# Inline process monitoring of moisture content in tetrahydrofuran

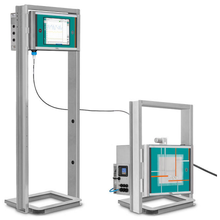
## Summary

Often, many solvents that are used daily in various manufacturing processes are not disposed of nor incinerated, but rather recovered and purified to save significant costs. Used solvents are mostly purified by distillation. Solvent recovery processes are very common in the chemical and pharmaceutical industries especially during the manufacture of Active Pharmaceutical Ingredients (APIs).

Tetrahydrofuran (THF) is one such organic solvent widely used in several industries. After THF solvent recovery, the quantification of residual water (the most common solvent impurity in THF) is an important measure for quality control in the pharmaceutical industry, for example.

This Process Application Note presents a method to accurately monitor low levels of moisture in tetrahydrofuran (THF) in «real-time» safely, reliably, and optimally with a 2060 *The* NIR Analyzer from Metrohm Process Analytics. Due to the hazardous and hygroscopic nature of THF, a single explosion-proof inline process analyzer is the preferred solution for industries to reduce chemical treatment, improve product quality, and increase profits.

## Configuration



**A472060040C - 2060 The NIR-REx Analyzer**

The 2060 The NIR-REx Analyzer is the next generation of process spectroscopy instruments from Metrohm Process Analytics. With its unique and proven design from the inside out, it delivers accurate results every 10 seconds. It can provide non-destructive analysis of liquids and solids directly in the process line or in a reaction vessel by using fiber optics and contact probes. It has been designed to connect up to five (5) probes and/or flow-cells. All five channels can be configured independently from each using our versatile embedded proprietary software.As part of the 2060 Platform, the 2060 The NIR-REx Analyzer enables the unique separation of the human interface (HI) and NIR cabinet by optical fibers. This remote configuration allows the placement of both cabinets at different locations around the plant depending on customer preference and area classifications.Additionally, this analyzer is IECEx certified and fulfills the ATEX EU Directives. It has been designed with an approved purge/pressurization system together with intrinsically electronic devices, preventing any potentially explosive fumes or gases from the ambient air entering the analyzer enclosure. Furthermore, it is available in three other versions: the 2060 The NIR Analyzer, 2060 The NIR-R Analyzer, and 2060 The NIR-Ex Analyzer.

## Introduction

Solvents are the medium for most chemical syntheses. They aid in heat and mass transfer, facilitate separations and purifications, and act as vehicles for surface coatings, pigments, and dyes.

If they are to be disposed of after use, some harsh solvents (e.g., halogenated solvents) must be treated in a separate manner to ensure their proper disposal. Rather than going through these tedious, costly, and environmentally harmful disposal processes, many industries have become more reliant on solvent recovery, involving the collection, purification, and reuse of spent solvents.

Solvent recovery processes are very common in the chemical and pharmaceutical industries, e.g., when manufacturing Active Pharmaceutical Ingredients (APIs). To keep production processes running efficiently and to **avoid side reactions**, manufacturers must ensure that the recovered solvents are of sufficient purity for their intended purpose.

Tetrahydrofuran (THF) is a heterocyclic organic compound. Due to its high polarity and wide liquid range (-108.4 to 66 °C), THF is a versatile solvent used extensively in many industrial processes. In the pharmaceutical industry, it is used for the fabrication of hormone and cough medicines, while in the chemical industry it is used during the manufacture of polyurethanes (e.g., polyvinyl chloride, PVC) [**1**].

The most common solvent impurity in THF is water. This interferes with many reactions, which is why the determination of the moisture content is crucial. Azeotropic separation is the main challenge for THF solvent recovery since this process requires more energy to break the water-THF azeotrope bond.

In many pharmaceutical processes, inline process monitoring is of vital importance to control the moisture content in various materials (**Figure 1a**). Out-of-specification water levels can impact the physical properties of pharmaceuticals, which can also negatively influence the product performance (e.g., shorter shelf life, binding errors).

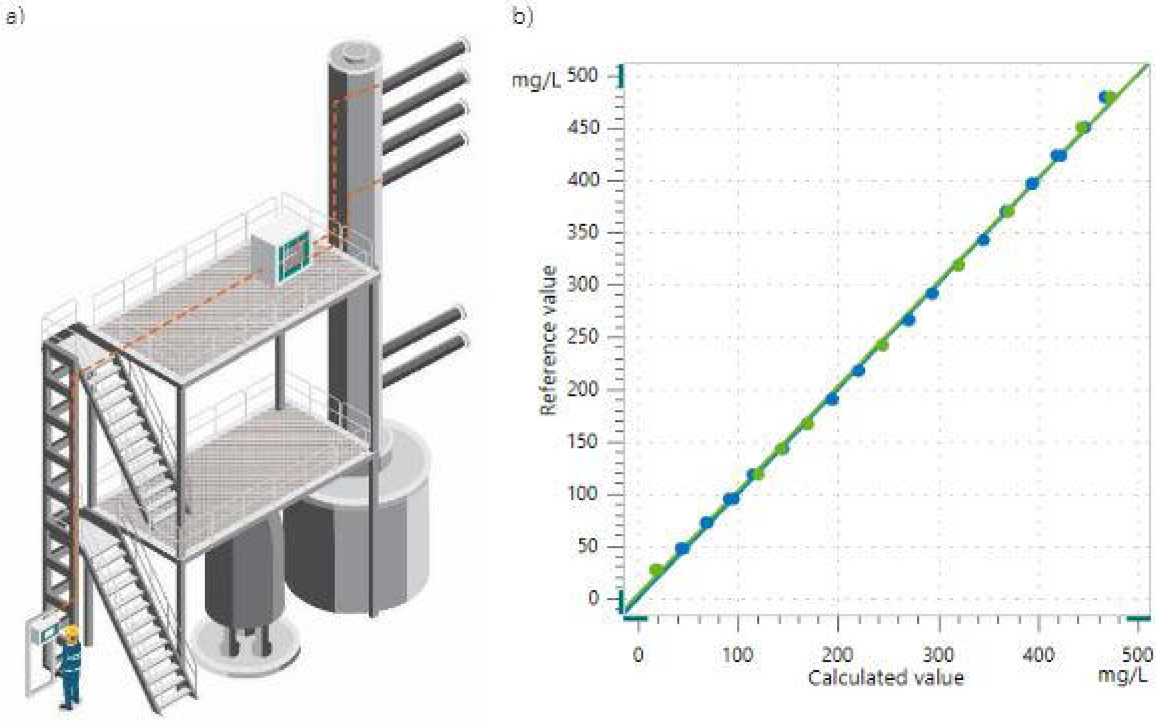



**Figure 1.** a) Illustration of a near-infrared spectroscopy (NIRS) system configuration for inline analysis of water content in recovered THF solvent streams. b) Correlation between the reference values from the primary method of Karl Fischer (KF) titration and the calculated values from the NIRS prediction model. Both the calibration (blue) and validation (green) data are shown.

Karl Fischer (KF) titration is generally used for moisture determination of substances in routine laboratory analysis. However, measuring the water content by this method is time-consuming and the sample is destroyed during analysis.

Manual laboratory methods can be quite cumbersome and can introduce bias depending on the analyst. Inline or online analysis of water content in recovered solvent streams gives the most precise results for high throughput API production. Near-infrared spectroscopy (NIRS) can provide a powerful alternative to manual laboratory methods for determining water in solvents. NIRS delivers results in almost «real-time» and does not require any sample preparation. Additionally, a single measurement provides information about several physical and chemical parameters so other chemicals (e.g., ethanol and isopropanol) can be monitored as well.

Metrohm Process Analytics offers analytical techniques relating to solvent characterization and qualification – near-infrared process analyzers. The 2060 *The* NIR-REx Analyzer configured for applications in ATEX areas (**Figure 2**) offers fast, reagent-free, nondestructive analysis of the water content in recovered solvents such as THF. Combination of KF titration as a reference method with NIRS enables efficient and high quality water determination even down to the mg/L (ppm) range directly in the manufacturing process.

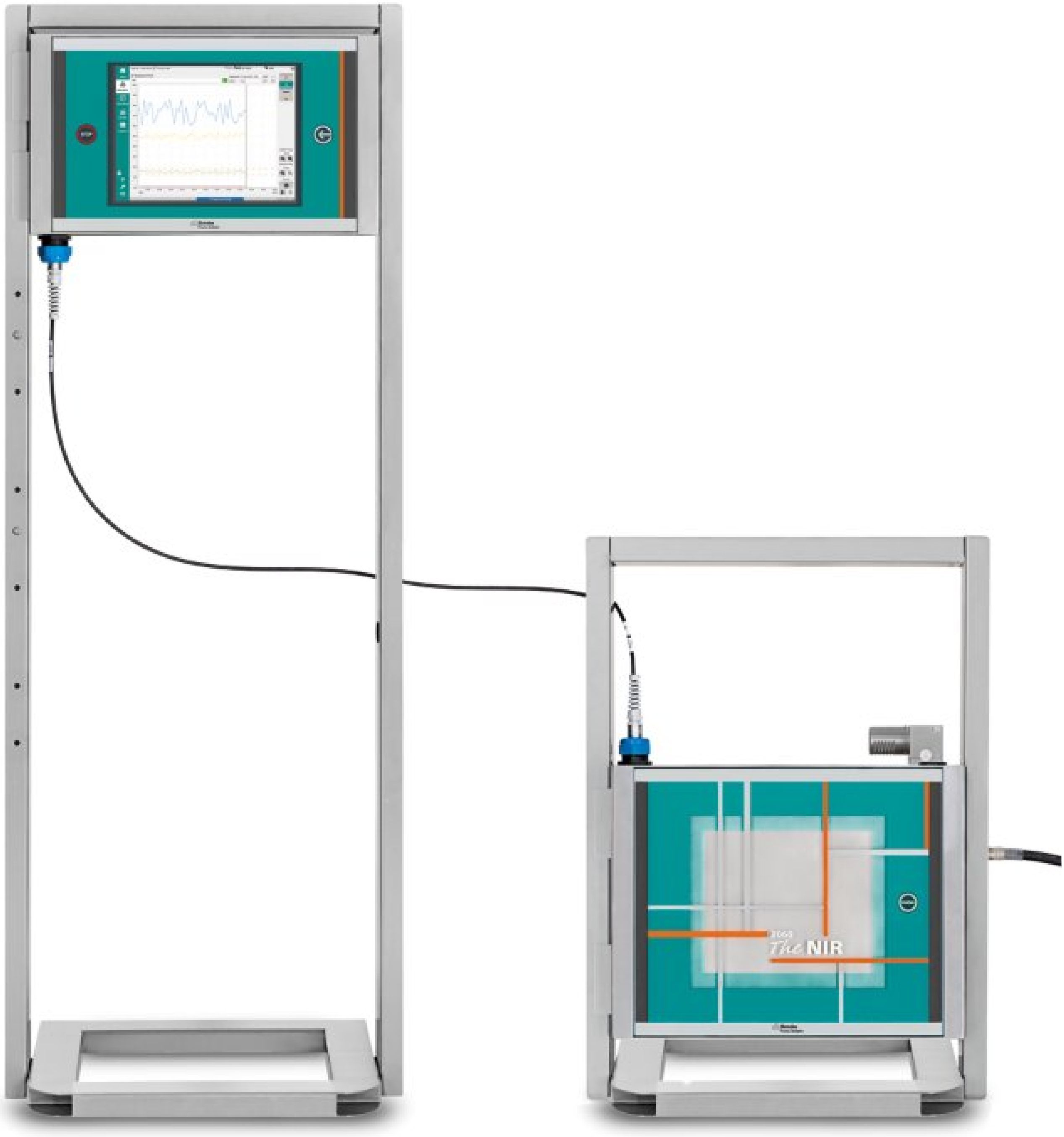



**Figure 2.** 2060 The NIR-REx Analyzer with fiber optic cable and probe.

## Application

38 THF samples with varying moisture levels determined by KF titration ranging from 20–500 mg/L were measured with NIRS to evaluate the correlation between moisture values and changes in spectral data. 28 samples were used to develop a prediction model and 10 samples were used for external validation purposes.

NIR spectra were collected in transmission mode on a 2060 *The* NIR-REx Analyzer in the wavelength range of 1000–2250 nm using a 10 mm Hellma flow cell. The OMNIS software package was used for data acquisition, data management, and development of the quantification method (**Figure 1b** and **Table 1**).

## Typical ranges

The parameters used for NIRS method development for analysis of moisture content in THF are listed in **Table 1**. A partial least squares (PLS) model using two factors shows a high correlation between the provided reference values and the calculated values ($R^2$ = 0.999) and low standard errors (**Figure 1b** and **Table 1**). Internal cross-validation was applied to verify the performance of the NIR prediction model during development.

**Table 1.** Parameters and results of the quantitative method development for moisture content in THF using NIRS.

| Parameters | Results |
|---|---|
| Range of $H_2O$ levels | 20–500 mg/L |
| Regression model | PLS with 2 factors |
| Pretreatment | Gap-Segment |

| | |
|---|---|
| Derivative order | 1 |
| Segment size | 11.5 nm |
| Gap size | 1.5 nm |
| Wavelength range | 1500–2000 nm |
| $R^2$ | 0.999 |
| SEC | 3.79 mg/L |
| SECV | 4.01 mg/L |
| SEP | 5.19 mg/L |

## Remarks

A reference method must still be in use. An appropriate range of samples covering the process variability should be analyzed by both methods (i.e., primary reference and NIRS) to build an accurate NIRS model. Correlations are made to process specifications. The correct NIRS probe must be placed in-situ in a manner that provides sufficient sample contact with the probe tip window. Correct probe design and proper placement in process equipment is highly important.

## Conclusion

NIRS analysis enables the comparison of «real-time» spectral data from the process to a primary method to create a simple, yet indispensable model for your process requirements. The Metrohm Process Analytics **2060 *The* NIR-REx Analyzer** can reliably measure low levels of moisture in THF streams. Additionally, it offers automated analysis results for different parts of a plant and helps to safeguard plant operations.

## Related documents

AN-NIR-016 Near-infrared spectroscopy for monitoring a single-pot granulator

AN-NIR-014 Following the progress of pharmaceutical mixing studies using near-infrared spectroscopy

AN-PAN-1048 Inline moisture analysis in a pilot scale granulation process by NIRS

AN-PAN-1050 Inline moisture analysis in fluid bed dryers by near-infrared spectroscopy

WP-017 Near-infrared spectroscopy in pharmacopoeias

## Benefits for NIRS in process

- **Optimize product quality** and increase profit with fast response times for process variations
- Greater and faster **return on investment**
- **No manual sampling needed**, thus less exposure of personnel to dangerous chemicals
- **Reduced cost** of hazardous waste disposal


## References

1. *Tetrahydrofuran (THF) Market*; CH 6125; Markets and markets, 2018.

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