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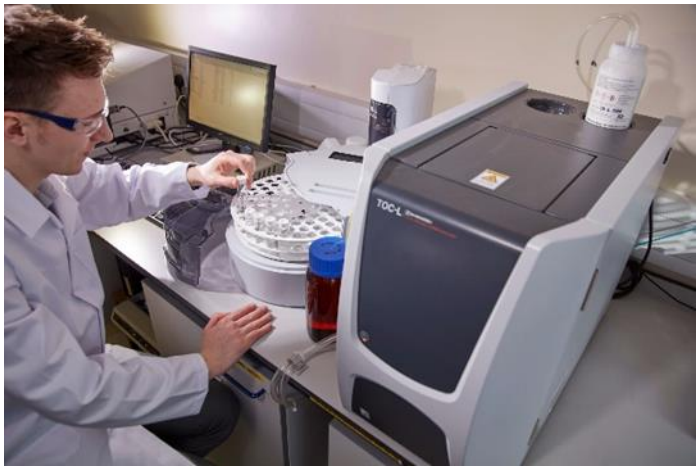
TOC + Headspace GC in Cleaning Validations

TOC combined with Headspace GC in Cleaning Validations

One of the major applications of Total Organic Carbon (TOC) analysis in the Pharmaceutical Industry is in Cleaning Validations, where it offers a relatively cheap and simple method to measure trace levels of organic carbon. The results, however, are not specific and if they do not meet the required specification, the use of more sophisticated and expensive techniques are required to accurately identify and quantify the source of the problem. One application for which we have for which we have used this technique is in demonstrating the removal of certain solvents used in a Clean in Place (CIP) procedure.

In the CIP process, the final rinse solution is sampled and analysed. Should the final rinse solution generate an Out of Specification (OOS) TOC result, then further analysis would be required to demonstrate that the failure to adequately remove solvents used in the CIP process were the cause of the OOS. We wanted to demonstrate the ability of the HS-GC method to separate and quantify more than one component whilst comparing the combined result against the TOC measurement.

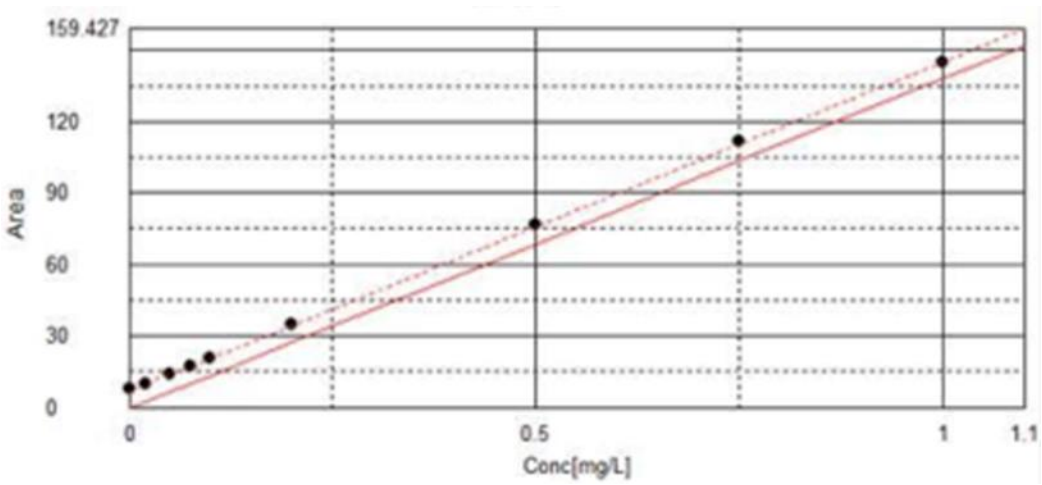


For the client, the purpose of the analysis was to demonstrate the removal of the solvent, 2-Propanol, at the end of the CIP process. To add a little more complexity to the study, we decided to add Ethanol to the mixture. This would enable us to demonstrate the ability of the HS-GC method to separate and quantify the two components whilst comparing the combined result against the TOC determination. It would also demonstrate that the technique could determine if the correct solvent had been used in the cleaning process.

Instrumentation commonly used to test water for the Pharmaceutical industry determine the TOC concentration by oxidising the organic molecules to produce carbon dioxide which is then measured by the instrument's detector. Butterworth Laboratories employ a Shimadzu TOC-L TOC analyser. The sample is firstly combusted in a furnace at 680°C, the combustion products dehumidified and then passed through a halogen scrubber. Finally the gases are passed through a non-dispersive infra-red (NDIR) detector which generates an analogue peak corresponding to the concentration of carbon. Samples can be introduced to the instrument manually or via an auto sampler. In addition to TOC measurement, the instrument is capable of measuring Total Carbon (TC), Inorganic Carbon (IC), and Non Purgeable Organic Carbon (NPOC) where required.

For this piece of verification work, NPOC was the determination of choice and the carbon dioxide from inorganic sources was removed by the addition of hydrochloric acid to the sample to a pH of <2 followed by use of a sparge gas.

The instrument was calibrated over a range of 25 to 1000ppb, using potassium hydrogen phthalate. Caffeine was run as quality control check standard.

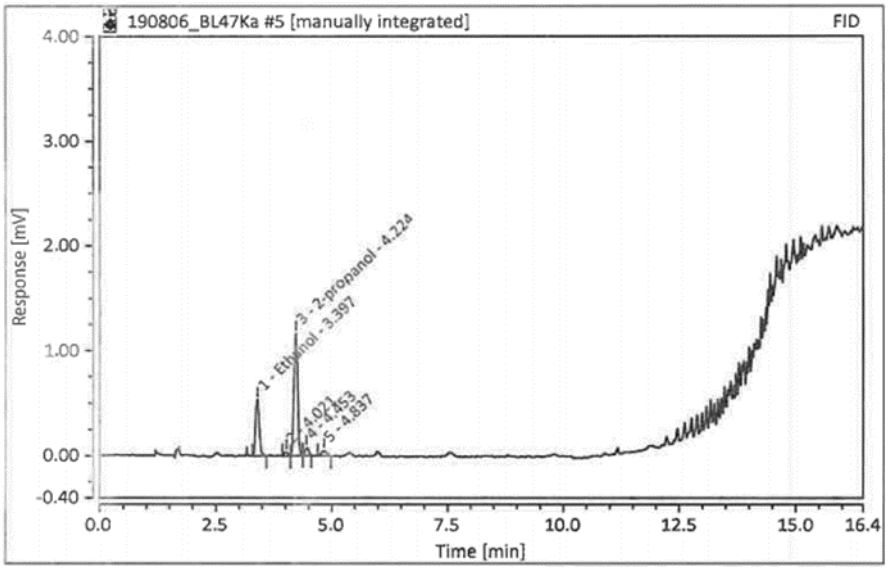


A series of test solutions containing both Ethanol and 2-Propanol were prepared from a mixed stock solution and analysed. The results obtained were:

Concentration of 2-Propanol mg/l	Concentration of Ethanol mg/l	Expected Concentration mgC/L	Calculated Result mgC/L	Recovery%
0.20	0.20	0.22	0.27	119
0.39	0.41	0.43	0.47	106
0.98	1.02	1.08	1.13	104
1.47	1.52	1.63	1.67	102
1.95	2.03	2.17	2.23	102

Note: %C in 2-Propanol = 60%; %C in Ethanol = 52%

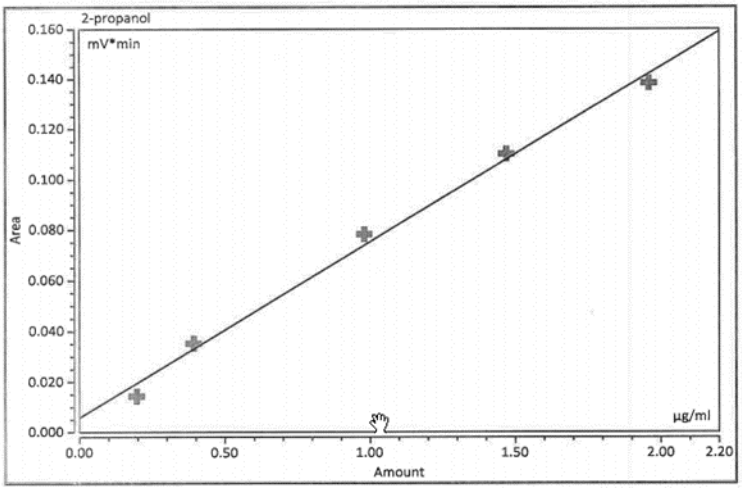
All solutions produced results close to those expected, although with a slight bias, particularly at low concentrations. GC Headspace, clearly identifies the two solvents, plus additional impurity peaks in the same test solutions. These impurities may explain the high bias in the low concentration solutions tested for TOC.



The equipment used for the HS-GC was a Perkin Elmer (PE) TurboMatrix HS110 headspace sampler and Perkin Elmer (PE) Clarus 580 Gas Chromatograph (GC) set up to measure Organic Volatile impurities to the USP <467> monograph.

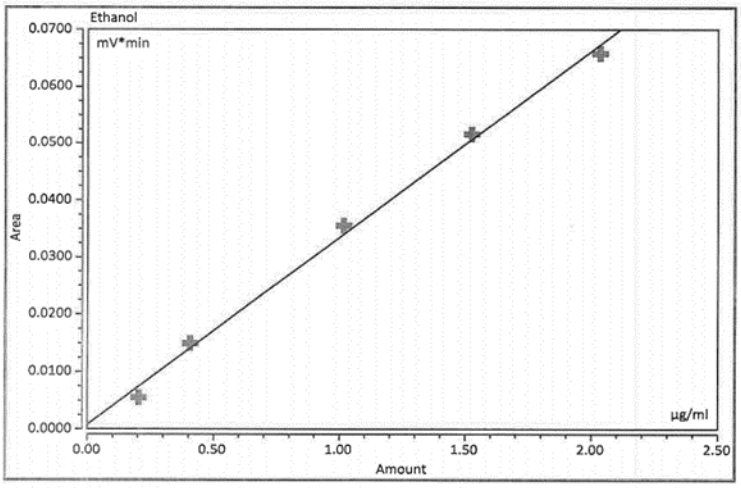
HS-GC Calibration data

2-Propanol



Component: **2-propanol**
Mode: Total
Fitting: Normal
Blank correction: Disabled
Weighting: No Weighting
Type: Lin, WithOffset
R-squared: 0.9935334
r: 0.9967615

Ethanol



Component: **Ethanol**
Mode: Total
Fitting: Normal
Blank correction: Disabled
Weighting: No Weighting
Type: Lin, WithOffset
R-squared: 0.9960489
r: 0.9980225

The results show the TOC may be used as a convenient screening tool for the determination of residual cleaning solvent in rinse solutions. Analysis is quick and relatively simple, taking approximately 4 minutes per determination. In the event that TOC is detected above control limits, GC with headspace sampler may be used to verify the source of organic carbon.

In this case the client believed from experience that the cause of the atypical/OOS results was almost certainly due to the presence of 2-Propanol, for which HS-GC is the most relevant form of confirmatory analysis. However, if this turned out not to be the case and 2-Propanol was not identified or did not account for all the TOC determined, this work demonstrated that HS-GC analysis may be able to indicate another source of contamination. However, it may also be true that other more complex techniques such as GC-MS or LC-MS have to be applied.

Author Biography

David Riches BSc CChem MRSC
Technical Director

David started his career at Sandberg LLP before joining Butterworth Laboratories as an Analytical Chemist in 1986 in the Microanalytical Department performing CHN analysis. David has progressed through various roles during his many years at Butterworth's, rising to his current position as Technical Director.