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Examples of NIR based real time release in tablet manufacturing

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Abstract

Real time release (RTR) of products is a new paradigm in the pharmaceutical industry. An RTR system assures that when the last manufacturing step is passed all the final release criteria are met. Various types of models can be used within the RTR framework. For each RTR system, the monitoring capability, control capability and RTR capability need to be tested. This paper presents some practical examples within the RTR framework using near-infrared and process data obtained from a tablet manufacturing process.

Keywords: Real time release; Near-infrared; Process models; Chemometrics; Process analytical technology; Multivariate statistical process control; Regression models; Tablet manufacturing

1. Introduction

The publication of the Food and Drug Administration (FDA) process analytical technology (PAT) initiative [1] has increased the interest for PAT in the pharmaceutical industry. One of the principles that are described in the guidance document is real time release (RTR). Real time release is the ability to evaluate and ensure the quality of in-process and/or final product based on process data [1]. In a recent paper [2] we presented a theoretical framework for RTR, in which four theoretical and distinct different models were suggested for a RTR system. In the present paper we will demonstrate (practical) examples of these four model types, using near-infrared and process data from a tablet manufacturing process.

1.1. Theory of real time release

An RTR system ensures that when the last manufacturing step is passed all the final release criteria are met. Three basic questions have to be addressed for such a system:

- Do we have a (preferably early) warning system if something is going wrong during manufacturing?—Monitoring capability.
- Do we have an idea how to adjust the process, and whether it is possible?—Control capability.
- If we monitor and control our processes, will the final product meet its quality criteria?—RTR capability.

Different approaches can be used in order to address these three questions. In this paper the combination of near-infrared and process data is demonstrated as an example of the theoretical considerations discussed earlier. Four distinct different models can be used to evaluate the data (Table 1) i.e. one multivariate statistical process control (MSPC) model and three different regression models.

1.1.1. Statistical model

In a statistical model, new measurements are compared statistically to historical data from normal operating conditions (NOC) batches that provided good quality products. A classical method which can be used for the statistical monitoring strategy is multivariate statistical process control (MSPC) based on developing a principal component analysis (PCA) model [3] on NOC batch data and two control charts for the operator based on D and SPE statistics [4,5]. Generally speaking the D statistics

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Table 1
Overview of the four different model types

Class	Model symbol	Description
(A) Statistical model	A	Statistical model comparing current process observations with historical process observations e.g. multivariate statistical process control (MSPC) models
(B) Regression models	B.1	Intermediate quality predictions. A regression model between predictors and intermediate quality parameters. For example, used for feedback control
	B.2	Final quality predictions. A regression model between predictors and final quality parameters at a point where the entire manufacturing process *has not been completed*. For example, used for feed forward control
	B.3	Final quality predictions. A regression model between predictors and final quality parameters when the entire manufacturing process has been completed. Used for RTR

describes the systematic variation in the data while the random variation is quantified as the squared prediction error (SPE). In case that a future measurement exceeds the limits in the control charts the operator can switch to the contribution plot [6] and identify the cause of the process disturbance.

1.1.2. Regression models

In the occasions where a quality parameter (being it an intermediate property or the final product) is available, a regression model can be developed. The regression models all relate some process measurements to a quality measurement at the end (final product quality) or halfway (intermediate quality parameter) of the process. The regression models all need a calibration model to be developed between predictors and a response e.g. quality parameter. Three different regression models can be made. These are explained in Table 1. Multivariate regression methods e.g. PLS [7], multi-block PLS [8], N-way PLS [9] and other regression techniques can be used to develop models for predicting intermediate and final product quality parameters.

In the results section examples of these models will be presented.

2. Experimental

2.1. Tablet manufacturing process

The manufacturing process consisted of several unit operations which are symbolized in Fig. 1. In the brackets are the symbols which are used in Fig. 1. First all compounds (see Table 2)

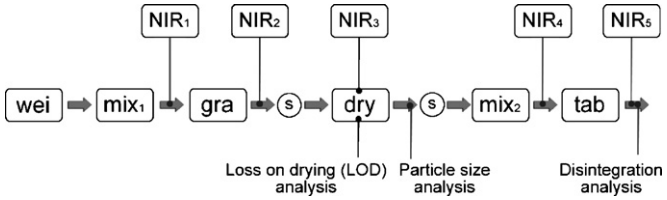

Fig. 1. Overview of unit operations, NIR measurements (symbolized with NIR boxes) and reference analysis points.

were weighed (wei). Then the active pharmaceutical ingredient (API), lactose, microcrystalline cellulose, polyvinylpyrrolidone and crosscarmellose were mixed (mix_1) in a high shear mixer. A prepared mixture of polyvinylpyrrolidone and water was added to the high shear mixer and granulation was performed (gra). The wet granules were removed and put through a sieve (s) before added into a fluid bed reactor where the granules were dried (dry). The dried granules were removed and again put through a sieve (s) and placed in a drum mixer. Gliding compounds were added and mixed with the granules (mix_2). The finalized granules were compressed into tablets (tab) with a weight of 180 mg.

2.2. Analysis

During drying, samples were removed from the fluid bed reactor and loss on drying analysis was performed, using a moisture analyzer (Mettler Toledo Halogen Moisture Analyzer HR73). After drying samples were subjected to particle size analysis using a Malvern Scirocco 2000 laboratory particle size analyzer. The mean tablet disintegration time was also determined for each batch using an automated disintegration testing instrument (Tablet Disintegration System PTZ Auto 2EZ, Pharma-Test Germany) (average of six tablets). Finally, NIR analysis was performed extensively throughout the entire process which will be described later in this chapter.

2.3. Batch overview

Six calibration batches with varying amount of API, i.e. 0 (placebo), 75, 85, 100, 115 and 125% of API label claim. In the calibration batches with API amount different from 100% label

Table 2
Batch formulation of main tablet, granulation liquid and glitter compounds

Compound	*g*
Main compounds	
API	175
Lactose	966
Microcrystalline cellulose	221
Polyvinylpyrrolidone	84
Crosscarmellose	97
Granulation liquid	
Polyvinylpyrrolidone	37
Purified water	372
Glitter compounds	
Magnesium stearate	8
Talc	16

Table 3
Batch overview

Batch	Description		
Placebo batch	A batch without API (also used for calibration)		
Calibration batches	Five batches with 75, 85, 100, 115 and 125% of API label claim		
DoE batches	Mixing time (min)	Granulation liquid flow (ml/min)	Drying temperature (°C)
#1	1	30	60
#2	1	30	50
#3	4	30	50
#4	1	90	50
#5	4	90	50
#6	1	30	70
#7	4	90	70
#8	1	90	70
#9	4	30	70
#10	2.5	60	60
#11	2.5	60	60
#12	2.5	60	60

claim the API was interchanged with lactose and microcrystalline cellulose keeping the ratio between those two components constant. Also a set of designed batches (DoE batches, all with 100% API label claim) were manufactured (Table 3). The tablets of all the calibration and DoE batches were weighing 180 mg. In the DoE batches three process variables; dry mixing time, granulation liquid flow and drying temperature were varied according to a full factorial design with two levels. This gave eight batches plus an extra training batch (#1), and three centre points (#10–12) in total twelve batches. All calibration batches and the placebo batch were having a mixing time of 2 min, granulation liquid flow of 90 ml/min and they were dried at 60 °C.

2.4. NIR analyzer and measurement details

All NIR measurements were performed with a new versatile FT-NIR Bruker Multi Purpose Analyzer (MPA) (Bruker Optics, Ettlingen, Germany). With this NIR analyzer the manufacturing process was investigated at several points (Fig. 1). In Fig. 1, the NIR measurement points are symbolized with boxes with NIR_i inside. NIR_3 is an online measurement of the drying step, while the other NIR measurements are obtained after the process step was finished. Table 4 contains details for the NIR measurements displayed.

Table 4
NIR measurement details

NIR_1, NIR_2 and NIR_4	Reflectance measurement with handheld probe. 16 scan pr spectrum. The region from 4000 to 12,500 cm^{-1} was scanned. Resolution 8 cm^{-1}
NIR_3	Reflectance measurement with process probe. Sixty-four scan pr spectrum. The region from 4400 to 12,500 cm^{-1} was scanned. Resolution 8 cm^{-1}
NIR_5	Transmission measurement. Thirty-two scan pr spectrum. The region from 5800 to 12,500 cm^{-1} was scanned. Resolution 8 cm^{-1}

2.5. Data analysis

All data analysis was done using MatLab [10], PLS toolbox [11] and in-house written m-files. The NIR spectra were imported into the MatLab environment after acquisition with the NIR instrument software. In the regression model examples B.1, B.2 and B.3 is the model performance evaluated by the root-mean-square error of calibration (RMSEC) and the root-mean-square error of cross-validation (RMSECV). The merits are calculated by the formula below:

$$\mathrm{RMSEC} = \sqrt{\frac{\sum_{i=1}^{n}(\hat{y}_i - y_i)^2}{n}}$$

where n is the number of calibration samples and $\hat{y}_i$ is the values of the predicted values when all samples are included in the model formation. The RMSECV is calculated as RMSEC, except the $\hat{y}_i$ are predictions for samples *not* included in the model formation.

3. Results and discussion

In this section, four examples of applications in a RTR system are discussed. Please note that, while the examples were investigated thoroughly, here we only discuss them briefly, since the main goal is to show how all these examples fit in a RTR scheme.

3.1. Example 1: statistical model

With this example it is demonstrated how two MSPC models based on NIR_1 or NIR_2 measurements could provide an early warning of manufacturing problems and separate good batches from the bad ones. Two DoE batches (#2 and #3) experienced particle size problems after the drying step and this is referred to as the manufacturing problem. The DoE batches #1, #4–6 and #8–12 had no manufacturing problems; these are referred to as normal operating condition (NOC) batches. NIR spectra from the NOC batches were used to develop the MSPC control charts. The DoE batches #2 and #3 with manufacturing problems and #7 without manufacturing problems were then used to validate the MSPC control charts. After drying DoE batch #2 granules had a large proportion of fines and a low average particle size while DoE batch #3 granules consisted of coarse particles. DoE batch #7 was known for having a particle size distribution similar to the other nine DoE batches i.e. good particle quality. These batches were called validation batches. Validation of MSPC models is done by showing that observations from batches with manufacturing problems are flagged above the control limits in the MSPC charts while observations from batches without manufacturing problems are below the control limits. It is an essential necessity for development and validation of a MSPC model that data exist for both NOC batches and batches with quality defects.

The first MSPC model used the raw NIR_1 spectra as input. The NIR_1 spectra from the NOC batches (on average fourteen spectra from each batch) were used in total 119 spectra. The spectra were collected in a 119×2281 matrix i.e. 119 spectra with 2281 spectral data points in each spectrum. The spectra

were mean centred and a PCA model was fitted to the spectra. The 95% confidence limit for the *D* statistic was calculated and used as warning limit in the *D*-chart [4]. For the residuals the 95% confidence limit was calculated and used as warning limit in the SPE-chart [12]. Now the NIR_1 spectra from the validation batches were mean centred and projected on the PCA model; their *D* statistics were plotted in the *D*-chart. The squared residuals were also calculated and plotted in the SPE-chart (Fig. 2). Fifteen spectra from DoE #2 (symbolized with stars), 13 spectra from DoE #3 (symbolized with triangles) and fourteen spectra from DoE #7 (symbolized with circles) are depicted in Fig. 2. These spectra are from independent measurement from different position in the powder mixture after the mixing step. Thus one should consider all the spectra of one batch as a whole. According to the control charts in Fig. 2, batches DoE #3 and DoE #7 have problems while batch DoE #2 seems to be ok (except for the sample 14 that just exceeds the SPE limit. Various ways of pre-processing and wavelength selection were tried out in order to see if a better result could be obtained but without success. The conclusion was that a MSPC model with NIR_1 was not good for identification of the two batches with quality defects.

Therefore an MSPC model and control charts were developed with NIR_2 as input. Again various pre-processing methods and wavelength selection were tried out and the best results obtained with 1st derivative and the wavelength region from 4700 to 5700 cm^{-1}. With the spectra from the NOC batches the control limits were developed for the charts. Then the *D* and SPE statistics of the validation spectra were calculated and plotted in the control charts (Fig. 3). Almost all data points from DoE #2 and DoE #3 spectra were flagged out in either the *D* or the SPE charts. All DoE #7 data points were below the control limits as expected (circles in Fig. 3).

This demonstrated how early warning and monitoring capability of manufacturing problems was achieved with a statistical model using NIR_2 data. Secondly, it was found that the granulation step is important when it comes to particle size quality. The next step would be to investigate whether the granulation process could be controlled to get consistent particle size quality.

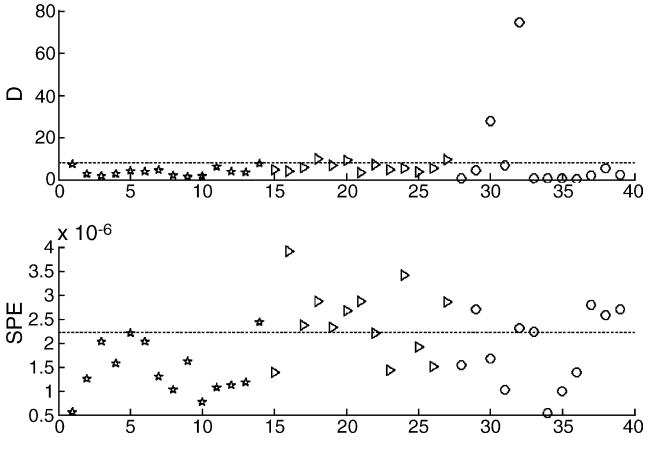

Fig. 2. The NIR_1 data from the validation batches plotted in the *D*-chart and the SPE-chart. DoE #2 observations are symbolized with stars, DoE #3 with triangles and DoE #7 with circles. The dotted lines in both charts are the 95% confidence limit.

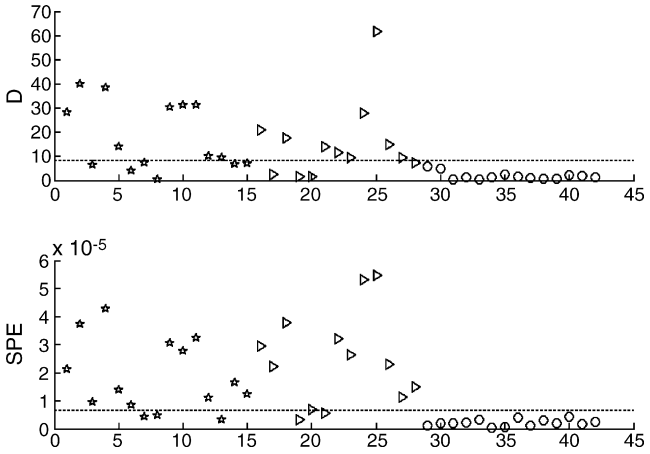

Fig. 3. The NIR_2 data from the validation batches plotted in the *D*-chart and the SPE-chart. DoE #2 observations are symbolized with stars, DoE #3 with triangles and DoE #7 with circles. The dotted lines in both charts are the 95% confidence limit.

3.2. Example 2: regression model B.1 (local prediction of quality)

Along the manufacturing chain several intermediate quality characteristics can be monitored. In some cases it is of vital importance that the intermediate quality is good in order to continue to the next process step and ultimately this will benefit a RTR system. Monitoring the water content during drying is an example of monitoring a local quality characteristic. The purpose of the drying process is to remove excess water in the granules and produce dried granules that are easily compressed into tablets. If the water content is not within a certain range, compression problems will occur and it might be necessary to discard the entire batch.

During drying in the fluid bed reactor, NIR spectra were automatically collected every half minute, with a process reflectance probe inserted in the reactor. Powder samples were removed from the fluid bed reactor during the drying from a sample port located in close proximity to the NIR probe port. The water amount in the samples was determined as % weight loss-on-drying (LOD) The spectrum that was recorded during the removal of the sample was assigned to the corresponding LOD reference value. A PLS model with three latent variables was developed using 28 calibration spectra representing all DoE batches. Many different pre-processing methods were investigated and also wavelength selection routines were applied in order to minimize non-relevant spectral variation and improve model statistics. As pre-processing method Savitzky–Golay 1st derivative with a second order polynomial fit using 17 spectral points was selected. The combined wavelength regions 4597–5450 cm^{-1} and 7500–12,500 cm^{-1} were used. These wavelength regions cover the water bands in the combinational and second overtone region in the NIR spectra. The first three latent variables explained 99.08% of the variation in *X* and 98.70% of *Y* variation. The cross validated predictions are presented in Fig. 4.

The NIR_3 spectra from the DoE batches were applied to the PLS model and drying (LOD) curves were predicted. Exam-

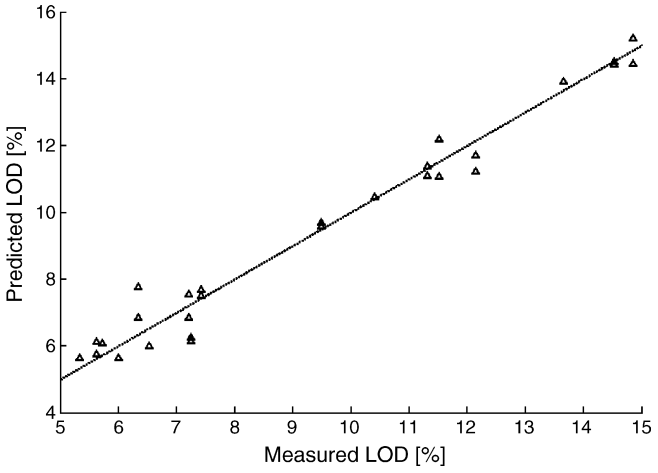

Fig. 4. Calibration line for three LV PLS model. Measured LOD values vs. predicted values from cross validation. The dotted line indicates perfect fit. With three LV the RMSEC was 0.37 and the RMSECV was 0.53.

ples of the drying curves from two DoE batches dried at 50 and 70 °C, respectively, are shown in Fig. 5. Both batches showed a steep decline in LOD the first five minutes because of high water evaporation caused by the airflow which always was 100 m^3/h the first 5 min and thereafter lowered to 50 m^3/h for the remaining drying. The drying of both batches was terminated when the product temperature reached 34 °C but due to the different drying temperature, the drying times differed from 23 to 38 min. Both drying curves showed a slight increase of the LOD near the end of the drying period. The increase can be explained with an increased diffusion of water from the core to the surface of the granules during what is known as the *equilibrium* period [13] where the granule temperature is increasing. The phenomenon is a process signature and can be utilized into end-point control of the drying process, which is the natural extension of this example of in-line local quality predictions.

With this example it was demonstrated how a regression model between in-line NIR spectra and LOD provided monitoring capability. Secondly, it is also possible to implement the regression model for real-time control of the drying time, which can provide control capability of the process.

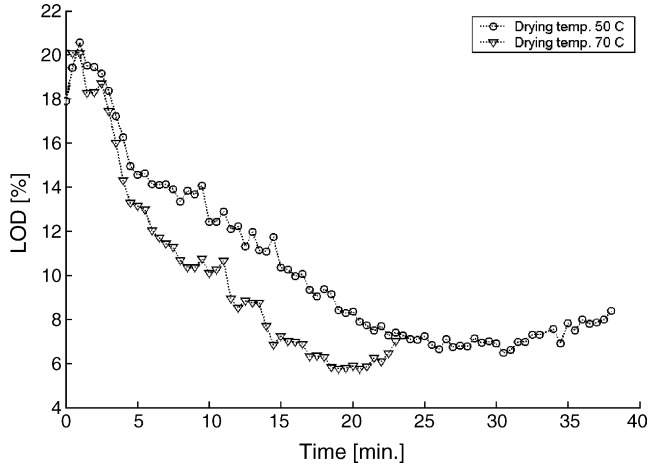

Fig. 5. Drying curves for two DoE batches with drying temperatures 50 °C (◯) and 70 °C (▽). Both batches were granulated with a granulation liquid flow of 90 ml/min.

3.3. Example 3: regression model B.2 (forecasting final quality and process control)

In any manufacturing system there will be variation in the process input e.g. raw material variation, environmental factors etc. which all affect the final quality, unless the manufacturing process can comprehend these variations or process control exists to minimize the influence of input variation. In the following it will be demonstrated how to develop a feed forward process control tool with regression models between process variables, process measurements and a final quality characteristic i.e. the mean disintegration time for the tablets.

In each batch the disintegration time was determined for six tablets. The average disintegration time (dis*T*) of six tablets was used as final quality variable. The average disintegration time ranged from 120 to 248 s. The standard deviation on the average disintegration time was approximately 30 s. Two PLS models were developed (models I and II) using process variables and NIR spectra as predictors. The NIR spectra consisted of more then 2250 spectral variables and in order to perform data fusion between a few process variables and thousands of spectral variables, the NIR spectra were first decomposed using PCA and the mean centred scores were then fused with the process variables.

Then the scores and process variables were auto scaled and a PLS model established between the predictors and the mean disintegration time.

The predictors for model I were; mixing time (mix), scores from the first three PCs of the PCA model of average NIR spectrum from the mixing (NIR1*) and the granulation liquid flow (gra) in total five predictors. For model II, the predictors also included the first three scores from three PCA models of (a) the average NIR spectrum of the granulation (NIR2*), (b) the last spectrum from the drying process (NIR3*) and (c) the average NIR spectrum from the glidant mixing step (NIR4*). Also the process variables; drying temperature (air*T*), drying time (dryTime) and upper punch force during tabletting (pun*F*) were used as predictors in model II. The predictors and models are depicted in Fig. 6.

Using the data from the twelve DoE batches two PLS models were developed. The models statistics are listed in Table 5. Leave one out cross validation (LOO CV) was used given the limited

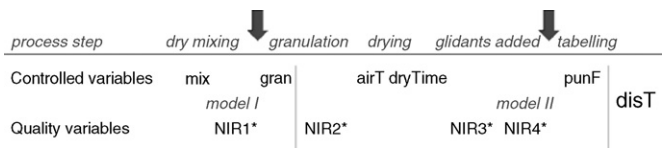

Fig. 6. Overview of controlled and quality variables used for modelling. The controlled variables are; mixing time of the dry powders (mix), the granulation liquid flow (gran), the air temperature in the fluid bed (air*T*), the drying time in the fluid bed (dryTime) and the average upper punch force during tabletting (pun*F*). The average NIR measurements after various process steps are denoted NIR* 1–4. The quality variable is the mean disintegration time of the final tablets (dis*T*).

Table 5
Model statistics for PLS models I and II

LV#	Model I				Model II			
	Expl. *X* variation	Expl. *Y* variation	RMSEC	RMSECV	Expl. *X* variation	Expl. *Y* variation	RMSEC	RMSECV
1	26.7	61.5	28.7	47.2	22.8	85.4	17.7	35.0
2	51.5	66.1	27.0	50.4	35.4	92.4	12.8	35.5
3	73.3	67.3	26.5	55.8	50.9	96.5	8.7	38.1
4	81.5	67.4	26.5	60.1	64.3	98.2	6.2	34.9
5	100.0	67.4	26.4	60.6	76.5	98.8	5.0	33.8
6					86.0	99.3	3.8	33.5

number of data points. The root mean squared error obtained from cross-validation (RMSECV) of model II was 35.0 with one latent variable (LV) and 85.4% of the *Y* variation explained compared to 61.5% for model I. So by adding more process information the prediction error decreased and a better model was established. The prediction error of model II was also close to the standard deviation for the reference analysis (approximately 30 s) so it might be difficult to improve the model further using the existing data. For both models only one PLS component was used. The *b* coefficients for the models are displayed in Figs. 9 and 11.

The measured versus predicted mean disintegration time for model II is depicted in Fig. 7. The prediction error was in some cases high which might be owed to the relative high standard deviation of the mean disintegration time. Secondly is the reference analysis performed on only a fraction of the total number of tablets produced in each batch. Generally, a larger number of batches and tablets pr batch should be used and secondly the experimental design space extended further in order to find a larger range of disintegration times. It is assumed that the correlation between the disintegration time and model predictions could then be improved. Also maybe the addition of other predictors e.g. raw material attributes could improve model predictions.

With the models, suggestions for feed forward process control can now be derived.

In Fig. 8 this is demonstrated with model I. Model I can be used by the operator just before the granulation is started and the operator wants to know how to set the granulation liquid flow. By using the mixing times and NIR measurements from the DoE batches and then inserting hypothetical values for granulation liquid flow from 30 to 90 ml/min, hypothetical mean disintegration times were then predicted with model I. The results showed that by increasing the granulation liquid flow the disintegration time would decrease. This could of course have been directly obtained from the negative b coefficient for granulation liquid flow and with model I the effect can be quantified.

With the model, the operator now has a process control tool to set the granulation liquid flow after the mixing step in order to control disintegration time (Fig. 9).

Before the operator starts the tabletting model II can be used to set the required upper punch force, in order to achieve a certain mean disintegration time of the final tablets. This was demonstrated by inserting different values for punch force in model II. The resulting predicted disintegration times are depicted in Fig. 10.

The results from this example are only indicative since more data should be available for a thorough treatment. Nevertheless does the example serve to demonstrate how to develop feed forward process control tools with regression models. The correlation between process variables and the final quality characteristic was illustrated by the b coefficients which showed ‘in

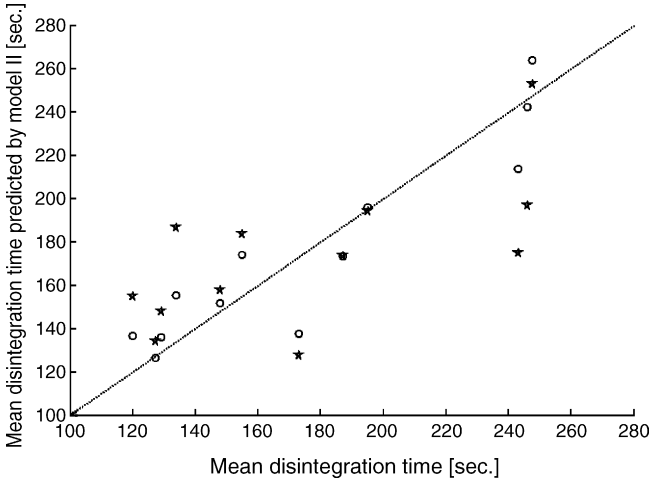

Fig. 7. Measured vs. predicted mean disintegration time for PLS model II. The values from calibration are symbolized with circles and the values from LOO CV are symbolized with stars. The dotted line symbolizes perfect fit.

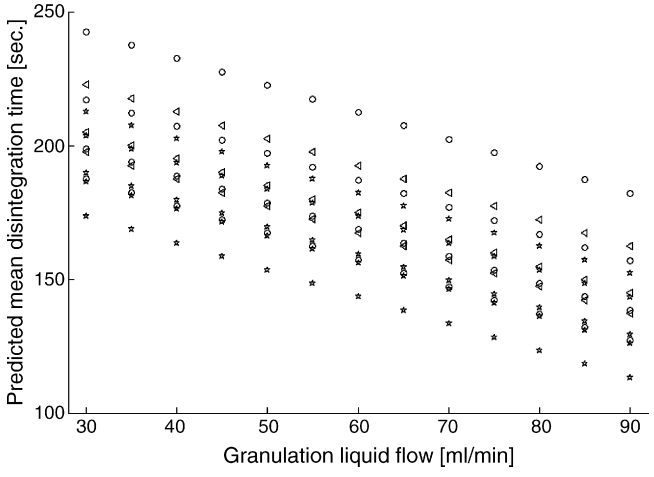

Fig. 8. Process control chart for setting of granulation liquid flow using model I at the first decision point. The DoE batches with mix time 1 min are symbolized with stars, 2.5 min are symbolized with triangles and 4 min with circles.

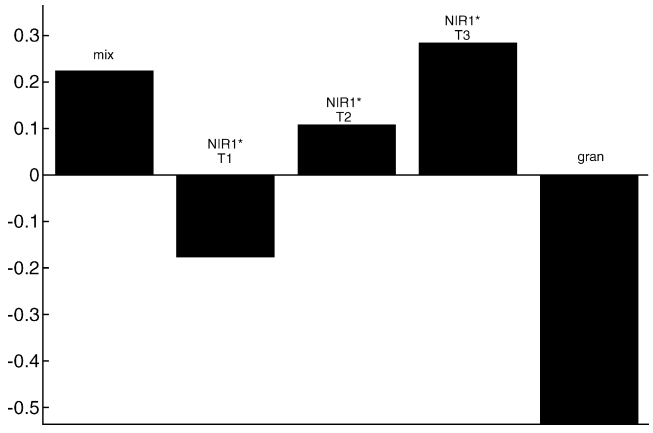

Fig. 9. The *b* coefficients for PLS model I.

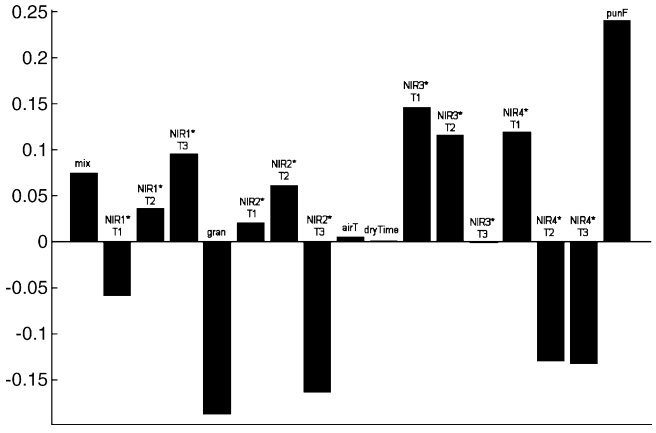

Fig. 11. The *b* coefficients for PLS model II.

which way to turn the knob' in order to force the direction of the quality parameter. The regression models could then be used to quantify the effect of 'the turn'. The results demonstrated how to get control capability.

3.4. Example 4: regression model B.3 (final quality predictions)

The most important quality characteristics for the customer are these of the final drug product. Measurements of final quality characteristics when the drug product leaves the manufacturing line in real-time or near real time would be an example of RTR (Fig. 11).

The content of active pharmaceutical ingredient (API) in the final tablets is a major quality parameter. Traditional quality control is performed on a small set of tablets i.e. 10 to 30 tablets in distant laboratories using time consuming analysis methods e.g. HPLC. This means that the batch is quarantined for 2–3 weeks before the analysis result is ready and the batch can be released to market. Secondly by only analyzing a small number of samples there is an increased risk that quality defects are not detected.

As an example of near real time quality control of the API content in individual tablets, a regression model was developed between NIR transmission spectra of the final tablets (NIR_5) and the API content. For each of the six calibration batches (Table 3) one calibration spectrum was made by averaging of 120 measured tablet spectra from each calibration batch. Then each calibration spectrum was assigned a reference value which was the average API content in the corresponding calibration batch and finally a regression model was build between the average calibration spectra and their reference values (which here was of course the weighing of the different compounds). This calibration method does not rely on reference analysis and the assumption for using this method is that by measuring a large number of samples from a batch the average content in all samples approach the average content of the entire batch.

A PLS regression model with one PLS component was constructed. A very low RMSECV of 0.066 and a correlation coefficient of 0.9999 were obtained. Fig. 12 shows the cross-validated predictions of mg API/tablets. By visual inspection of

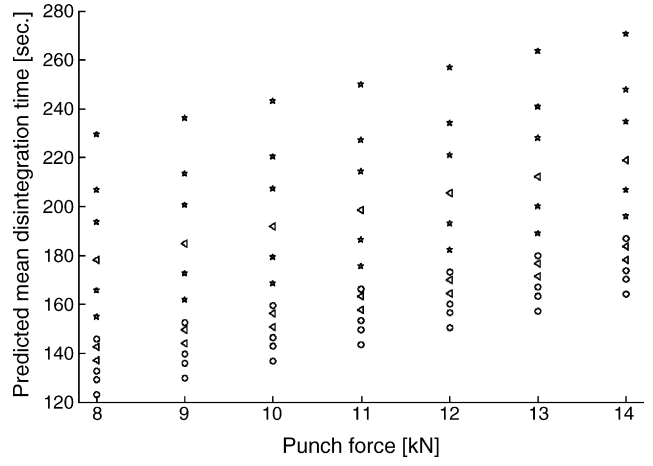

Fig. 10. Predicted mean disintegration time as a function of various hypothetical upper punch force values (pun*F*) for the twelve DoE batches. The batches with gran = 30 ml/min are symbolized with stars, 60 ml/min are symbolized with triangles and 90 ml/min symbolized with circles.

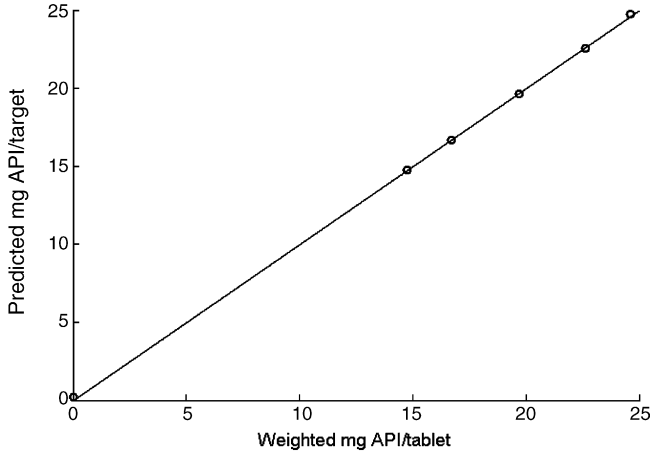

Fig. 12. PLS model with one component using the wavelength region from 7500 to 12,500 cm^{-1}. The predicted values from cross validation, of the calibration spectra vs. their reference values. The R^2 is 0.9999; the RMSECV is 0.066 which is 0.3%.

Table 6
Assay predictions (mg API/tablet) for 12 DoE batches

DoE #	Mean			Variance		
	Start	Mid	End	Start	Mid	End
1	19.2	19.2	19.1	0.03	0.02	0.03
2	19.4	19.4	19.4	0.03	0.02	0.02
3	19.6	19.5	19.6	0.03	0.03	0.04
4	19.6	19.6	19.6	0.03	0.03	0.02
5	19.6	19.7	19.8	0.04	0.02	0.04
6	19.5	19.5	19.5	0.03	0.04	0.02
7	19.8	19.5	19.5	0.05	0.06	0.02
8	19.6	19.6	19.5	0.02	0.02	0.03
9	19.4	19.4	19.5	0.04	0.02	0.01
10	19.6	19.7	19.6	0.02	0.03	0.01
11	19.6	19.5	19.4	0.02	0.03	0.03
12	19.5	19.6	19.5	0.02	0.04	0.03

The mean and variance are calculated for 30 tablets from the start, mid and end of tabletting process. The target content is 19.7 mg API/tablet.

the regression vector, the pre-processed calibration spectra and the pure API spectrum it was evident that it was the variation of the API that was modelled.

From each of the DoE batches 90 tablets were measured with transmission NIR. The 90 tablets were removed from the tabletting process in the following way; 30 tablets from the start, 30 tablets from the mid and 30 tablets from the end of the tabletting process. With the PLS model the assay (mg/tablet) was predicted in all tablet samples. The average and variance of the 30 assay predictions from the start, mid and end are listed for all DoE batches (Table 6). It was discovered that there was very little variation in the API content.

Though the API content was not varying much, few batches showed some variation in the API content. As an example the assay content of the 90 tablets from DoE batch #7 is depicted in Fig. 13. It was discovered that there was generally more API in the tablets in the beginning of the tabletting process compared to the mid and end of the process. Also the variance was higher in the start of the process. This behaviour would be difficult to identify and control if only a few samples were analyzed using classical methods. The reason for the changes in API content during the tabletting process could be explained by a mild segregation of the powder granules when flowing into the tabletting machine.

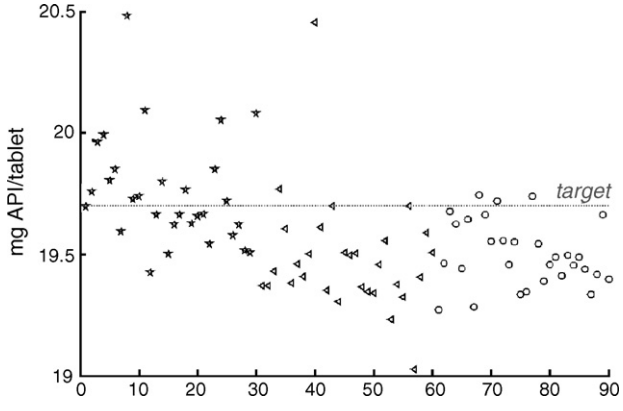

Fig. 13. Ninety assay predictions from DoE batch no. 7, 30 from start (star), mid (triangle) and end (circle), respectively. The average API content was higher in the first part of the tabletting compared to the mid and end of the tabletting process.

The last example showed how RTR capability of the tablets could be achieved. Secondly, by analyzing a large number of samples trends in the process were discovered. This would be difficult using classical sampling schemes were only a few samples are analyzed.

4. Conclusions

An approach to RTR has been shown in this paper. Starting with the three levels of capability, each process step can be evaluated for its appropriateness in the RTR system. For a pharmaceutical tabletting process, examples for monitoring capability, control capability and RTR capability are provided. Different types of models are used to provide early warnings of future manufacturing problems.

Four different models were demonstrated using NIR and process data. First a MSPC model of NIR spectra from the granulation step, demonstrated how an early warning of future manufacturing problems could be given. In the second example (*local quality predictions*) a quantitative NIR model for in-line prediction of loss-on-drying in the drying process was demonstrated. The example showed monitoring capability and suggestion for process control was discussed.

For an RTR system it is important that the manufacturing process and process control can minimize the effect of input variation to the process that affects the final quality. In the third example (*forecasting final quality and process control*) it was tried out to establish process control models and forecast the disintegration time of the final tablets.

The last regression example (*final quality predictions*) demonstrated how the API content in individual tablets can be determined with transmission NIR which can be applied at-line the tabletting process.

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