# PE6019 Sample Exam Questions

The following is a selection of the type of exam questions that the exam may typically include. The exam will take 90 minutes and you are required to answer three from a choice of four questions of the type given below.

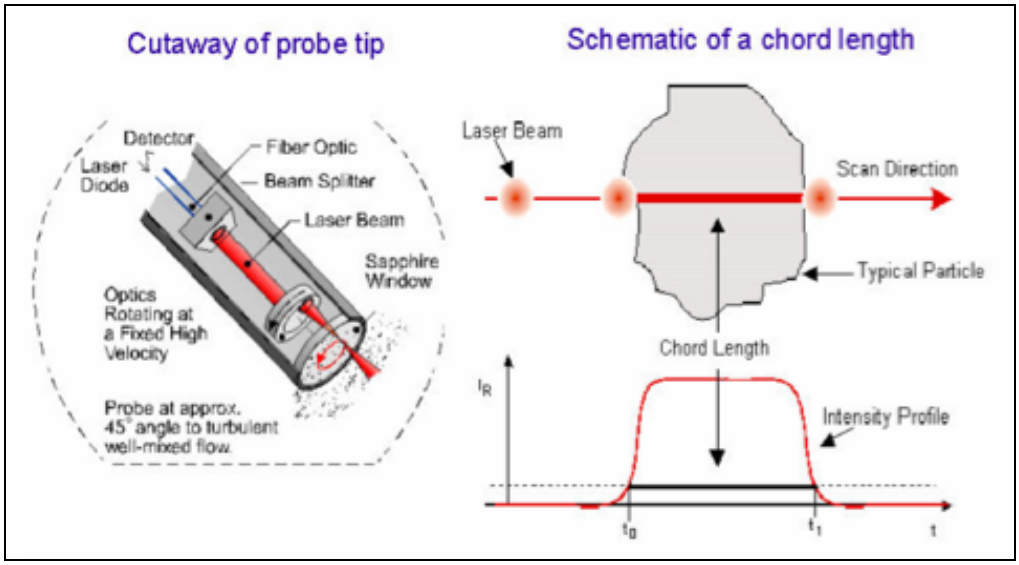
**Q1.**
Describe how PAT could be applied to a crystallisation process. Provide a brief description of two analysers you could choose from. Make use diagrams where appropriate.

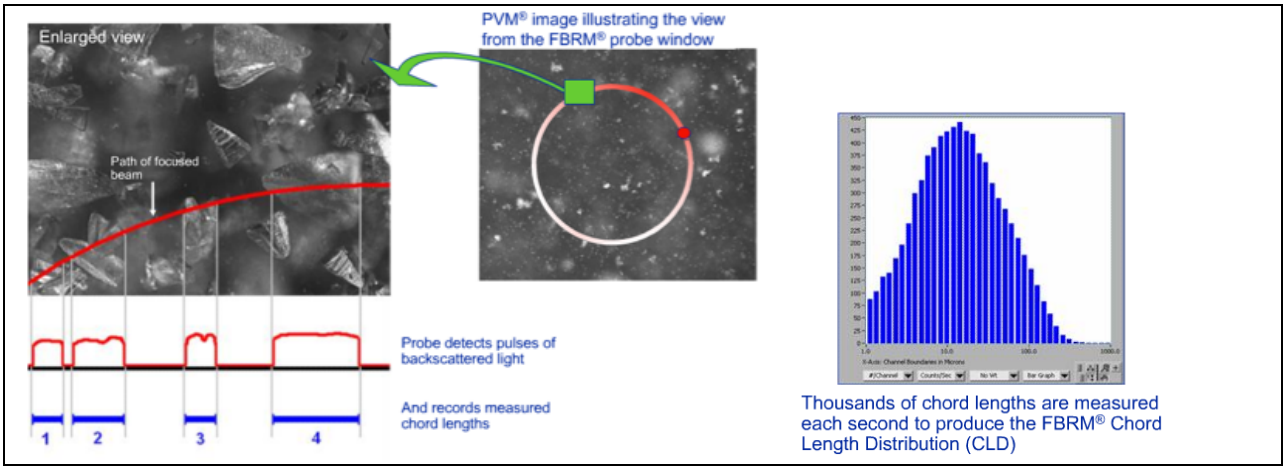
a. Describe how these analytical techniques work and what they measure. (40 marks)
b. Describe how this data facilitates process understanding. (40 marks)
c. Describe how these analysers would be installed in a plant vessel, taking into account probe type, location and orientation. (20 marks)

**Answer**

**a)**
**FBRM to measure particle size:**

The principal of operation of the Focused Beam Reflectance Meaurement (FBRM) is illustrated in the figure below. A light beam rotates at high speed and is focused into the particle suspension to be monitored. When the focused beam crosses a particle in front of the probe, a signal is backscattered into the probe. The length of the scanned chord is determined in the electronics of the system and presented as a chord length distribution histogram. This chord length distribution provides a representation of the particle size distribution (PSD), particle counts and particle dimension information.






**Raman to detect polymorphs:**

Raman scattering is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. Raman spectroscopy relies upon inelastic scattering (Raman scattering) of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. Infrared spectroscopy yields similar, but complementary, information. Typically, a sample is illuminated with a laser beam. Light from the illuminated spot is collected with a lens and sent through a monochromator. Wavelengths close to the laser line, due to elastic Rayleigh scattering, are filtered out while the rest of the collected light is dispersed onto a detector.

The Raman effect occurs when light impinges upon a molecule and interacts with the electron cloud of the bonds of that molecule. The incident photon excites one of the electrons into a virtual state. For the spontaneous Raman effect, the molecule will be excited from the ground state to a virtual energy state, and relax into a vibrational excited state, which generates Raman scattering.

*Could also have selected NIR to monitor solution concentration.*

**b)**

**FBRM & Raman Application to Crystallisation Monitoring:**

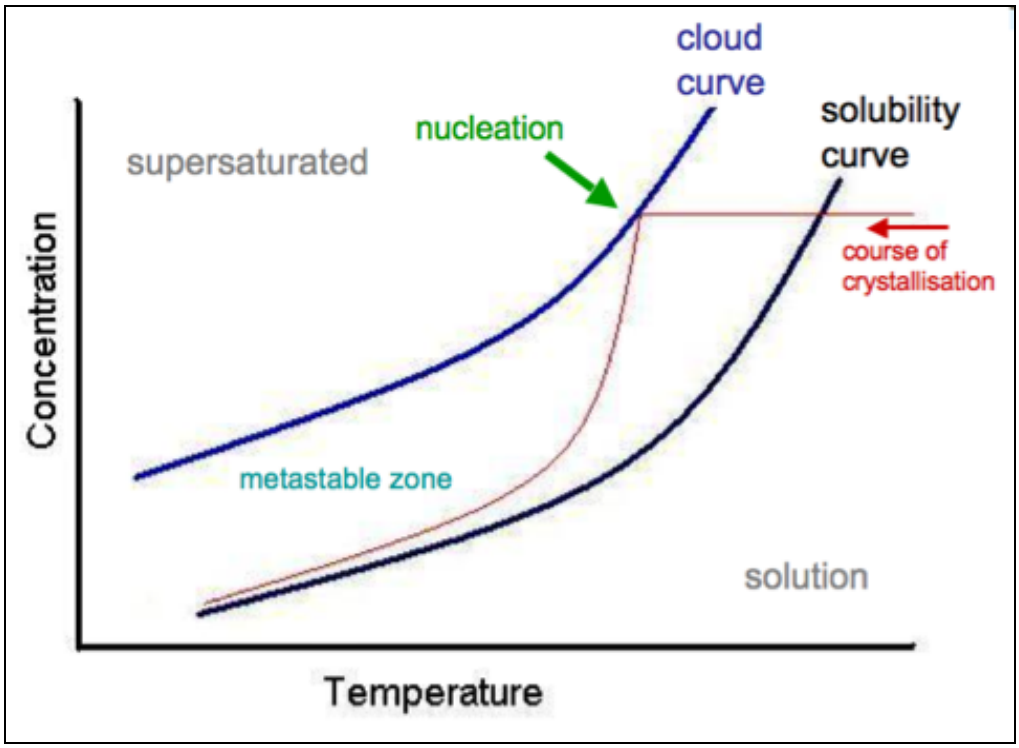
Batch crystallization is widely used for the separation and purification of solids. A well designed batch crystallization process can be scaled successfully to production scale, giving the desired crystal size distribution, yield and purity. Before this scale-up can be successful, understanding the kinetics of the crystallization process and the impact of process variables, such as temperature and mixing, on the process is key. The use of in-process particle dimension and shape instruments, allows direct measurement of crystals in the crystallizer, removing the need for sampling which can be unrepresentative. By measuring in process, one has a quantitative picture of the whole process and can have an immediate impact by helping:

- Maximize product yield
- Increase throughput
- Assure crystal quality and purity
- Design robust operating conditions
- Eliminate downstream processing bottlenecks (e.g. filtration probems)
- Meet final crystal dimension specifications consistently
- Ensure a smooth scale-up from laboratory to production

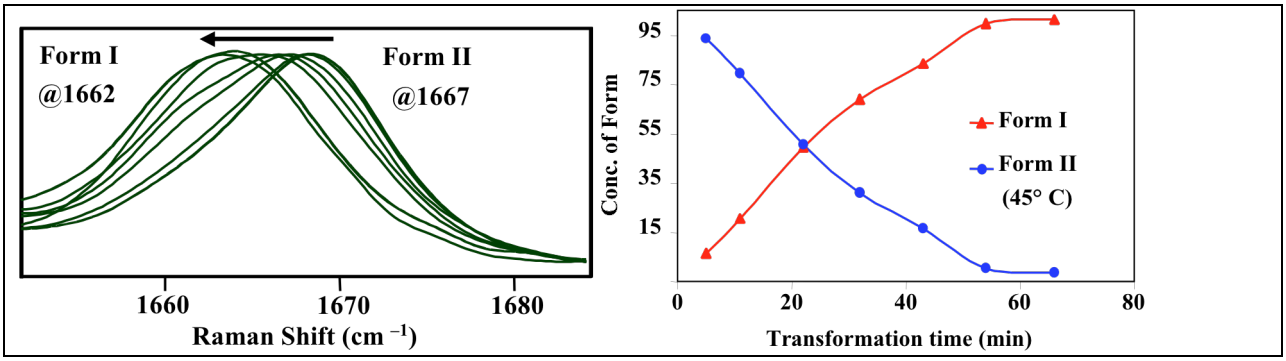
FBRM has become an industry standard for gaining understanding with respect to the crystallistion process from the development laboratory through pilot studies to full scale production. It is possible to use the same analytical machine in lab vessels as in full-scale vessels. In order to successfully scale-up a crystallization process two important properties of the system need to be understood:

- Nucleation
- Growth

In order to determine the primary data for any crystallization process it is recommended to determine these properties at lab-scale by means of deriving a plot of the metastable zone. This plot (as illustrated in the figure below) consists of a nucleation curve and a supersolubility (or cloud) curve. The difference between these lines in the metastable zone. Crystal growth is maintained in a control state by ensuring that the process follows a path downwards through this region. Failing to do this can result in unexpected crystal habits, undesirable polymorphs or difficult to isolated crystals. Scale-up exacerbates the non-robust nature of many crystallization processes. This is why using an in-line particle size technique (such as FBRM) can prove so vital in developing crystallistion processes. FBRM has the ability to detect the onset of nucleation (primary or secondary events). FBRM can also track the realtime growth of crystals in a suspension. This offers the ability to determine the effect of scale-up or process changes on the crystallisation process behaviour.




In addition to tracking particle size, it is also frequently important to monitor the polymorph generated in a crystallization process. Nucleation can result in the formation of different polymorphic forms of the same compound. In addition polymorphic transformations are not uncommon following nucleation. A key feature of Raman spectroscopy is its ability to determine differences in polymorphic forms of the same compound. The following figure illustrates an example whereby this raman could be applied to track the polymorphic conversion in a crystallization process.




**c)**

Process analysis can be performed in a number of ways, namely:

In-line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive.

On-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream, e.g. using a pump in a loop.

At-line: Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.

Off-line: The traditional in process control (IPC) approach of taking grab samples and analysing in a laboratory removed from the plant.

Clearly for the truest measure of what is happening in situ, while also being highly responsive the following hierarchy is preferable:

## In-line > On-line > At-line > Off-line

The FBRM probe should be installed in an area of good fluid flow and at an angle to this flow. This will provide a continual fresh supply of material to the sample window, in addition to facilitating cleaning of the window. Probes of varying lengths are available or it is possible to install in a dip pipe. Locating near the agitator in the area of maximum mixing is most desirable.

Raman can be installed in a number of ways. For example:

- Dip-pipe from vessel top.
- Through sidewall of vessel.
- Recirculation loop.
- Withdraw to sampler on vessel top.

**Q2.**
Consider the four principal spectroscopic techniques utilised in PAT.

a. Name four categories of spectroscopic technique. Provide a short paragraph describing each of these (35 marks).
b. Briefly describe a common industrial applications for each these in a pharmaceutical process (30 marks)
c. Describe the relative merits and limitations of these techniques as they apply to installations in plant vessels (35 marks).

**a)**

**Mid-IR:**

If infra-red (IR) light is shone through a sample of an organic compound some frequencies get absorbed by the compound. A detector on the other side of the compound would show that some frequencies pass through the compound with almost no loss, but other frequencies are strongly absorbed. How much of a particular frequency gets through the compound is measured as percentage transmittance. A transmittance of 100% would mean that all of that frequency passed straight through the compound without any being absorbed. In practice, that never happens: there is always some small loss, giving a transmittance of perhaps 95% as the best you can achieve. A transmittance of only 5% would mean that nearly all of that particular frequency is absorbed by the compound. A very high absorption of this sort tells you important things about the bonds in the compound.

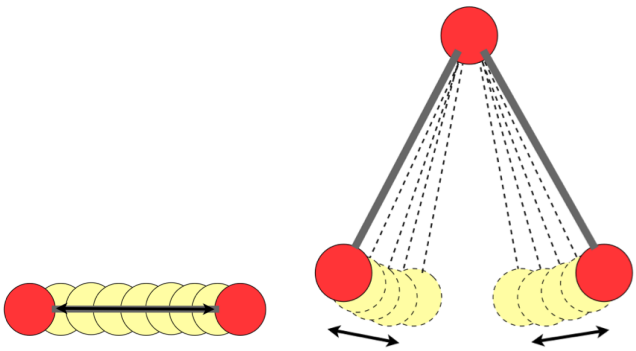
Each frequency of light (including infra-red) has a certain energy. If a particular frequency is being absorbed as it passes through the compound being investigated, it must mean that its energy is being transferred to the compound. Energies in infra-red radiation correspond to the energies involved in bond vibrations.

Near Infra-Red

Near-infrared (NIR) spectroscopy and imaging are capable of providing nondestructive and fast analysis of chemical and physical properties of a wide range of material types. In combination with multivariate data analysis these two methods open many interesting perspectives for both qualitative and quantitative analysis. Currently, NIR is used in both off-line and in-line applications in different pharmaceutical industrial process control applications.

Near infrared (NIR) is the region of the electromagnetic spectrum extending from 780 – 2 500 nm (12 800 – 4 000 cm-1). Different atomic and molecular groupings absorb characteristic wavelength "fingerprints" in the infrared region.

NIR spectra are primarily the consequences of overtones and combinations of the many fundamental absorption bands of the mid and far infrared regions. The overtones are anharmonic, which makes NIR spectra complex and overlapping. Anharmonicity is the deviation of a system from being a harmonic oscillator. Due to energy considerations, most of the overtones found in the NIR spectrum arise from the X–H stretching modes (O–H, C–H, S–H and N–H). Being quantum mechanically forbidden transitions, the overtones represent a 10 to 1000 times weaker band, than the fundamental mid-IR vibrational bands. The absorption in the infrared region is a result of molecular vibrational and rotational states. The background of vibrational spectroscopy is the concept that atom-to-atom bonds within molecules vibrate with frequencies that may be described by the laws of physics and are, therefore, subject to calculation. When the material comes into contact with radiation, it absorbs energy and is excited to a higher energy level. The difference in the energetic state of the material may be described by quantum mechanical calculations.



*Stretching and vibrational models of molecules.*

**Raman**

Raman scattering is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. Raman spectroscopy relies upon inelastic scattering (Raman scattering) of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. The shift in energy gives information about the phonon modes in the system. Infrared spectroscopy yields similar, but complementary, information. Typically, a sample is illuminated with a laser beam. Light from the illuminated spot is collected with a lens and sent through a monochromator. Wavelengths close to the laser line, due to elastic Rayleigh scattering, are filtered out while the rest of the collected light is dispersed onto a detector.

Spontaneous Raman scattering is typically very weak, and as a result the main difficulty of Raman spectroscopy is separating the weak inelastically scattered light from the intense Rayleigh scattered laser light.

The Raman effect occurs when light impinges upon a molecule and interacts with the electron cloud of the bonds of that molecule. The incident photon excites one of the electrons into a virtual state. For the spontaneous Raman effect, the molecule will be excited from the ground state to a virtual energy state, and relax into a vibrational excited state, which generates Raman scattering.

**UV**

According to the Beer-Lambert Law, absorbance is proportional to concentration, and so one would expect a straight line. That is true as long as the solutions are dilute. Despite UV spectrometers being very commonly used in a range of off-line analytical applications, only limited use is made of this technique in-line. An offline straight line correlation is first developed in which absorbance is plotted versus concentration for a range of solutions of known concentration. For each solution, measure the absorbance at the wavelength of strongest absorption.

**b)**

*A very wide range of answers are possible in this section.*

**mid-IR for Reaction Monitoring**

The manufacture of API involves performing a series of synthetic chemical reactions. Traditionally at production scale the end point of reaction is determined by a single off-line analytical test. No information is gathered during the process. Indeed, the reaction has either already succeeded or failed by the time the result is obtained. Chemical reactions are quite often complex and may involve a number of intermediates. mid-IR offers the ability to potentially view real time trends for raw materials, intermediates, reaction products and undesirable byproducts. This is also a powerful tool during the development stage of a process from lab through scale-up to full-scale production.

Before mid-IR can be applied to a process, an initial scan must be performed in order to determine what wavelengths are responsive to changes in reaction components. This may involve a lab test whereby the reaction is performed and data then analysed. Alternatively this may be supplemented with spiking experiments, whereby the reaction components are introduced to a solution in order to see if changes in wavelength occur.

**NIR Raw Material Identification:**

NIR is capable of the chemical identification of raw materials in real-time without the need for sample preparation. Identification involves the recording of the spectrum of an unknown sample and the comparison of its spectrum to a reference one. A decision is made on the identity of the unknown applying a spectral reference library approach. Raw materials such as API for use in tabletting or the bulk solvents for chemical sythesis can all be identified in this manner. Testing can be performed at the point of arrival or point of use for any material. The analysis need not be performed by a trained analytical scientist. As NIR is not sensitive to many transparent plastic packaging materials and glass, it may be possible to perform the tests through sample bags without the need for potential exposure to hazardous material.

**Raman monitoring of crystallizations:**

It is frequently important to monitor the polymorph generated in a crystallization process. Nucleation can result in the formation of different polymorphic forms of the same compound. In addition polymorphic transformations are not uncommon following nucleation. A key feature of Raman spectroscopy is its ability to determine differences in polymorphic forms of the same compound. The following figure illustrates an example whereby this raman could be applied to track the polymorphic conversion in a crystallization process.

Raman can also be used to monitor the substrate concentration in the crystalllisation solution. This provides a means of tracking the rate of crystallisation as the solid precipitates.

**UV for Cleaning Monitoring**

One process application in which UV finds use is in the on-line monitoring of API residue in cleaning solvent. Typical cleaning of a process vessels involves circulating heated solvent in a loop. The ability to monitor this concentration in real time permits evaluation of the success, or otherwise, of the solvent dissolution of the residual compound in the vessel.

**c)**

*Much of the answer to this question is captured in the table below. In addition the answer to this question should capture such topics as:*

- *Cost*

- *Use of fibre optics (e.g. NIR is most favourable here)*
- *Range of data available (e.g. UV only good for low concentrations; Raman good for polymorphs, etc.)*
- *Ease of building models (e.g. mid-IR easier than multivariate NIR)*
- *Interference from ambient light (a problem for UV an Raman)*

| | Near IR | Mid IR | Raman | UV/Vis |
|---|---|---|---|---|
| Spectral Range (cm-1) | 12,800-4,000 | 4,000-400 | 4,000-50 | 105-5,000 |
| Information Content | Bonds with dipole moments. Predominantly O-H, N-H, C-H vibrations, though other bonds may be observed. | Bonds with dipole moments. More info than NIR (i.e. not just O-H, N-H, C-H). | Bonds must contain weak dipole moment (polarisable). Bonds observed are non-polar. | Absorption process resulting from electron transitions. |
| Polymorph Detection? | 😐 | 😐 ☹ | ☺ ☺ ☺ | ☹ |
| Spectrum Interpretation | 😐 Spectra broad + overlapping. Chemometrics essential | ☺ Spectra interpreted by functional groups. | ☺ Spectra interpreted by functional groups. | ☹ Broad peaks. Poor chemical discrimination. |
| Aqueous Systems? | ☹ | ☹ ☹ | ☺ | ☺ |
| Fibre Optic Interface? | ☺ | ☹ 😐 | ☺ | 😐 |
| Cost Rating | € € | € € € | € € € € | € |

**Q3.**
Describe two analytical techniques which can be applied to monitor the drying of pharmaceutical material. Make use diagrams where appropriate.

a. Describe how these techniques work and what they measure. (40 marks)
b. Describe the relative merits and limitations of these techniques (30 marks).
c. Describe how a drying correlation is developed from spectroscopic data. (hint: chemometrics) (30 marks)

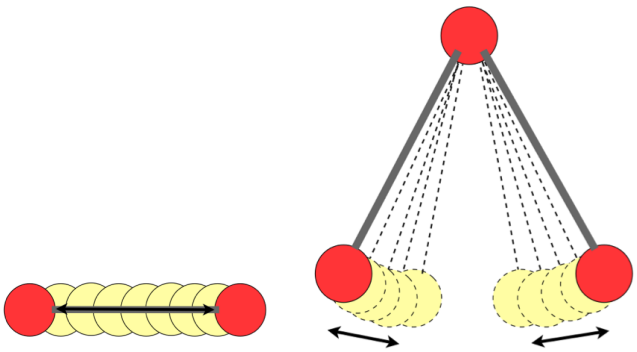
**a)**

Near Infra-Red

Near-infrared (NIR) spectroscopy and imaging are capable of providing nondestructive and fast analysis of chemical and physical properties of a wide range of material types. In combination with multivariate data analysis these two methods open many interesting perspectives for both qualitative and quantitative analysis. Currently, NIR is used in both off-line and in-line applications in different pharmaceutical industrial process control applications.

Near infrared (NIR) is the region of the electromagnetic spectrum extending from 780 – 2 500 nm (12 800 – 4 000 cm-1). Different atomic and molecular groupings absorb characteristic wavelength "fingerprints" in the infrared region.

NIR spectra are primarily the consequences of overtones and combinations of the many fundamental absorption bands of the mid and far infrared regions. The overtones are anharmonic, which makes NIR spectra complex and overlapping. Anharmonicity is the deviation of a system from being a harmonic oscillator. Due to energy considerations, most of the overtones found in the NIR spectrum arise from the X–H stretching modes (O–H, C–H, S–H and N–H). Being quantum mechanically forbidden transitions, the overtones represent a 10 to 1000 times weaker band, than the fundamental mid-IR vibrational bands. The absorption in the infrared region is a result of molecular vibrational and rotational states. The background of vibrational spectroscopy is the concept that atom-to-atom bonds within molecules vibrate with frequencies that may be described by the laws of physics and are, therefore, subject to calculation. When the material comes into contact with radiation, it absorbs energy and is excited to a higher energy level. The difference in the energetic state of the material may be described by quantum mechanical calculations.



*Stretching and vibrational models of molecules.*

**Mass Spectrometry**

If something is moving and you subject it to a sideways force, instead of moving in a straight line, it will move in a curve, deflecting from its original path due to the sideways force.

The extent to which the moving object deflects is dependent upon its mass. If you knew the speed of the object and the size of the force exerted, you could calculate the mass of the object. The less the deflection, the heavier the object. The exact same principal can applied to atomic sized particles.

Atoms can be deflected by magnetic fields, provided the atom is first turned into an ion. Electrically charged particles are affected by a magnetic field although electrically neutral ones aren't.

The sequence is as follows:

***Stage 1: Ionisation***

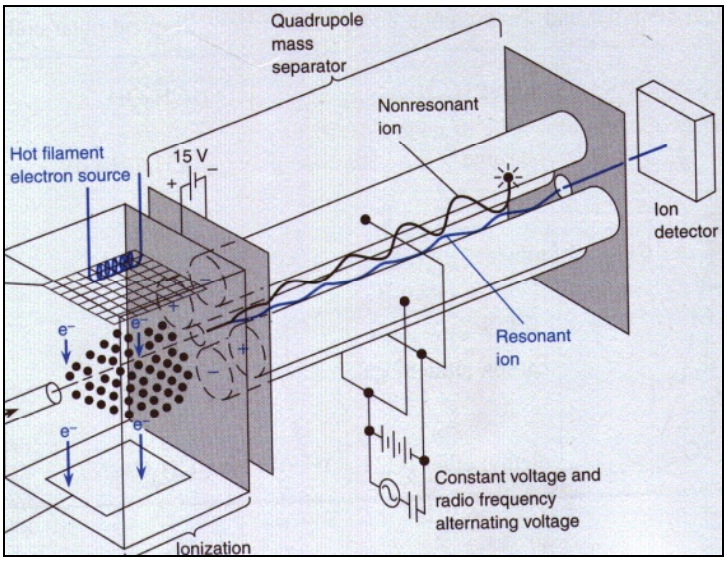
This serves to convert neutral gas molecules and atoms to positive ions. The atom is ionised by knocking one or more electrons off to give a positive ion. This is true even for things which you would normally expect to form negative ions (chlorine, for example) or never form ions at all (argon, for example). Mass spectrometers always work with positive ions.

***Stage 2: Mass Filter***

This separates the ions produced in the ion source.

***Stage 3: Detection***

The beam of ions passing through the machine is detected electrically.




**b)**

**NIR**

NIR has a number of advantages:

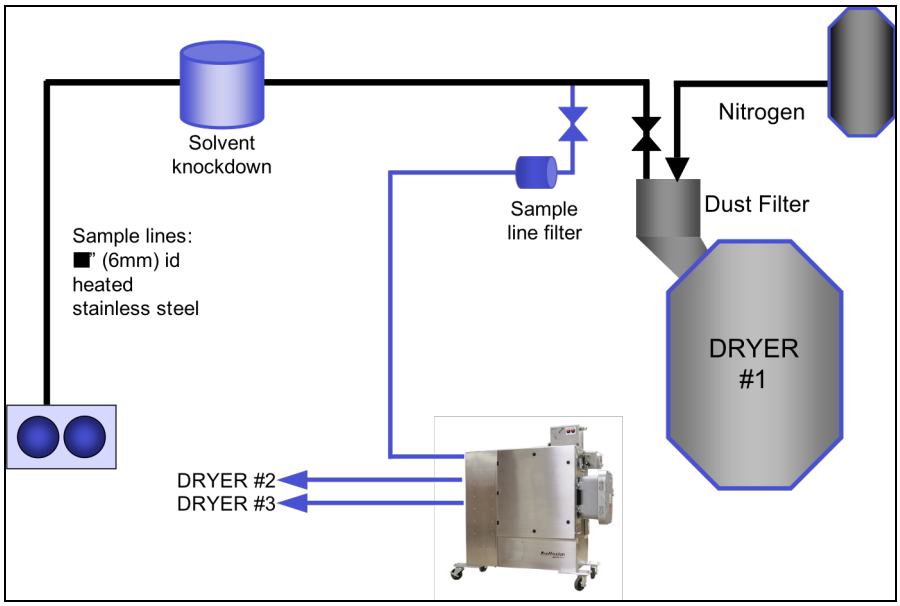
- As the NIR probe is in direct contact with the solid material in the dryer, this technique provides a direct measurement of the solvent present in the cake.

- The multivariate chemometric techniques employed in developing a correlation will ignore the influence of such process variables: as particle size, temperature, gas flowrate etc.
- Fibre optics of reasonable length can be used in order to facilitate remote location of the spectrometer.
- One spectrometer unit can be used for several probes.

The disadvantages of NIR include:

- Knowledge of chemometrics required.
- Analysis is based on a correlation against traditional off-line analysis (e.g. KF), and as such can never provide greater accuracy than the primary analytical technique.
- Probes can be prone to fouling (though purged or removable options are available).

An example of how a typical mass spec set-up might look is illustrated below. Note that a single analyzer can be configured to monitor a range of dryers in the same facility. The lines between the dryer and mass spec analyser require heat tracing in order that the evaporated solvent remains in the vapour phase.




*Mass spectrometer plant installation.*

Mass Spec advantages:

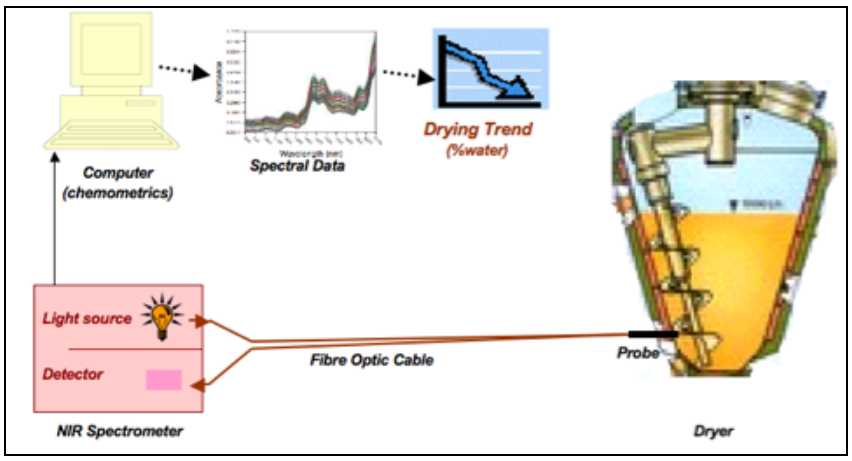
- Easy to use. Does not require chemometric model development.

Mass Spec disadvantages:

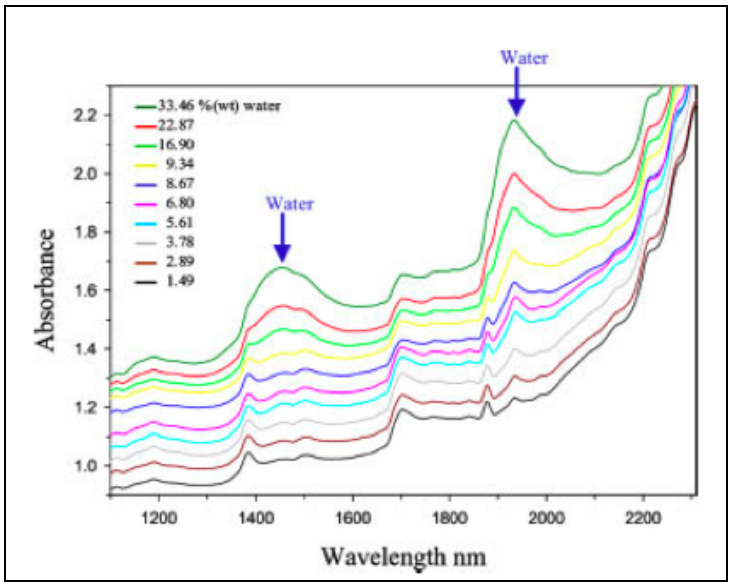
- Not a direct measurement technique, as is looking at off-gas rather that product itself.
- Influenced by variation in gas flowrate to dryer.
- Possibility of false positive results should gas flow rate drop.
- Heat tracing required on lines to prevent condensation of solvent.
- Attention should be paid to the potential for mass spectrometer peaks to overlap. For example, the mass spectrum of one of the fragments of nitrogen has the potential to occur at the same mass (28) as carbon monoxide.

**c)**

Developing an NIR method for monitoring solvent in a wet cake involves the building a correlation against the off-line analytical technique (e.g. KF or HPLC). A PLS (Partial least squares) chemometric model is determined which then permits a regression model to be derived. Once implemented the operator will be provided with a simple univariate trend for moisture content.




*NIR dryer monitor schematic.*




*NIR spectra for samples with different water content.*

Partial Least Squares (PLS) is the chemometric technique most frequently used for the developing linear type relationships to a particular process or product quality (e.g. water or solvent content). Building a correlation involves removing a series of samples from a dryer for a number of batches. Analysis is performed on these using a traditional primary technique (e.g. HPLC, KF). NIR spectra from each of these sample instances is then used in a chemometric software package in order to build a correlation against the off-line technique.

The principal steps involved in building a PLS correlation might include the following:

- Spectral Region Selection
- Data Preprocessing
- Determining the Number of Factors for the Model:

Spectral Region Selection:

One of the best features of factor analysis-based models is the ability to use the entire spectrum for building a calibration. This gives advantages over other methods, mainly, the averaging effect of using a large number of data points makes more robust calibrations, and the ability to build models with little or no prior knowledge of the spectra of the constituents of interest. When setting up a chemometric model, it is very easy to simply select the entire range of the training spectra as the set of data to use for calibration. The PLS model will certainly be able to figure out the regions in the spectra that are most important for calibration based on the information in the training set. However, the performance of the calibrations can usually be improved by some intelligent masking of regions which are obviously useless. Selecting regions where it is known peaks for the solvent of interest reside will facilitate model development.

Data Preprocessing:

One of the major problems in applying chemometric models to spectra is the fact that the acquired spectrum of a sample is dependent on many different, sometimes uncontrollable, factors. For example, samples of powdered solids are usually measured by diffuse reflectance. Light scattering off the particles causes every spectrum, even of remeasurements of the same sample, to look a little bit different due to the particle size distribution and alignment with the incident beam of light. While the quantitative information related to the constituents is still contained within the spectral data, it may not be immediately apparent. Chemometric models can sometimes correct for these effects by adding extra loading vectors, but generally, the models will perform better if they can be removed or at least minimized before running the data through the calculations. Since they are applied to the data before it is used in the model, they are often called Preprocessing Algorithms.

There are a variety of methods that can be used to remove the non-constituent related aberrations in the data. Most algorithms are targeted at removing a specific interference (Multiplicative Scatter Correction, MSC, for example, specifically attempts to remove the effects of light scattering). Other preprocessing techniques include baseline correction and performing derivatives.

Determining the Number of Factors for the Model:

One of the most difficult tasks in using PLS is determining the correct number of loading vectors (factors) to use to model the data. As more and more vectors are calculated, they are ordered by the degree of importance to the model. Eventually the loading vectors will begin to model the system noise (which usually provides the smallest contribution to the data).

**Q4.**
The FDA describe four primary categories of PAT tool. Describe each of these in turn providing the following information:

a. Briefly describe two examples (or sub categories) within each category. (50 marks)
b. Describe how each of these tools help improve product quality. (40 marks)
c. List five potential motivations for the initiation of a PAT project. (10 marks)

**a) Pat Tools Categories and examples**

In the FDA PAT framework, the PAT tools can be categorized according to the following:

· Multivariate tools for design, data acquisition and analysis
· Process analyzers
· Process control tools
· Continuous improvement and knowledge management tools

***Multivariate tool, Example 1: DOE***

DOE is a systematic approach to investigation of a system or process. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a pre-defined output are then assessed.

DOE is important as a formal way of maximizing information gained while minimizing the resources required. It has more to offer than 'one change at a time' experimental methods, because it allows a judgement on the significance to the output of input variables acting alone, as well input variables acting in combination with one another.

***Multivariate tool, Example 2: Chemometrics***

The word chemometrics means the performance of calculations on measurements of chemical data. Most recently the common usage of the word refers to using linear algebra calculation methods to make either quantitative or qualitative measurements of chemical data, primarily spectra.

***Analyser tools:***

Available tools have evolved from those that predominantly take univariate process measurements, such as pH, temperature, and pressure, to those that measure biological, chemical, and physical attributes. Indeed some process analyzers provide nondestructive measurements that contain information related to biological, physical, and chemical attributes of the materials being processed. These measurements can be:

1. at-line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.

2· on-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

3· in-line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

***Control tools:***
It is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical quality attributes. Process monitoring and control strategies are intended to monitor the state of a process and actively

manipulate it to maintain a desired state. Strategies should accommodate the attributes of input materials, the ability and reliability of process analyzers to measure critical attributes, and the achievement of process end points to ensure consistent quality of the output materials and the final product.

Design and optimization of drug formulations and manufacturing processes within the PAT framework can include the following steps (the sequence of steps can vary):

1· Identify and measure critical material and process attributes relating to product quality

2· Design a process measurement system to allow real time or near real time (e.g., on-, in-, or at-line) monitoring of all critical attributes

3. Design process controls that provide adjustments to ensure control of all critical attributes

4· Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes

***Improvement & Management, Example 1:***

Risk-Based Approach

Within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product. For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change (e.g., no need for a regulatory submission). Thus, a focus on process understanding can facilitate risk-based regulatory decisions and innovation. Note that risk analysis and management is broader than what is discussed within the PAT framework and may form a system of its own.

***Improvement & Management, Example 2:***

Real Time Release

Real time release is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data. Typically, the PAT component of real time release includes a valid combination of assessed material attributes and process controls. Material attributes can be assessed using direct and/or indirect process analytical methods. The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes. The FDA consider real time release to be comparable to alternative analytical procedures for final product release.

**b) Improved Quality**

***Multivariate tools:***

From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many development strategies that can be

used to identify optimal formulations and processes. The knowledge acquired in these development programs is the foundation for product and process design. This knowledge base can help to support and justify flexible regulatory paths for innovation in manufacturing and postapproval changes.

When used appropriately, these tools enable the identification and evaluation of product and process variables that may be critical to product quality and performance. The tools may also identify potential failure modes and mechanisms and quantify their effects on product quality.

***Analyser tools:***

Process analyzers typically generate large volumes of data. Certain data are likely to be relevant for routine quality assurance and regulatory decisions. In a PAT environment, batch records should include scientific and procedural information indicative of high process quality and product conformance. For example, batch records could include a series of charts depicting acceptance ranges, confidence intervals, and distribution plots (inter- and intrabatch) showing measurement results. Ease of secure access to these data is important for real time manufacturing control and quality assurance. Installed information technology systems should accommodate such functions.

Measurements collected from these process analyzers need not be absolute values of the attribute of interest. The ability to measure relative differences in materials before (e.g., within a lot, lot-to-lot, different suppliers) and during processing will provide useful information for process control. A flexible process may be designed to manage variability of the materials being processed. Such an approach can be established and justified when differences in quality attributes and other process information are used to control (e.g., feed-forward and/or feed-back) the process.

***Control tools***

Where PAT spans the entire manufacturing process, the fraction of in-process materials and final product evaluated during production could be substantially greater than what is currently achieved using laboratory testing. Thus, an opportunity to use more rigorous statistical principles for a quality decision is provided. Rigorous statistical principles should be used for defining acceptance criteria for end point attributes that consider measurement and sampling strategies. Multivariate Statistical Process Control can be feasible and valuable to realizing the full benefit of real time measurements. Quality decisions should be based on process understanding and the prediction and control of relevant process/product attributes.

Systems that promote greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to demonstrate validation, i.e. production and process controls are designed to ensure quality. In a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.

**Continuous Improvement and Knowledge Management**

Continuous learning through data collection and analysis over the life cycle of a product is important. These data can contribute to justifying proposals for postapproval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the Agency.

Opportunities need to be identified to improve the usefulness of available relevant product and process knowledge during regulatory decision making. A knowledge base can be of most benefit when it consists of scientific understanding of the relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes) as well as a means to evaluate the applicability of this knowledge in different scenarios (i.e., generalization). Today's information technology infrastructure makes the development and maintenance of this knowledge base practical.

**c)**

- Lack of true process understanding
- Improve process cycle time
- Move towards real time release
- Reduce material waste
- Eliminate potential exposure to highly toxic material
- Eliminate potential batch contamination
- Control critical quality attributes
- Improve response time to process problems