Reaction monitoring in a pharmaceutical process using near infrared closed-loop control

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Introduction

A closed-loop reaction control system utilising near infrared (NIR) methodology has been implemented for a pharmaceutical conversion process within a manufacturing facility at the GlaxoSmithKline site at Ulverston in the UK. This site specialises in the manufacture of Cephalosporins (antibiotics), which are APIs in the production of such drugs as Zinnat and Zinacef; both anti-infectives. The product stream that manufactures Zinnat was chosen as the target for online reaction control, due to cost drivers associated with generic drug competition.

Calibration models were constructed, validated and implemented for the detection of the endpoint of the reaction between the intermediate stage API in this product stream and the reagent forming the additional side-chain in the resulting product. An intermediate species, which is not isolated in the process, is formed and monitored during the reaction, before subsequent conversion to the final API product (Reaction 1 below). In order to incorporate NIR for monitoring of this reaction, a modification of the standard processing method was employed, although no regulatory action was generated by this change.

A	+	**B**	→	**(C)**	→	**D**	
Starting material		Side-chain reagent		Intermediate Species		Product	(1)

The ability of this analysis method to detect the end-point of the reaction in a reproducible and accurate manner was demonstrated simply by equivalence of the quality of the final API product [D] produced by this modified process method to that typically seen in the standard processing method.

This closed-loop control method is now in beneficial use for the process in question and affords significant raw material savings to the business due to a reduction in the quantity of side-chain reagent [B] required, whilst providing a useful insight into the state of the reaction under control. Other additional benefits afforded by this technology include reduction in the variability of the resultant product quality and the reduction of health and safety hazards associated with the reagent

The production of the API was historically carried out using a significant theoretical molar excess of reagent [B]. This was due to variable levels of protic species present in the inputs used in this stage. As the reagent reacts preferentially with these protic species, an excess of it is required to ensure adequate conversion through to the product [D].

In order to incorporate spectroscopic monitoring of this reaction, a modification of the standard processing method was required. The standard processing method utilised a large excess of [B], which was batched in its entirety into a reaction vessel before [A] was added. Reaction time in the

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vessel was typically 15minutes. This method did not enable the end-point of the reaction to be monitored as the order and manner of addition of the reagents made this impossible.

Consequently, a modified process method was proposed: This retained the current addition order of [A] to [B], but only the theoretical stoichiometric quantity of [B] required for complete reaction is present in the reaction vessel initially. Further [B] required for complete conversion of residual [A] to [C] is then added in a secondary process step at a constant level and rate until the analysis method shows that conversion is complete in real-time as illustrated in Figure 1below

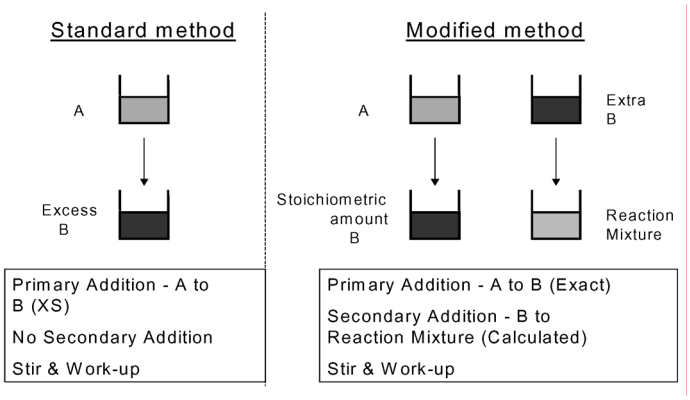


Figure 1. Comparison of standard and modified process methods.

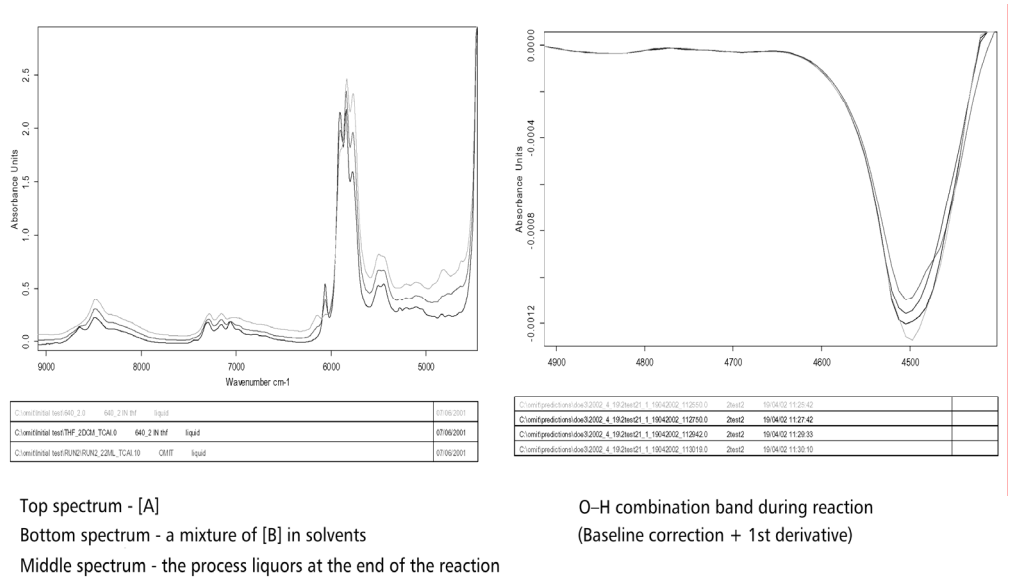
Raman studies

An investigation using RAMAN spectroscopy showed that the reaction between [A] and [B] to form [C] is completed within 1 minute of addition. The conversion of [C] to [D] takes place within a similar time period. As these reactions appeared to be practically instantaneous, there was not enough time to capture the RAMAN data for this reaction with sufficient signal to noise ratio, since scan times of one minute are typically used. Therefore this aspect ruled out the use of Raman in following the change of species with respect to time.

However, by comparison of RAMAN spectra, it was shown that the intermediate [C] produced by addition of [A] to [B] was spectrally identical to that produced by addition of [B] to [A].

NIR studies

The initial feasibility study using NIR showed clearly that by using a combination of NIR spectra and chemometrics, it was possible to characterise and interpret the reaction. It also demonstrated that defined wavelength regions could be correlated with the levels of [A] and [C] and that these could be used as a predictive tool to accurately determine the reaction end point. Figure 2 illustrates the spectra obtained with a transflectance probe and In-Ga-As detector.



Top spectrum - [A]
Bottom spectrum - a mixture of [B] in solvents
Middle spectrum - the process liquors at the end of the reaction

O–H combination band during reaction
(Baseline correction + 1st derivative)

Figure 2. NIR spectra produced during the reaction

By comparison of these spectra, it can be seen that different spectral bands exist for the main components of the reaction, i.e. [A] (green spectrum) and [B] (blue spectrum). As the reaction proceeds towards completion, a different spectrum again is observed, which is strongly influenced by the formation of [C] (red spectrum). These differences, although small, enable the different components within the reaction to be tracked and the end-point to be detected.

Calibration model construction

The original calibration models were built using theoretical conversion values between the starting material [A] and product [C] components as each reaction progressed. These were calculated using the levels of protic species present in all of the reaction inputs being used and the known level of reagent [B] being added over a set time during each batch. Table 1 below illustrates the philosophy employed for construction of the calibration models.

Table 1. Typical conversion data used for calibration model construction.

	[A]	[B]	[C]
Time 1	31.8%	68.2%	0.0%
Time 2	30.3%	69.7%	0.0%
Time 3	28.8%	71.2%	0.0%

Time 23	0.0%	100.0%	5.6%
Time 24	0.0%	100.0%	6.3%

During validation of the models, the predicted conversion values from the NIR models were used as a guide only for end of reaction indication and these were continuously assessed throughout the project lifecycle.

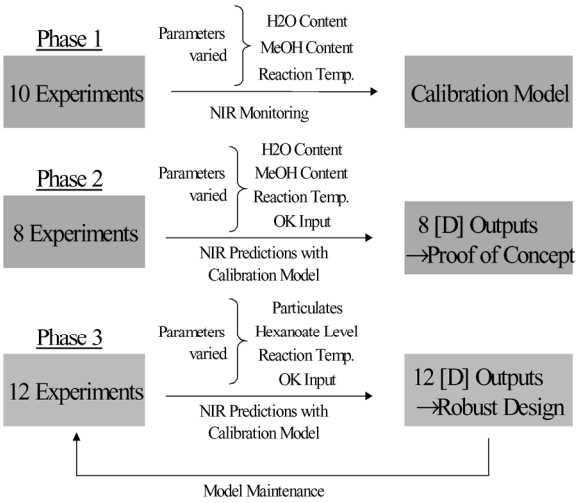


Figure 3. Calibration model construction.

The models were validated and updated accordingly using a series of spectra gathered from a combination of Calibration Model both laboratory and plant batches subjected to experimental design variation in the usual iterative process. Key reaction parameters were adjusted in combination to assess the effects of these parameter changes on the ability of the NIR models to predict the reaction end-point accurately and reproducibly. This approach also ensures that the calibration models incorporate all elements of process variability that may reasonably be expected to be present in the reaction on a plant scale.

Calibration models produced gave coefficients of regression of 0.96 and 0.94 for [A] and [C] respectively. Predictions for levels of [B] were removed from the analysis method, as there was significant difficulty using these figures to aid end-point identification. This was due to the fact that the reagent [B] is used up instantaneously in the reaction and is therefore difficult to track. The predictions for [B] were therefore considered surplus to requirements. Calibration models for [A] and [C] can be seen below.

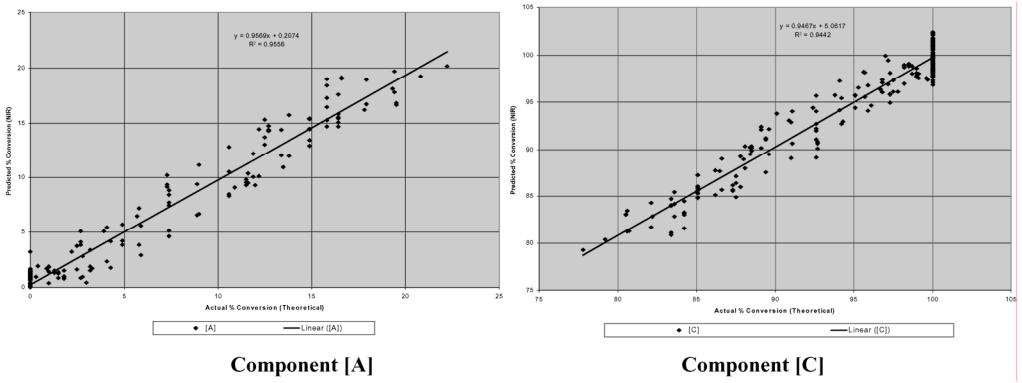


Figure 4. Calibration models for components [A] and [C].

In subsequent reactions, the predicted concentration values for each component from the models were continuously assessed for accuracy. Nominated selections of these reactions were added to the calibration models to ensure that all elements of process variability present in the reaction were incorporated into the analysis method. Any necessary adjustments to the method that were required in order to improve predictive capability were superseded by revalidation of the method. This iterative process resulted in robust calibration models. Real-time plots were produced during reactions, which allowed the reaction state to be monitored and the end-point to be determined.

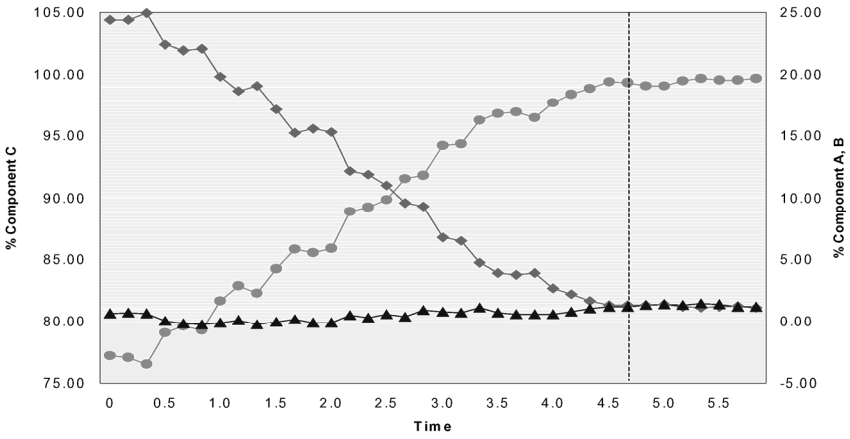


Figure 6. Real-time prediction plots for reaction components [A], [B] and [C].

The production of standard control batches during this experimental work has shown that there is no discernible difference between material produced by the standard process method and that produced by the modified method.

Statistical algorithm

In order to allow the reaction end-point to be detected with a high degree of certainty, a statistical algorithm was developed, which translates prediction levels for the components present into a form where an end-point trigger can be identified. The basis of this algorithm is the rate of change of component values and is applied with respect to a constant time interval during the reaction. The algorithm incorporates changes in [A] and [C] only; changes in [B] were difficult to quantify and did not aid detection of the end-point. Full details of the algorithm can be seen below.

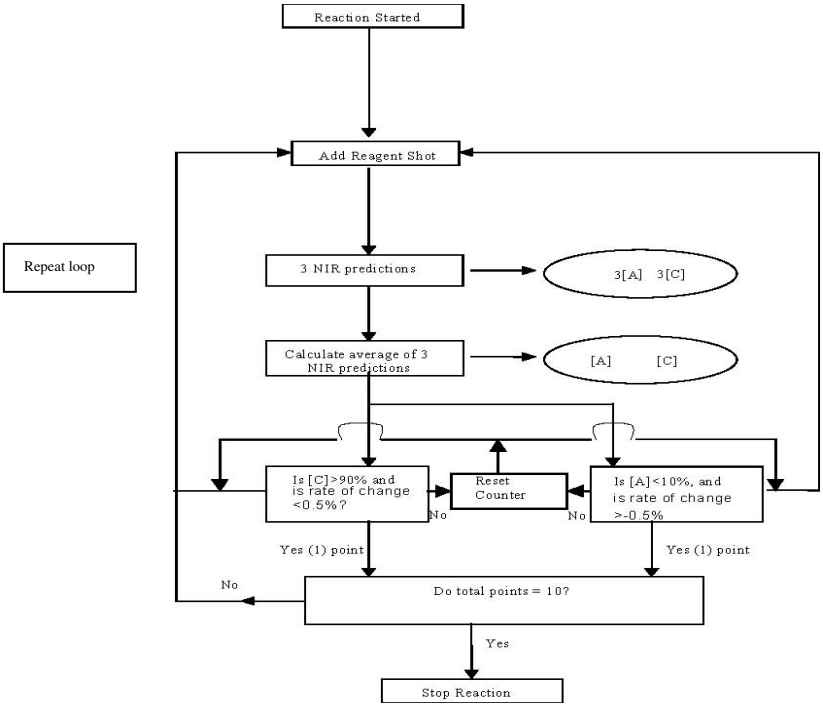


Figure 6. Statistical algorithm used to detect end of reaction

Component averages were calculated from a sub-set of three predictions for each component over a time period of 30seconds. The use of the algorithm cycle was dependent on the prediction levels of the components, so that a batch could not reach an end-point unless a certain level of conversion from [A] to [C] had been reached, as detailed in the adjacent schematic.

Conclusion

This reaction control system has now been in use for approx. 250 batches and has afforded a reduction in reagent use of around 20%. The system continues to manage the variability present in the process inputs whilst maintaining product quality.