



Application Note AN-PAN-1060

Inline process monitoring of moisture content in tetrahydrofuran

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.

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).

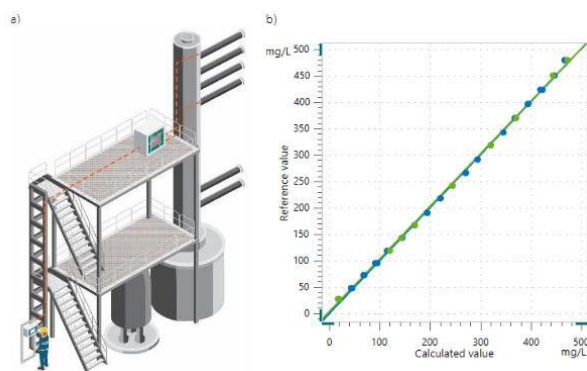


Figure 1. a) Illustration of a near-infrared spectroscopy (NIRS) system configuration for inline analysis of water content in recovered THF solvent streams. b) Correlation between the reference values from the primary method of Karl Fischer (KF) titration and the calculated values from the NIRS prediction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

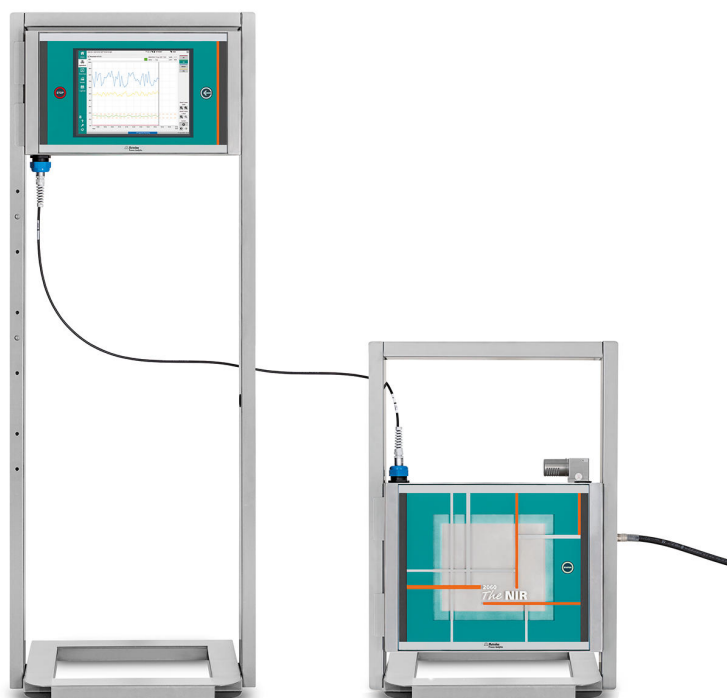


Figure 2. 2060 *The* NIR-REx Analyzer with fiber optic cable and probe.

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.

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

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**).

($R^2 = 0.999$) 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 ₂ O 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.

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

- **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

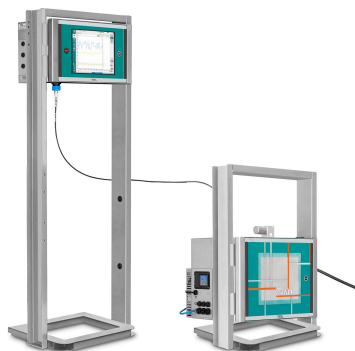
1. *Tetrahydrofuran (THF) Market*; CH 6125; Markets and markets, 2018.

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CONFIGURATION



2060 The NIR-REx Analyzer

2060 *The* NIR-REx は、Metrohm Process Analytics 製の次世代プロセス分光分析計です。その独自で定評のある完全な設計により、10 秒ごとに正確な結果を出します。この装置は、光ファイバーまたは接触式プローブを用いた、プロセスラインまたは反応容器における直接液体または固形物の非破壊分析を提供します。五 (5) つまでのプローブおよび/またはフローセルを接続できるように設計されています。弊社独自開発の多機能な組込ソフトウェアを使用して、5 つのチャンネルをすべて互いに独立して設定することができます。

2060 プラットフォームの一部として 2060 *The* NIR-REx Analyzer は、光ファイバーを用いてヒューマンインターフェース (HI) と NIR キャビネットの独自の分離を可能にします。このリモートコンフィグレーションにより、顧客嗜好とエリア区分によって異なる、工場周辺の異なる場所に二つのキャビネットを配置することができます。

加えて、このアナライザーは IECEx 認証を取得し、ATEX EU 指令を満たしています。本装置は、あらゆる潜在的な爆発性ヒュームまたはガスが周囲の空気からアナライザーのカバーに入り込むのを防ぐ、本質的な電子装置とともに、検定済みパージ/加圧システムで設計されています。さらに、他の三つのバージョンで使用可能です: 2060 *The* NIR Analyzer、2060 *The* NIR-R Analyzer、および 2060 *The* NIR-Ex Analyzer。