

The calibration of an on-line near infrared spectrometer for the quantitative in-process control measurement of the composition of foul and recovered organic solvents at a multi-purpose solvent recovery plant

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Introduction

Organic solvents are essential ingredients in the manufacturing process of drug substance material. For every product produced by the pharmaceutical industry, however, a quantity of effluent waste exists which must be disposed of in a regulated manner. Companies deal with this foul solvent waste in a number of ways, namely,

- 1) controlled incineration of the liquid waste on- or off-site
- 2) allow a third party to dispose of the liquid waste
- 3) on-site recovery of the foul solvent.

The choice of a multi-purpose Solvent Recovery Plant, for solvent re-use, provides both a cost-effective and environmentally beneficial approach. At SmithKline Beecham, an automated Multi-Purpose Solvent Recovery Unit (MPSRU), consisting mainly of two fractional distillation columns, was constructed to deal with the ever increasing volumes of foul dichloromethane, toluene and methanol emanating from existing drug manufacturing processes. The MPSRU was commissioned in 1997, using off-line analytical methodologies. The principal tests consisted of capillary gas chromatography (GC) for assay/residual solvents and Karl Fischer (KF) titration for residual water. A battery of other tests such as infrared (IR) and specific gravity identification were also included on the solvent recovery specification.

Near infrared (NIR) spectrometry is an ideal technique for quantitative solvent measurement. Due to low absorptivity constants, direct, i.e. on-line analysis, is possible. Moreover, NIR wavelengths may be transmitted efficiently via fibre-optic cables, hence remote monitoring is possible. A Brimrose Luminar 2060 Analyser has been installed remotely at the MPSRU with fibre optic cables extending from between 45 and 70 metres to both fractional distillation columns at the feed tank and three column points (Column Reflux Stream, Vapour Side Draw and Liquid Side Draw Streams). The 2060 Analyser uses acousto-optic tunable filter (AOTF) technology, which allows 20 spectra scans/second, sequentially, through each of eight channels via a multiplexer device.

The analyser has been calibrated by correlating sample spectra with off-line GC and KF analyses at exact time points and using chemometric software packages to produce working models. The characteristic accuracy data (correlation coefficients, standard error of prediction) for each solvent stream is

contained within the text of this paper. The models have been set up to replace the off-line GC/KF testing at column start-up to provide a rapid and accurate in-process control (IPC) monitoring.

Experimental

In order to build robust working models two important criteria had to be satisfied.

- 1) the spectra collected from all four sampling points were to be included in the models. This was to ensure that concentration ranges of all solvents were built into the model.
- 2) large numbers of samples (> 60 samples) were necessary to build up workable and robust models.

A plan was devised to carry out so-called “dummy runs” whereby column operating conditions (for example, flow rate) were changed to vary the concentration of major or minor components. Samples were collected at regular time intervals, labelled and analysed by the In-Process Control Analytical Team. Three main tests were used to mass balance the contents of the solvent samples. These were:

- 1) Capillary gas chromatography which separates and quantitates 12 known solvents.
- 2) Karl Fischer titration to determine the residual water content.
- 3) Residue on evaporation testing in the case of foul methanol samples (approximately 5% drug by-products present).

The spectra were retrospectively correlated with the analytical results and the data was subjected to principal component analysis (PCA) and partial least squares (PLS) chemometric packages (Camo Unscrambler Software). Outliers were removed to improve the fit of the regression model and the optimised model was used to predict the concentrations of solvents during column recovery operation.

Instrumentation

Figures 1 and 2 below.

Results

Models for the three routinely recovered solvents, dichloromethane, toluene and methanol have been built. Tables 1–3 give a statistical summary of each stream and the relevant impurities. In most cases a good fit (correlation coefficient of > 0.9) was achieved. For dichloromethane and methanol, a sample population of 94 samples were used. For toluene a smaller population of 64 samples was used. The models may be made even more robust by carrying out additional dummy runs and adding the results of the analysed samples to the existing models.



Figure 1. NIR probe in field. 10 mm pathlength, 70 metre fibre length, SS316 construction, Ansi Flange 10 fittings.

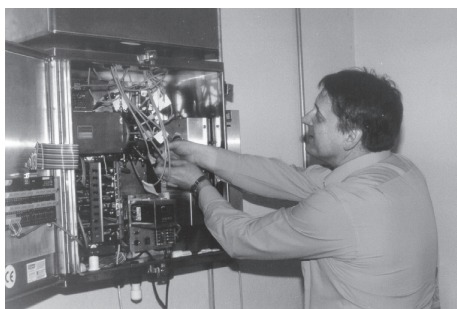


Figure 2. Luminar 2060 installation. 8 channel multiplexer, single fibre 600 micron diameter, I/O board for modbus connection to process system (Provox).

The dichloromethane (MDC) was used as a case study to show the effectiveness of the model when predicting the concentration of solvent in a column start-up operation. Figures 3 and 4 show the spectra and related regression coefficients of the MDC component. Figure 5 shows the correlation of predicted v. measured concentrations in the foul material range of between 70 and 90%. Good correlation and low *SEP* values are observed. Figure 6 shows a similar plot for a typical impurity (i.e. methanol). The correlation is lower but acceptable for the concentrations being measured (0–0.2%).

The model for MDC was then utilised on-line, using the Brimrose real-time Prediction Server. On-line results were generated every few seconds and the results put into a real time trend line. These trend lines are shown in Figure 7 (MDC recovered at the liquid side draw stream). The main compo-

Table 1. NIR statistical model results (MDC).

MDC		
	<i>SEP</i>	Correlation
MDC feed	0.5	0.99
MDC recovered	0.5	0.99
Ethyl acetate	0.06	0.98
Ethanol	0.03	0.92
Acetone	0.2	0.98
Methanol	0.01	0.95
Toluene	0.7	0.98
Water	0.01	0.97

Table 2. NIR statistical model results (methanol).

Methanol		
	<i>SEP</i>	Correlation
Methanol feed	1.17	0.99
Methanol recovered	1.17	0.99
DMF	0.26	0.89
Ethyl acetate	0.92	0.97
Ethanol	0.84	0.94
Water	0.72	0.98
MDC	0.17	0.98
Solids	0.8	0.88
TEA	0.04	0.8

Table 3. NIR statistical model results (Toluene).

Toluene		
	SEP	Correlation
Toluene feed	0.98	0.99
Toluene recovered	0.5	0.99
Ethanol	0.07	0.99
Water	0.05	0.99
Methanol	0.006	0.99
THF	0.78	0.99
Heptane	0.12	0.99

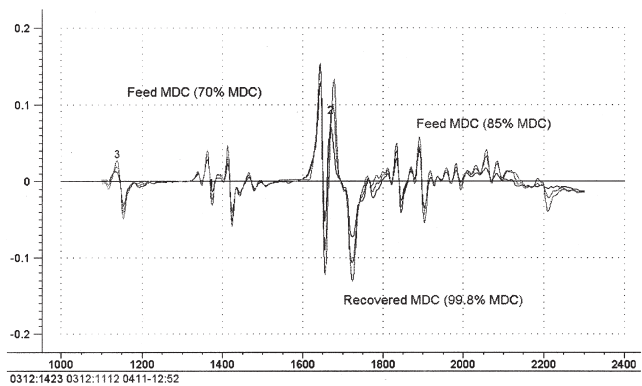


Figure 3. MDC spectra.

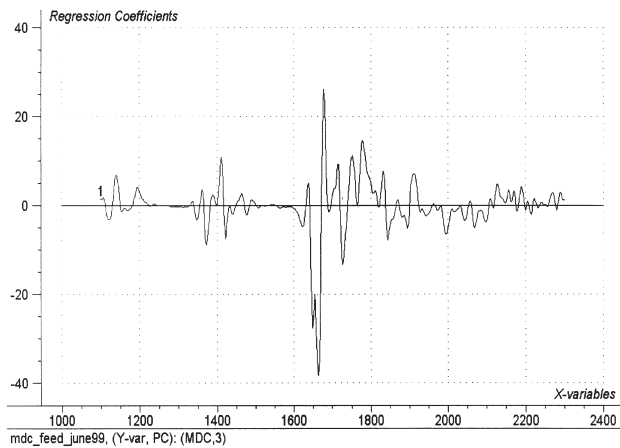


Figure 4. MDC regression coefficients.

ment can be read from the left-hand side of the graph and respective impurities from the right-hand side.

The process screen (Figure 8) allows the various solvent concentrations to be monitored at any time during the column recovery operation. The upper position of the real time predictor gives quantitative data for recovered material (MDC 99.22%, methanol 0.03%, etc.). The lower position deals with foul material (MDC 79.88%, methanol 0.04%, etc.). This information may be used to further optimise the recovery procedure.

Table 4 shows the correlation of NIR and the reference procedure for two recovered MDC samples. Obviously, more samples are required to demonstrate the reliability of the analyser but the on-line application was commissioned three days before the NIR conference.

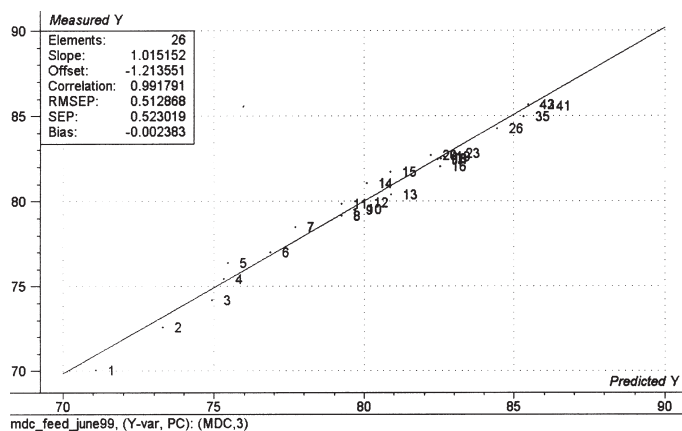


Figure 5. MDC correlation plot.

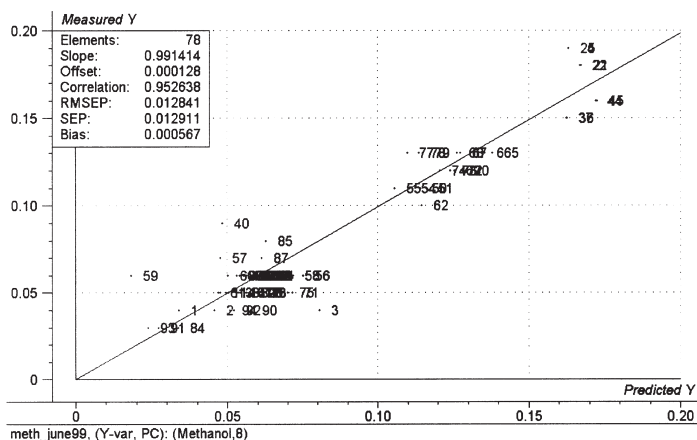


Figure 6. Methanol correlation plot.

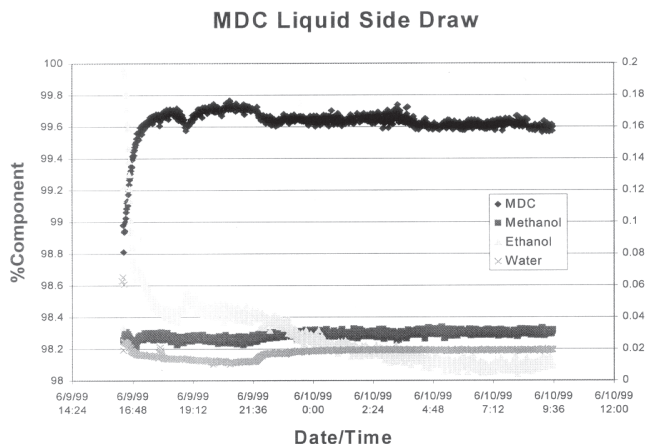


Figure 7. Real time trend lines.

Conclusions

This paper demonstrates the applicability of on-line NIR for multi-solvent analysis at a drug manufacturing site's solvent recovery facilities. Calibration of the analyser is achieved by dedicating the plant to "dummy runs" to obtain a maximum number of samples in a relatively short space of time. These samples contain varying concentrations of solvents and help build up a series of robust models. The Brimrose real-time Prediction Server has been set up to replace the off-line analytical testing and preliminary results indicate excellent correlation between the reference methodologies and the NIR technique.

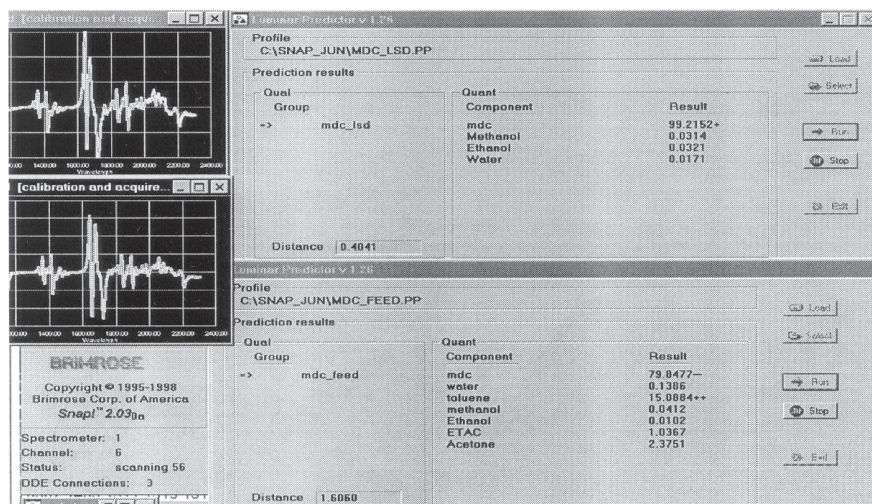


Figure 8. Example of process screen.

Table 4. Correlation of NIR and reference procedure for two recovered MDC samples.

NIR v. reference analysis technique				
	MDC	Methanol	Ethanol	Water
Sample 1 Reference	99.9	0.03	0.01	0.01
Predicted 1	99.6	0.03	0.01	0.02
Sample 2 Reference	99.8	0.03	0.0	0.01
Predicted 2	99.6	0.03	0.01	0.02

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