

In Pharmaceuticals, Quality Assurance and Control

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Abstract

In the pharmaceutical industry, Quality Assurance (QA) and Quality Control (QC) play critical roles in ensuring the safety, efficacy, and consistency of pharmaceutical products. Quality Assurance refers to the proactive, system-wide approach that focuses on preventing defects in the manufacturing process by adhering to regulatory standards and guidelines. This includes the establishment of standard operating procedures (SOPs), training, audits, and risk management practices. In contrast, Quality Control is a reactive function that involves the testing, inspection, and verification of raw materials, in-process materials, and finished products to ensure they meet predefined specifications. Together, QA and QC provide a framework that ensures compliance with Good Manufacturing Practices (GMP) and international regulatory requirements, thus safeguarding public health. This paper explores the interplay between QA and QC, emphasizing the importance of integrating both functions into the pharmaceutical development cycle to guarantee high-quality products while maintaining efficiency in production.

The integration of various instruments and analytical techniques is crucial for both QA and QC processes. Instruments such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), UV-Vis Spectrophotometers, Mass Spectrometers, and Dissolution Apparatus are widely used for quality testing. These instruments allow for the precise measurement of active ingredients, the identification of impurities, and the determination of physical properties such as dissolution rates, which are vital for product performance.

Advanced instruments like Automated Microbial Testing Systems and Particle Size Analyzers are also used to ensure sterility and the correct formulation of dosage forms. By incorporating sophisticated instruments into the pharmaceutical QA and QC processes, manufacturers can achieve greater accuracy, consistency, and efficiency, leading to the production of pharmaceutical products that consistently meet regulatory requirements and ensure patient safety.

This paper highlights the role of QA and QC in the pharmaceutical industry, focusing on the critical instruments used in these processes, and discusses the impact of these technologies in maintaining high standards of product quality and regulatory compliance.

Keyword- Equipments HPLC, UV Visible Spectroscopy, Tablet Compression equipment, FBD, Dissolution equipment

INTRODUCTION TO THE QUALIFICATION OF HPLC EQUIPMENT

Equipment qualification is a formal process that provides documented evidence that an instrument is fit for its intended use and kept in a state of maintenance and calibration consistent with its use. The entire qualification process consists of four parts:

- Design qualification (DQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

References offer comprehensive guidance on general definitions, overall objectives, and the selection of appropriate parameters and criteria for each qualification step. The type of equipment and its intended use dictate the specific procedures and the frequency of necessary certifications. This article focuses on the qualification procedures for HPLC systems, while also touching on processes for qualifying other instruments such as capillaries and UV/Vis spectrophotometers. Future installments in this series will cover

the qualification of mass spectrometers and electrophoresis equipment. The primary focus of this paper is on the qualification of hardware components. Software and computerized system qualifications are discussed in the referenced materials. To ensure practical relevance, a real-life scenario from a QA/QC laboratory is used. Although the templates provided in this article can be adapted to different applications, users should customize the acceptance criteria and qualification parameters to suit their specific needs.[1]

a) Principle of HPLC

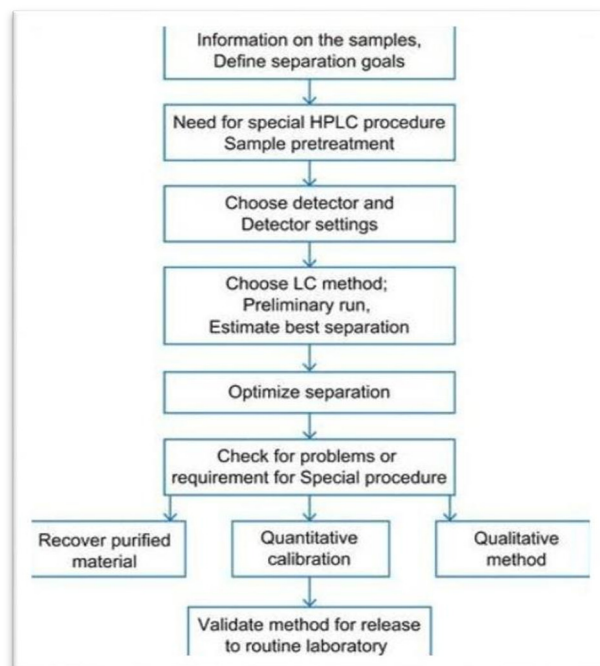
In High-Performance Liquid Chromatography (HPLC), a small amount of liquid sample is introduced into a column packed with fine particles, typically ranging from 3 to 5 microns in diameter. A high-pressure pump drives a liquid, known as the mobile phase, through the column. As the sample travels through the column, its individual components interact differently both chemically and physically with the stationary phase (the packed particles). These varying interactions cause the components to separate from each other as they move through the column.

As the separated components exit the column, their quantities are detected by a flow-through device known as a detector. The signal produced by this detector is referred to as an HPLC chromatogram. While HPLC operates on the same basic principles as traditional liquid chromatography (LC), it offers significant improvements in terms of speed, sensitivity, efficiency, and ease of use. A typical HPLC system consists of a solvent reservoir, a pump, an injector, a column, a detector, and a data processing or display system (such as an integrator or computer). Although traditional LC laid the foundation, HPLC is now the preferred method for analytical applications due to its superior performance. Basic liquid chromatography is still used for preparative purposes, as illustrated in the diagram above. The column, where the actual separation happens, is the main part of the system.[2]



Figure 1: High-Performance Liquid Chromatography (HPLC)

b) Method Development On HPLC:

**Table 1: Method Development On HPLC**

- i. Understanding the Physicochemical Properties of the drug molecule.
- ii. Selection of chromatographic conditions.
- iii. Developing the approach of analysis.
- iv. Sample preparations
- v. Method optimization
- vi. Method validation [3]

c) Parameters:

Several factors are used as standards for analyzing a particular substance accurately. Changes in these parameters can greatly affect the results. The most commonly used metrics include internal diameter, pore size, particle size, and pump pressure. These parameters can be adjusted depending on the chemical composition and properties of the substance being analyzed.

- Internal diameter:

The internal diameter (ID) of an HPLC column plays a key role in determining both the column's sensitivity and the amount of analyte it can handle. Larger ID columns are commonly used in industrial applications, such as purifying pharmaceutical products for later use. In contrast, smaller ID columns enhance sensitivity and minimize solvent consumption, although they have a lower sample loading capacity.

- Particle size:

In most traditional HPLC methods, the stationary phase is usually bonded to the surface of small, spherical silica particles (tiny beads). While using smaller particles generally improves separation efficiency and provides a larger surface area, it also requires significantly higher pressure, as the optimal linear velocity increases with the inverse square of the particle diameter.

- Pore size:

To enhance surface area, many stationary phases are designed to be porous. Larger pores provide better kinetic performance, especially for larger analytes, while smaller pores contribute to a greater overall surface area. The pore size is crucial because it influences how effectively analyte molecules can penetrate the particle and interact with its internal surface. This is particularly important given that the ratio of external to internal surface area is roughly 1:1000, meaning most molecular interactions occur within the interior of the particle.

- Pump pressure:

While the pressure capabilities of pumps can differ, their effectiveness is typically assessed by their ability to deliver a consistent and repeatable flow rate. Advances in modern HPLC systems have enabled them to function at significantly higher pressures, allowing for the use of much smaller particle sizes often less than

2 micrometers in the columns.[3]

d) Advantages:

1. HPLC's widespread use in science is no coincidence. Its main strength lies in its versatility, as it can analyze a wide range of substances, from tiny natural atoms and particles to large proteins and polymers.
2. Using an HPLC lab can lead to the production of better products, provide deeper insights into competitors' offerings, and allow for the resolution or postponement of product reviews.

e) Disadvantage:

1. HPLC can be an expensive technique.
2. It demands a power source, various costly reagents, and regular upkeep.
3. Identifying problems or creating new methods can be complex.[4]

f) Application:

1. Pharmaceutical Applications: HPLC is used for quality control, studying dissolution, and managing medication stability.
2. Environmental Applications: It helps in identifying structures, monitoring unknown pollutants, and analyzing components in drinking water.
3. Forensic Applications: HPLC is employed to measure drug and steroid concentrations in biological samples, as well as to analyze textile dyes.[5]

g) Conclusion:

Method development and validation are ongoing, interconnected processes that ensure accurate measurement and define the limits of measurement performance. The selectivity of the separation process is largely influenced by the organic content and pH of the buffer and mobile phase. HPLC technology is recognized for its high selectivity, sensitivity, low detection limit, and cost-efficiency. Furthermore, parameters such as gradient slope, temperature, flow rate, and the type and concentration of mobile-phase modifiers can be optimized. As per ICH guidelines, the refined method is validated based on various factors, including specificity, precision, accuracy, detection limit, and linearity.[6]

INTRODUCTION TO THE QUALIFICATION OF UV-VISIBLE SPECTROSCOPY

Ultraviolet-Visible (UV-Vis) spectroscopy is a versatile analytical method commonly used in areas such as pharmaceuticals, environmental monitoring, food safety, and chemical analysis. It works by measuring the absorbance or transmission of UV and visible light through a sample, offering important insights into its molecular structure and concentration. UV-Vis spectroscopy plays a key role in quantitative analysis, enabling the determination of analyte concentrations in solutions using Beer-Lambert's law.

a) Phases of Qualification:

I. Installation Qualification (IQ):

Objectives: The purpose of IQ is to ensure that the spectrophotometer is correctly installed and meets the manufacturer's specifications.

Activities: This phase involves verifying the installation environment, confirming that all necessary components are present, and ensuring the instrument is calibrated according to the manufacturer's guidelines. Relevant documentation, such as installation records and equipment manuals, is also reviewed.

II. Operational Qualification (OQ):

Objectives: The goal of OQ is to demonstrate that the instrument functions correctly and consistently under normal operating conditions.

Activities: In OQ, tests are carried out to assess parameters like wavelength accuracy, photometric accuracy, linearity, and noise levels. Acceptance criteria are defined for each parameter to ensure that the instrument operates within the specified limits.

III. Performance Qualification (PQ):

Objectives: PQ ensures that the UV-Vis spectrophotometer performs reliably and accurately with real samples in typical laboratory conditions.

Activities: This phase generally includes analyzing standard solutions and sample matrices to evaluate parameters such as precision, sensitivity, and detection limits. Long-term stability testing may also be conducted to assess the instrument's performance over an extended period.

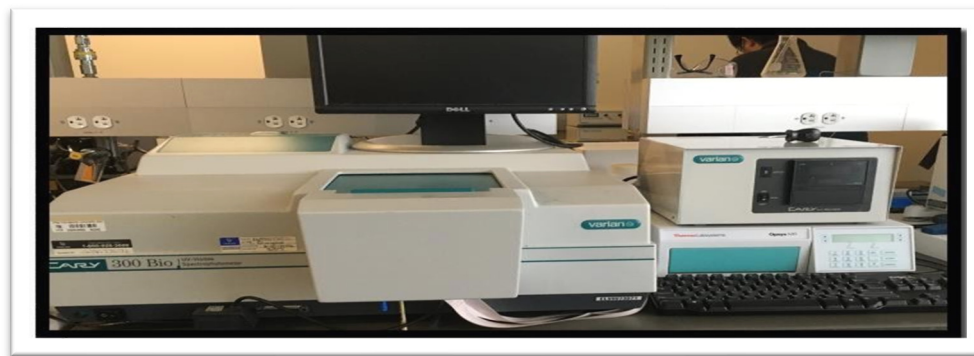


Figure 2: UV-Visible Spectroscopy

UV-Visible Spectroscopy

Spectroscopy Methods: This is a branch of research that investigates the interaction between matter and electromagnetic radiation. It serves as one of the most powerful techniques for examining atomic and molecular structures and is used across a wide range of sample analyses. Optical spectroscopy encompasses the portion of the electromagnetic spectrum that spans from 100 Å to 400 μm. The electromagnetic spectrum is divided into several regions, including:

Table 2: Electromagnetic spectrum

ICH Guidelines (ICHQ2R1) for Analytical Procedure and Validation:

The method used for analysis is referred to as the analytical technique. The procedures needed to perform each

Region	Wavelength
Far (or vacuum) ultraviolet	10-200nm
Near ultra violet	200-400nm
Visible	400-750nm
Near infra-red	0.75-2.2 μm
Mid infra-red	2.5-50μm
Far infra-red	50-1000μm

analytical test should be clearly detailed. This may include, but is not limited to: the sample, preparation of the reference standard and reagents, use of the equipment, creation of the calibration curve, application of calculation formulas, and more.

a) Types of Analytical Procedures to be Validated: ICH Guidelines (ICHQ2R1) for Analytical Procedure and Validation:

The method used to carry out the analysis is referred to as the analytical technique. The procedures required to carry out each analytical test should be thoroughly explained. This might involve, but not be restricted to: the sample, the preparation of the reference standard and the reagents, the usage of the equipment, the creation of the calibration curve, the application of the calculation formulas, etc.

Types of Analytical Procedures to be validated: The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests
- Quantitative tests for impurities 'content
- Limit tests for the control of impurities [7]

b) System Suitability

- Method validation and system suitability are distinct concepts. System suitability is used to evaluate the performance of the components of an analytical system, ensuring that it meets the requirements of

the method. System suitability tests are performed regularly on a specific system to verify its effectiveness, while method validation occurs only after method development is completed. Unlike chromatography systems, UV-visible spectroscopy systems currently lack a well-established system suitability definition.

- To assess performance, a single standard with a concentration equal to 100% of the expected component concentration should be used for measurement and calibration. Then, both the standard and a diluted version (50% of the original concentration) should be measured and quantified. The results of both samples should fall within a specific percentage of the known concentration. Repeating the measurement of the standard verifies the accuracy of the initial measurement. This process can be automated in the HP 8453 system by using one standard and two control samples (the standard and the 50% dilution) and setting an acceptable error range for the control samples. The system automatically flags any control result that falls outside the specified range.
- Measure the standard first, followed by a series of dilutions, and for each concentration, calculate the extinction coefficient (absorbance/concentration). The values of the extinction coefficient should not vary by more than a specified percentage. The HP 8453 system's Automation feature can be used to automatically perform this with up to three standards. One of the calibration results is the percentage deviation of each standard from the calibration curve. This percentage deviation reflects the variation in the extinction coefficient for each standard. [8]

c) Calibration and Validation Methods:

Since the spectrometer (ISA T4) does not offer a global calibration, two calibration methods were compared to evaluate the studied parameters:

- Local calibration was performed using the ISAI software, following the manufacturer's guidelines. Four wavelengths ($n = 4$) were selected for these calculations, and the MLR method served as the basis for the ISAI software.
- Local PLS calibration was carried out using a package from the R library. The collected data was divided into two sets: one for calibration (80%) and one for validation (20%). After the calibration techniques were developed, they were used to predict the new data. The robustness of the calibration function was then assessed by comparing the predicted data with the actual laboratory results (validation) [9].

d) Procedure:

In ultraviolet-visible (UV-Vis) spectrophotometers, a light source is employed to illuminate a sample with light covering the visible wavelength range, typically from 190 to 900 nm. The spectrophotometer then measures the light absorbed, transmitted, or reflected by the sample at each wavelength. Some spectrophotometers extend their wavelength range into the near-infrared (NIR) region, which spans from 800 to 3200 nm.

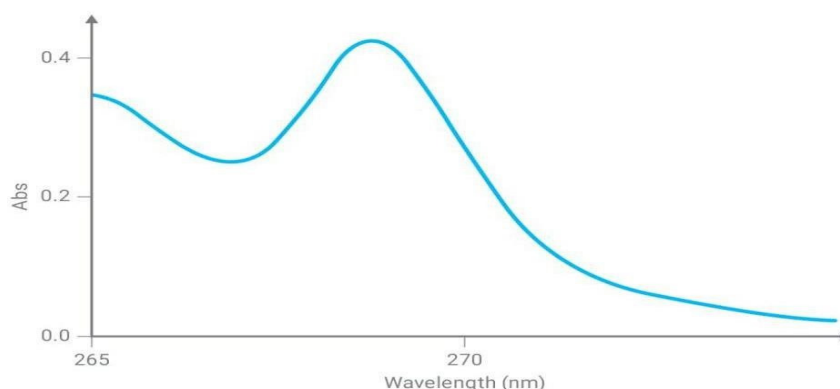


Figure 3: Absorbance Peak

A UV absorbance spectrum displaying a peak at approximately 269 nm allows for the determination of both the chemical and physical properties of a sample. Typically, this spectrum can be used to:

- Identify molecules in solid or liquid samples.
- Determine the concentration of a specific molecule in a solution.

- Characterize the absorbance or transmittance of a liquid or solid across a range of wavelengths.
- Analyze the reflectance properties of a surface or assess the color of a material.
- Study chemical reactions or biological processes.

UV-Vis spectrophotometers can be paired with various accessories and sample containers to perform a wide range of measurements. There are attachments available for different sample types (e.g., solids vs liquids), measurement settings, and capabilities. Due to its versatility, UV-visible spectrophotometry has been utilized for over a century across various industries, including biotechnology, pharmaceuticals, chemistry, petrochemicals, and material testing and research.

e) The Linear Range of a UV-Vis Instrument:

The maximum absorbance that an instrument can measure at a specific wavelength is determined by its design and the measurement settings used. As absorbance increases, the signal-to-noise ratio decreases because less light reaches the detector. By understanding the limitations of your system, you can avoid calibrations and sample measurements that fall outside its capabilities. To ensure measurements stay within the instrument's linear range, a liquid sample can be diluted. Alternatively, using a cuvette with a shorter path length can also help.

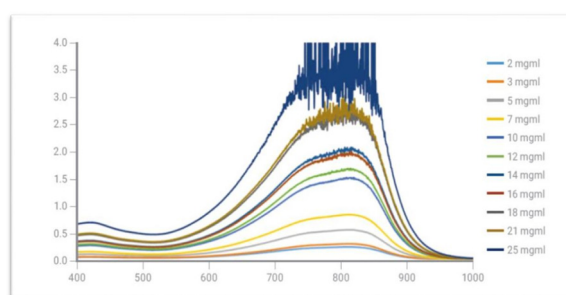


Figure 4: The Linear Range of AUV Visible

Ultraviolet/Visible (UV/Vis) spectroscopy is commonly used in analytical chemistry for both quantitative and qualitative analysis. While spectroscopic studies often focus on solutions, solids and gases can also be analyzed. The core principle of quantitative absorption spectroscopy involves using the Beer-Lambert equation to compare the absorption of a sample solution with that of a set of standards at a specific wavelength. According to the Beer-Lambert law, the absorbance of a solution is directly related to both the path length and the concentration of the absorbing species in the solution. Consider a monochromatic light beam with intensity I_0 striking a sample surface at normal incidence. As the light passes through the sample, its intensity decreases to I after traveling through a path length b , which contains N molecules per cm^3 . The Beer-Lambert law describes the relationship between light attenuation as it passes through the substance and the properties of the substance, as shown in the equation: $\frac{I}{I_0} = e^{-\sigma N b}$ [11]

f) Application:

UV-Visible Spectroscopy has many different applications:

- Detection of impurities
- Structural elucidation of organic compounds
- Quantitative analysis
- Qualitative analysis
- Chemical analysis
- Quantitative analysis of pharmaceutical substance
- Dissociation constant of acids and bases
- Molecular weight determination
- As HPLC detector
- Deviations from the Beer-Lambert law [12]

g) Conclusion:

Ultraviolet-visible spectroscopy is a cost-effective method for determining the identity, strength, quality,

and purity of substances. It involves two primary processes that enable both qualitative and quantitative analysis of samples. This technique can also be applied in areas such as wastewater treatment, kinetic studies, and ongoing monitoring by analyzing and comparing spectral data over time. UV-Visible spectroscopy is an effective tool for confirming the successful removal of certain dyes or dye by-products from wastewater. It is also highly valuable for monitoring air quality and verifying the authenticity of food products. This technique serves as an analytical method for detecting various ions, suitable for both qualitative and quantitative analysis. In addition, it has applications across a wide range of industries. Based on the information presented, it can be concluded that UV/Vis spectroscopy is a highly reliable method in analytical chemistry for the quantitative analysis of numerous analytes, including biological macromolecules, complex organic compounds with extensive conjugation, and transition metal ions. [13]

INTRODUCTION TO THE QUALIFICATION OF TABLET COMPRESSION EQUIPMENT

Tablet compression is a crucial step in pharmaceutical manufacturing, where powdered substances are compressed into solid tablet forms. This process significantly impacts the quality, effectiveness, and stability of the final product. Due to the complexity of tablet formulation and strict regulatory requirements in the pharmaceutical industry, it is essential to qualify the tablet compression equipment to ensure consistent performance.

a) Phases of Qualification

The qualification process for tablet compression equipment generally consists of three primary phases:

I. Installation Qualification (IQ):

Objective: The purpose of IQ is to confirm that the tablet compression equipment has been correctly installed in accordance with the manufacturer's guidelines.

Activities: This phase involves inspecting the installation site, verifying the presence and proper functioning of all necessary components, and confirming that the equipment is installed in a suitable environment (e.g., controlled temperature and humidity). Relevant documentation, such as equipment specifications and installation manuals, is also reviewed.

II. Operational Qualification (OQ):

Objective: The goal of OQ is to verify that the tablet press operates within predefined parameters and performs reliably during typical use.

Activities: In this stage, the equipment is tested for key operational factors such as compression force, tablet weight, thickness, and ejection force. These tests ensure the machine consistently produces tablets that meet established acceptance criteria under standard working conditions.

III. Performance Qualification (PQ):

Objective: The aim of PQ is to ensure that the tablet compression equipment consistently produces tablets that meet predefined quality standards under normal production conditions.

Activities: This phase usually includes processing actual production batches using the intended formulations and evaluating the finished tablets for key quality attributes such as dissolution rate, hardness, and content uniformity. In some cases, extended performance testing may also be carried out to confirm the equipment's reliability and consistency over time.



Figure 5: Tablet compression machine

b) Parameters:

Tablet compression machines, also known as tablet presses, are widely used in the pharmaceutical industry to compress powdered substances into solid tablets. These machines form tablets of the desired shape, size, and hardness by applying pressure to the powder blend inside a die cavity. To ensure tablet quality and consistency, it is crucial to monitor and control several key parameters. The main parameters, along with their typical reference ranges, are outlined below:

I. Compression Force (Pressure):

Definition: The amount of force exerted on the powder blend during the compression stage to form it into a tablet.

Typical Range:

Low: 5–10 kN (suitable for softer tablets)

High: 10–100 kN (used for harder tablets)

Impact on Tablets: Applying greater compression force usually leads to harder tablets; however, excessive pressure can cause issues such as capping or inconsistent tablet weight. [14]

II. Pre-Compression Force:

Definition: A preliminary, lighter force applied before the main compression to eliminate trapped air and begin consolidating the powder.

Typical Range: 5–10% of the main compression force.

Impact on Tablets: Pre-compression minimizes capping, improves uniformity, and enhances the bonding between powder particles. [15]

III. Tablet Weight:

Definition: The weight of each tablet, which should remain consistent across all units produced.

Typical Range: Generally, between 50 mg and 1000 mg, depending on the specific formulation requirements.

Effect on Tablet: Fluctuations in tablet weight may point to problems such as improper powder filling, worn dies, or inconsistent compression pressure. [16]

IV. Tablet Thickness:

Definition: The total height or thickness of a tablet after it has been compressed.

Typical Range: Generally, between 2 mm and 12 mm, depending on the tablet's design.

Effect on Tablet: Maintaining uniform thickness is crucial for consistent dissolution rates and consumer satisfaction. [17]

V. Tooling (Punch and Die) Parameters:

Definition: Refers to the design, condition, and functionality of the punches and dies used to shape the tablets.

Effect on Tablet: Damaged or worn tooling can lead to inconsistencies in tablet weight, thickness, and overall appearance. Regular inspections and maintenance are essential to avoid these issues. [18]

VI. Fill Depth (or Die Fill):

Definition: The volume of powder loaded into the die cavity before compression takes place.

Typical Range: Usually ranges from 0.5 mm to 5 mm, depending on tablet formulation and size.

Effect on Tablet: Insufficient fill depth can produce tablets with low weight or uneven hardness. [19]

VII. Ejection Force:

Definition: The amount of force needed to push the compressed tablet out of the die cavity.

Typical Range: Generally, falls between 100 and 200 N.

Effect on Tablet: Excessive ejection force can lead to issues like tablet chipping or cracking. This can be reduced by using appropriate lubrication and properly designed tooling. [20]

VIII. Speed (Tablet Press Speed):

Definition: The rate at which the tablet press operates, typically expressed in tablets per minute (TPM).

Typical Range: Single-station presses usually run at 30–250 TPM, while multi-station presses can operate at much higher speeds.

Effect on Tablet: Operating at higher speeds may cause inadequate powder filling, insufficient consolidation time, and variability in tablet hardness. [21]

IX. Dwell Time:

Definition: The duration that the tablet remains under compression during the pressing process.

Typical Range: Generally, ranges from 0.2 to 1 second.

Effect on Tablet: Too short a dwell time can lead to poorly formed tablets, while excessive dwell time may result in over-compression or increased wear on the tooling. [22]

X. Lubrication:

Definition: The use of lubricants (commonly magnesium stearate or stearic acid) either in the powder blend or directly on the tooling to reduce friction during tablet formation and ejection.

Effect on Tablet: Adequate lubrication prevents sticking and reduces tool wear. However, excessive lubricant can weaken tablet hardness, while insufficient lubrication may cause increased wear and sticking issues. [23]

XI. Moisture Content:

Definition: The amount of moisture present in the powder formulation, expressed as a percentage.

Typical Range: For most formulations, moisture content should be maintained below 5–10%.

Effect on Tablet: Elevated moisture levels can negatively affect powder flow, leading to issues like capping, sticking, or incomplete compression.

XII. Granulation (Particle Size and Distribution):

Definition: Refers to the properties of the powder blend, specifically the size and distribution of the particles.

Typical Range: Ideal particle sizes are generally between 100–500 microns.

Effect on Tablet: A consistent particle size distribution enhances powder flow and ensures uniform tablet formation. Too many fine particles can reduce flowability, while overly coarse particles may cause uneven compression.

XIII. Tablet Hardness:

Definition: The amount of force needed to break a tablet.

Typical Range: Usually measured in kilogram-force (kgf), with standard values ranging from 4–12 kgf, depending on the formulation.

Effect on Tablet: Tablets should have an appropriate level of hardness to withstand handling without breaking while still being able to disintegrate effectively in the digestive system.

c) Process:

In both the food and pharmaceutical industries, tablet presses are used to compress powdered or granulated substances into tablets of specific shapes and sizes. The process generally includes stages like compression, granulation, formulation, and quality assurance. Below is an overview of the tablet compression process, referencing standard practices.

I. Formulation and Granulation:

Before compression can take place, a suitable tablet formulation must be developed. This formulation includes the active pharmaceutical ingredient (API) and various excipients—inactive substances that help form the tablet and support drug delivery. Common excipients include binders, fillers, lubricants, disintegrants, and glidants.

Granulation is the process of converting powders into granules, which improves flow and compressibility. There are two primary methods of granulation:

- **Wet Granulation:** A liquid binder is added to the powder blend to form granules, which are then dried.
- **Dry Granulation:** This method does not involve any liquid. Instead, the powder is compressed into slugs or sheets, which are then milled into granules.

II. Tablet Compression Process:

Tablet compression is generally performed using a rotary tablet press or a single-punch press. The process includes the following key steps:

a. Powder Feeding:

The hopper of the tablet press is loaded with the granulated or powdered blend. A dosing mechanism ensures that a specific amount of material is delivered into the die cavity for each tablet.

b. Die Cavity Filling:

The tablet press features a rotating turret that holds the dies and punches. During this step, the lower punch is positioned within the die, while the powder is filled into the cavity using a feeding system such as a cam or rollers. The upper punch remains elevated during this stage.

c. Compression:

- The upper punch then moves downward to compress the powder within the die cavity against the lower punch.
- This step forms the tablet and the compression force is adjustable, depending on the required tablet hardness and disintegration time.
- Proper compression is critical to ensure the particles bond without causing defects like capping (where part of the tablet separates), cracking, or other structural issues.

d. Ejection:

- Once compression is complete, the punches separate, and the lower punch rises to push the finished tablet out of the die.
- The tablet is then released from the machine, ready for further processing or packaging.

e. Tablet Weight and Thickness Control:

The weight of each tablet is primarily controlled by adjusting the amount of powder that fills the die cavity. Tablet thickness is managed through modifications to the punch settings and the applied compression force.

III. Post-Compression Handling:

Once tablets are compressed, they may undergo additional steps such as coating or further testing. If coating is required, the tablets are transferred to equipment like a coating pan or a fluidized bed coater, where a protective layer is applied. Coating serves various purposes, including improving taste, protecting active ingredients from degradation, and enabling controlled or delayed release.

IV. Quality Control:

Maintaining quality throughout the tablet compression process is essential to ensure each tablet meets specified standards. Standard quality control assessments include:

- **Tablet Weight Uniformity:** Verifies that the tablet weight stays within the acceptable range.
- **Hardness Testing:** Measures the tablet's resistance to breaking under pressure.
- **Friability Testing:** Assesses the tablet's ability to withstand mechanical stress during handling.
- **Disintegration Time:** Confirms the tablet dissolves properly within the digestive system.
- **Content Uniformity:** Ensures consistent dosage of the active ingredient in each tablet.

d) Types of Tablet Compression Machines:

Tablet presses vary by design and scale of production:

Single-Punch Press: Ideal for small-scale production and simple tablet formulations. It operates with a single set of punches, creating one tablet per cycle.

Rotary Tablet Press: Designed for high-volume manufacturing. These machines feature a rotating turret equipped with multiple stations for powder filling, compression, and ejection, capable of producing

thousands of tablets per minute. [24]

e) Applications of Tablet Compression Machines in the Pharmaceutical Industry:

- **Tablet Manufacturing:** Tablet compression machines are primarily used to produce medicinal tablets, which are one of the most common forms for administering active pharmaceutical ingredients (APIs) to patients.
- **Controlled-Release Tablets:** These machines are essential for creating controlled-release formulations, where the release of the active ingredient is gradually delayed or extended over time.
- **Coated Tablets:** Compression machines are also used to manufacture coated tablets, which may have controlled release properties or provide protection to the active ingredient.
- **Granulation Process:** The granulation process, which involves combining raw materials to form granules before tablet compression, is another key use of tablet compression machines [25].

f) Conclusion:

Understanding the critical parameters in tablet compression such as compression force, tablet weight, ejection force, and tablet hardness is vital for producing tablets with the desired characteristics. Additionally, controlling aspects like fill depth, speed, and lubrication is necessary to ensure consistency and avoid defects in the final product. A well-managed tablet compression process guarantees the effective delivery of active pharmaceutical ingredients (APIs) while maintaining both patient safety and product stability. Tablet compression machines, including both single-punch and rotary presses, play an indispensable role in the pharmaceutical industry by producing a wide array of tablet formulations, ranging from simple to complex designs, such as controlled-release and coated tablets. The qualification and optimization of these machines are essential for the success of pharmaceutical production, ensuring that each batch of tablets adheres to the highest standards of quality and reliability. By following these qualification and process guidelines, pharmaceutical companies can guarantee the production of tablets that are safe, effective, and meet all regulatory requirements

INTRODUCTION TO THE QUALIFICATION FLUIDIZED BED DRYER

In manufacturing environments, validation test procedures are essential for ensuring the equipment and processes that may affect product quality are properly validated. These tests are carried out in accordance with approved qualification procedures. The necessary activities and responsibilities for qualification and validation are detailed in the Validation Master Plan. All steps of the validation process for facilities, equipment, processes, process controls, and cleaning comply with current European Community Guidelines for GMP and FDA regulations, as well as the cGMP guidelines for finished pharmaceutical manufacturing.

I. Design Qualification (DQ):

FBD (Fluid Bed Dryer) operates by using a blower or fan to introduce the fluidizing air stream. An air heater raises the temperature to the desired level, and the air travels upward through the wet materials, which are contained in a drying chamber with a wire mesh support at the bottom.

Capacity: 5–200 kg

Drying time: 20–40 minutes

II. Installation Qualification (IQ):

An Installation Qualification (IQ) ensures the equipment is correctly installed. This process verifies that the installation adheres to the manufacturer's specifications and ensures compliance with any design changes made during installation. Electrical codes must also be met. Key activities in IQ include:

- Verifying the authorized purchase order.
- Checking the invoice for correctness.
- Confirming the supply and manufacturer.
- Verifying the serial number and model number.
- Inspecting the area for visible damage.
- Ensuring installation meets the manufacturer's recommended specifications.

III. Operational Qualification (OQ):

Operational Qualification (OQ) determines whether the equipment functions within the predefined tolerance and operational limits.

Steps involved in OQ include:

- Checking the alarm system functionality.
- Meeting the calibration requirements as outlined by the validation team or in the equipment handbook.
- Running the equipment at low, medium, and high speeds to confirm operational control according to the operation manual.

IV. Performance Qualification (PQ):

After installation, the equipment is tested to confirm its functionality and operating parameters. Calibrated tools, such as air flow monitors, temperature probes, and hydrometers, are essential for this process. For PQ validation, placebo materials are used.

Key steps in PQ:

- Monitor the drying cycle parameters under minimum and maximum load conditions.
- Check temperature, relative humidity, fluidization pressure, and differential air pressure during the drying process.
- Once the drying process is complete, reset the timer to "0" to stop the process. These parameters must be documented prior to operation [26].

a) Principle

The operation of fluid bed dryers is based on the fluidization process, which transforms a material from a solid-like state to a dynamic, fluid-like state. This process involves injecting hot air or gas into the material-holding chamber via a perforated distribution plate. The gas forces its way through the gaps between solid particles, and as the air velocity increases, the upward force on the particles overcomes the gravitational forces, causing them to rise. This results in the particles being suspended in a fluid-like state, often resembling a boiling liquid, which is known as fluidization. The particles, once static, now behave like a flowing liquid. The hot air or gas surrounds each particle, ensuring an even and efficient drying process. During this process, hot air is forced through a bed of moist particles, accelerating the drying rate by transferring heat to the particles as they become fluidized.

b) Construction

The fluidized bed reactor is constructed using a 304 stainless steel pipe with a 3-inch diameter and a height of 5 feet. Stainless steel 304 is selected for its cost-effectiveness and suitability, as it has a melting point of 1450 °C, far higher than the operating temperature of the reactor. This material can withstand temperatures up to 870–925 °C, ensuring that it maintains resistance to oxidation during occasional high-temperature use. The reactor's temperature must be kept below this threshold to prevent the formation of ash, which could disrupt fluidization and hinder the reactor's operation. The reactor is externally heated using three sets of ceramic heaters, each creating a separate heating zone to reach the required temperature for gasification and fluidized bed combustion. For each experiment, 2.7 kg of sand is used as the fluidizing medium.

c) Parameters

In industrial applications, a Fluidized Bed Dryer (FBD) is commonly used in industries such as chemical manufacturing, food processing, and pharmaceuticals to dry granular or powdered materials by suspending particles in an upward stream of hot air or gas. The key physical parameters of a fluidized bed dryer include:

I. Airflow Rate

Definition: The rate at which hot air passes through the particle bed to maintain fluidization.

Units: m³/h or m³/s

Effect on Drying: Higher airflow rates typically improve fluidization and drying efficiency. However, excessive airflow can cause particle entrainment, leading to material loss.

II. Particle Size and Distribution

Definition: The size and distribution of particles being dried, which influence the fluidization behavior.

Units: μm (micrometers) or mm

Effect on Drying: Smaller particles are easier to fluidize and require lower air velocities, while larger particles need higher velocities for fluidization. A uniform particle size distribution ensures consistent drying.

III. Bed Height (or Bed Depth)

Definition: The height of the material bed within the dryer.

Units: m (meters) or cm (centimeters)

Effect on Drying: A higher bed height allows for processing larger quantities of material, but it may also necessitate higher airflow rates to maintain fluidization.

IV. Temperature

Definition: The temperature of the air used to fluidize the particles.

Units: $^{\circ}\text{C}$ or $^{\circ}\text{F}$

Effect on Drying: Temperature influences the drying rate and moisture evaporation from the particles. It must be precisely controlled to avoid overheating or degrading the material being dried.

V. Humidity of the Air (or Dew Point)

Definition: The moisture content of the air entering the dryer, which directly influences the drying process.

Units: % RH (Relative Humidity) or g/m^3

Effect on Drying: High humidity in the air reduces the drying rate because the air's ability to absorb moisture becomes limited. This slower absorption hampers the overall drying efficiency.

VI. Drying Rate

Definition: The speed at which moisture is removed from the material during the drying process.

Units: kg of moisture removed per kg of dry material per unit of time (e.g., $\text{kg}/\text{kg}\cdot\text{h}$)

Effect on Drying: A higher airflow rate and increased temperature typically accelerate the drying rate. However, excessively high temperatures may cause overheating or degradation of the material being dried.

VII. Pressure Drop

Definition: The pressure difference across the fluidized bed during operation.

Units: Pa (Pascal), or mm of water column

Effect on Drying: A higher pressure drop often indicates increased resistance to airflow, typically caused by a denser material bed or smaller particle size. It can also suggest poor fluidization, which could lower the efficiency of the drying process.

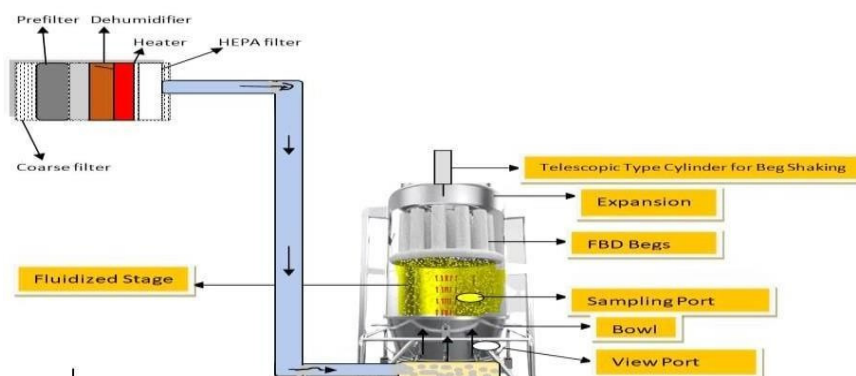


Figure 6: Fluidized bed dryer

d) Working of Fluidized Bed Dryer

- i. Hot air, under high pressure, is forced through a perforated bed containing wet solid particles to

operate the fluidized bed dryer.

- ii. The particles begin to suspend in the air as the hot air moves faster than the particles' settling velocity.
- iii. To achieve the desired loss on drying (LOD), the moisture content of the solid particles decreases as they are suspended in the heated air.
- iv. The evaporated moisture is carried away from the wet solid particles by the drying vapors.
- v. To conserve energy, the outgoing air may sometimes be recycled.

e) Types of Fluidized Bed Spraying Techniques

Fluidized bed technology has evolved with modifications, leading to three main spraying techniques:

- I. Top Spray Process
- II. Bottom Spray Process
- III. Tangential Spray Process

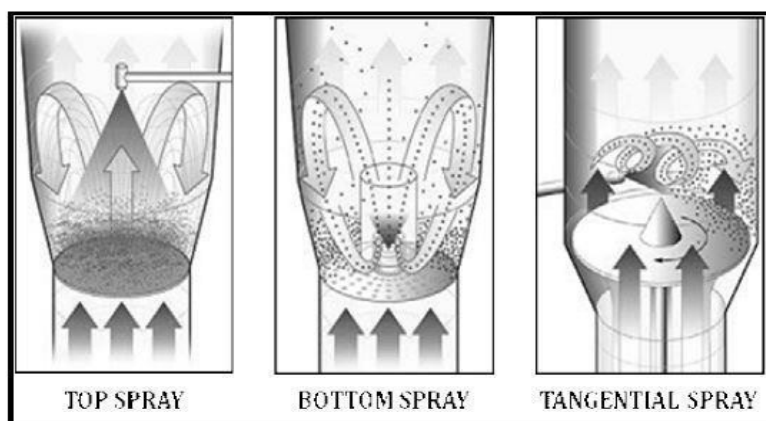


Figure 7: Types of fluidized bed spraying techniques

I. Top Spray Process:

The top spray process is one of the most widely used methods for wet granulation and has been employed for over 30 years in various industries such as food, detergent, fertilizer, and pharmaceuticals. A top-spray system consists of three key components: an exhaust system with a filter housing, an air handling system (which may include options for humidification and dew point management or dehumidification), and a product container with an expansion chamber.

II. Bottom Spray Process:

In the bottom spray process, a cylindrical product container with perforated plates is utilized. The container has a coating partition elevated just above the perforated plate. A nozzle, located in the center beneath the partition, dispenses the coating solution. The plate features large holes at the edges and smaller holes throughout, except for the central larger ones. This technique is particularly effective for producing sustained, controlled, prolonged, and delayed/enteric releases, and it creates a high-quality, repeatable film. The method can handle solvents, emulsions, suspensions, aqueous solutions, films, and hot melts, and is used to coat tablets, pellets, capsule shells, and small particles, in batches ranging from a few hundred grams to 600 kilograms.

III. Tangential Spray Process:

The tangential spray process is similar to the bottom spray process, with the key difference being that a motor-driven rotor disc provides the production motion. In this process, spraying nozzles are positioned tangentially within the chamber. A major advantage of this method over top and bottom spraying is the ability to attach a powder feeder to reduce exposure of the compound to solvents or water. This technique is ideal for producing pellets with a high dosage loading in a relatively short time and is also used for making spheres (spheronized granules) from powders. It is often applied in modified release medication coating and layering.

f) Advantages of Fluidized Bed Dryer (FBD):

- i. Efficient heat and mass transfer rates, leading to faster moisture removal, if the gas-particle constant is optimal.
- ii. High thermal efficiency is often achieved if part of the thermal energy for drying is supplied by an internal heat exchanger.
- iii. Lower initial and ongoing costs.
- iv. Reduced drying contact time.

g) Disadvantages of Fluidized Bed Dryer (FBD):

- i. Considerable pressure drops occur due to the need to suspend the entire bed in gas, resulting in high energy consumption.
- ii. Increased gas handling is required because substantial exhaust gas recirculation is necessary for high thermal efficiency operation.
- iii. Inadequate fluidization and flexibility, especially if the feed is too wet.
- iv. Fluidized bed dryers are not ideal for drying organic solvents.

h) Application:

I. Pharmaceutical Industry:

Fluidized bed dryers are widely used in the pharmaceutical sector for the drying of powders, granules, and other small particles, ensuring consistent quality and efficient processing.

II. Chemical Industry:

In the chemical industry, fluidized bed dryers are employed to dry various chemical powders and materials, ensuring uniform moisture removal and high-quality production.

III. Plastic Resin Industry:

Fluidized bed dryers are used to dry plastic resins, providing effective moisture control and enhancing the properties of the resins during the manufacturing process.

IV. Food Industry:

The food industry benefits from fluidized bed dryers for drying food ingredients, powders, and other small particles, maintaining product quality and safety.

i) Conclusion:

Fluidized Bed Dryers are crucial technology for industries requiring efficient and high-quality drying of powders, granules, or small particles. Their ability to provide uniform drying and fast processing times makes them indispensable in pharmaceutical, chemical, and food processing sectors. However, the performance of FBDs requires careful control of parameters such as airflow, temperature, and particle size. Due to their versatility and efficiency, Fluidized Bed Dryers remain a preferred choice for a wide range of drying applications.

INTRODUCTION TO THE QUALIFICATION OF DISSOLUTION EQUIPMENT

Background and Significance

Dissolution testing plays a crucial role in pharmaceutical development by ensuring the effective release of active pharmaceutical ingredients (APIs) from their formulations. The certification of dissolution testing instruments is vital to ensure that test results are accurate and reliable, meeting the required regulatory standards.

a) Importance of Dissolution Testing

Dissolution testing is an essential quality control measure in the pharmaceutical industry, evaluating the in vitro release of APIs from different formulations. This testing helps to:

- i. Assess bioavailability and bioequivalence
- ii. Determine product stability and shelf-life
- iii. Optimize formulation development
- iv. Ensure compliance with regulatory requirements



Figure 8: Dissolution Equipment

b) Physical Parameters:

- i. Vessel Shape and Size
- ii. Vessel Material (e.g., glass, stainless steel)
- iii. Stirrer Design (e.g., paddle, basket)
- iv. Stirrer Speed (RPM)
- v. Stirrer Depth
- vi. Temperature Control Range (e.g., $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$)
- vii. Heating/Cooling System

c) Sampling System

I. Vessel Shape and Size

- Influences the homogeneity of the sample, mixing effectiveness, and dissolution rate.
- The vessel's shape and size should be suitable for the test, ensuring enough space for the dissolving medium.

II. Vessel Material

- The material should be inert and non-reactive to ensure chemical stability, durability, and ease of cleaning.
- The vessel material should be compatible with the dissolving medium.

III. Stirrer Design

- Affects the dissolution rate, flow dynamics, and mixing efficiency.
- The stirrer design should ensure uniform mixing and minimize vortex formation.

IV. Stirrer Speed (RPM)

- Impacts shear stress, mixing efficiency, and the dissolution rate.
- The stirrer speed should be maintained within a ± 1 RPM tolerance, and its speed must be verified.

V. Stirrer Depth

- Affects the dissolution rate, flow dynamics, and mixing efficiency.
- The stirrer depth should be adjustable to ensure optimal mixing.

VI. Temperature Control Range

- Affects test accuracy, chemical reactions, and the dissolution rate.

- The ideal temperature control range is $\pm 0.5^{\circ}\text{C}$, and this should be confirmed.

VII. Heating/Cooling System

- Ensures consistent and accurate temperature regulation.
- The system should effectively manage temperature control and minimize fluctuations.

VIII. Agitation Mechanism

- Affects the dissolution rate, flow dynamics, and mixing efficiency.
- The agitation system should ensure even mixing, and its effectiveness should be verified.

IX. Vessel Lid Design

- The lid design should prevent contamination, reduce evaporation, and ensure proper sealing.
- The integrity of the seal must be ensured by the vessel lid design.

X. Sampling System

- Ensures accurate analysis, representative samples, and minimizes contamination.
- The sampling system should guarantee that samples are representative.
- Verification of the sampling system is necessary.

d) Qualification Stages

The qualification process typically consists of four stages:

I. Design Qualification (DQ): Verifies that the equipment design meets both user requirements and manufacturer specifications.

II. Installation Qualification (IQ): Confirms the correct installation and integration of the equipment.

III. Operational Qualification (OQ): Demonstrates that the equipment operates consistently and accurately.

IV. Performance Qualification (PQ): Verifies the equipment's performance under various conditions.

e) Benefits of Qualification

Qualifying dissolution equipment ensures:

- Reliable and accurate test results
- Compliance with legal and regulatory requirements
- A reduced risk of errors and unpredictability Enhanced product quality
- Increased lab productivity

f) Industry Standards and Guidelines

Several industry standards and guidelines offer guidance on dissolution equipment qualification:

- ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical Dissolution Systems
- ISPE Guide: Pharmaceutical Dissolution Testing
- AAPS Dissolution Testing Focus Group: Best Practices for Dissolution Testing

Design Qualification (DQ)

Objective: To ensure the dissolution testing equipment's design meets user and manufacturer specifications.

Method:

- Review of the manufacturer's records
- Confirmation of design requirements
- Documentation of the design review

Installation Qualification (IQ)

Objective: To confirm that the dissolution testing equipment is correctly installed and meets the manufacturer's requirements.

Method:

- Installation checklist

- ii. Verification of component installation
- iii. Documentation of installation details
- iv. Comparison against manufacturer standards

Operational Qualification (OQ)

Objective: To ensure the dissolution testing device meets user requirements and functions as intended.

Method:

- i. Preparation of Standard Operating Procedures (SOPs)
- ii. Employee training
- iii. Operational testing
- iv. Documenting test results
- v. Confirmation of critical functionality

Performance Qualification (PQ)

Objective: To confirm that the dissolution testing device operates reliably and meets user specifications.

Method:

I. Physical performance verification (loaded condition):

- Head plate coplanarity
- Dissolution solution temperature
- Stirrer RPM
- Stirrer timer
- Stirrer wobbling
- Stirrer basket paddle depth
- Integrity and mesh size of the basket
- Jar centering
- Stirrer vibration
- Rinsing volume

II. Chemical performance verification (loaded condition):

- Geometric mean
- Percentage of coefficient of variation (CV)

g) Advantages

- i. Accurate results: Provides precise dissolution rates, ensuring the purity of medicinal products.
- ii. Effective testing: Automates the testing process to reduce human error and manual work
- iii. Flexibility: Supports various vessel materials, sizes, and shapes.
- iv. Temperature control: Maintains temperature at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, which is physiologically relevant.
- v. Real-time monitoring: Allows continuous tracking of dissolution profiles.
- vi. Compliance: Meets FDA, EU GMP, and ICH regulations for pharmaceutical dissolution testing.

h) Disadvantages

- i. Expensive: High initial investment and ongoing costs.
- ii. Complexity: Operation and maintenance require specific training.
- iii. Calibration requirements: Regular calibration is necessary to ensure accuracy.
- iv. Limited capacity: Restrictions on batch testing.
- v. Vibration and noise: Vibration and noise from the equipment can impact results.
- vi. Maintenance: Regular maintenance is required to prevent equipment failure.

i) Conclusion

After completing a comprehensive qualification process, the dissolution testing equipment was deemed suitable for its intended purpose. The design certification confirmed that the equipment complies with the standard specifications for laboratory instruments. The operational qualification tests verified that the equipment operates within predefined acceptable limits, demonstrating its functionality and performance. As part of a complete preventive maintenance plan, semi-annual system suitability tests will be performed,

or tests will be conducted following any significant changes to the equipment, such as relocation or replacement.

The results of this work confirm that the dissolution testing apparatus:

- i. Operates in accordance with the user manual.
- ii. Performs programmed functions as outlined in the Standard Operating Procedures (SOPs).
- iii. Meets predefined acceptance criteria for performance qualification and calibration.

Thus, the dissolution apparatus is considered qualified and is deemed acceptable for use in dissolution testing

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