Quality by design (QbD)

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Introduction

Quality By Design (**QbD**) is defined as

"a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management"

The quality by design (QbD) **principle**

> Once a system has been tested to the extent that the test results are predictable, further testing can be replaced by establishing that the system was operating within a defined design space.

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Introduction

Background

- The concept of Quality by Design was first outlined founded by Joseph M Juran.
- He said quality can be planned and that most problems related to the way that quality was planned (or not!) in the first place.
- The concept of QbD was adopted by FDA and mentioned in the **ICH Q8 guidance**, which states that "quality cannot be tested into products, i.e., quality should be built in by design".
- Quality was defined by the ICH Q8 as "The suitability of either a drug substance or drug product for its intended use."

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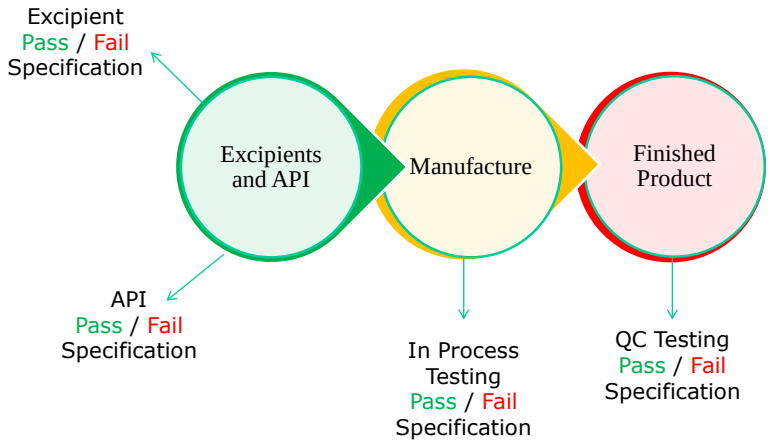
Traditional Approach – Quality By Testing



- Acceptance criteria set on limited data eg 1 batch.
- Testing must be performed for batch to be released.
- Failing batch only investigated at end of process

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QbD elements

1. Define target product quality profile
2. Design and develop product and manufacturing processes
3. Identify critical quality attributes, process parameters, and sources of variability
4. Control manufacturing processes to produce consistent quality over time

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QbD elements

Define target product quality profile (TPQP)

- Target Product Quality Profile (TPQP) is a term denoting the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label.
- For example, a typical TPQP of an immediate release solid oral dosage form would include:
  - Tablet Characteristics
  - Identity
  - Assay and Uniformity
  - Purity/Impurity
  - Stability
  - Dissolution

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QbD elements

Design and develop product and manufacturing processes

Product Design and Development

- In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance (Preformulation).
- These biopharmaceutical properties include:
  - **physical**: (particle size, shape, and distribution), polymorphism, aqueous solubility as function of pH, hygroscopicity, and melting points, mechanical properties …)
  - **Chemical** (pKa, chemical stability, excipient compatibility)
  - **biological** properties (partition coefficient, membrane permeability, and/or oral bioavailability)

QbD elements

Design and develop product and manufacturing processes

Process Design and Development

- **Process design is**
- the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing.
- This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables.

QbD elements

Identify critical quality attributes, process parameters, and sources of variability

- Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture.
- **Critical quality attributes (CQA)** are physical, chemical, biological, or microbiological property or characteristic of drug product that must be controlled directly or indirectly to ensure the quality of the product.
- **Critical process parameters (CPP)** are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range.

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QbD elements

Identify critical quality attributes, process parameters, and sources of variability

- Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time.
- In process robustness studies, effects of variations in process parameters for a candidate process are evaluated.
- **The analysis of these experiments :**

1. identifies critical process parameters that could potentially affect product quality or performance,
2. establishes limits for the critical process parameters within which the quality of drug product is assured.

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Table II. Typical Unit Operations, Process Parameters, and Quality Attributes for Tableting[a]

Pharmaceutical Unit Operation	Example Process Parameter	Potential Quality Attributes
Mixing	Type and geometry of mixer	Blend uniformity
	Order of addition	Particle size distribution
	Mixer load level	Bulk/tapped density
	Number of rotations (time and speed)	Moisture content
	Agitating bar (on/off pattern)	Flow properties
Milling	Impact/cutting/screening mills	Particle size
	Mill type	Particle size distribution
	Speed	Particle shape
	Blade configuration and type	Bulk/tapped density
	Screen size and type	Flow properties
	Feeding rate	Polymorphic form
	Fluid energy mill	
	Number of grinding nozzles	
	Feed rate	
	Nozzle pressure	
	Classifier	
Compaction[b]	Compression speed and force	Target weight
	Pre-compression force	Weight uniformity
	Feed frame type and speed	Content uniformity
	Hopper design, height, and vibration	Hardness
	Tablet weight and thickness	Thickness
	Depth of fill	Tablet porosity
	Punch penetration depth	Friability
		Visual attributes
		Moisture content

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QbD elements

Identify critical quality attributes, process parameters, and sources of variability

- Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process.
- When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability.

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QbD elements

Control manufacturing processes to produce consistent quality over time

- Under the QbD for drug product, the effects of raw materials including both drug substance and excipients, and process parameters on the product quality are studied thoroughly and become well understood.
- This means that manufacturers have knowledge of the operating range as well as the proven range of critical raw material attributes and process parameters.
- **The operating range is defined as**
- the upper and/or lower limits for raw material attributes and process parameter values between which the attribute and parameter are routinely controlled during production in order to assure reproducibility.

QbD elements

Control manufacturing processes to produce consistent quality over time

- The proven range is defined as the upper and/or lower limits for process parameter values between which the parameter is known to produce a high quality product that delivers the therapeutic benefit claimed on the label.
- **The proven range can be established based on:**

1. historical and/or experimental data.
2. scientific and operational judgment and expertise.

- Within the QbD, design space is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide quality assurance

QbD elements

Control manufacturing processes to produce consistent quality over time

- Working within the FDA approved design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.
- The design space for manufactured drugs is likely established at small scale batches using design of experiments (DOE) and prior knowledge, and may need to be verified at commercial scale.
- The control space (or normal operating ranges) is defined as the upper and/or lower limits for the critical raw material attributes and process parameters between which the parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space.

Example on design space

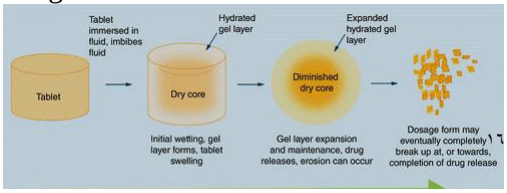
- Optimization of pentoxifylline extended-release hydrophilic matrix tablets.

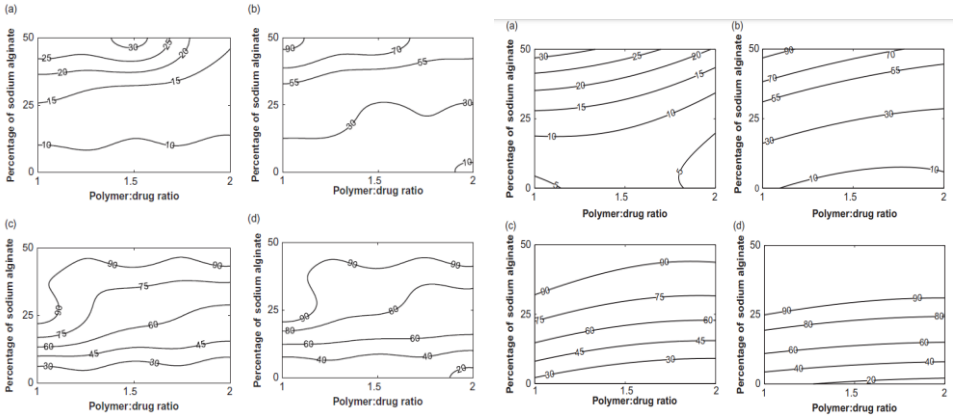
Specifications (*USP Test 1*)

Time (hours)	Amount dissolved
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

Formulation factors

1. the matrix former (polymer): drug weight ratio
2. *the percentage* of sodium alginate in the matrix former





Before using second-order polynomial equations

After using second-order polynomial equations

Contour plots showing the effects of formulation factors on percentage of pentoxifylline released after (a) 1, (b) 4, (c) 8, and (d) 12 hours, predicted by SVR.

MATLAB platform Support Vector Regression

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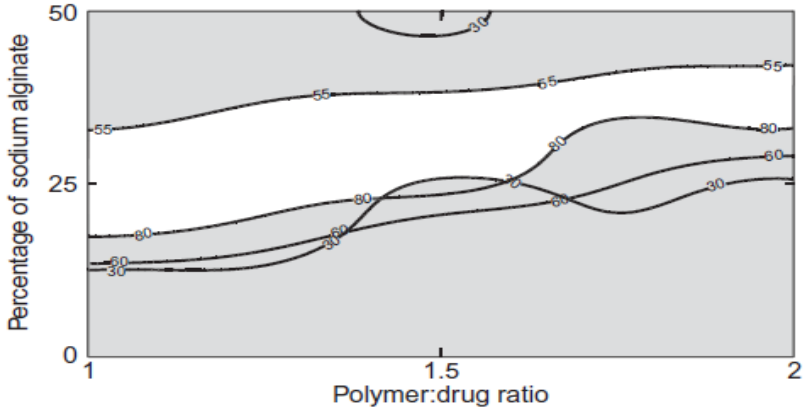

Superimposed of the 4 contour plots derived by using SVR predicted release data

Drug Development and Industrial Pharmacy, 2011, 37(1): 80–8

Optimization of extended-release hydrophilic matrix tablets by support vector regression

Optimization of matrix tablets by SVR

Nizar Al-Zoubi , Kyriakos Kachrimanis , Khaled Younis and Stavros Malamataris

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QbD elements

Control manufacturing processes to produce consistent quality over time

- Full establishment of QbD requires process control of critical steps to ensure that quality is maintained.
- Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality
- Pharmaceutical scientists have begun to use PAT for process understanding and process control.
- The FDA has approved a number of applications which implemented PAT.
- The use of PAT is expected to assist the implementation of QbD

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Process Analytical Technology (PAT)

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Introduction

- Since the late 1990s the FDA has been advocating the use of process analytical technology (PAT) in pharmaceutical development and manufacturing.
- The agency was interested in decreasing patient risk through improved control of pharmaceutical processes.
- Process analytical technology (PAT) has been defined by the US FDA as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA).

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Process Analytical Technology (PAT) Tools

Analytical Techniques

- Process analytical technology is based on the use of in-line/on-line or off-line tools to determine product quality.
- Ideally, test results need to be available in a timely manner to allow for feedback control.
- several techniques have been introduced into pharmaceutical development. These techniques include:
  - spectroscopy
  - acoustics
  - chromatography
  - laser diffraction
  - optical techniques

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Analytical Techniques

Spectroscopic techniques

- One advantage of these tools over other analytical chemistry techniques (i.e., HPLC, GC, etc.) is the high speed at which the measurements can be done (typically on the order of seconds).
- In addition, vibrational spectroscopy, with the exception of some UV-Vis applications, is usually a non-destructive analytical technique requiring minimal or no sampling preparation. Therefore, measurements can be made in-process or on a final product, without affecting the product yield or quality.

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Analytical Techniques

Spectroscopic tools

Examples

- ***UV-Vis Spectroscopy:*** reaction monitoring, dissolution testing, vessel cleaning, and color determinations.
- ***Near-infrared Spectroscopy:*** Polymorph identification; Crystalline versus amorphous phase identification; Blend uniformity, Wet granulation monitoring, Roller compaction monitoring, Drying end point, Coating end point and uniformity; and Potency in tablets or capsules.
- ***Mid-infrared Spectroscopy***
- ***Raman Spectroscopy:***

the category of vibrational spectroscopy. inelastic (Raman) scattering of a molecule irradiated by a monochromatic light, usually from a laser light

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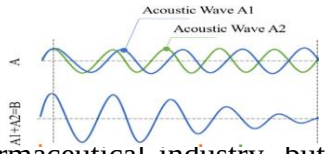
Analytical Techniques



Acoustic tools

- Acoustic measurements are new to the pharmaceutical industry, but are widely used in other industries.
- There are two types of acoustic measurements: active and passive.

➢ Active acoustic techniques involve sending a sound wave into a sample, and collecting the sound waves that are transmitted through the sample.

- The attenuation of the acoustic waves, and the change in their velocity as the waves pass through the sample, are related to the physical and thermal properties of the sample material. For example, changes between incoming and outgoing sound waves can be correlated to the density, porosity, concentration, etc., of the sample.

➢ Passive acoustic techniques are based on collecting sound waves emitted during a process, and correlating those acoustic emissions to steps in the process or product attributes.

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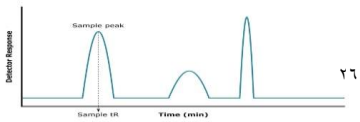
Analytical Techniques

Chromatography

- Chromatography, liquid or gas, has been widely employed in the pharmaceutical industry for quality assurance of in-process samples and final product.
- **Chromatography is known for**

1. its characteristics of high resolution and detection power,
2. making it suitable for detecting multiple components in a complex mixture
3. high accuracy, precision, specificity, and sensitivity.

- Therefore, chromatography is used almost exclusively for:
  - analysis of complex mixtures, such as fermentation broths,
  - and for trace analysis.



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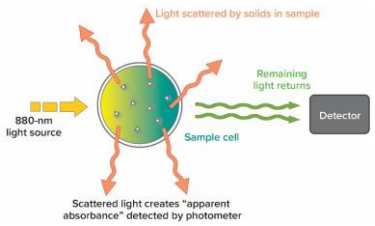
Analytical Techniques

Laser Diffraction Tools

One of the most established tools for characterizing and monitoring the size distribution of pharmaceutical products is laser diffraction.



Optical Tools

- These include several techniques such as <u>turbidity</u> measurements. **Used For:**

1. determining particulate levels in liquid flows (for example to monitor filter breakthrough).
2. determine the presence of microbiological contamination in pharmaceutical water,
3. with bioprocesses.

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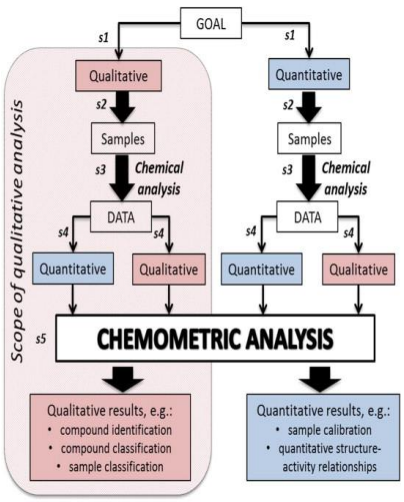
Process Analytical Technology (PAT) Tools

Chemometrics and MultivariateAnalysis

- Chemometrics can be defined as " the use of statistical and mathematical techniques to analyze chemical data. "
- <u>Multivariate data</u> analysis allows for analysis of the multidimensional data, so that all significant variations are accounted for.
- Multivariate data analysis is necessary whenever the data obtained is in more than two dimensions.



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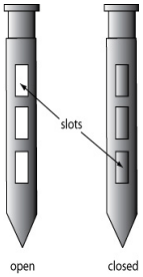
Process Analytical Technology (PAT) Applications

Blending (mixing)

- Blending is one of the most common unit operations in solid dosage manufacturing.
- Depending on the process, several blending steps may be needed, each requiring a uniform powder product.
- To ensure the blend is uniform, current industry standards require obtaining unit dose samples from either the blender or from a drum after the material has been discharged from the blender.
- Sampling involves using a sample thief to obtain a powder sample from different locations in the powder bed.
- The blend is considered uniform if the potency of the samples is between 85% and 115% of the theoretical value.



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Process Analytical Technology (PAT) Applications

Blending (mixing)

- **Real-time NIR** and **Raman spectroscopy : These are continuous** measurements used in determining blend uniformity
- Because the powder in the blender is continuously moving, each spectra collected is from a different powder sample.
- The spectra obtained from the blending run can be analyzed in several ways.

Uses: 1. to blend uniformity data

2. Physical information : particle size, density,

moisture content

3. The hardness of tablets has been correlated to the NIR spectra obtained during blending.

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Process Analytical Technology (PAT) Applications

Blending (mixing)

Advantages:

- Because the measurements and analysis are done in realtime, the blend end point can be determined in realtime.
- This is especially beneficial for processes whose blend uniformity is sensitive to the raw materials or to upstream unit operations (Biologics, e.g. Antibodies).

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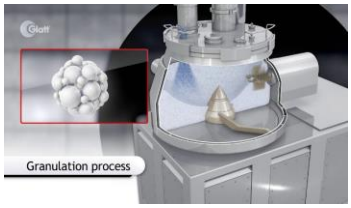
Process Analytical Technology (PAT) Applications

Wet Granulation

- Techniques that have been used to monitor granulation processes include:
  A. power output,
  B. acoustic emission,
  C. thermal effusivity,
  D. NIR spectroscopy.



- Power curves from a high shear granulator shaft have been used for decades to determine the end point of granulation.
- The power can be correlated to the quality of the granules, and provide a real-time inline tool for ensuring consistent granules are produced from batch to batch.

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Process Analytical Technology (PAT) Applications

Near-infrared Monitoring of Fluid-bed Drying

- Typically, drying is controlled based on empirical experience, where drying is conducted for a fixed amount of time at a given set of conditions or until the exhaust temperature reaches a predetermined temperature.
- At the end of drying, a sample of the granulation is pulled, and tested for moisture using offline gravimetric or other instruments.
- If the moisture level is within the desired range the drying process is terminated, otherwise, the granulation is redried until the desired moisture level is achieved.

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Process Analytical Technology (PAT) Applications

Near-infrared Monitoring of Fluid-bed Drying

- NIR spectroscopy provides an opportunity to make the drying process more efficient through real-time moisture monitoring.
- Water exhibits high absorption in the NIR spectral region, making NIR spectroscopy a viable technique for directly monitoring moisture content.
- In order to use NIR to monitor moisture, a calibration model must be created from spectral data collected during the drying process and/or from the laboratory, and correlated to moisture data from a referee method (e.g., Karl Fischer or loss on drying (LOD%)).

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Process Analytical Technology (PAT) Applications

Near-infrared Monitoring of Fluid-bed Drying

- When the calibration model is applied to NIR spectra collected during the drying process, real-time moisture values are calculated, and the drying process is continued until the desired moisture level is achieved.
- Terminating the drying process at the desired moisture content eliminates the need for redrying, thus reducing overall cycle time.
- real-time moisture monitoring allows for reducing or extending the drying time as needed, based on changes in the granulation properties to ensure the target moisture level is obtained every time.

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Process Analytical Technology (PAT) Applications

Encapsulation

- The main product quality attributes in encapsulation are content uniformity, and capsule weight.
- Monitoring encapsulation is challenging, due to the speed of the encapsulator and the need to monitor the powder inside the capsule before the cap is closed.
- Because of these challenges, vendors of encapsulation technology have led the effort of implementing online techniques.
- Both NIR and soft X-ray techniques have been used in real-time on commercial encapsulators to monitor content uniformity and fill weight, respectively.

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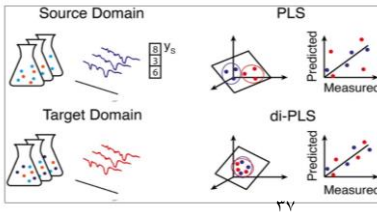
Process Analytical Technology (PAT) Applications

Encapsulation

- More simple applications involve the use of vibrational spectroscopy via a fiber optic probe to monitor the content uniformity in the hopper or powder bowl, and determine if segregation is occurring.
- These techniques, combined with inline capsule weight checkers, can give an indication if either the content uniformity or the weight are varying, and provide an opportunity for feedback control.'
- Partial least squares regression(PLS)



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Process Analytical Technology (PAT) Applications

Compression

- The main product quality attributes of the tablets are content uniformity, hardness, weight, and dissolution profile. NIR has been used to build PLS models that can predict the drug content, hardness, and dissolution profile for tablets.
- These PLS models require substantial chemometric method development.
- In addition, real-time measurements of all tablets exiting a tablet press are challenging, due to the spectrometer speeds needed, and the need for modification of existing equipment.
- For these applications, at line instruments are often used. Commercial atline instrumentation can acquire NIR spectra and perform, weight, thickness, and hardness testing, in a few minutes per tablet.

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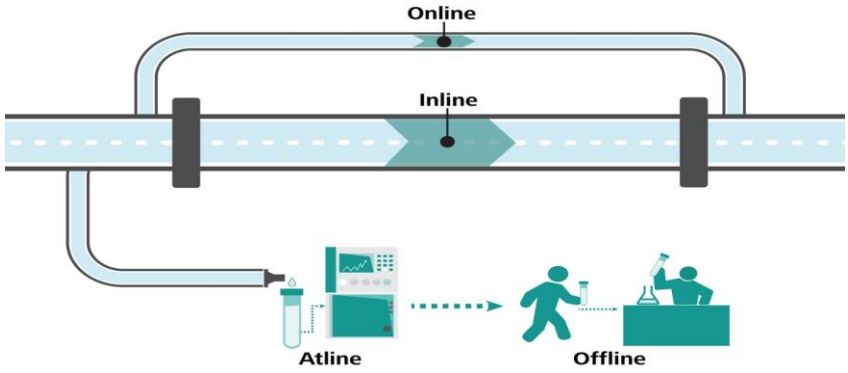

Inline: For inline analysis, a sensor can be placed in a process vessel or stream of flowing material to conduct the analysis.
Online: Analysers which are connected to a process, and conduct automatic sampling, can be called online (or on-line) analysers or sometimes inline (or in-line) analysers.
This means that online and inline analyses permit continuous process control.
Offline and atline analyses, on the other hand, are characterized by manual sampling followed by discontinuous sample preparation, measurement and evaluation. The material properties can change during the time between sampling and the availability of the results, so direct process control is not possible ٣٩