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QUALITY SYSTEM CERTIFICATION
DNV·GL
ISO 9001

The Benefits of Refractive Index (RI) in Development and Production of Active Pharmaceutical Ingredients (APIs)

JOINING FORCES FOR LIQUID MEASUREMENTS

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- End of 2018, **Vaisala**, a global leader in weather, environmental and industrial measurements acquired **K-Patents**, an industry leader in in-line liquid concentration measurements.
- Following the acquisition, K-Patents is part of Vaisala's Industrial Measurements Business Area.
- The acquisition provides new, unexplored opportunities and innovations by combining two technology leaders, their product knowledge and resources as well as production excellence, R&D efficiency and ways of working by LEAN principles.

Anticipated advantages of the merger:

- State-of-the-art production capability
- On-time delivery (OTD) excellence
- R&D resources and knowledge
- Technology collaboration
- New innovations
- LEAN way of working
- Sustainable practices and procedures
- ISO 14001:2015 Environmental Certification

General Rules for Selecting in-line Pharma Measurement Equipment

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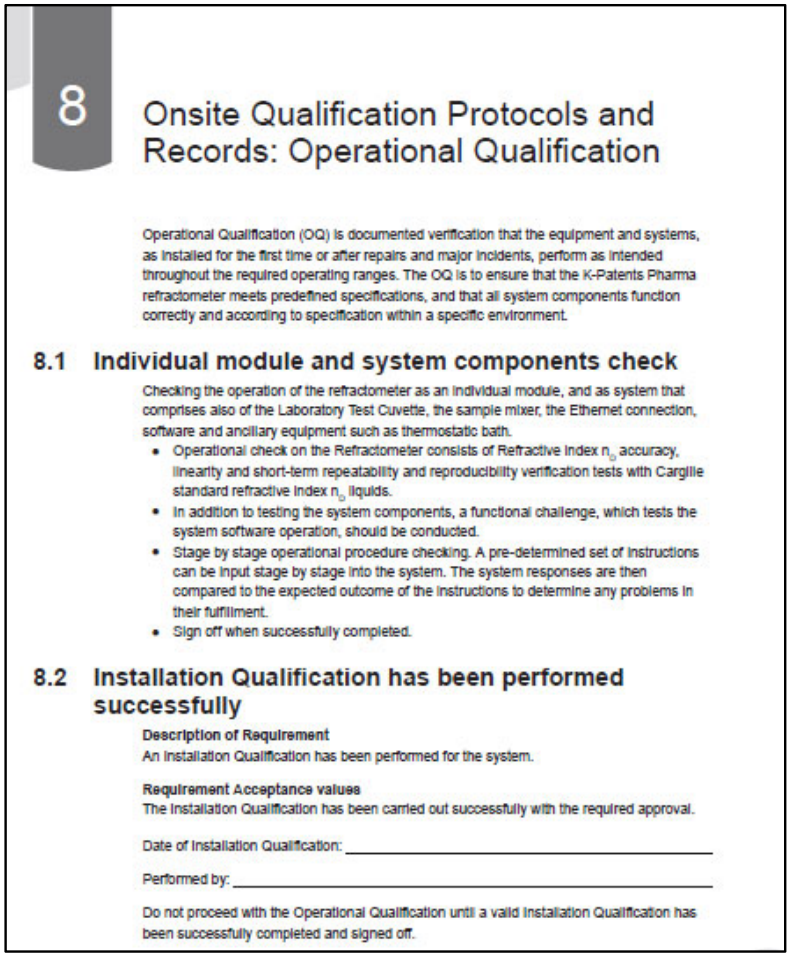
- Equipment qualification documentation
- Scalability of measurement solution
- Pharma grade contact materials
- Data recording and storage according to FDA 21 CFR Part 11
- Process equipment calibration and verification.

1. Documentation

- Does the supplier provide proper documentation (e.g. IQ / OQ documents) for completion of equipment qualification?
  - Installation Qualification, Operational Qualification and Performance Qualification protocols are normally required to document that the correct process equipment model and parts have been ordered, delivered and installed, and also to check that the equipment meets its performance specification and is able to reliably measure typical samples using the selected measurement method.
  - The complete qualification process must be fully documented.



8 Onsite Qualification Protocols and Records: Operational Qualification

Operational Qualification (OQ) is documented verification that the equipment and systems, as installed for the first time or after repairs and major incidents, perform as intended throughout the required operating ranges. The OQ is to ensure that the K-Patents Pharma refractometer meets predefined specifications, and that all system components function correctly and according to specification within a specific environment.

8.1 Individual module and system components check

Checking the operation of the refractometer as an individual module, and as system that comprises also of the Laboratory Test Cuvette, the sample mixer, the Ethernet connection, software and ancillary equipment such as thermostatic bath.

- Operational check on the Refractometer consists of Refractive Index n_D accuracy, linearity and short-term repeatability and reproducibility verification tests with Cargille standard refractive index n_D liquids.
- In addition to testing the system components, a functional challenge, which tests the system software operation, should be conducted.
- Stage by stage operational procedure checking. A pre-determined set of instructions can be input stage by stage into the system. The system responses are then compared to the expected outcome of the instructions to determine any problems in their fulfillment.
- Sign off when successfully completed.

8.2 Installation Qualification has been performed successfully

Description of Requirement
An Installation Qualification has been performed for the system.

Requirement Acceptance values
The Installation Qualification has been carried out successfully with the required approval.

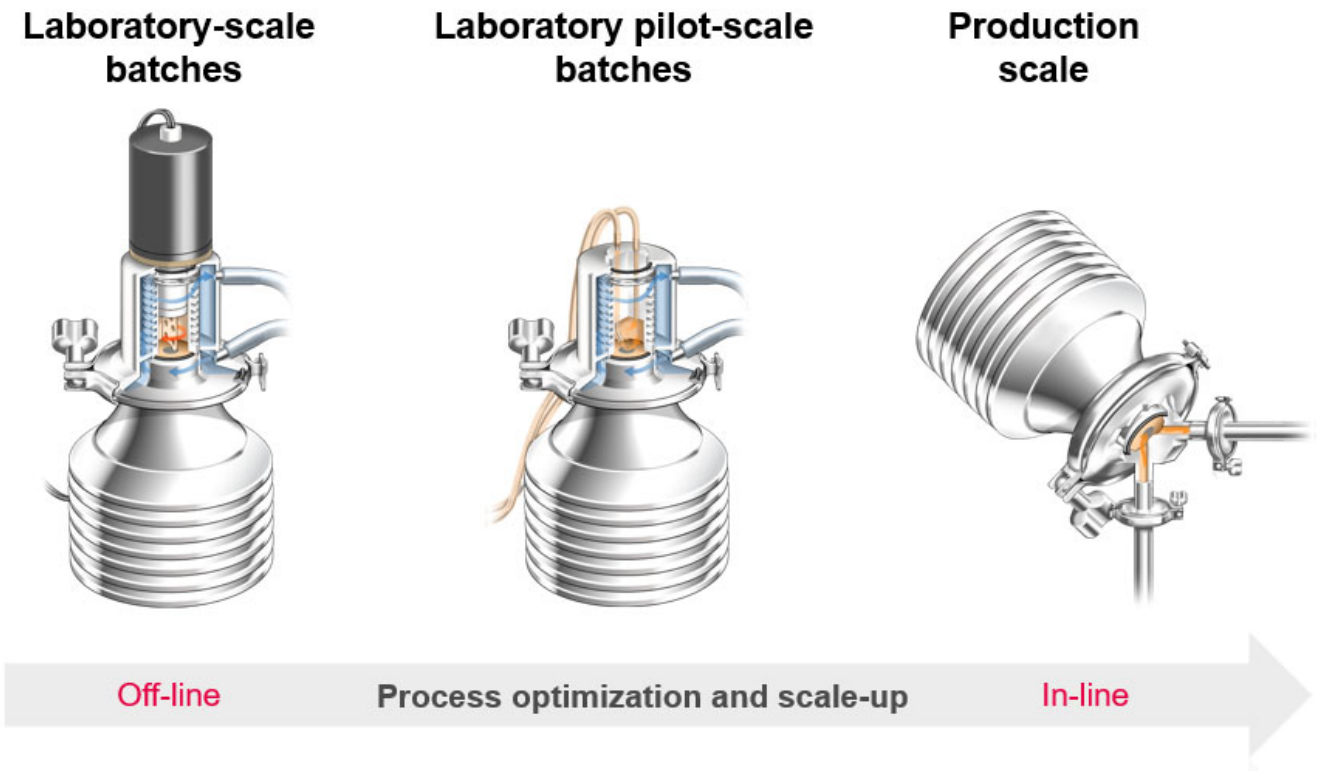
Date of Installation Qualification: _____

Performed by: _____

Do not proceed with the Operational Qualification until a valid Installation Qualification has been successfully completed and signed off.

2. Scalability

- The process equipment used at early testing stages may not represent the process scale design
- Gain confirmation the equipment picked is scalable so that it is applicable from lab scale to full-scale production
- **Example of a scalable solution** is shown below:



3. Pharma Grade Contact Materials

- Steel parts are made of 316L stainless steel
- Product contact surface finishes are electropolished, and surface roughness is Ra max 0.38 micrometers
- USP Class VI Elastomers are tested for materials' biocompability and toxigology safety (no extract that is harmful for human health)
- No animal derived ingredients (ADI) are used in processing or machining

- **Traceability** of these materials is proven by proper marking/labelling procedures and documentation!

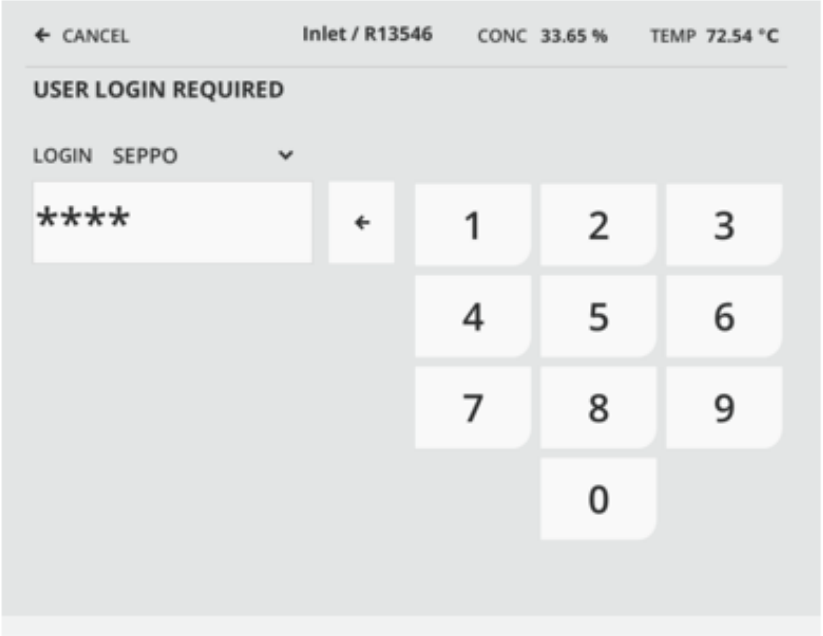
- Product contact surfaces are EHEDG tested and 3-A Sanitary approved
- Meet Clean-in-place (CIP) and sterilization-in-place (SIP) standards

4. Electronic Data Capture and Storage

- **FDA 21 CFR Part 11** requires pharmaceutical companies to use electronic data recording and storage, rather than paperwork, to collect and maintain quality control and production records.

- In case of instrument measurements, every reading taken with the instrument must be **logged** and **permanently stored electronically**, and the data is **password-protected** ensuring alteration accountability (i.e. which operator makes an alteration) and tracking.

User authentication with user ID and password



5. NIST Traceable Calibration and Accuracy

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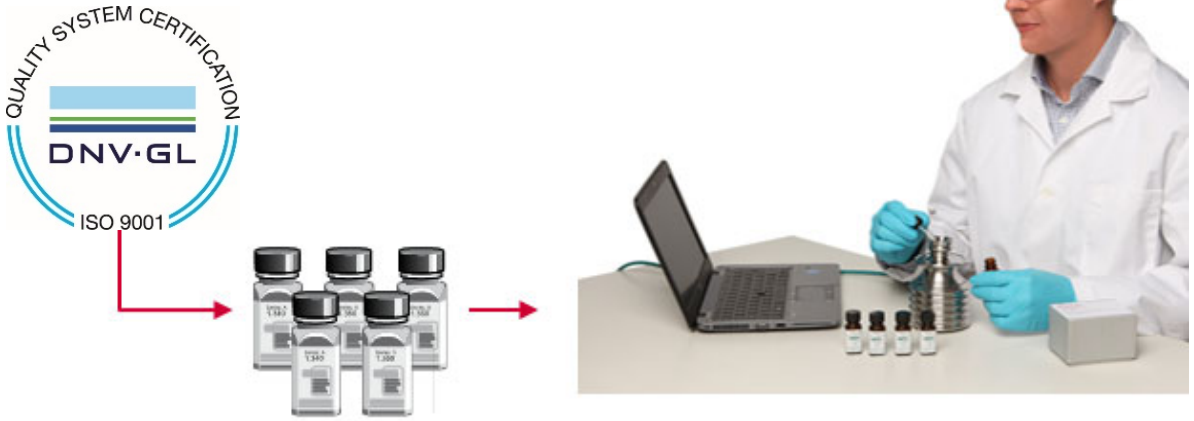
- Process equipment must be capable of producing valid results; and properly calibrated versus a suitable standard.

- Verification is recommended to be performed once every 6-12 months (or more frequently if specified in the client's own quality system) as a routine quality control check.

- **General rule of equipment selection:** The purchase of stable and accurate measuring equipment can reduce the frequency of calibration and increase confidence in the company's metrology program.



PRINCIPLE

Refractive Index n_D measurement

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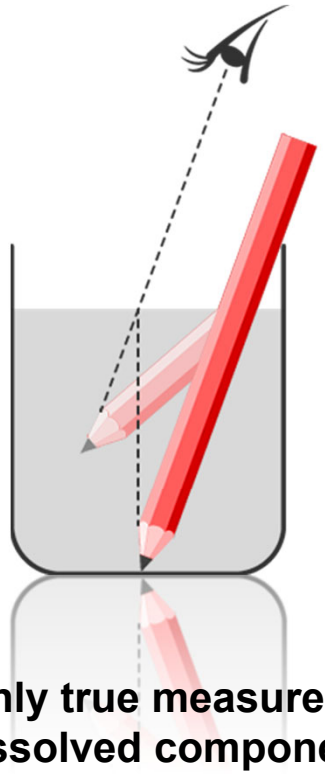
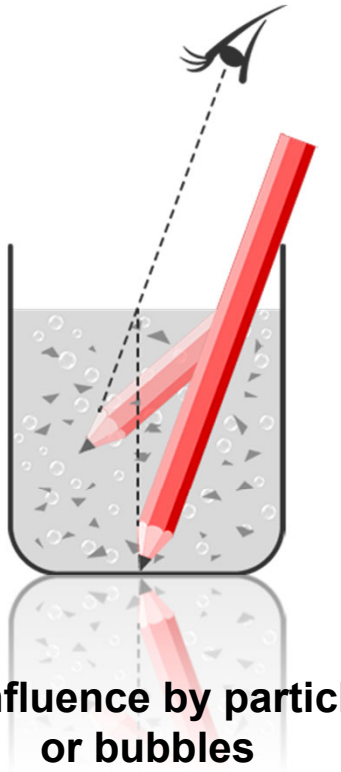


The only true measurement of dissolved components



No influence by particles or bubbles

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REFRACTIVE INDEX n_D and TEMPERATURE T are measured

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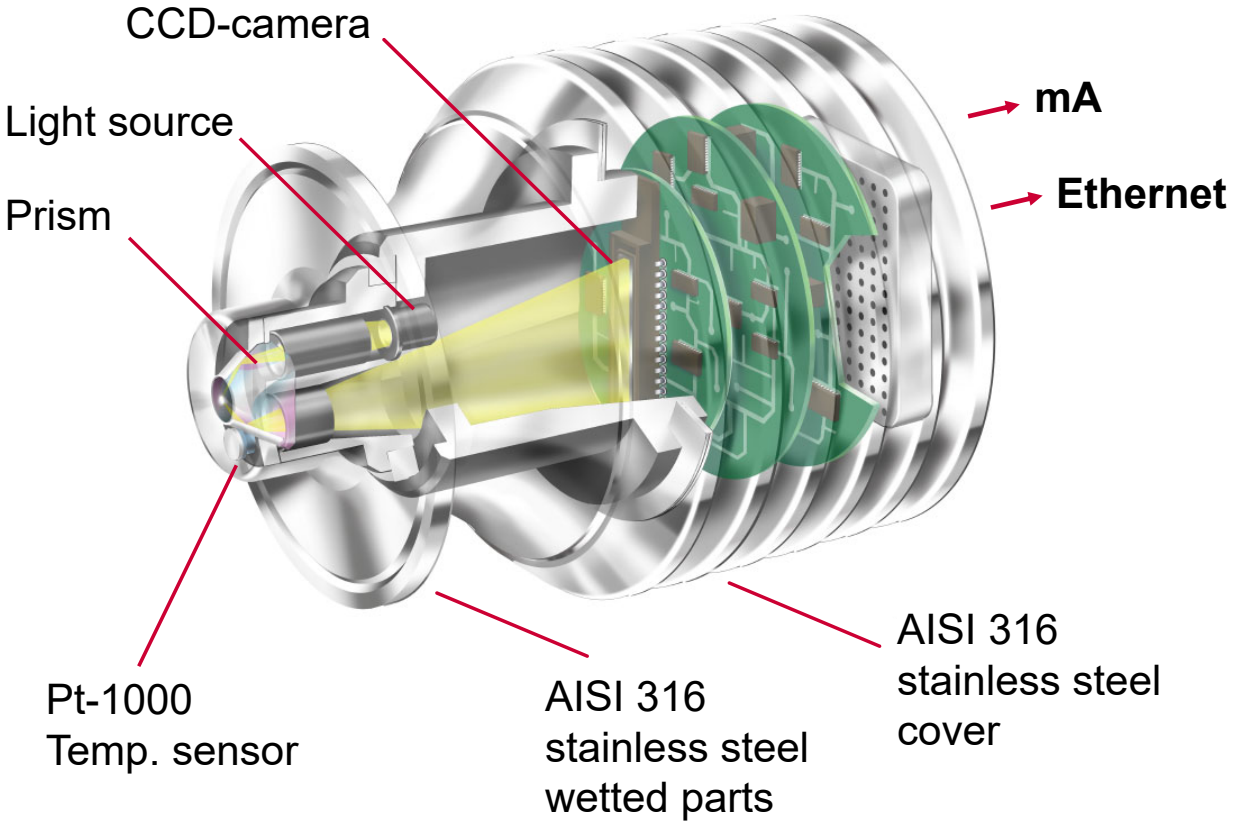

PRINCIPLE

Critical Angle Measurement

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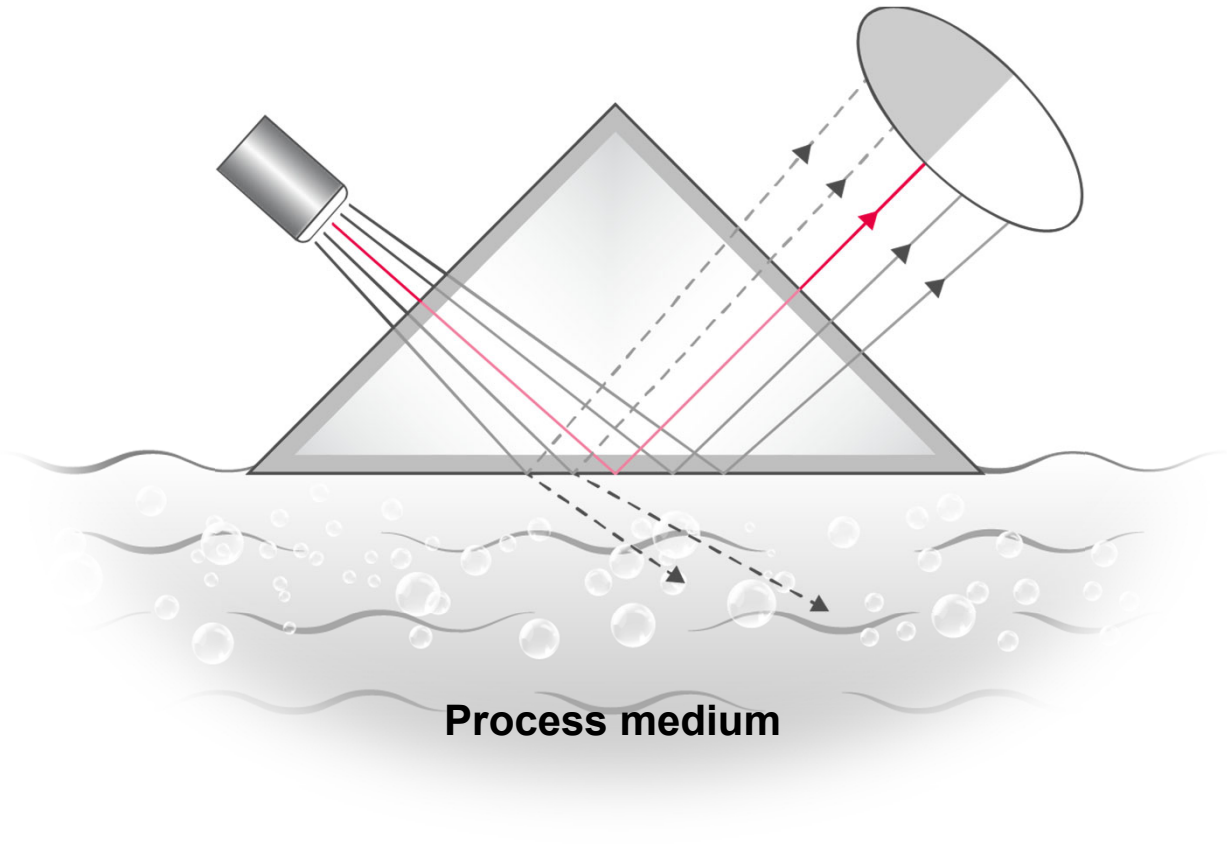

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No Measurement Error

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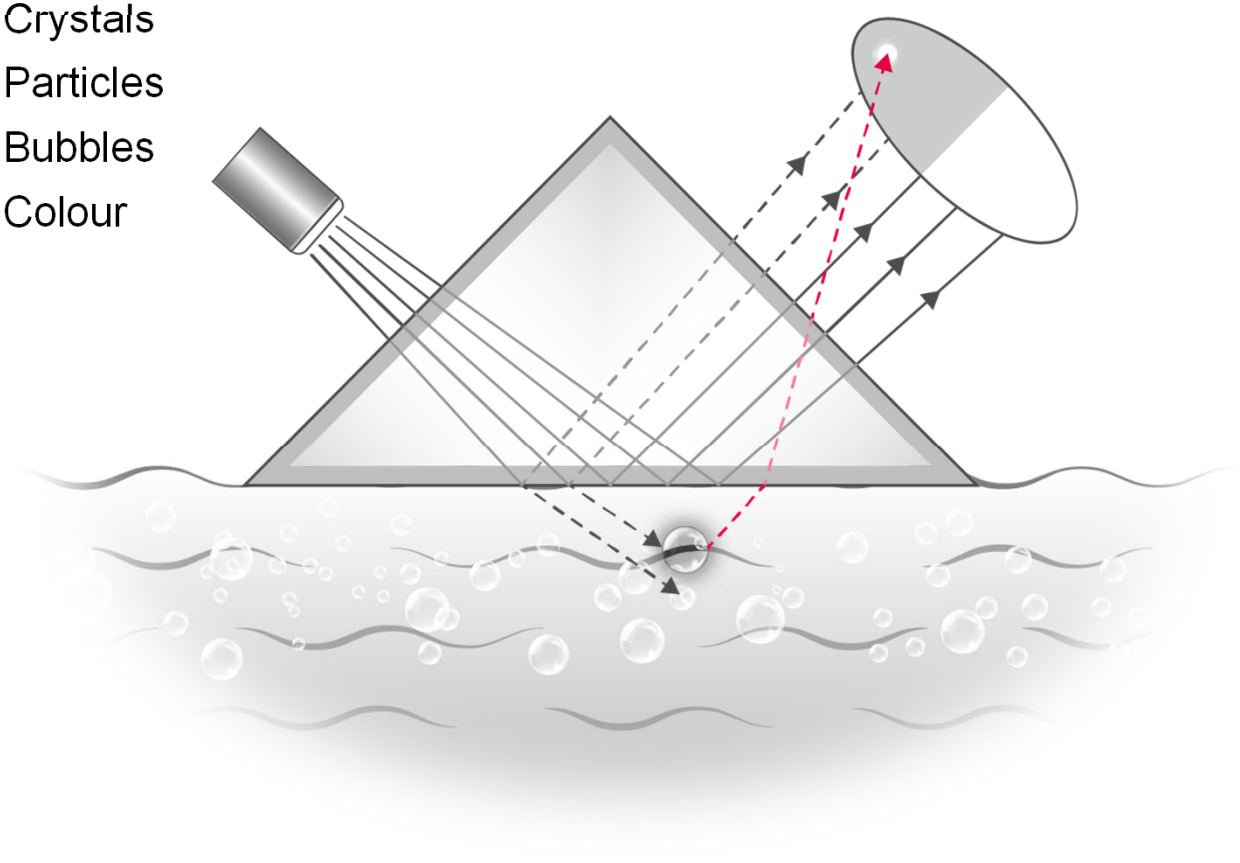
Caused by:

- Crystals
- Particles
- Bubbles
- Colour

Light reflected from a bubble



PRINCIPLE

Borderline Detection by Digital Camera

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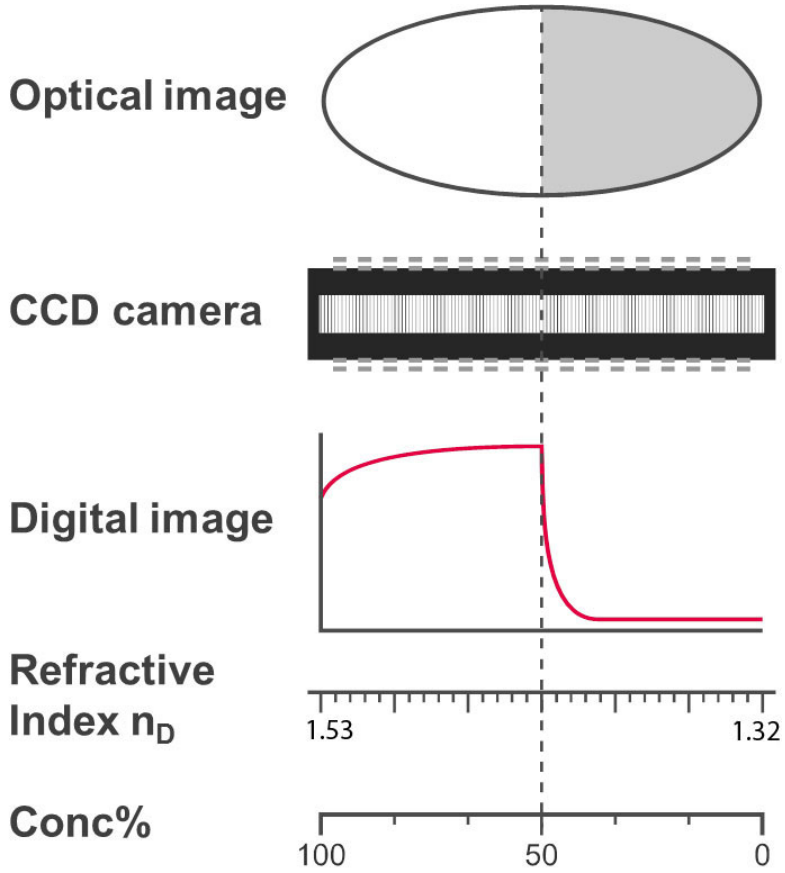

K-PATENTS PROCESS REFRACTOMETER

The best way to measure concentrations

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- Accurate
- No calibration drift
- Maintenance free

The Benefits of Refractive Index (RI) in Development and Production of Active Pharmaceutical Ingredients (APIs)

Why Refractive Index (RI) Measurements?

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- Selective, true measurement of dissolved material in a liquid.
- Uninfluenced by bubbles, particles, color
- Each liquid has a distinctive RI value
- Perfect for liquids identification and monitoring purity and concentration of chemicals, solvents and pharmaceuticals

K-PATENTS® Pharma Refractometer in the Development of APIs – from Lab to Full Scale

Case studies on developing API manufacturing operations:

- 11 identified applications where refractive index can be applied

In close cooperation with a major European pharmaceutical producer

Development Objectives

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- Reduce drug development time
- Increase production capacity and stability
- Achieve high product quality and reliability
- Demonstrate compliance to regulations

Tools

- PAT principles, specially the *need for scientific knowledge*
- Refractive index measurements for process understanding and knowledge of critical process parameters (CPPs) and quality attributes
- All according to FDA´s Process Validation Guidelines

Process Validation and Qualification

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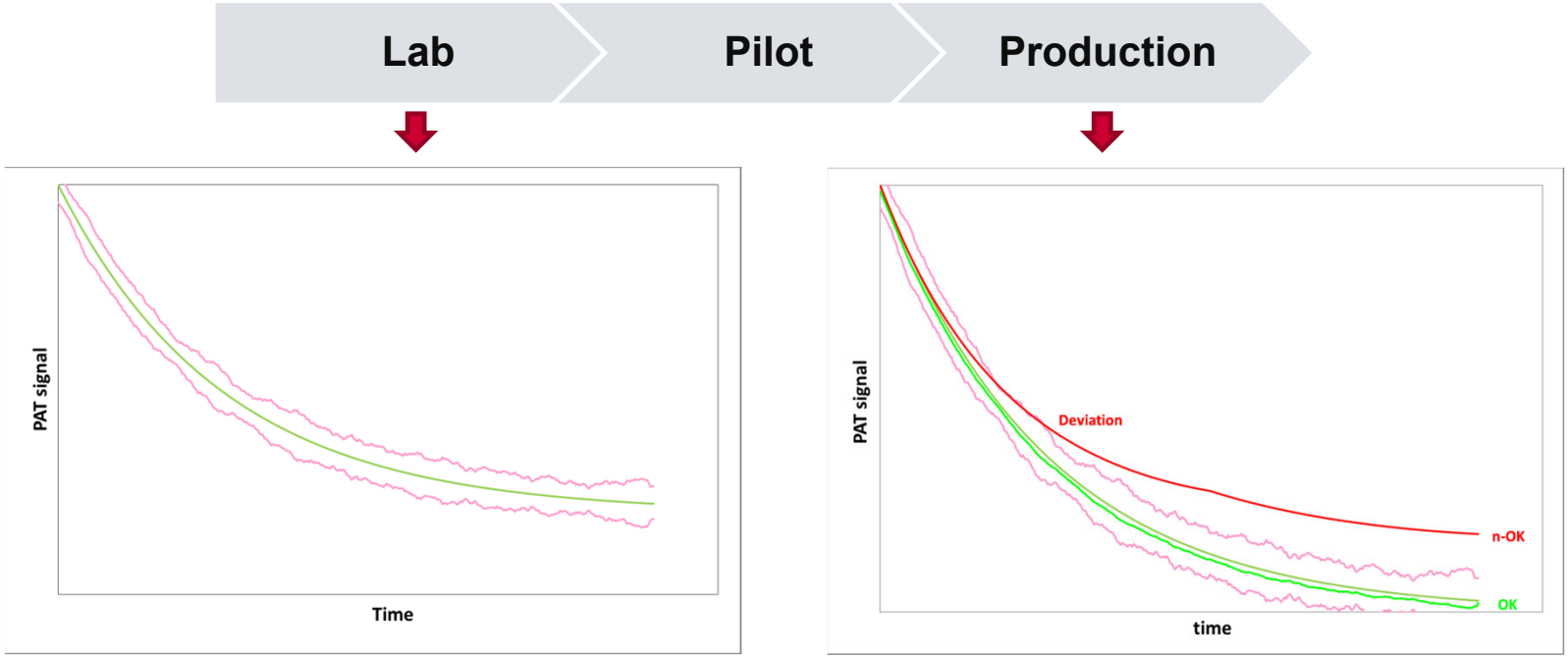
- The main goal is **process equivalence** from drug discovery to full production
- Find ideal **process profile** for consistent production process
- Control critical parameters to ensure same process profile



Typical API Production Process

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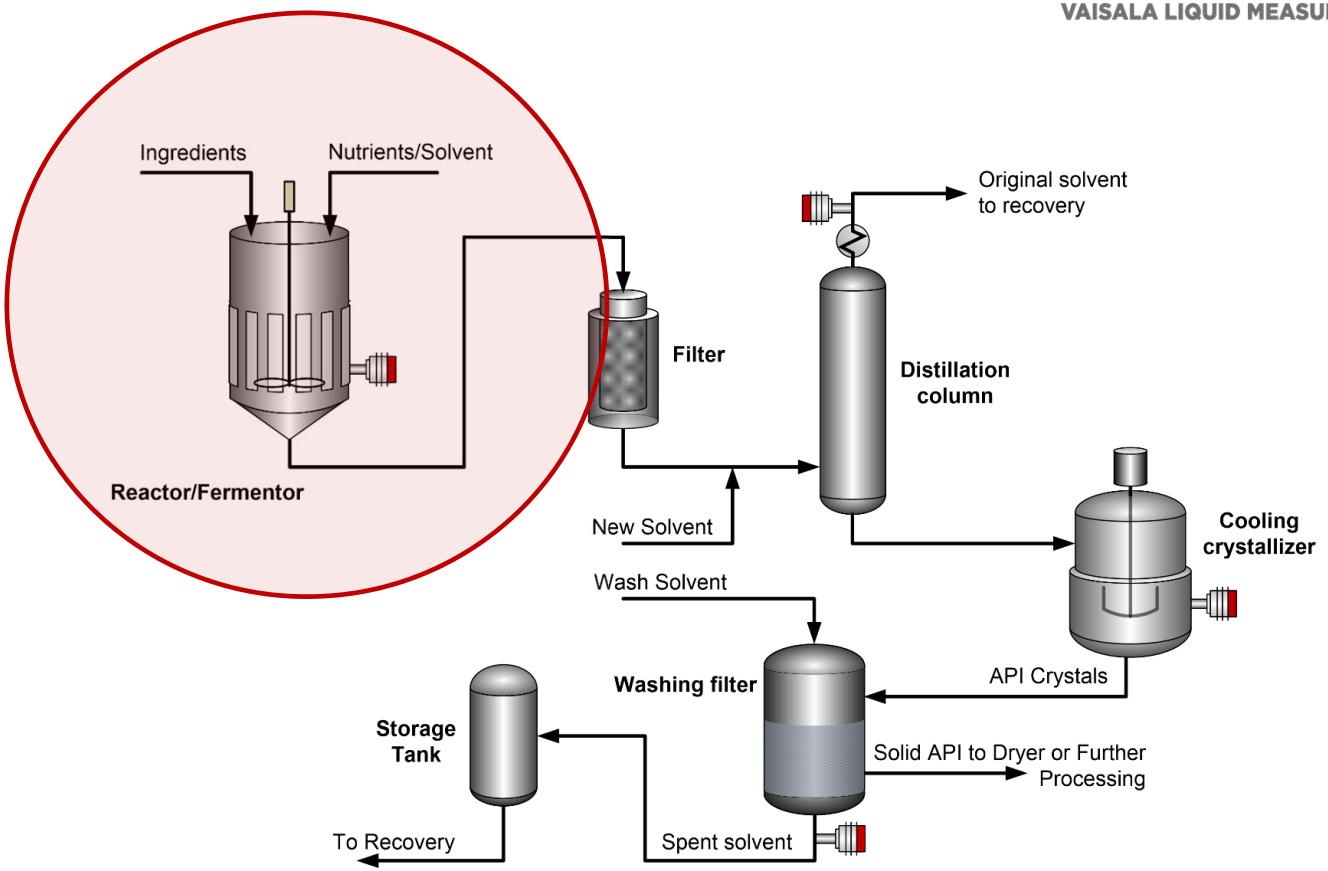
Common steps:

1. **Reaction/ Fermentation/ Extraction**
2. Solvent swap
3. Cooling crystallization
4. Filter cake washing



Monitoring reaction, fermentation or extraction progress

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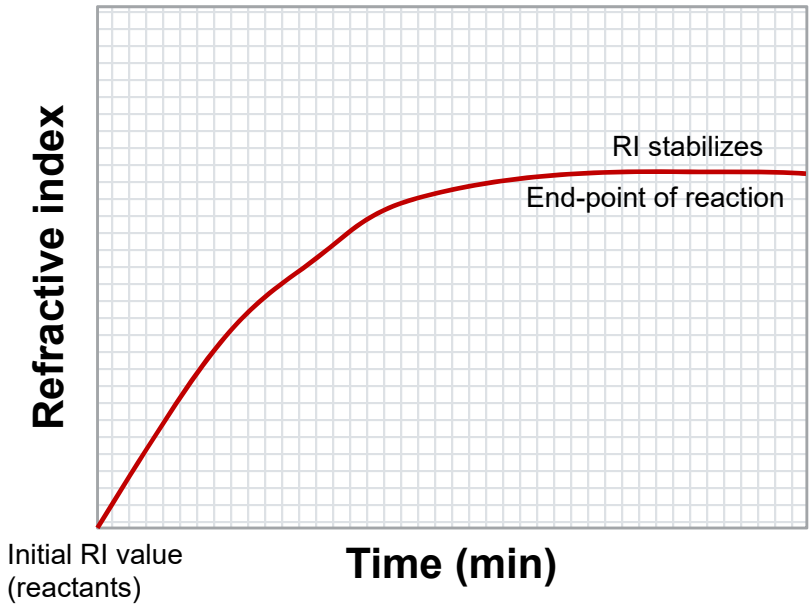
- As each material has an specific RI value, during a reaction the total RI of the reactants mixture will change from its original value towards a RI corresponding to products
- Changes in RI can be used as a measure of degree of reaction
- End-point of reaction can be determined



Pharmaceutical Extraction

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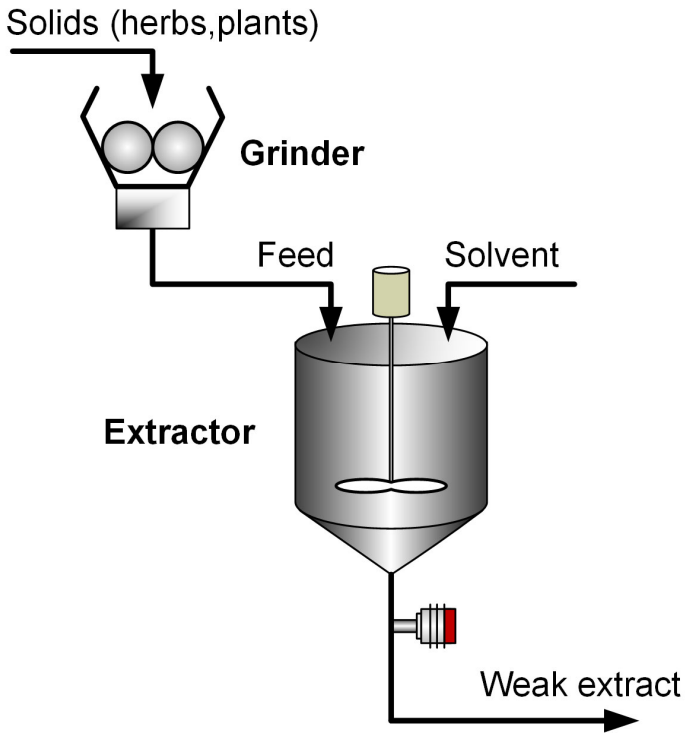
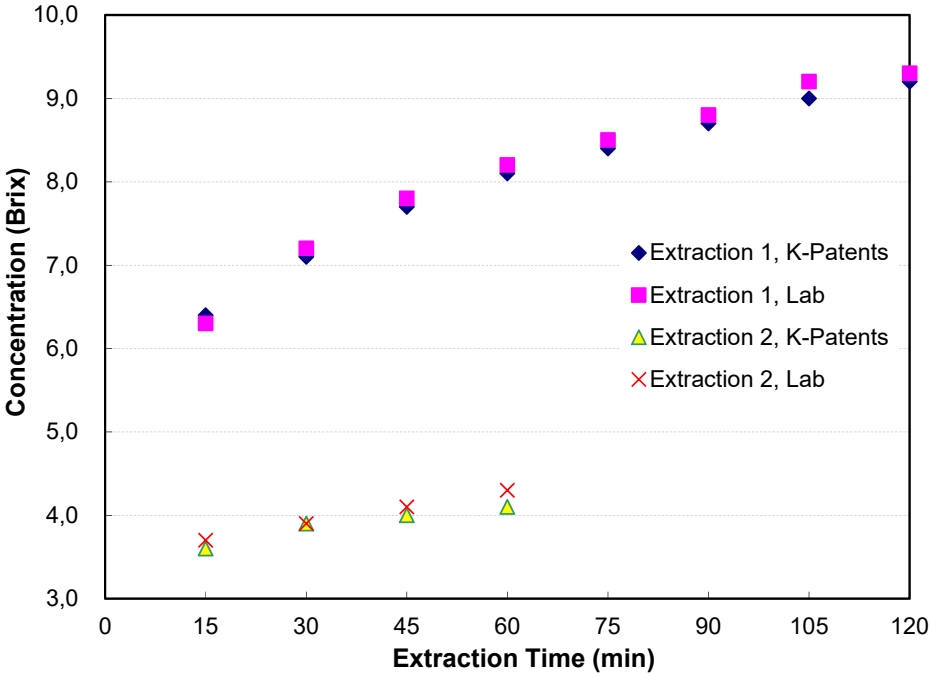
- Goal is to extract and isolate products from natural sources to be used as APIs or precursors in a synthesis
- Obtain a high concentration and purity of the extract

Some challenges:

- Measurement in real-time of extraction
- Suspended solid residues in the extract

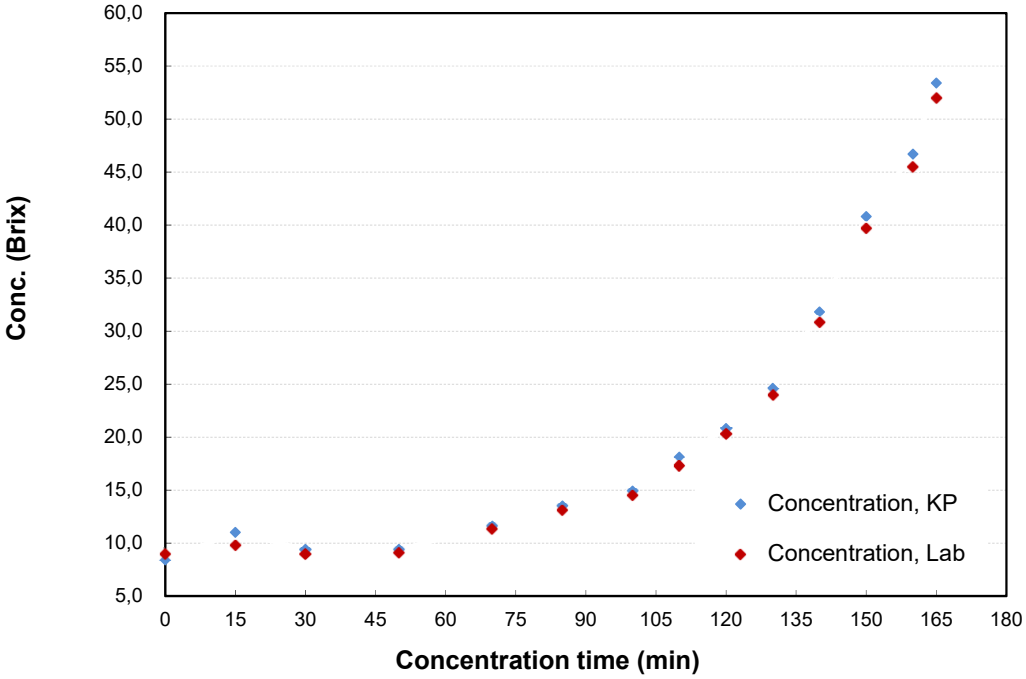


Example 1: Real-time Monitoring of Extract Concentration



*Measurement directly in the extractor

***Data from a Herbal Extract Plant.



**Measurement in the line after low temperature evaporator

Typical API Production Process

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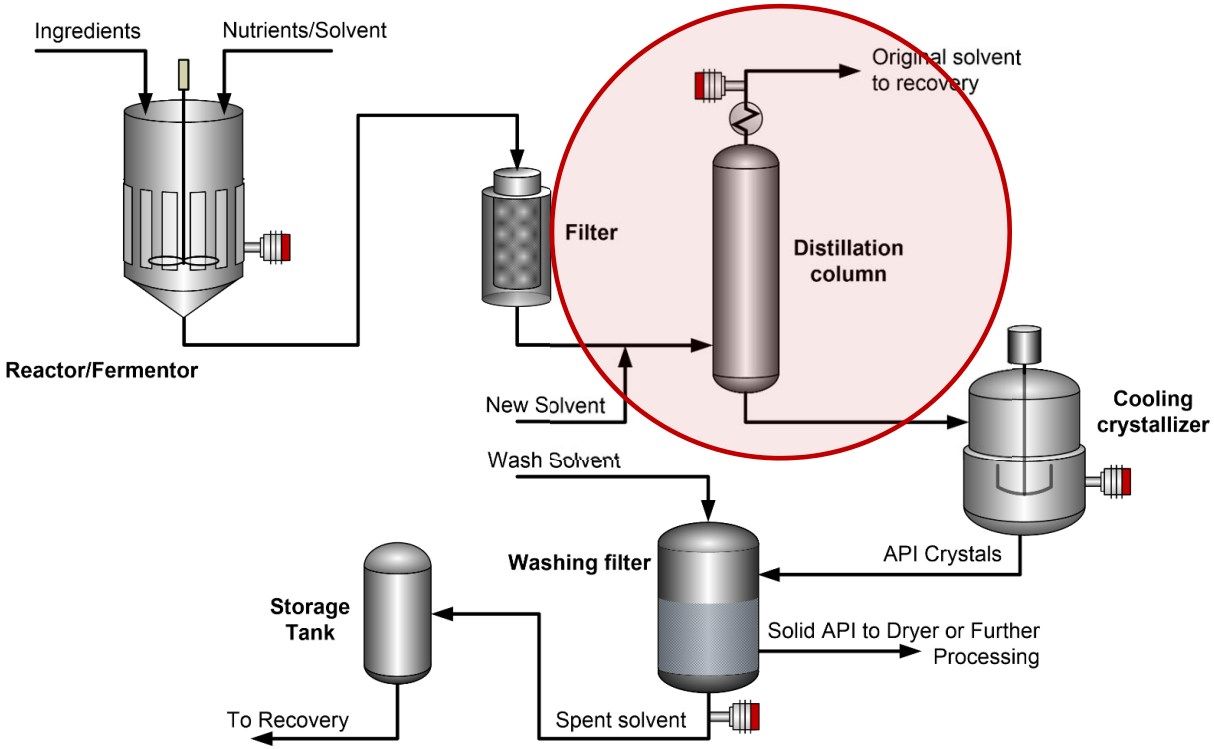
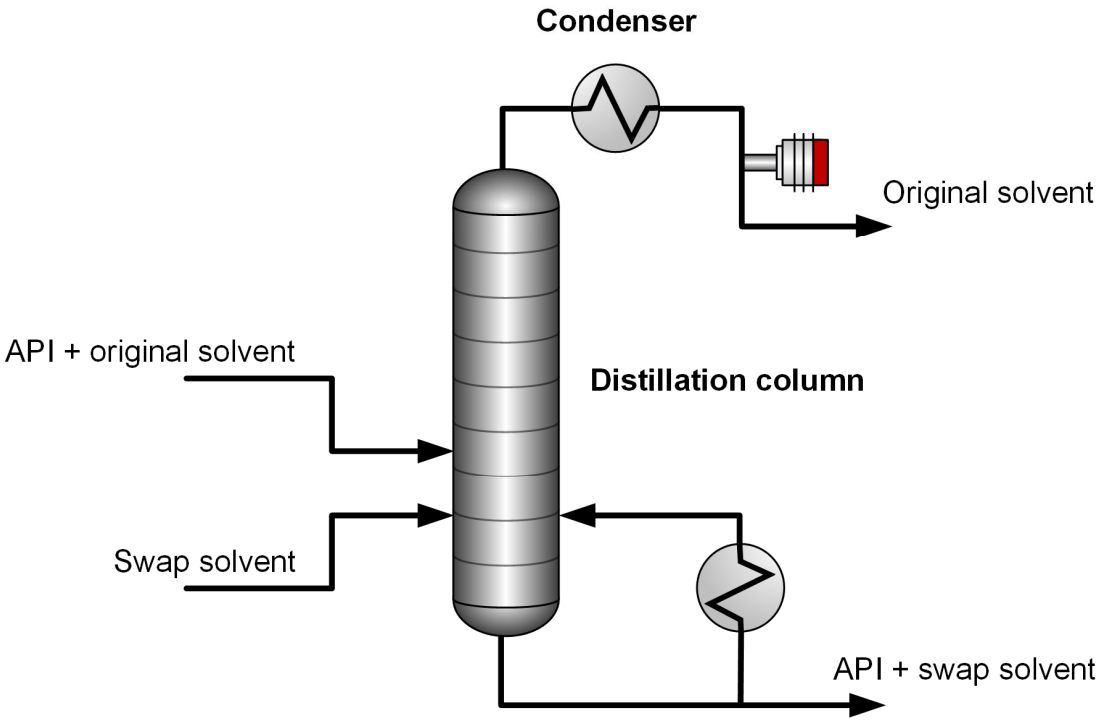
Common steps:

1. Reaction/ Fermentation/ Extraction
2. **Solvent swap**
3. Cooling crystallization
4. Filter cake washing



Solvent Swap

- Aims to replace the original solvent by a swap solvent that will make downstream processing easier, e.g. by distillation
- Concentration should be monitored to add more swap solvent and to ensure the correct concentration is achieved



Example 2: Scale-up of Solvent Swap Operations (1/2)

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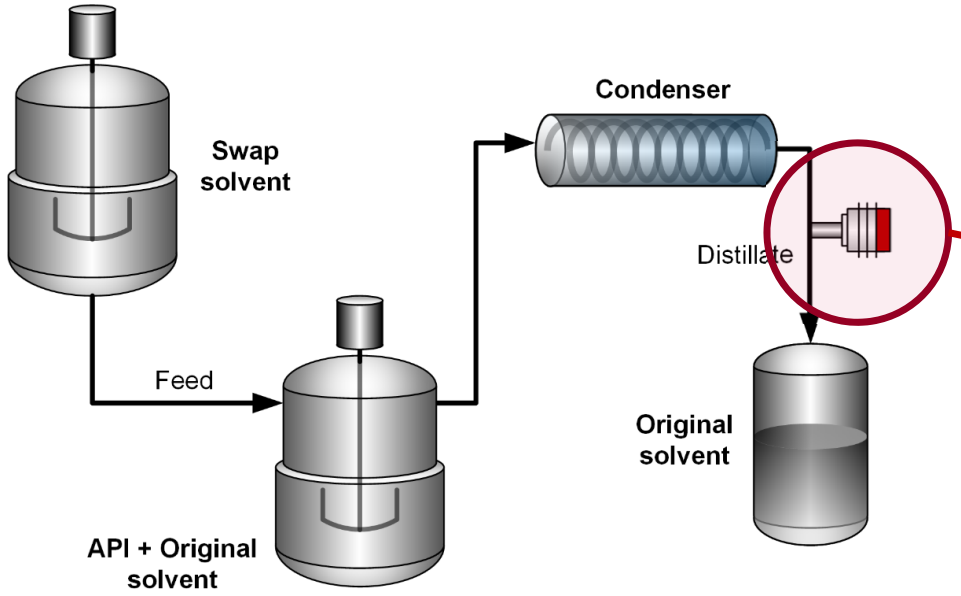
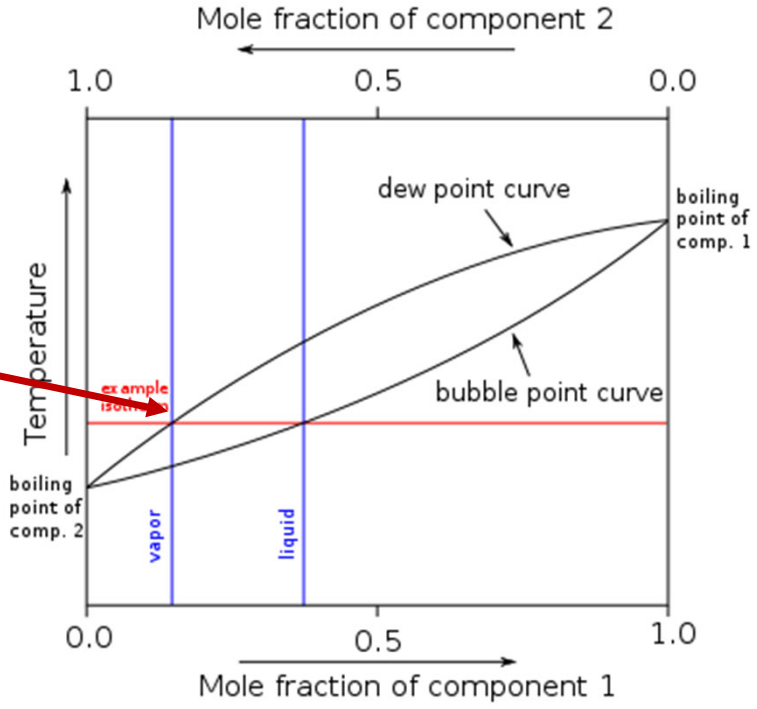
1. Finding the process profile





Vapor-Liquid Equilibrium (VLE) Data

Example 2: Scale-up of Solvent Swap Operations (2/2)

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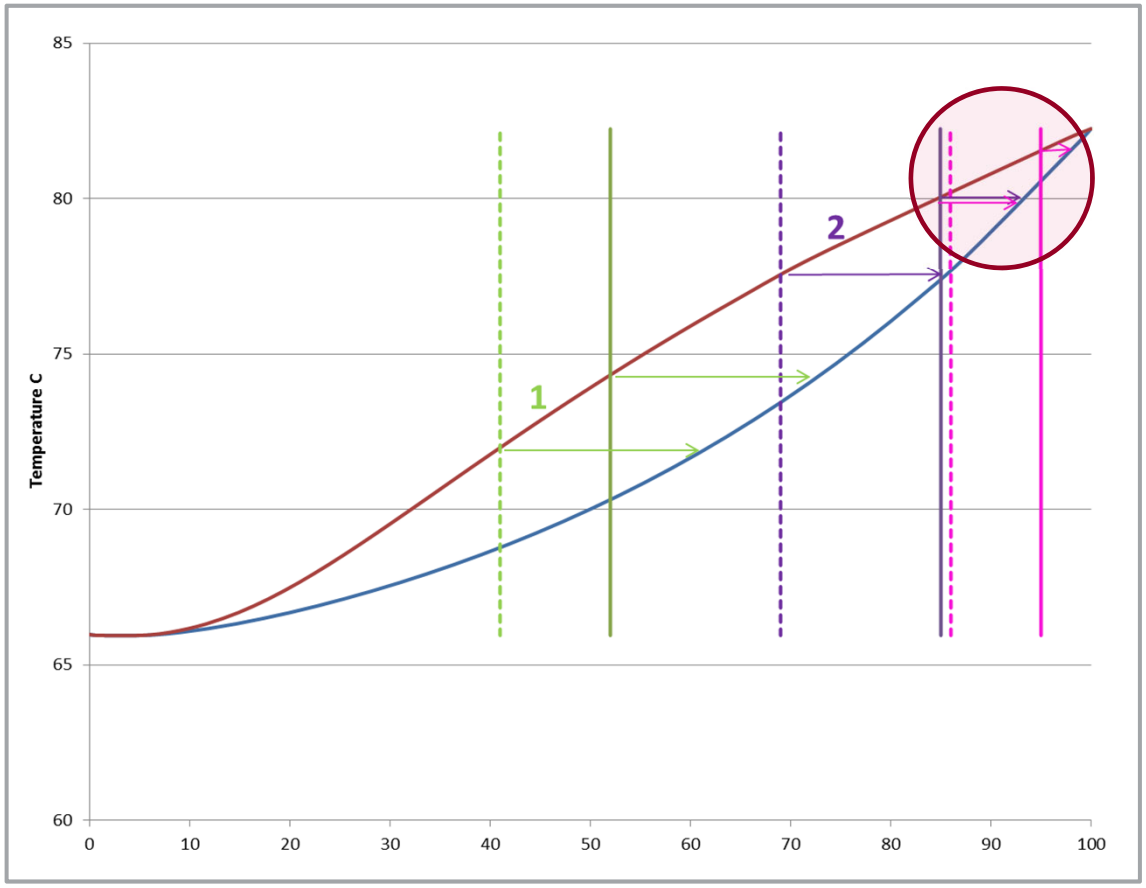
2. Troubleshooting during scale-up

RI values at each swap step		
Lab	**Plant 1**	**Plant 2**
1.404	1.411	1.404
1.392	1.405	1.392
1.379	1.389	1.384
1.378	1.382	1.379
1.3769	*Add. swap*	1.377

1 swap step was eliminated and the yield increased in 6-7 %!



Typical API production process

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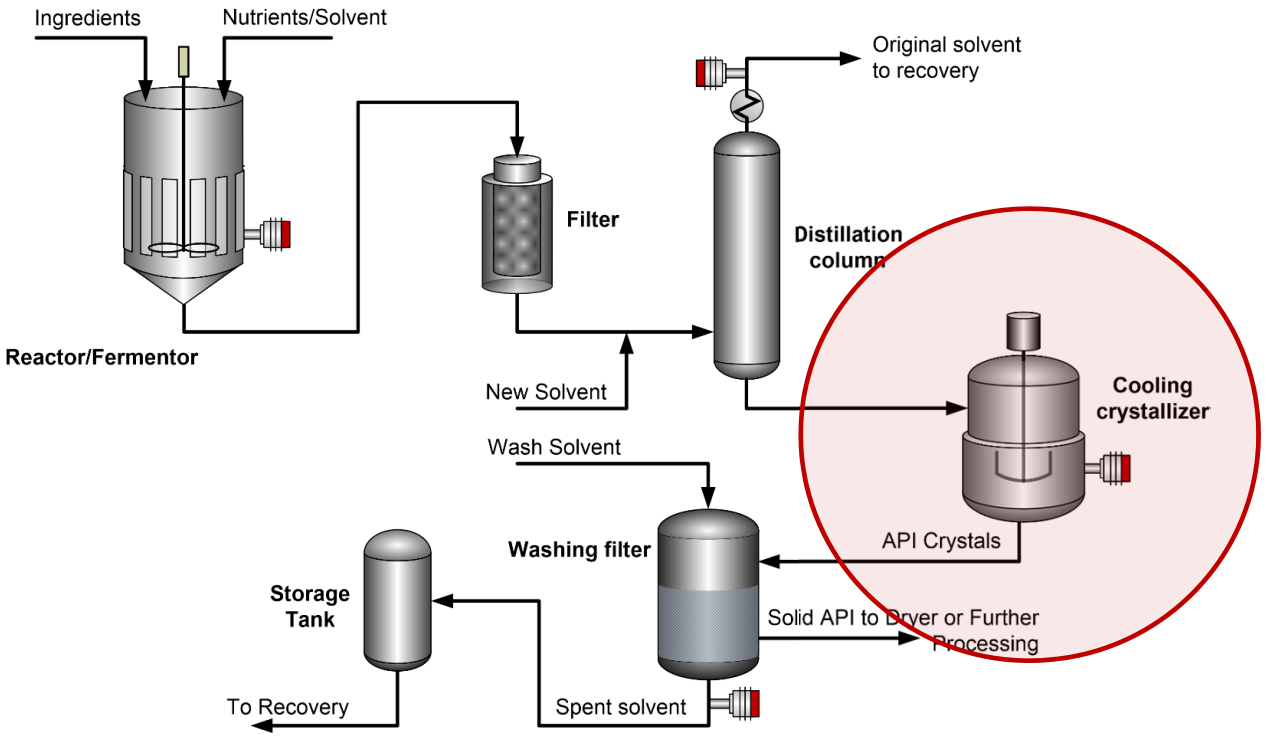

Pharmaceutical Crystallization

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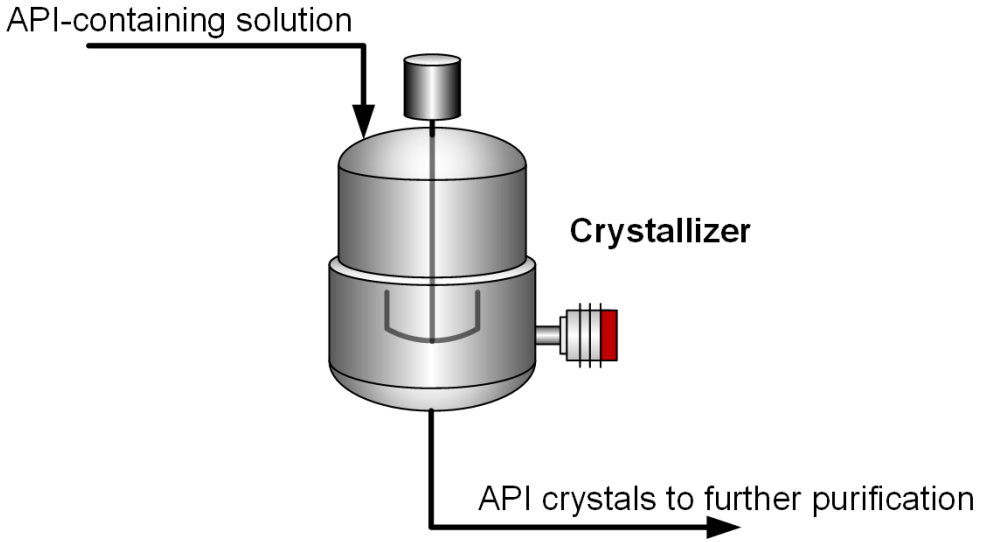
- Aims to recover the API from the liquid phase and to obtain a pure crystal product
- Need to avoid fines and conglomerates
- **Challenges:**
- How to control crystallization?
- How to ensure good quality crystals and PSD?
- How to monitor mother liquor saturation and determine seeding point?



Need for a selective measurement of the liquid phase!

Understanding Crystallization

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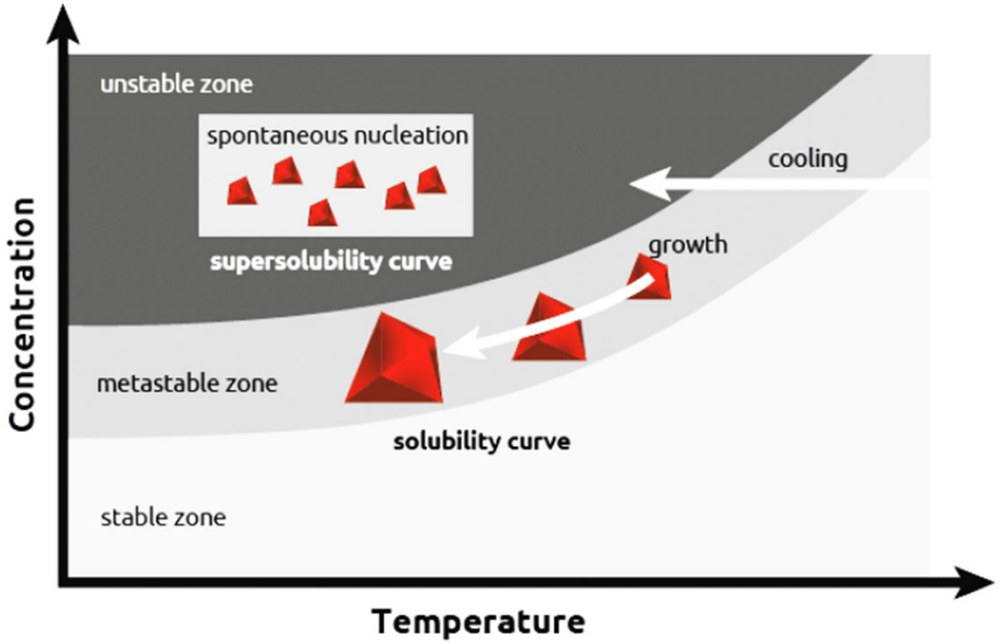
- **Supersaturation** is defined as the state at which any solution contains more dissolved solid (solute) than can be found in saturation conditions.
- This mean crystallization can only happen if the conditions of the liquid are taken above that saturation point (metastable zone).



* As crystallization happens there is a mass (solute) transfer from the liquid to solid, and crystals grows. This changes concentration.

** Good crystal PSD can be obtained in the metastable zone, close to the solubility curve.

Example 3: Crystallization Control (1/2)

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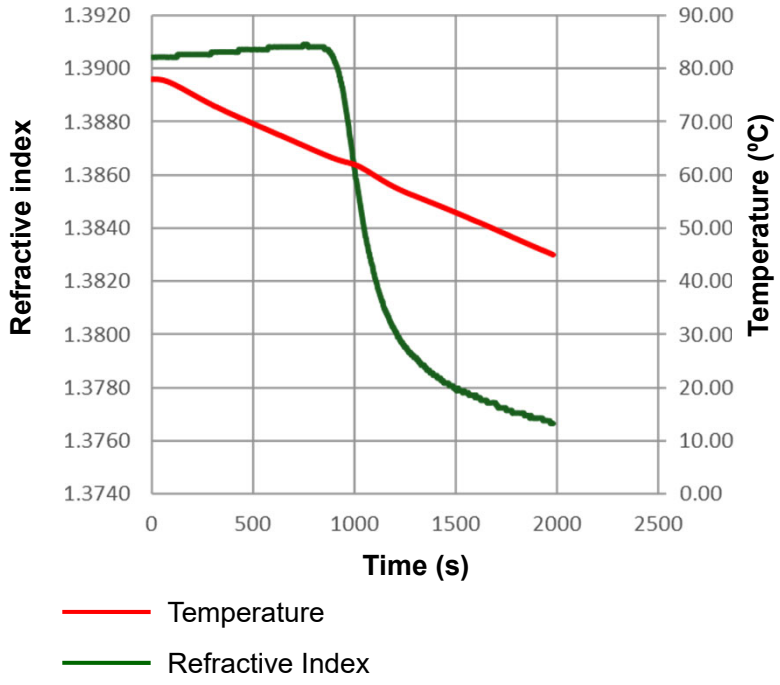
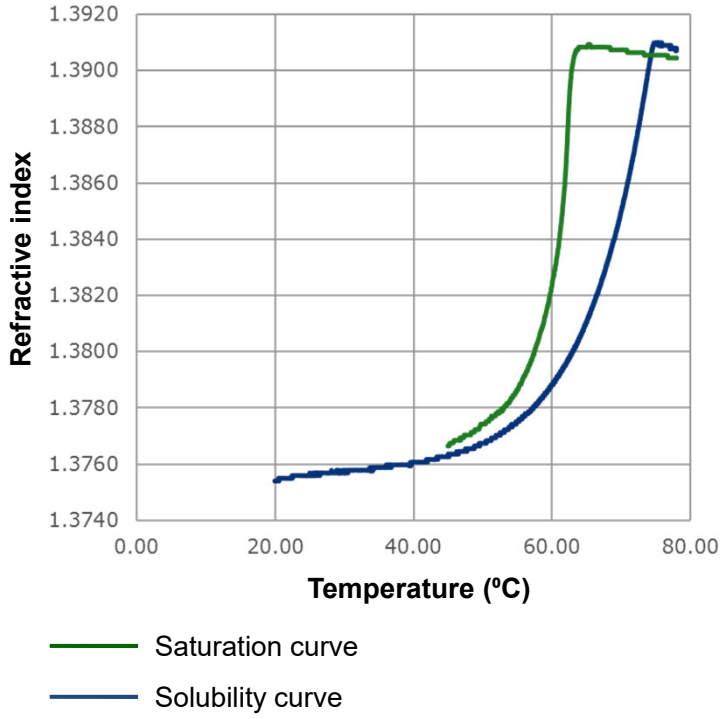
How to monitor and control crystallization with refractive index?

Spontaneous nucleation





Example 3: Crystallization Control (2/2)

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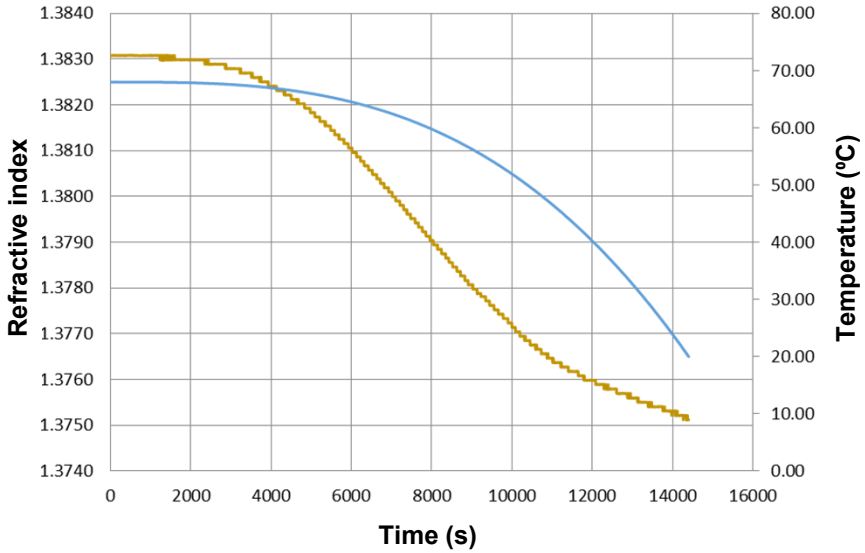
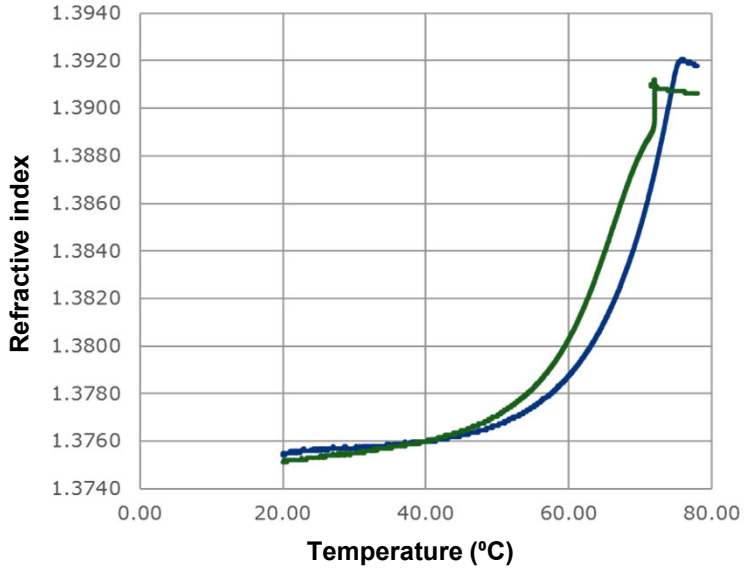
Cooling crystallization control, seeding and T control.





Typical API Production Process

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Common steps:

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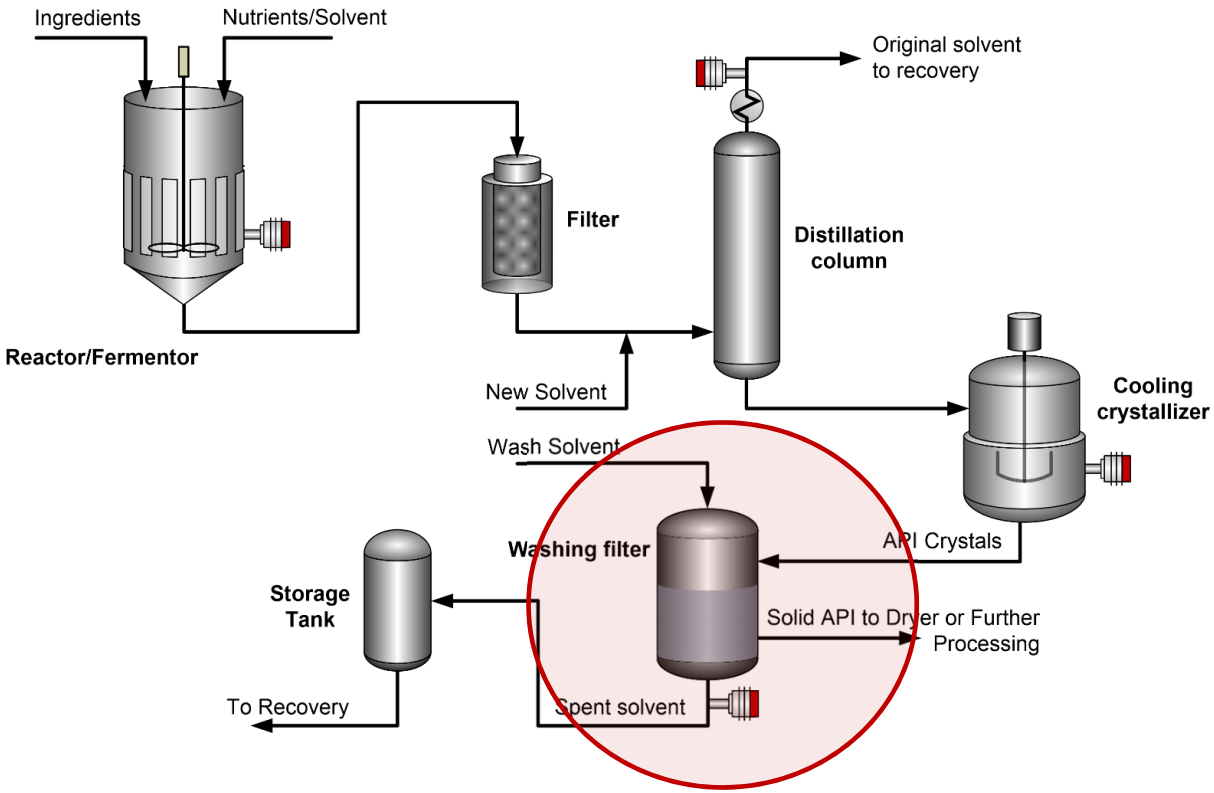
4. **Filter cake washing**

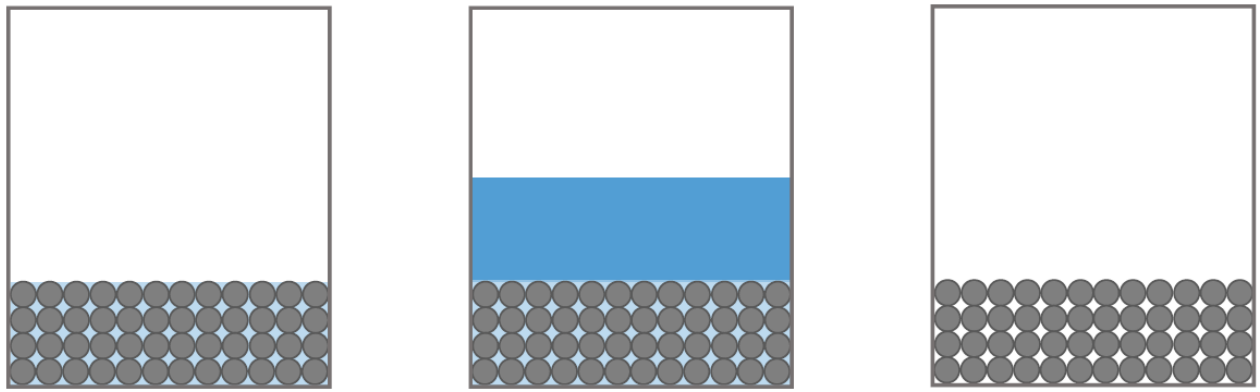


Filter Cake Washing

- Wash API crystals with solvent
- Remove impurities and mother liquor from filter cake
- Avoid dissolution of API in the solvent

Selection of correct washing solvent is critical to

- remove all mother liquor
- product dissolution
- maximize yield



1. Mother liquor is filtered out. A cake is formed with residual liquor in voids.

2. Washing solvent is applied to wash the cake.

3. Mother liquor is replaced by washing solvent.

Example 4: Understanding Cake Washing Operations

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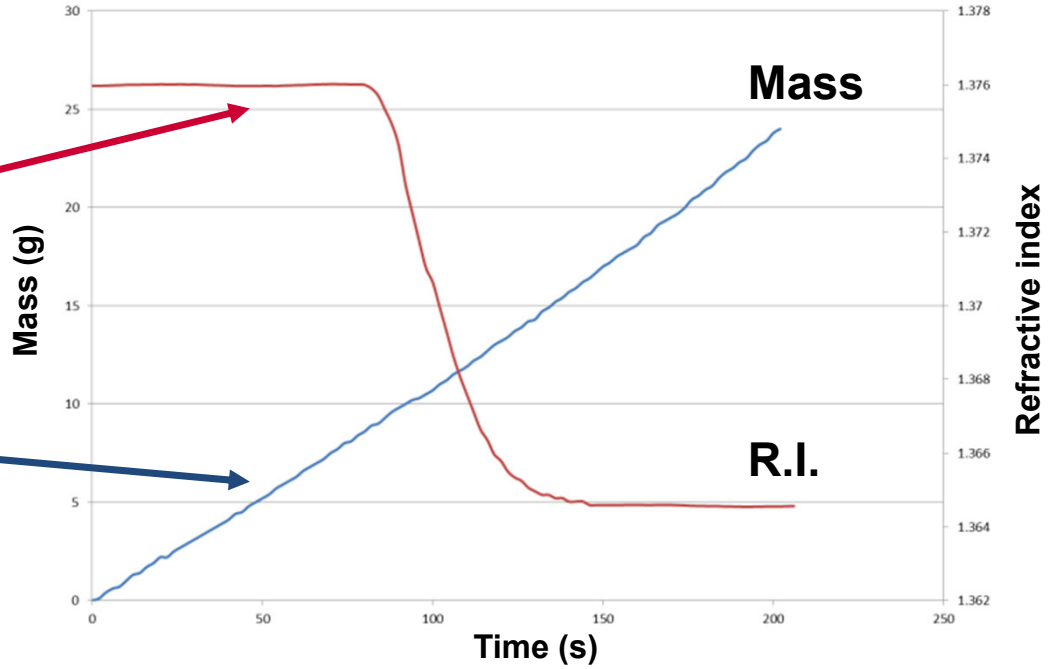
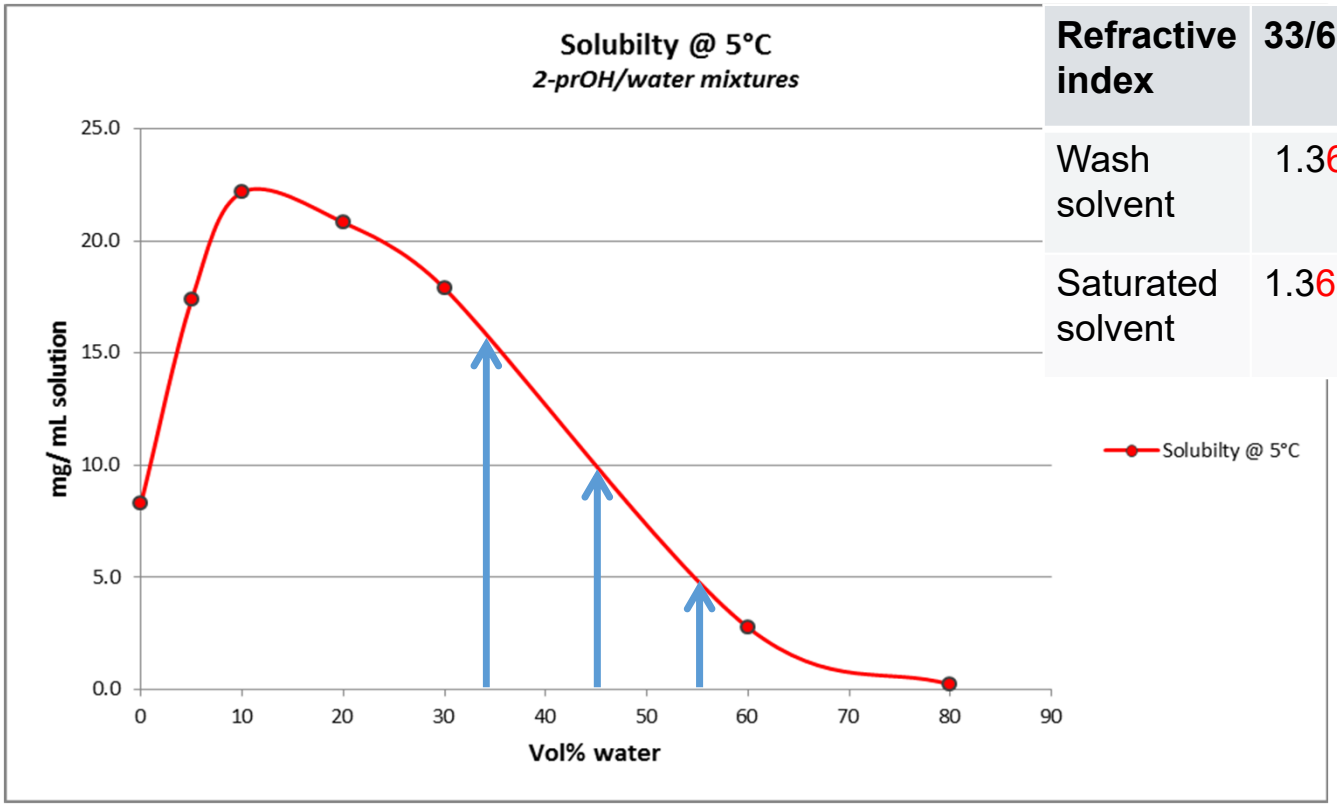
Process design and optimization questions:

- How much solvent is needed?
- Is it a displacement wash type?
- What are critical-to-quality parameters?
- What control tools can be used?



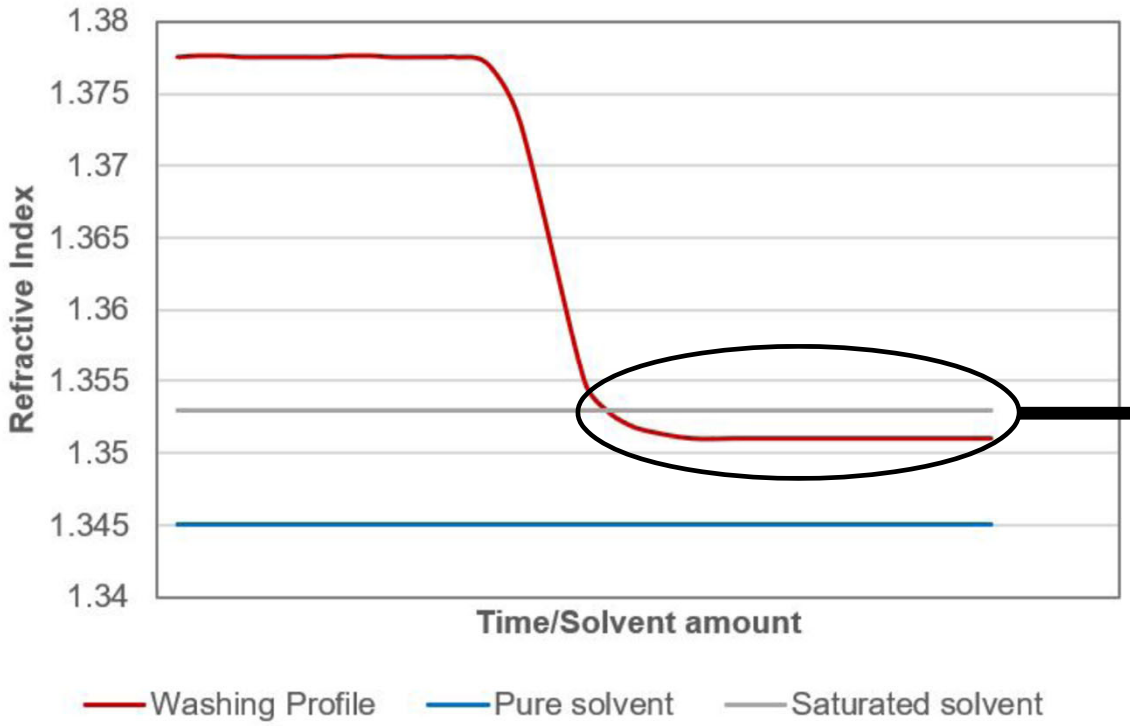
Example 5: Evaluation of Different Solvents

- **Pure washing solvent** and **saturated (with API) solvent** have different R.I. values



Refractive index	33/66	45/55	55/45
Wash solvent	1.3682	1.3639	1.3583
Saturated solvent	1.3689	1.3643	1.3582

Example 6: Process Troubleshooting



The measured refractive index value is closer to the saturated value than pure value. Some of the product is washed away. Lost yield!”

K-Patents Pharma Refractometer as a PAT Tool in Cake Washing Operations

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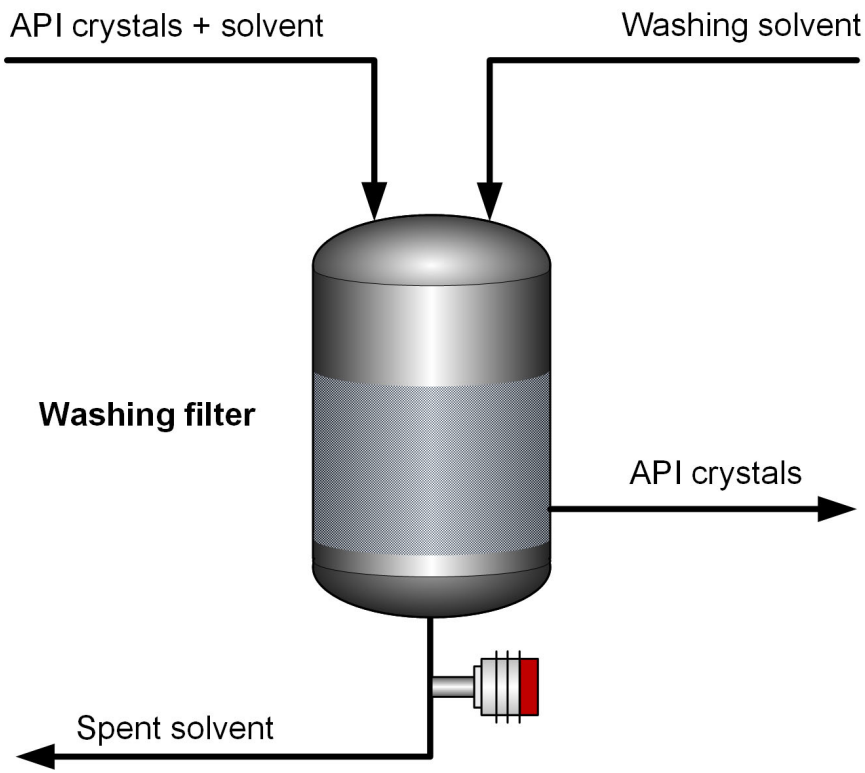
Lab scale:

- PAT tool for process understanding and process design
- Process profiles
- Solvent and API solubility evaluation
- Washing conditions, end-point of washing

Pilot and full scale:

- Reliable data for scale-up
- Process troubleshooting
- Continuous process optimization (minimizing operational costs, maximizing yield)



Conclusions

- Equipment qualified and validated in main API applications
- Refractive index is a valuable and easy tool for process understanding and troubleshooting
- The measurements are accurate and reproducible, allowing for consistent production
- Great savings in drug development and process design time

Read more about K-Patents applications in
www.kpatents.com/applications