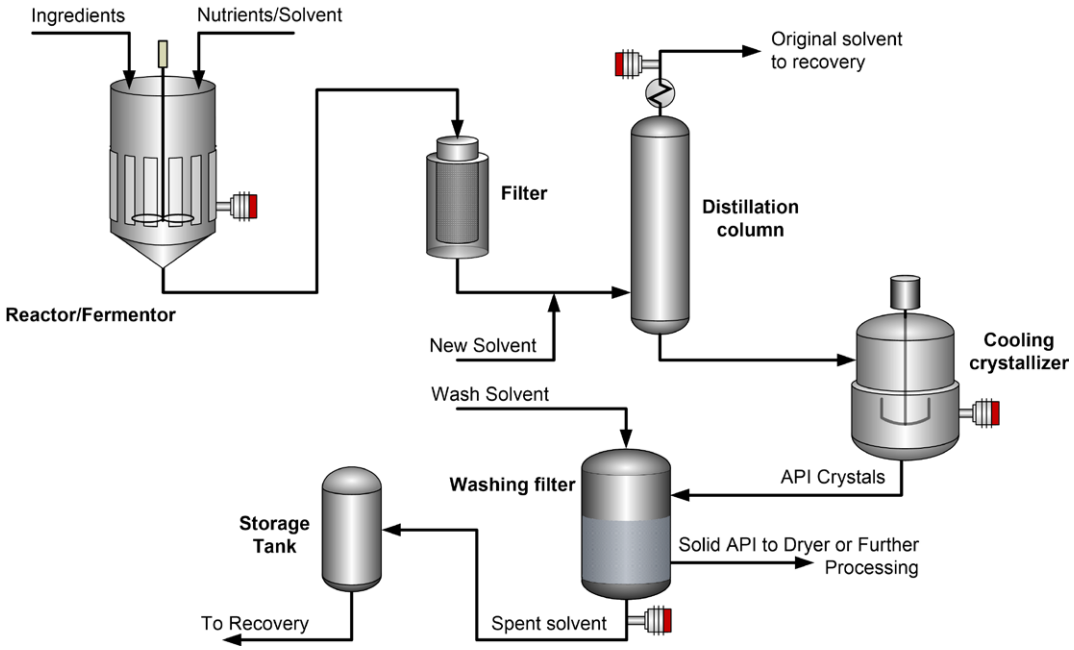
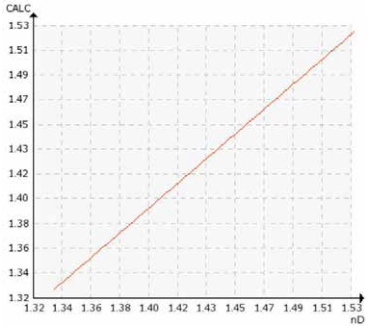


ACTIVE PHARMACEUTICAL INGREDIENT (API), SOLVENTS

Typical end products

Active Pharmaceutical Ingredients (APIs) for medical treatment or the manufacture of other drugs.

Chemical curve: R.I. at Ref. Temp. of 20˚C



Introduction

Active Pharmaceutical Ingredients (API) are specialty chemicals that have a disease-curing value. These APIs are manufactured through different steps usually including reaction, separation and purification.

Traditionally, manufacture has been performed by batch processes because of their simplicity and flexibility. However, as demand for drugs increases, pharmaceutical companies are moving towards continuous operation and larger scale production. Different guideline changes and initiatives have been put into action to reduce production costs while increasing efficiency, productivity and product safety. For instance, the *Process Analytical Technology* (PAT) initiative promotes the use of in-line measurements throughout the entire manufacturing process.

Reaction

The API can be obtained by a variety of processes, such as chemical synthesis, natural product extraction and fermentation. The reactions can be carried out in batch or continuous reactors, that are usually equipped with jacket and agitator.

The first step is the addition of the raw materials and solvents to the reactor. These are mixed, cooled or heated, and they are let to react for a certain time to obtain the API product. The ratio of raw materials, process conditions, and reaction time are defined by the specific product formulation.

Vaisala K-PATENTS® Pharma Refractometer provides a real-time refractive index measurement that is used to follow the degree of conversion and determine the end-point of the reaction. In fermentation, the refractometer's signal can also be used to detect the need for the further addition of nutrients and to control automatically the feeding valve (see also application note *Pharmaceutical Fermentation*).

Separation and purification

After the reactor, the API undergoes a series of steps for its separation and purification. Common downstream operations are solvent swap, crystallization, filter cake washing and drying.

Solvent swap or solvent exchange

Solvent swap is performed to remove the solvent used in an earlier step (original solvent), and to replace it with another solvent (swap solvent) that is more suitable for the next processing step. This can be done, for example, by batch distillation.

The new solvent is usually added to the product from the reactor, and the mixture is heated. As the components reach their boiling points, the most volatile solvent (the original solvent) is evaporated from the mixture, leaving behind the API mixed with the new solvent. As distillation progresses, the concentration of the solvents should be monitored to ensure a pure product or original solvent.

It can be challenging to measure the concentration of the mixture inside the vessel as the swap takes place. In such cases, the Pharma Refractometer is installed after the condenser to measure the concentration of the condensed vapor. As there is vapor-liquid equilibrium (VLE) inside the vessel, the concentration of the swap solvent can be then determined with the aid of VLE data, the temperature and the information provided by the refractometer (see also application note *Solvent Swap*).

Crystallization

Recovery of the API to a solid state and further purification is commonly achieved by crystallization. Consistent crystal morphology and good particle size are required when crystallizing the API. Poor quality crystals are difficult to process and may require costly recycling and reprocessing.

The Pharma Refractometer measures continuously the concentration of the mother liquor as it is saturated. The refractometer provides useful information to monitor supersaturation and determine the seeding point. Due to our unique digital sensing technology, the measurement is not affected by bubbles or crystals formed during the process. The accurate information from the refractometer guarantees a consistent product quality.

Moreover, the measurement of the Pharma Refractometer is highly accurate and repeatable and can also be used for obtaining the solubility curve of an API (see also application note *Pharmaceutical crystallization*).

Filter cake washing

Filtration and washing is required for efficient removal of the mother liquor and to obtain pure solids. Filter cake washing is achieved by filtration of the product from crystallization while applying a separate washing solvent.

Refractive index is a valuable tool for the development, monitoring and control of cake washing operations. At laboratory scale, and at a development stage, the Pharma Refractometer provides valuable information for understanding the washing process, creating washing profiles and to find the most suitable washing solvent.

Because each liquid has a different refractive index value, the refractometer can detect immediately the interface between the original solvent and the washing solvent. This indicates the end-point of washing, thus reducing the amount of solvent used. The refractive index of pure solvent and saturated solvents can also be studied and used as reference to determine if the washing conditions are not optimal, and if some product is washed away. This ultimately increases the yield and productivity (see also application note *Filter Cake Washing*).

Process fingerprint and troubleshooting

Refractive index has proven to be a useful tool not only for API process monitoring and control, but also for process understanding, evaluation, and troubleshooting.

The precise measurement of the refractometer can be used for finding the *process profile* or *fingerprint*. This is a reference during scale-up to confirm that the process behaves as designed and to assure there is process equivalence.

Refractive index can also provide the basis to understand the interaction between the raw materials, formulation, and conversion yields, as well as to identify Critical Process Parameters (CPPs). The data from the refractometer can be used to set the correct range limits for CPPs and to determine acceptable process variations.

Instrumentation and installation

Vaisala K-PATENTS® Pharma Refractometer PR-43-PC is the ideal in-line process analyzer for pharmaceutical processing in accordance with the PAT framework. The refractometer provides measurement of the refractive index of the medium, which can be used at any step in the development and production of an API. The scalability feature of the PR-43-PC

helps the drug manufacturer to reduce development time and improve product reliability throughout the complete process analysis. The measurement by the refractometer is accurate and very repeatable, providing assurance at any scale.

For larger scales, Vaisala K-PATENTS® Sanitary Probe Refractometer PR-43-AP can be used. The refractometer is also available with special materials and alloys for corrosive mediums. The refractometer is constructed of pharma grade materials, and the product surface finishes are electro-polished.

The refractometer is available with 3-A Sanitary and EHEDG certifications. Appropriate equipment with hazardous and intrinsic safety approvals are available when required.

Instrumentation	Description
	Pharma refractometer PR-43-PC for hygienic installations. The PR-43-PC is installed in the main processing line or vessel and no by-pass arrangements are required. Optional laboratory test cuvette (LTC) for off-line laboratory testing and validation.
	Sanitary Compact Refractometer PR-43-AC for hygienic installations in small pipe line sizes of 2.5 inch and smaller. The PR-43-AC refractometer is installed in the pipe bend. It is angle mounted on the outer corner of the pipe bend directly, or by a flow cell using a 3A Sanitary clamp, I-clamp or Varinline® connection.
	Sanitary Probe Refractometer PR-43-AP for hygienic installations in large pipes, tanks, cookers, crystallizers and kettles and for higher temperatures up to 150°C (300 °F). The PR-43-AP refractometer is installed in the pipe line or vessel through a 2.5 inch or 4 inch Sanitary clamp, I-clamp, APV Tank bottom flange or Varinline® connection.
	Process Refractometer PR-43-GP is a general industrial refractometer for pipes and vessel installations. The PR-43-GP can be installed with 2, 3 and 4 inch flange and 3 inch Sandvik L coupling process connections and a variety of flow cells for pipe sizes of 1 inch and larger.
User Interface	Selectable multichannel MI, compact CI or a web-based WI user interface options allow the user to select the most preferred way to access and use the refractometer measurement and diagnostics data.
Measurement range	Refractive Index (nD) 1.3200 – 1.5300, corresponding to 0-100 % by weight.