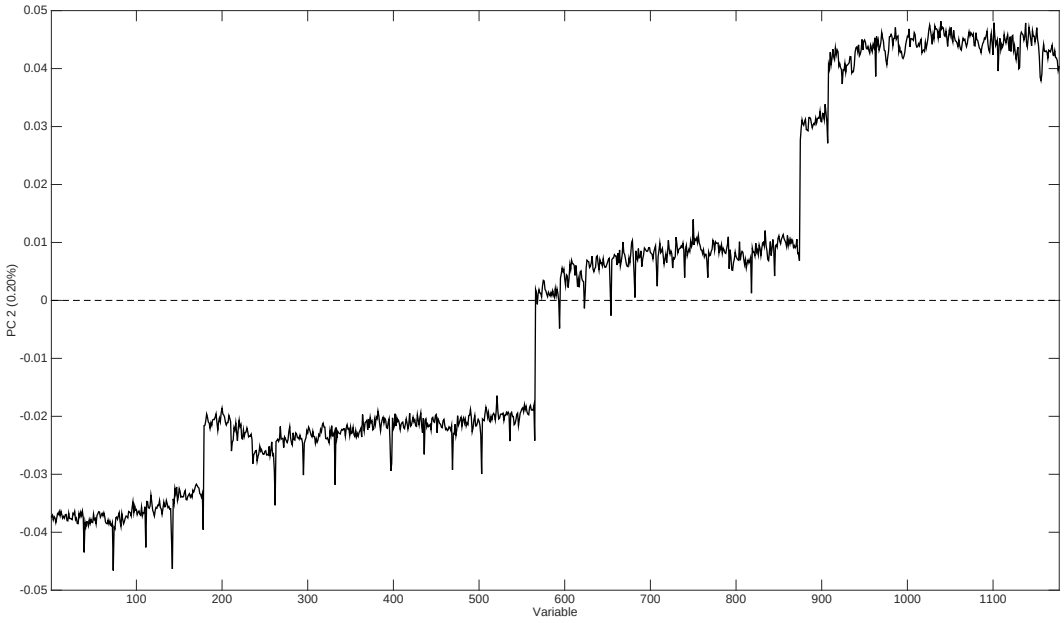

Figure 5: Principal Component 2 for Sodium Saccharin Run 1 at levels 10%, 20%, 30%

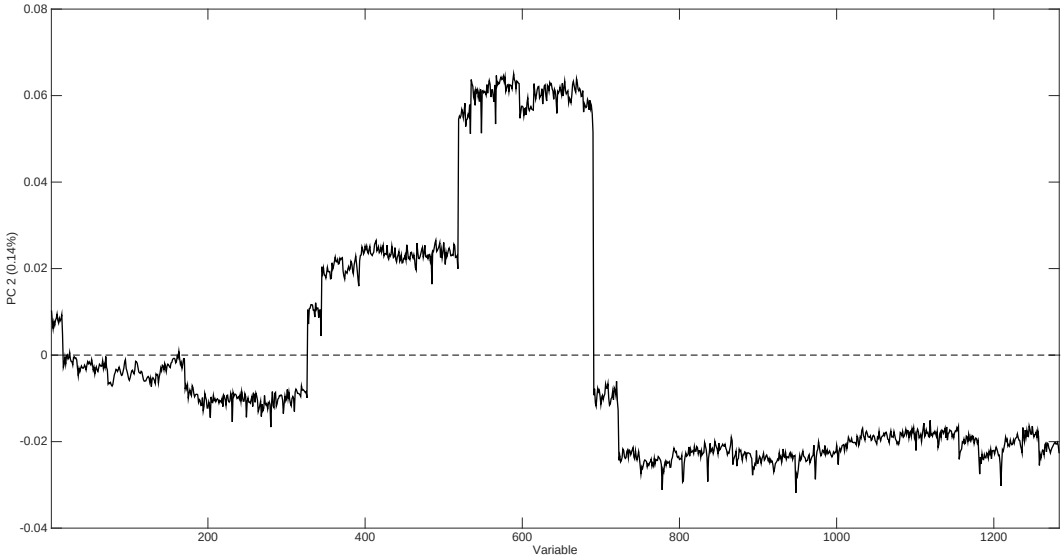

Figure 6: Principal Component 2 for Sodium Saccharin Run 2 at levels 10%, 20% and 30%, 5% and 7.5%

Here it is principal component 2 that contains information of saccharin variation and principal component 1 contains information on the average trend of all samples. It can be seen that there are clear indications of the change in saccharin levels visible in the scores plot that were far more difficult to see in the raw and pre-treated spectral plots.

Again, the same degree of discrimination of saccharin level is evident in run 2. These results look promising, with the different sodium saccharin levels being easily definable and quite steady but the spikes which appear in each cell are of concern. Though when looked at closely these are only one or two data points associated with the start and end of each cell before the NIR probe stops recording. Clearly these points need removing from the logged data in the pre-processing steps.

4.2 Calibration Modelling using On-line NIR Measurements

4.2.1 Offline Analysis

In building a calibration model it is necessary to determine an off-line analysis method, i.e. reference method to quantify tablet composition. This measure is then used with the pre-processed spectroscopic data to develop a partial least squares based calibration model. The quality measurement of interest was percentage of saccharin present in the granule samples taken during process operation. An off-line UV spectrometry method was developed that involved the liquid dilution of the granule samples to an absorbance between zero and one so that the Beer-Lambert law could be applied, the filtration of the non-soluble component of the placebo and then finally the measurement of the sample. After analysing the sodium saccharin/placebo mix with the UV spectrometer it was found that there was an absorbance peak at 269nm that was only affected by the saccharin. It was the absorbance at this peak from which the calibration line was developed and which realised the further quantification of the amount of sodium saccharin present. The calibration line (R^2 1) is given in Figure 7.

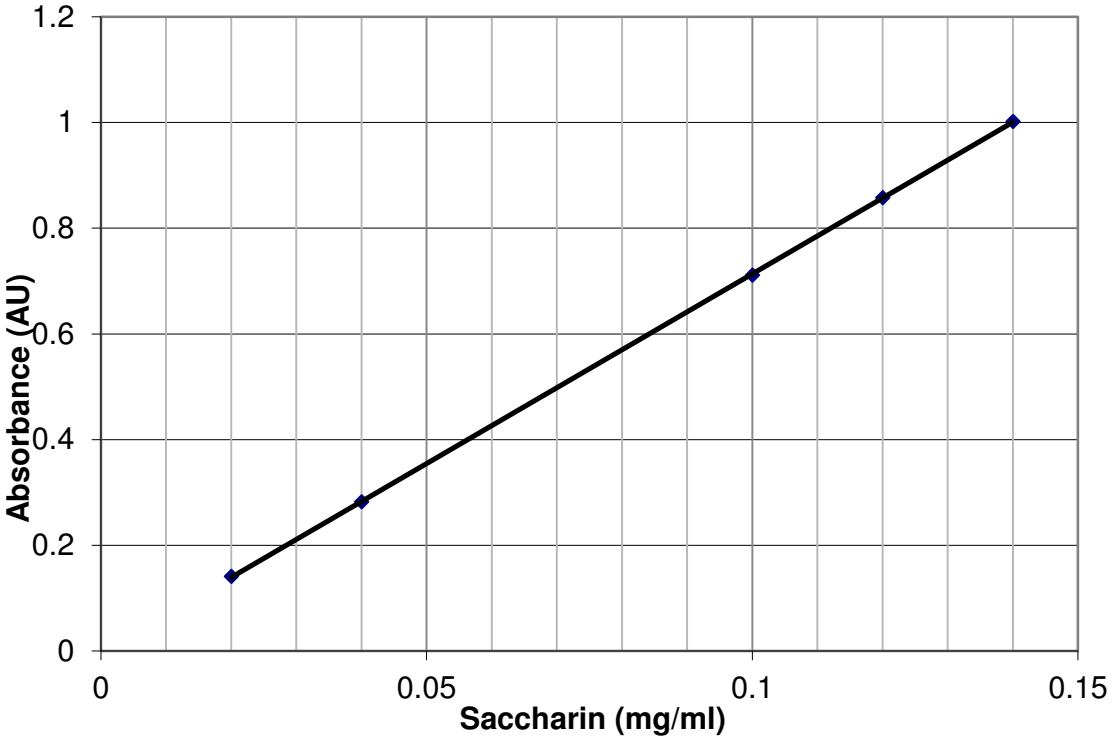

Figure 7: Sodium Saccharin UV Spectrometer Calibration Line, y = 7.177x – 0.0039; R^2=1

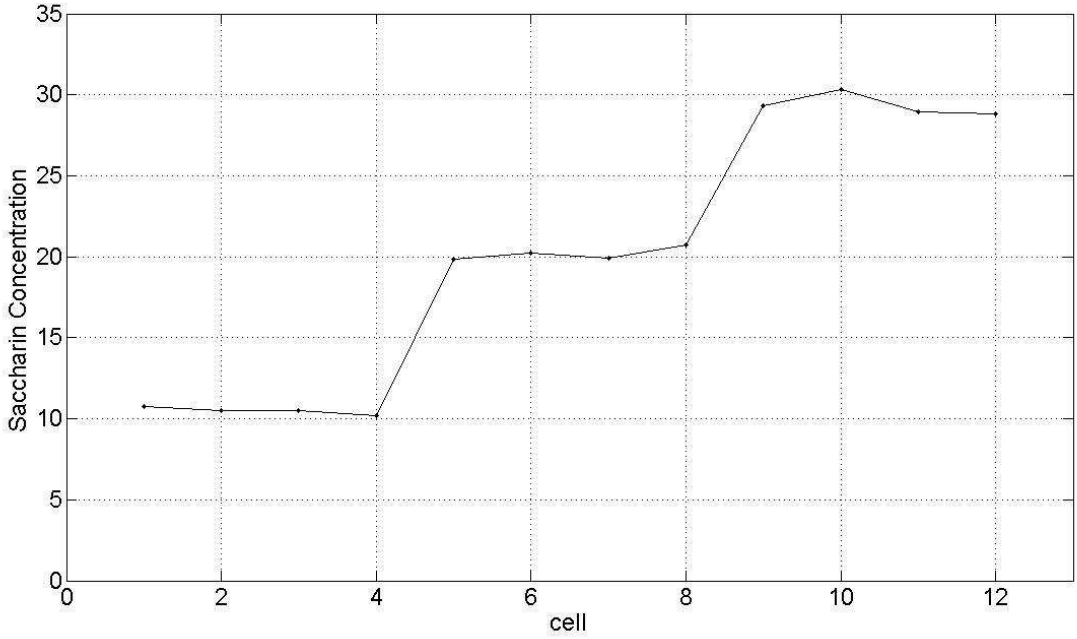

Figure 8 – Saccharin Concentration from run 1

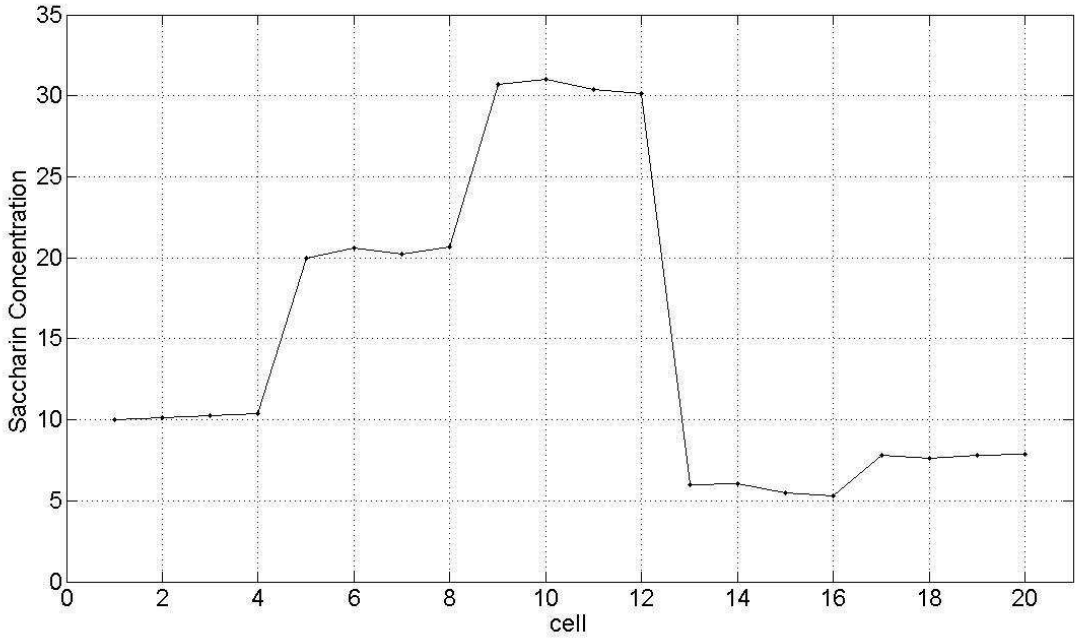

Figure 9 – Saccharin Concentration from run 2

Figure 8 and 9 show the results from the offline analysis for all the cells analyzed. For each cell, three samples were taken and for each sample the UV measurement was repeated three times thus each point in Figures 8 and 9 is an average of nine values. As can be observed the variability from cell to cell for particular saccharin concentrations are relatively low, but there is slightly more saccharin present than would have been expected. It is likely that at the higher saccharin concentrations there will be a larger error due to the dilutions that were needed. For the 20% and 30% saccharin a further dilution was required to keep the absorption below a value of one which will increase the error. As a consequence of doing the extra dilution, the saccharin concentration obtained needs to be multiplied by a dilution factor in order to get the true saccharin concentration; this will magnify any errors present.

4.2.2 NIR Calibration Modelling

An NIR calibration model based on the data generated from the offline analysis was constructed. The offline analysis produced the average blend uniformity for the sample taken from the cell. It is assumed that the sample is representative of the whole cell. The spectra recorded within each cell were averaged to produce one spectrum for each cell. The data set was split into a calibration set and a validation set. The calibration set contained all the samples from Run 2 excluding cells F8C4 and F10C4 (so that they could be included in the validation dataset). The rest of the samples were used as a validation set, which consisted of all the samples from Run 1 and cells F8C4 and F10C4. The calibration model was then built using PLS based on the average blend uniformity and the spectra. Five latent variables were retained explaining in excess of 99% variation. Finally, the measure used to assess the model fit was the Root Mean Square Error of Prediction RMSEP:

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{N} (x_i - \hat{x}_i)^2}{N}} \qquad (2)$$

where x_i represents a specific measurement, $\hat{x}_i$ the prediction for that sample and N is the number of samples. The PLS model was then built and the results are shown in Figures 10 and 11. Figure 10

shows the ability of the model to be able to predict both the calibration and the validation dataset using the calibration model. It can be seen that distinct clusters occur for each concentration.

The differences in RMSE can be seen from applying different pre-processing techniques in different combinations in Table 5 and it can be seen that SNV and Savitzky-Golay first derivative gave the lowest validation errors.

Table 5: The effect of different pre-processing techniques on model accuracy

Pre-Processing	**Calibration + Validation Sample RMSE (%)**	**Validation Samples REMSEP (%)**
SNV	0.618	0.857
SNV + Savitzky-Golay 1st Derivative	0.412	0.483
SNV + Savitzky-Golay 2nd Derivative	0.410	0.548
Savitzky-Golay 1st Derivative	0.884	1.26
Savitzky-Golay 2nd Derivative	0.952	1.37
Multiplicative Scatter Correction	1.29	1.83

Using this data the final model was build using SNV and a Saviztky-Golay first derivative. The results of this are shown in Figures 10 and 11.

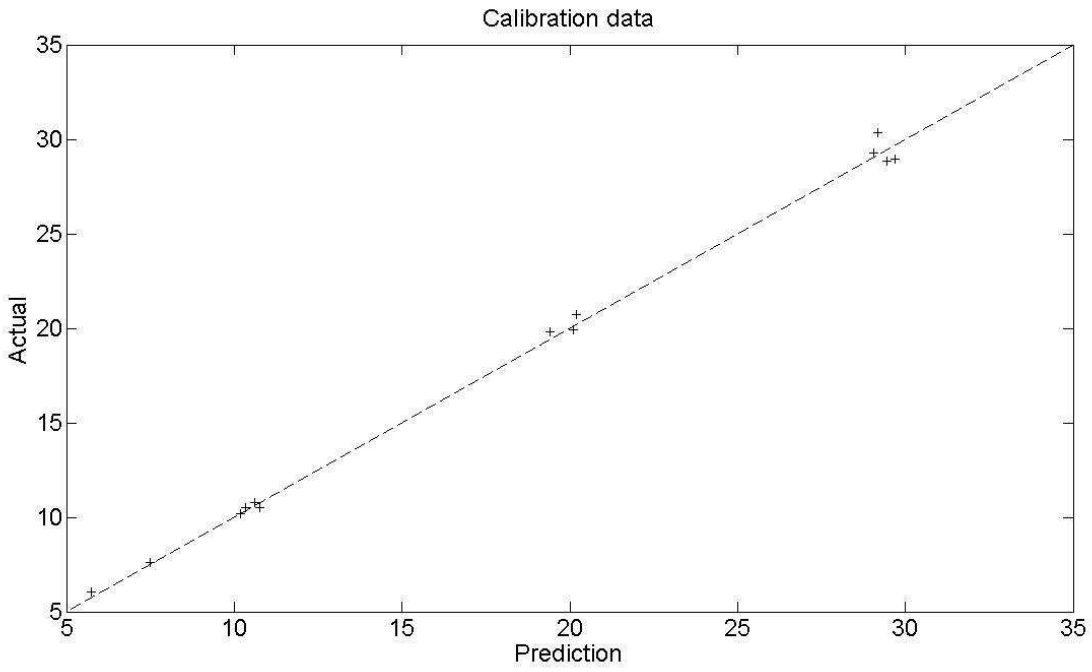

Figure 10: Actual concentration vs. predicted concentration for the calibration and validation data sets. RMSE = 0.412%

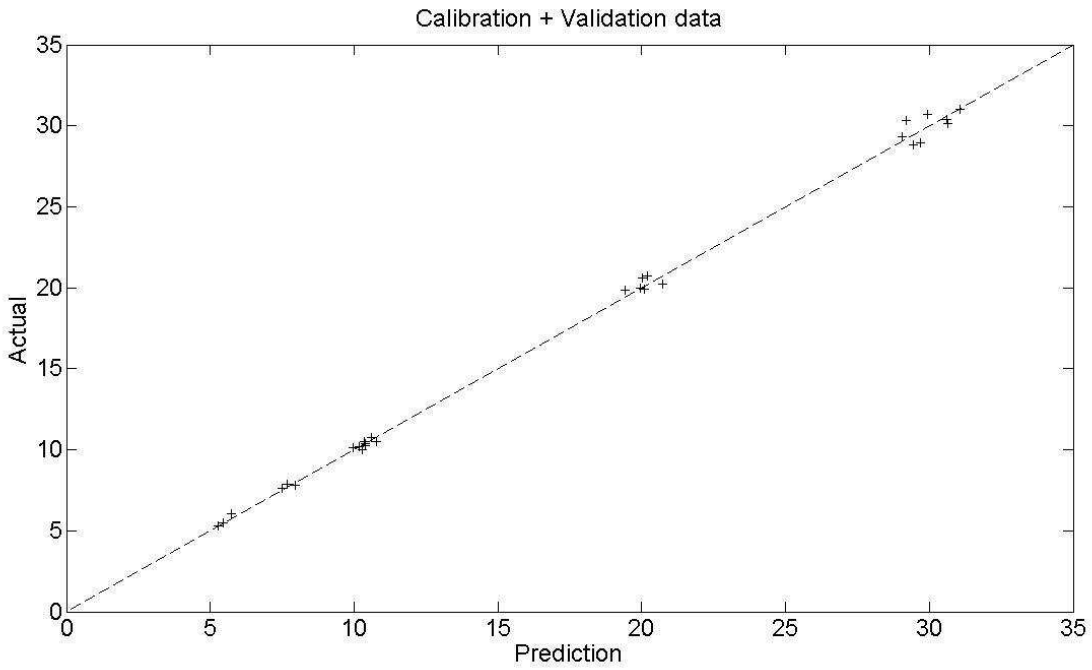

Figure 11: Actual concentration vs. predicted concentration for validation data. RMSEP = 0.483%

Figure 11 shows the ability of the model to predict the concentration of cells with known saccharin content. The prediction error is slightly higher when looking just at validation data as would be expected. The lower concentrations are predicted with smaller errors as can be observed from the fact that the clusters are tight and lie on the ideal line. This is confirmed from the RMSEP for the saccharin concentration (Table 6).

Table 6: Calculated RMSEP for each saccharin concentration

Target Saccharin Concentration	**RMSE (%)**
5 %	0.165
7.5%	0.139
10 %	0.170
20 %	0.500
30 %	0.641

4.3 Online Blend Uniformity Monitoring Using the Calibration Model

The PLS model was then used to show the monitoring ability of the probe on the saccharin concentration within the same run. It is important to highlight the difference, where before the PLS model was being used to predict the average saccharin concentration over a cell, the model is now being used to predict the saccharin concentration from each NIR reading taken. It is difficult to quantify how accurate this is as there is no offline data to cross validate this with. However, it is important to note that both Figure 12 and Figure 13 both follow the same trends found in the offline measurements that can be seen in Figures 8 and 9. This is particularly important for Run 1 as this is validation data that was not used to build the PLS model.

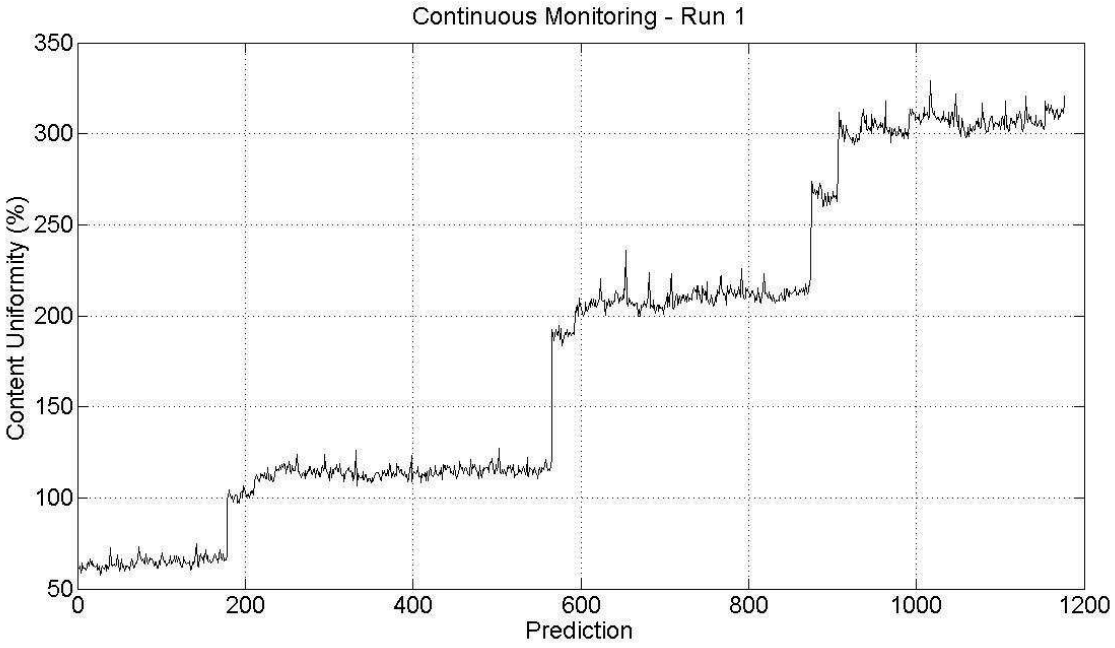

Figure 12. Prediction for all NIR readings during Run 1

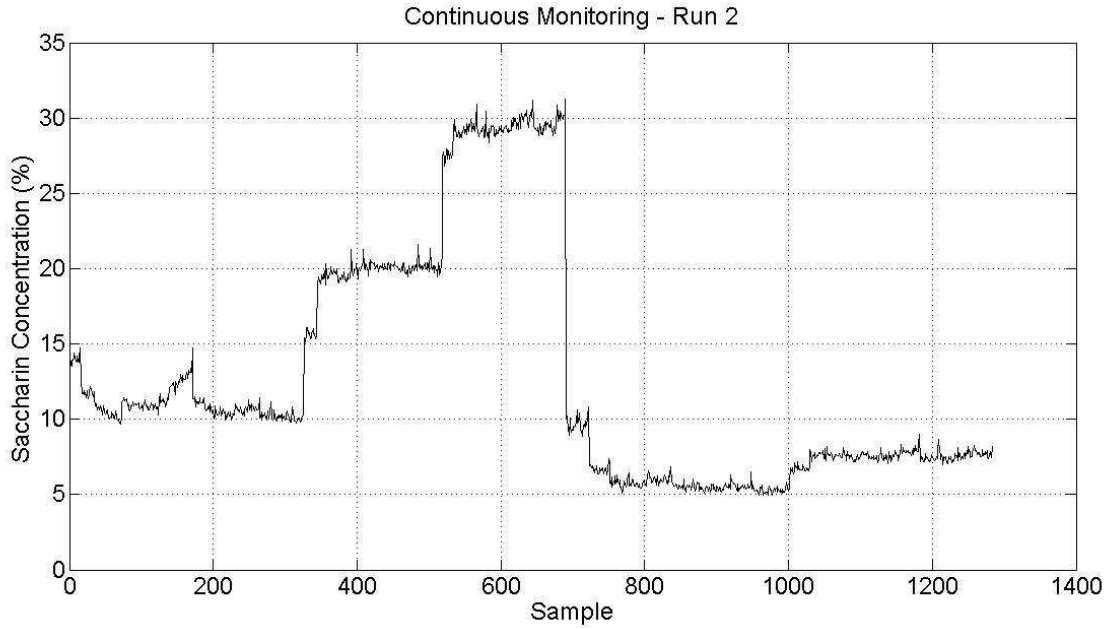

Figure 13. Prediction for all NIR readings during Run 2

By calculating the sample mass the NIR probe has measured in one dryer cell, it is also possible to look at the blend uniformity measured online at a unit dose scale. The total measured sample mass over one cell can be seen in Table7:

Table 7: Granule Properties

Granule	**Bulk Density (g/cm^3)**	**No. of NIR Samples Taken**	**Measured Mass (mg)**

Placebo Granule 10% Saccharin	0.599	32	153.2

Figure 14-15 show the monitoring of both the assay and the uniformity of the saccharin concentration within each cell at a sub unit dose scale of scrutiny. The assay stays within the potency limits in both runs, the only cells which breach the +/-10% limits are those which involve a transition in concentration, where the exact concentration of saccharin is not known.

The uniformity stays within limits for the entirety of run 1, however run 2 has a couple of cells where the uniformity isn't with specification. The first 10% concentration period in run 2 has a couple of disturbances which can be seen in Figure 13 where the measured concentration is higher than expected and it is these disturbances which push the RSD up. The lowest concentration set point at 5% saccharin also has a relatively high RSD, which was due to the feeder struggling to maintain its set point at such low concentrations. This could be rectified by using a feeder with a more suitable set up when dosing very small mass flow rates.

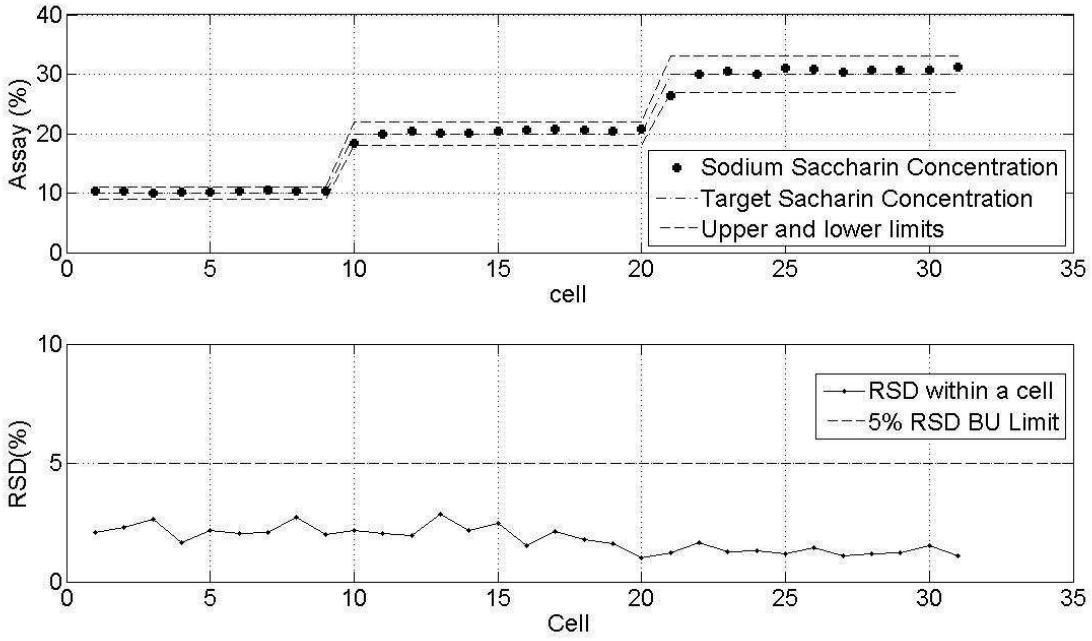

Figure 14: Online monitoring using NIR analysis of Sodium Saccharin showing Assay and RSD on Run 1. Boundary conditions are positioned at +/- 10% of the target set point for the Assay and 5% limit for the RSD.

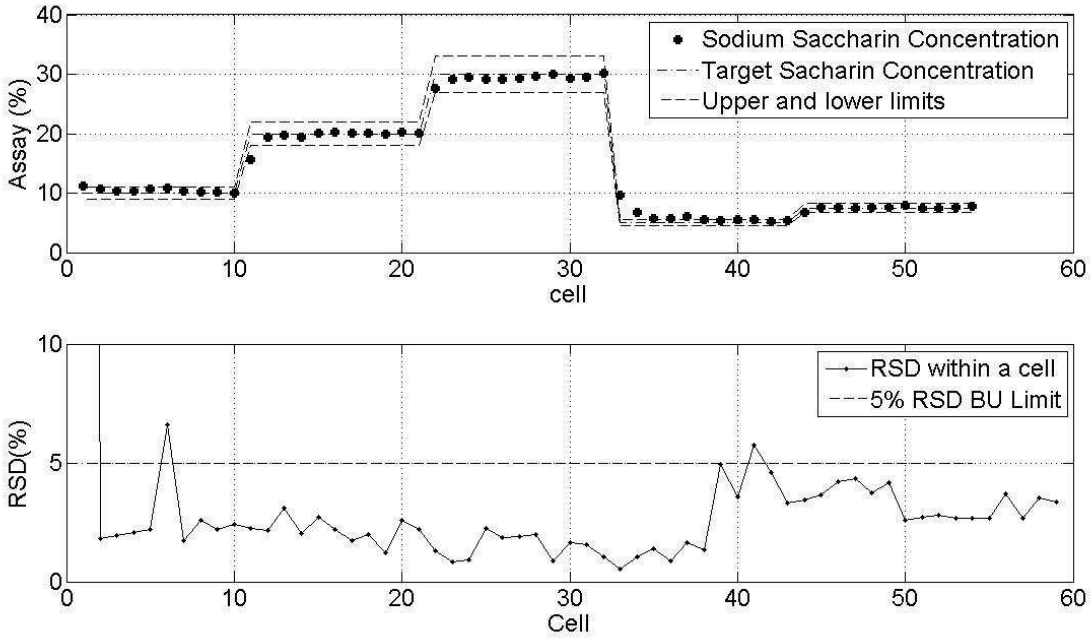

Figure 15: Online monitoring using NIR analysis of Sodium Saccharin showing Assay and RSD on Run 2. Boundary conditions are positioned at +/- 10% of the target set point for the Assay and 5% limit for the RSD.

There are advantages to measuring the blend uniformity at both unit dose scale, and at the sample size scale. The unit dose scale gives a better indication of the blend uniformity that will be seen in the final tablets. At the sample size scale however it could be possible to see if there will be poor intra-tablet uniformity.

It is possible to compare different sample sizes and the effect that this has on the RSD. It is worth noting that as long as all the data is used; changing the scale of scrutiny will not change the final assay, only the RSD.

The effect of changing the scale of scrutiny can be seen in Figure 16 and 17, where 1, 10, 20 and 30 samples from each condition are used to calculate the blend uniformity over each concentration.

Table 8: Calculated Sample Size for Varying Number of Samples in Averaging

No Samples	Calculated Sample Size (mg)
1	15.7
10	50.7
20	89.7
30	128.7

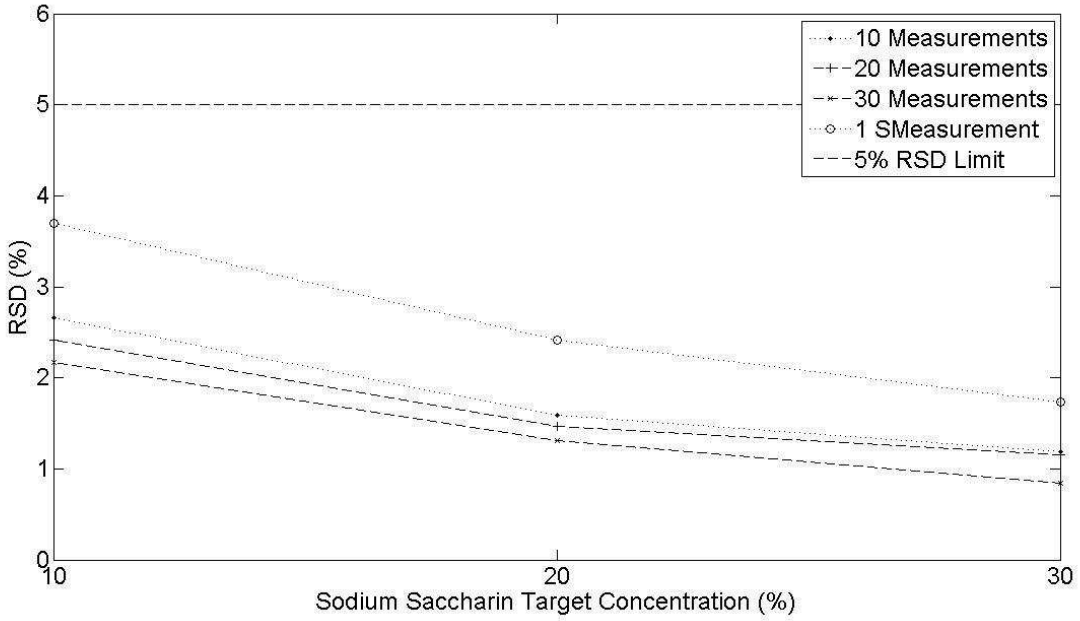

Figure 16: Effect of increasing the number of measurements per average to move from single measurements towards a unit dose scale of scrutiny for Run 1

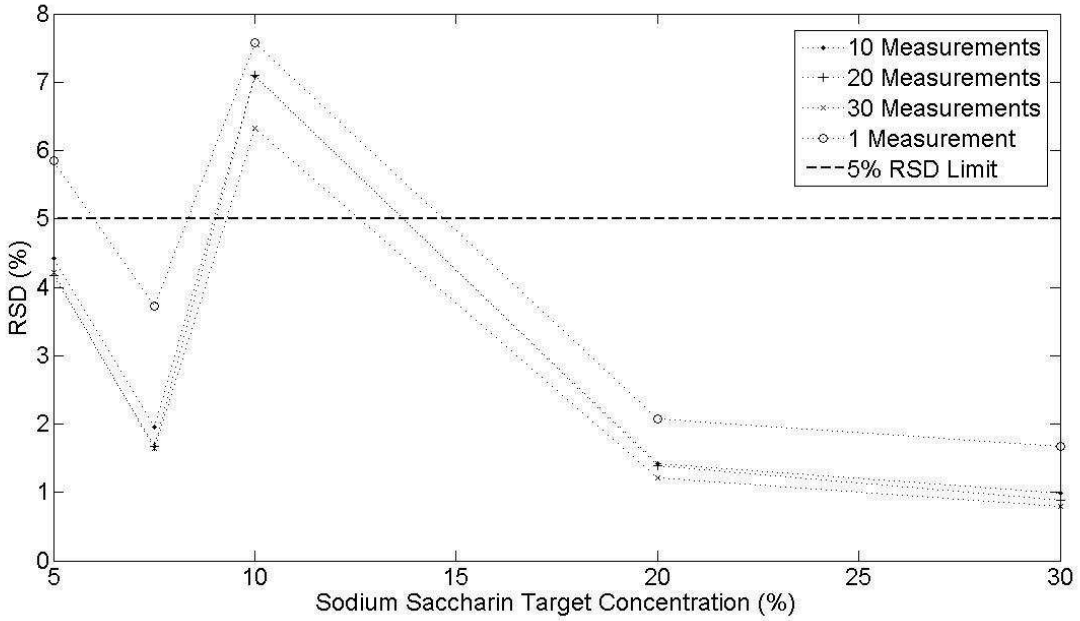

Figure 17: Effect of increasing the number of measurements per average to move from single measurements towards a unit dose scale of scrutiny for Run 2

As the number of samples used is increased in order to move towards a unit dose scale of scrutiny, it would be expected that the RSD would decrease. However, the RSD will only decrease towards the population RSD. Figure 16 and Figure 17 show that it is important to measure based on unit dose scale

of scrutiny in order to quantify the real variability and not a variability amplified by spectral noise and intra tablet variability.

5. Conclusions

Process Analytical Technologies are potentially a valuable tool for improving the monitoring and control of processes. They offer a move from a control strategy that is predominantly based on off-line laboratory analysis, to one where on-line measurement can rapidly indicate deviations and allow appropriate action to be taken. Unfortunately, the complexity of the physical system makes calibration model construction problematic and traditional methods are compromised unless care is taken in probe implementation and data preprocessing.

This paper has demonstrated that it is possible to monitor blend uniformity of a continuous tableting line using online NIR spectroscopy. It has been shown that through the use of PLS regression it is possible to detect deviations in the blend uniformity. This paper also highlights the need to analyze the data generated by the NIR probe at the correct scale of scrutiny. If the wrong scale of scrutiny is used, then the variability may be amplified or filtered leading to incorrect judgements of the product quality. In arriving at the results described this is not the only issue that arises in application. The quality of the results is significantly impacted by the mathematical signal pre-processing approaches chosen to move from raw data to prediction. An 'optimal' set of methods is not easily identifiable and requires significant data and knowledge of the approach to configure the processing steps. Importantly, what is 'optimal pre-processing' for one application is not necessarily so for another. One of the greatest challenges we faced in moving from first implementation of the probe to a working system was that decisions such as pre-processing proceed in parallel with probe commissioning, data gathering and experimental design thus in moving towards 'optimal' probe functionality it can be difficult to identify where attention needs to be focused. Such considerations are discussed further in a comprehensive technology review bringing together the experiences of multiple teams [29].

Looking beyond the scope of this paper, a relatively straightforward early warning scheme for deviations can subsequently be implemented through applying statistical process control the form of which is discussed by Silva et al [30]. It is also demonstrated that if the need is to implement a control system to compensate for disturbances, a quantitative calibration model can be constructed for closed loop control or use in a feedforward scheme.

The availability of more frequent measurements of critical quality attributes has the potential to make a paradigm shift in the control philosophy employed. A move towards a more responsive control policy than that accepted by regulatory authorities in the past offers the opportunity for greater product consistency and increased productivity through greater insight into deviations. This is particularly crucial in the case of a continuous processing line where the batch-wise demonstration of consistency is no longer applicable and the measurement of instantaneous composition is required.

While this paper has concentrated on on-line implementation of NIR measurements as part of a control strategy, the benefits of PAT may arise without full implementation. The understanding gained by on-line implementation in the design stage may result knowledge that allows an effective control system to be designed that does not require permanent on-line NIR implementation.

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