APPLICATION NOTE
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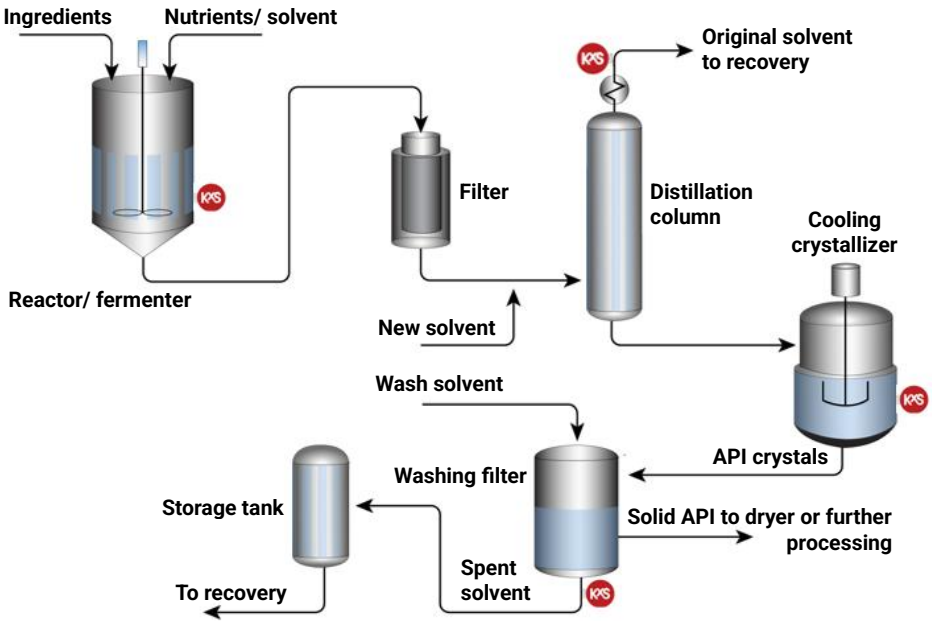
BIOPROCESSING AND PHARMACEUTICALS 2.03.02
Overview of Active Pharmaceutical Ingredient (API) applications

Active Pharmaceutical Ingredients (APIs), solvents

Benefits of R.I. measurement

- Continuous inline monitoring of reactions, crystallization, solvent swap, and washing operations
- Real-time process control for enhanced product consistency and yield
- Supports PAT/QbD frameworks and accelerates scale-up and validation
- Robust optical technology unaffected by bubbles, solids, or turbidity
- Minimizes solvent consumption and reduces need for reprocessing
- Enables development of solubility curves and process fingerprinting for improved understanding



Overview

Active Pharmaceutical Ingredients (APIs) are high-value specialty chemicals with therapeutic properties, used either directly in medical treatment or as building blocks for final drug formulations.

API manufacturing involves multistep processes such as reaction, separation, purification, and crystallization. These operations are increasingly shifting from traditional batch methods to continuous processing, driven by growing demand and regulatory initiatives such as the FDA's Process Analytical Technology (PAT) framework. PAT encourages the use of in-line measurements to ensure product quality, efficiency, and safety across the production lifecycle.

KxS Technologies provides inline refractive index (RI) measurement solutions to support real-time process monitoring, enhance product consistency, and reduce batch failure risk in both pilot and large-scale API production.

Refractive index measurement applications

Reaction monitoring

API synthesis begins with the addition of raw materials and solvents into a reactor—either a batch reactor or continuous reactor equipped with jacketed heating and agitation. The mixture is reacted under carefully controlled conditions to produce the desired API.

KxS refractometer provides real-time monitoring of RI to track the degree of conversion and detect the reaction endpoint. In bioreactor fermentation, it supports nutrient feeding control and metabolic monitoring.

Solvent swap

Solvent swap replaces the original solvent with another better suited for subsequent processing. During distillation, real-time monitoring is critical to prevent cross-contamination.

KxS refractometers can be installed in-line after the condenser to analyze the condensed vapor's concentration. With knowledge of vapor-liquid equilibrium (VLE) and process temperature, users can accurately determine solvent composition, ensuring a clean and efficient solvent swap.

Crystallization

Accurate supersaturation control during crystallization is key to forming APIs with consistent morphology and particle size.

KxS refractometers provide continuous RI monitoring of the mother liquor to detect saturation levels and determine the optimal seeding point. The digital image-based sensing method remains unaffected by bubbles or crystals, ensuring reliable readings during the entire crystallization process.

Filter cake washing

Efficient washing removes residual mother liquor from API crystals. KxS refractometers detect the interface between wash solvent and process solvent by measuring their distinct RI values.

This enables endpoint detection of the wash phase, minimizing solvent use and preventing product loss.

Additionally, RI values of pure and saturated solvents can be used to validate solvent purity and washing effectiveness.

Process fingerprinting and scale-up

Refractive index data supports comprehensive process understanding and troubleshooting. During scale-up, it provides a fingerprint for verifying that the process replicates expected performance, facilitating smooth technology transfer and validation.

KxS RI measurements help identify Critical Process Parameters (CPPs), define acceptable process variability, and confirm process robustness during development and manufacturing.

Instrumentation and installation considerations

KxS DCM-20 Hygienic Refractometer models are designed to meet the stringent requirements of pharmaceutical and bioprocessing applications:

- Standard 1” Ingold process connection – For seamless integration into bioreactors and fermenters and Sanitary Tri-Clamp SFC flow cells – For hygienic in-line pipe installations.
- Measurement output: Dual 4–20 mA analog and Modbus TCP digital protocols.
- ADI-free, pharma-grade wetted materials and surface roughness.
- Validation support: KxS provides IQ/OQ/PQ documentation and protocols tailored for pharmaceutical customers.
- KxS also offers a lab test cuvette for use with DCM-20-H15-P120 refractometers. This set up is designed for FDA-regulated industries as an additional off-line testing and validation tool. Using the lab cuvette allows liquid concentration measurements to be obtained in laboratory studies to validate the analytical method for its intended purpose and application in inline pilot and full-scale production.
- 3-A Sanitary 46-04 symbol authorization and EHEDG Type EL Class I certificate.
- Hazardous area certification (ATEX/IECEx Zone 2)