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PROCESS VALIDATION OF CRITICAL STEPS INVOLVED IN MANUFACTURING OF SOLID DOSAGE FORMS IN PHARMACEUTICAL INDUSTRY

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Abstract

Quality is an important prerequisite when we consider any product. Therefore the drug must be manufactured to the highest quality levels. End product testing by itself does not guarantee of product quality. Every step of manufacturing procedure should be validated. Process validation performs this task to build quality in to the product. Process validation had proven to be an important tool for quality management soon emerged several regulatory guidelines and publication on validation and today for the pharmaceutical industry successful validation is prerequisite. The principles of planning, organizing and performing process validation are similar to those for qualification. It should be done in accordance with process validation protocols; data should be collected and reviewed against predetermined acceptance criteria, and reflected in process validation reports.

Keywords: Process validation, critical parameters, validation protocol.

Introduction

Definition:

Established documentary evidence which provides a high degree of quality assurance that a specific process will produce a product meeting its predetermined specification and quality attributes, FDA Guidelines 1987.

Validation studies are performed for analytical tests, equipment, facility systems such as air, water, steam, and for processes such as the manufacturing processes, cleaning, sterilization, sterile filling, lyophilisation, etc.

Validation is an essential part of good manufacturing practices (GMP). It is therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that

The manufactured products will consistently meet their product specifications. United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered. Process controls include raw materials inspection, in-process controls and targets for final product. The purpose is to monitor the on-line and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for controls is established to monitor its performance.

Documentation associated with validation includes:

- Standard Operating Procedures (SOPs)
- Specifications
- validation master plan (VMP)
- Qualification protocols and reports
- Validation protocols and reports.

Standard Operating Procedure:-

Standard Operating Procedures are issued specifically instruct employees in area of responsibility, work instructions, appropriate specifications and required records. These outlines procedures must be followed to claim compliance with GMP principles or other statutory rules and regulations.

The general aspects covered under the SOP's are preparation and maintenance of work area like washing and sterilization, decontamination and testing area. Even the work done in laboratory were documented, even the details of the equipments and their maintenance were also involved.

The general format of the SOPs involves:

- Title
- Code
- Objective
- Scope
- Definitions
- Description
- Safety

- Documentation
- Effective date, review date' version number
- Footer: Prepared by, Reviewed by, Approved by, Authorized by.
- References

Validation Master Plan:

VMP is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

VMP is a summary intention document stating the scope of the validation and outlining the methods to be establishing the performance adequacy. The validation master plan should provide an overview of the entire validation operation, its organizational structure its being the list inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It even holds the Calibration and qualification of equipments, summary and conditions of Validation Protocol.

The format and content should include:

- Objective
- Approach
- Scope and justification
- Acceptance Criteria
- Support programs
- Organization
- Schedules
- Documentation formats

Validation protocols:

As a minimum the protocols should include the following significant background information:

- The objectives of the study
- The site of the study
- The responsible personnel
- Description of SOPs to be followed
- Equipment to be used; standards and criteria for the relevant products and processes
- The type of validation
- The processes and/or parameters
- Sampling, testing and monitoring requirements
- Predetermined acceptance criteria for drawing conclusions.

The Validation Report:

A written report should be available after completion of the validation. If found acceptable, it

Should be approved and authorized (signed and dated). The report should include at least the

Following:

- Title and objective of study
- Reference to protocol
- Details of material
- Equipment
- Programmes and cycles used
- Details of procedures and test methods
- Results (compared with acceptance criteria)
- Recommendations on the limit and criteria to be applied on future basis.

Importance of process validation:

- Assurance of quality
- Process optimisation
- Reduction of quality cost.
- Reduction in rejections.
- Increased output.
- Reduced testing in process and in finished goods.
- More rapid and reliable start-up of new equipments
- Easier scale-up form development work.
- Easier maintenance of equipment.
- Improved employee awareness of processes.

Types of validation:

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

Prospective validation:

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive productions - size (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors.

Each experiment should be planned and documented fully in an authorised protocol. All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined. Using this defined process a series of batches should be produced.

Concurrent validation:

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation. This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

- In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- The decision to carry out concurrent validation must be justified, Documented and approved by authorised personnel.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation:

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control.

This type of validation of a process for product already in distribution.

Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

Revalidation:

Re-validation provides the evidence that Changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality.

Revalidation becomes necessary in certain situations.

- Changes in raw materials
- Changes in the source of active raw material manufacturer.
- Changes in packaging material
- Changes in the process
- Changes in the equipment
- Changes in the plant/facility.

Phases in process validation

The activities relating to validation studies may be classified into three phases:

Phase 1

Pre-validation phase or the Qualification phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial, scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment qualification, Installation qualification, master production documents, Operational qualification, Process capability.

Phase 2

Process validation phase (Process Qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the “Worst case” conditions.

Phase 3

Validation Maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures. At this stage the Validation Team also assures that there have been no changes/deviations that should have resulted in requalification and revalidation**.**

Process Validation of solid dosage forms:-

The policy and approach to process validation should be documented, e.g. In a validation master plan, and should include the critical process steps and Parameters.

- Process validation should normally begin only once qualification of support systems and equipment is completed. In some cases process validation may be conducted concurrently with performance qualification.
- Process validation should normally be completed prior to the manufacture of finished product that is intended for sale (prospective validation). Process
- Validation during routine production may also be acceptable (concurrent validation).

Critical factors:-

- Critical factors or parameters that may affect the quality of the finished product should be identified during product development. To achieve this, the production process should be broken down into individual steps, and each step should be evaluated (e.g. on the basis of experience or theoretical considerations).
- The criticality of these factors should be determined through a "worst-case" challenge where possible. These critical parameters of the process have been identified, and machine settings, component specifications and environmental conditions have been determined and specified.
- Numerous factors should be considered when developing and validating solid dosage forms:

1. Pre-blending
2. Granulation
3. Drying
4. Milling
5. Lubrication
6. Compression
7. Coating

Strategy for Industrial Process Validation of Solid Dosage Forms:

The strategy selected for process validation should be simple and straightforward. The following five points gives strategy for process validation:

1. The use of different lots of raw materials should be included. i.e. active drug substance and major excipients.

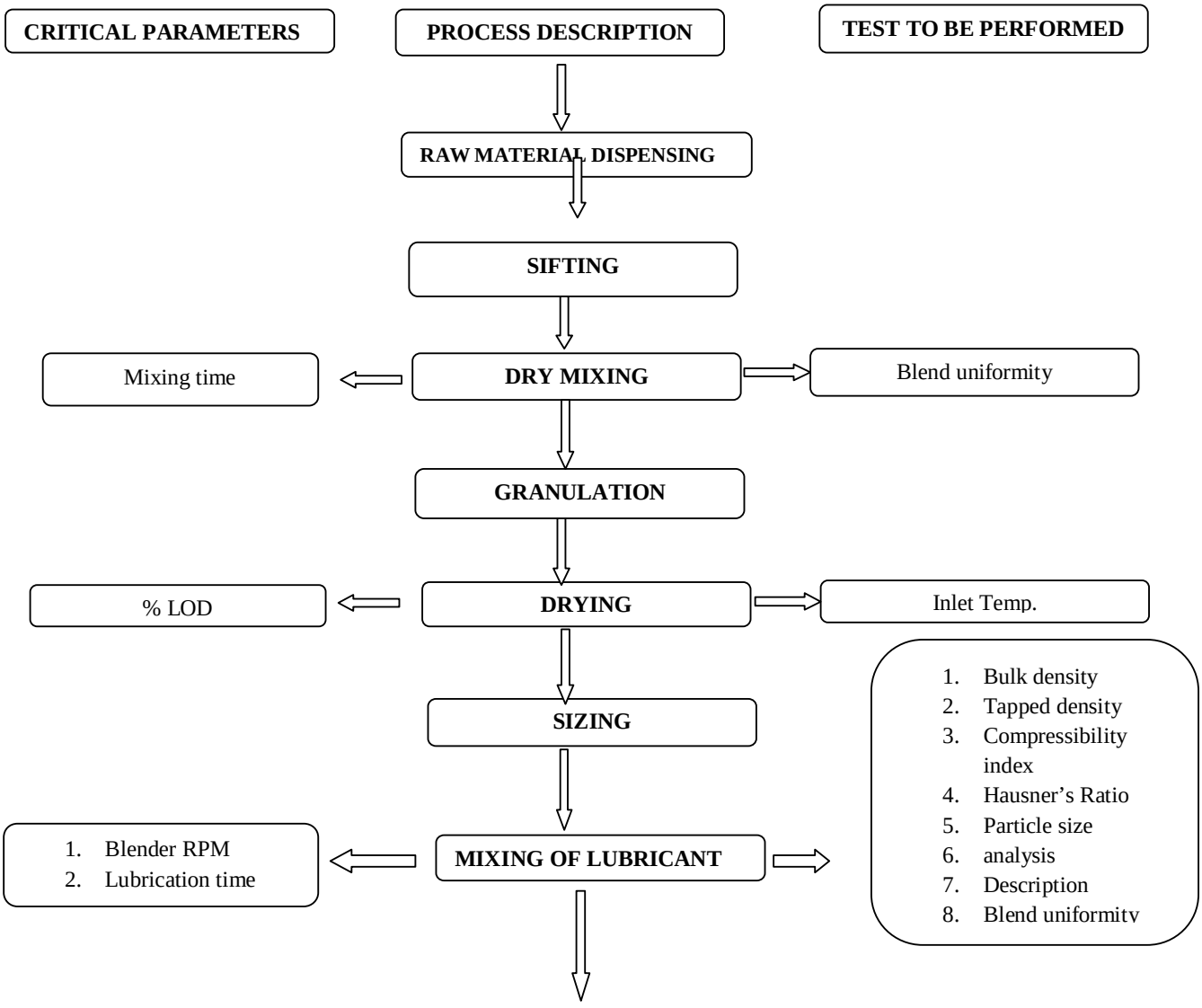
2. Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).

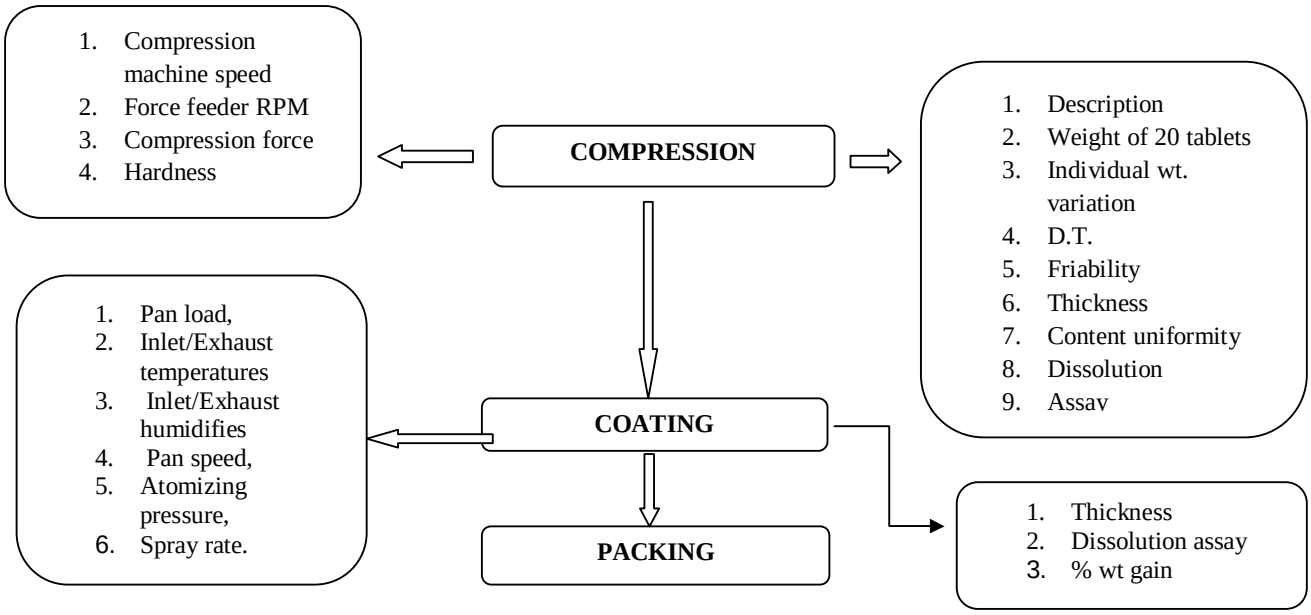
3. Batches should be manufactured in the equipment and facilities designated for eventual commercial production.

4. Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.

5. Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process requalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team.

PROTOCOL FOR PROCESS VALIDATION OF SOLID DOSAGE FORMS (TABLETS) PROCESS REVIEW:





Process Evaluation and Selection:

Determine the unit operations needed to manufacture the tablets.

1. Mixing or Blending

The mixing or blending unit operation may occur once or several times during the tablet manufacture. For example, a direct compression formulation may involve one blending step in which the drug and the excipients are blended together prior to compression. A wet granulation formulation may require two mixing/blending steps:

(1) Prior to granulating to have a uniform drug/excipients mixture, and

(2) After milling the dried granulation to add other excipients, such as the lubricant. Some or all the items provided in this section may therefore be pertinent for validation, depending on the mixing or blending objective. The following physical properties of the drug and excipients are factors in creating a uniform mix or blend:

- Bulk density
- Particle shape
- Particle size distribution
- Surface area

Materials that have similar physical properties will be easier to form a uniform mix or blend and will not segregate as readily as materials with large differences. Items to consider:

a) **Mixing or blending technique**: Diffusion (tumble), convection (planetary or high intensity), or pneumatic (fluid bed) techniques can be used to mix or blend materials. Determine the technique that is required for the

formulation or process objective. It may be different, depending on whether you are mixing the drug and excipients for a direct compression formulation or adding the lubricant (e.g., magnesium stearate) to the granulation.

b) **Mixing or blending speed:** Determine the intensity (low/high shear) and/or speed (rpm) of the mixing or blending. Mixing the drug and excipient will require more intense mixing than adding the lubricant to the final blend. Mixing or blending time: How much mixing or blending is required to obtain a uniform mixture? The mixing or blending time will be dependent on the mixing or blending technique and speed. Experiments should be done to determine if the materials can be over mixed, resulting in demixing or segregation of the materials. Demixing can occur due to the physical property differences (e.g., particle size distribution and density). For example, demixing can occur in a direct compression formulation in which the drug substance is micronized (5 microns) and the excipients are granular (500–1000 microns).

c) **Drug uniformity:** Content uniformity is usually performed to determine the uniformity of drug throughout the mix or blend. Representative samples should be taken throughout the mix or blend. The sampling technique and handling of the materials are key in obtaining valid content uniformity results. Segregation of the sample can occur by over handling, resulting in inaccurate results. For the final blend (blend prior to compression), the sample taken should be equivalent to the weight of a single tablet.

d) **Excipient uniformity:** Besides drug uniformity, excipients need to be uniform in the granulation or blend. Two key excipients are:

- Lubricant: The lubricant needs to be distributed uniformly in the mixture/granulation for the high-speed compression operation. Uneven distribution of the lubricant can result in picking and sticky problems during compression. It can also lead to tablet performance problems (low dissolution due to excessive lubricant in some tablets).
- Colour: The colorant(s) need(s) to be evenly distributed in the mixture so that the tablets have a uniform appearance (e.g., color, hue, and intensity). The coloring agent may need to be prescreened or more uniformly dispersed in the blend prior to compression to avoid speckling or shading of the color.
- Equipment capacity/load: The bulk density of materials or granules will affect the capacity of the equipment. If an excipient in the formulation affects the density of the final blend to a greater extent than any other ingredient, then a well-controlled density specification for that excipient may be warranted. Test different-sized loads in the

mixer/ blender (e.g., 30, 50, and 70% of working volume) for optimal mixing or blending. Undercharging or overcharging a blender can result in poor drug or tablet lubricant distribution.

2. Wet Granulation

What type of wet granulation technique will be used? Will it be low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air)? Each technique will produce granules with different physical properties and will require monitoring of different processing parameters. Wet granulation parameters to be considered during development and validation are:

a. **Binder addition**: Should the binder be added as a granulating solution or dry like the other excipients? Adding the binder dry avoids the need to determine the optimal binder concentration and a separate manufacture for the binder solution. Binder concentration: The optimal binder concentration will need to be determined for the formulation. If the binder is to be sprayed, the binder solution needs to be dilute enough so that it can be pumped through the spray nozzle. It should also be sufficiently concentrated to form granules without over wetting the materials.

b. **Amount of binder solution/granulating solvent**: How much binder or solvent solution is required to granulate the material? Too much binder or solvent solution wills over wet the materials and prolong the drying time. The amount of binder solution is related to the binder concentration.

c. **Binder solution/granulating solvent addition rate:** Define the rate or rate range at which the binder solution or granulating solvent can be added to the materials. Can the granulating solution be dumped into the mixer or does it have to be metered in at a specific rate?

d. **Mixing time**: How long should the material is mixed to ensure proper formation of granules? Should mixing stop after the addition of the binder or solvent solution or should additional mixing be required? Granulations that are not mixed long enough can form incomplete or weak granules. These granules may have poor flow and compression properties. On the other hand, over mixing the granulation can lead to harder granules and a lower dissolution rate.

e. **Granulation end point:** How is the granulation end point determined? Is it determined or controlled by granulation end point equipment (e.g., ammeter or wattmeter)? Is it controlled by specifying critical processing parameters? For example, a drug or excipient mixture may be granulated by adding a predetermined amount of

water (granulating solution) at a certain rate. The granulation is completed after mixing for a set time after the water has been added.

3. Wet Milling:

Does the wet granulation need to be milled to break up the lumps and enhance drying of the granulation? Wet granules that have a wide aggregate range can lead to inefficient drying (long drying times and partially dried large granules or lumps).

Factors to consider are:

a. **Equipment size and capacity:** The mill should be large enough to delump the entire batch within a reasonable time period to minimize manufacturing time and prevent the material from drying during this operation.

b. **Screen size:** The screen needs to be small enough to delump the material, but not too small to cause excessive heating of the mill, resulting in drying of the granulation.

c. **Mill speed:** The speed should be sufficient to efficiently delump the material without straining the equipment.

d. **Feed rate:** The feed rate of the wet granulation is interrelated to screen size and mill size and speed.

4. Drying

The type of drying technique (e.g., tray, fluid bed, and microwave) required for the formulation needs to be determined and justified. The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution, and stability.The optimal moisture content of the dried granulation needs to be determined. High moisture content can result in (1) tablet picking or sticking to tablet punch surfaces and (2) poor chemical stability as a result of hydrolysis. An over dried granulation could result in poor hardness and friability. Moisture content analysis can he performed using the conventional loss-on-drying techniques or such state-of-the-art techniques as near infrared (NIR) spectroscopy. Parameters to consider during drying are:

a) **Inlet/outlet temperature**: The inlet temperature is the temperature of the incoming air to the dryer, while the outlet temperature is the temperature leaving the unit. The inlet temperature is critical to the drying efficiency of the granulation and should be set high enough to maximize drying without affecting the chemical/physical stability of the granulation. The outlet temperature is an indicator of the granulation temperature and will increase toward the inlet temperature as the moisture content of the granulation decreases (evaporization rate).

b) **Airflow:** There should be sufficient airflow to ensure removal of moisture laden air from the wet granulation. Insufficient airflow could prolong drying and affect the chemical stability of the drug. Airflow and the inlet/outlet temperature are interrelated parameters and should be considered together.

c) **Moisture uniformity**: The moisture content could vary within the granulation. Heat uniformity of the dryer (e.g., tray), amount of granulation per tray, and incomplete fluidization of the bed are factors that could affect the moisture uniformity of the granulation.

d) **Equipment capability/capacity**: The load that can be efficiently dried within the unit needs to be known. A larger load will require more moisture to be removed on drying and will affect the drying time. In the case of fluid bed drying, a maximum dryer load is that load above which the dryer will not fluidize the material.

5. Milling

The milling operation will reduce the particle size of the dried granulation. The resultant particle size distribution will affect such material properties as flow, compressibility, disintegration, and dissolution. An optimal particle size/size distribution for the formulation will need to be determined. Factors to consider in milling are:

a) **Mill type:** What mill type (e.g., impact or screen) should be used? Each has several variants, depending on the means to reduce the particles. The type of mill can generate a different particle size/size distribution. Particle size testing will need to be conducted and the results examined when substituting mill types.

b) **Screen size:** The selected screen size will affect the particle size. A smaller screen size will produce a smaller particle size and a greater number of fines.

c) **Mill speed**: What is the optimal mill speed? A higher mill speed will result in a smaller particle size and possibly a wider particle size distribution. It can also generate more heat to the product, depending on the screen size and feed rate, which could affect the stability of the product.

d) **Feed rate**: The feed rate is dependent on the mill capacity, screen size, and mill speed.

6. Tablet Compression: Compression is a critical step in the production of a tablet dosage form. The materials being compressed will need to have adequate flow and compression properties. The material should readily flow from the hopper onto the feed frame and into the dies. Inadequate flow can result in “rat holing” in the hopper and/ or segregation of the blend in the hopper/feed frame. This can cause tablet weight and content uniformity problems. As for the compressibility properties of the formulation, it should be examined on an instrumented tablet press.

Factors to consider during compression are as follows:

a) **Tooling:** The shape, size, and concavity of the tooling should be examined based on the formulation properties and commercial specifications. For intagliated (embossed) tablets, factors such as the position of the intagliation on the tablet and the intagliation depth and style should be examined to ensure that picking of the intagliation during compression or fill-in of the intagliation during coating does not occur.

b) **Compression speed:** The formulation should be compressed at a wide range of compression speeds to determine the operating range of the compressor. The adequacy of the material's flow into the dies will be determined by examining the tablet weights. Is a force feeder required to ensure that sufficient material is fed into the dies?

c) **Compression/ejection force:** The compression profile for the tablet formulation will need to be determined to establish the optimal compression force to obtain the desired tablet hardness. The particle size/size distribution or level of lubricant may need to be adjusted in order to have a robust process on a high-speed compressor.

The following in-process tests (as discussed in Sec. V) should examined during the compression stage:

- Appearance
- Hardness
- Tablet weight
- Friability
- Disintegration
- Weight uniformity

7. Tablet Coating

Tablets may be coated for various reasons.

- Stability
- Taste masking
- Controlled release
- Product identification
- Aesthetics
- Safety–material handling

Tablet coating can occur by different techniques (e.g., sugar, film, or compression). Film coating has been the most common technique over recent years and will be the focus of this section. Key areas to consider for tablet coating include the following:

a) **Tablet properties**: Tablet properties such as hardness, shape, and intagliation (if required) are important to obtain a good film-coated tablet. The tablet needs to be hard enough to withstand the coating process. If tablet attrition occurs, the tablets will have a rough surface appearance. For shape, a round tablet will be easier to coat

than tablets will multiple sides or edges because of the uniformity of the surface. For intagliated tablets, the intagliation style and depth should be developed to prevent fill-in or chipping of the intagliation.

b) **Equipment type:** The type of coater will need to be selected. Conventional or perforated pan and fluid bed coaters are potential options.

c) **Coater load:** What is the acceptable tablet load range of the equipment? Having too large a pan load could cause attrition of the tablets because of the overall tablet weight in the coater. In the case of a fluid bed coater, there may not be sufficient airflow to fluidize the tablets.

d) **Pan speed**: What is the optimal pan speed? This will be interrelated to other coating parameters, such as inlet temperature, spray rate, and flow rate.

e) **Spray guns**: The number and types of guns should be determined in order to efficiently coat the tablets. The spray nozzles should be sized properly to ensure even distribution over the tablet bed and to prevent clogging of the nozzles. The location and angle of the spray gun(s) should be positioned to get adequate coverage. Having the guns positioned too close together can lead to a portion of the tablets to be over wet.

f) **Application/spray rate:** The optimal application/spray rate should be determined.

Spraying too fast will cause the tablets to become over wet, resulting in clumping of tablets and possible dissolution of the tablet surface. Spraying too slowly will cause the coating materials to dry prior to adhesion to the tablets. This will result in a rough tablet surface and poor coating efficiency.

g) **Tablet flow:** The flow or movement of the tablets in the coater should be examined to ensure proper flow. There should be sufficient tablet bed movement to ensure even distribution of the coating solution onto the tablets. The addition of baffles may be required to provide adequate movement of tablets for tablet coating.

h) **Inlet/outlet temperature and airflow:** These parameters are interrelated and should be set to ensure that the atomized coating solution reaches the tablet surface and then is quickly dried.

i) **Coating solution**: The concentration and viscosity of the coating solution will need to be determined. The solution will need to be sufficiently diluted in order to spray the material on the tablets. The concentration of the coating solution will also determine the amount and volume of solution to be applied to the tablets. The stability of the coating solution should be investigated to establish its shelf life.

j) **Coating weight:** A minimum and maximum coating weight should be established for the tablet. Sufficient coating material should be applied to the tablets to provide a uniform appearance; however, it should not be great enough to cause fill-in of the intagliation.

k) **Residual solvent level:** If solvents are used for tablet coating, the residual solvent level will need to be determined. Appearance testing of the tablets is critical during the coating operation. Items to look for include the following:

- Cracking or peeling of the coating
- Intagliation fill-in
- Surface roughness
- Color uniformity

Coating efficiency should be determined for the coating operation. The efficiency will determine the amount of coating solution overage that may be required.

Table 1:- Different Process validation Parameters involved in the manufacturing of a tablet:

Sr. No	PROCESS STEPS	CONTROLLED VARIABLES	TEST
1	Pre-blending	Blending time. RPM, Load size, Order of addition.	Blend uniformity
2	Granulation	Mixing speed, Amount of granulating fluid, Feed rate granulation time, Load.	Drug distribution, water content, size
3	Drying	Initial temperature, Outlet temperature, Drying temperature.	Particle size distribution, densities, LOD
4	Milling	Screen size, Milling Speed, Feed rate.	Particle size, bulk and tap densities'
5	Lubrication	Blending time, Blender speed, Load size.	Particle size distribution, bulk and tap densities, flow properties
6	Compression	Compression rate, Granule feed rate, Pre-compression force, and Compression force.	Appearance, hardness, thickness. Friability, Assay
8	Coating	Pan load, Inlet/Exhaust temperatures, Inlet/Exhaust humidifies, Pan speed, Atomizing pressure, Spray rate.	Thickness, dissolution assay, % wt gain,

Responsibility:

The validation working party is convened to define progress, coordinate and ultimately, approve the entire effort, including all of the documentation generated. The working party would usually include the following staff members, preferably those with a good insight into the company's operation.

- Head of quality assurance
- Head of engineering
- Validation manager
- Production manager
- Specialist validation discipline

Table-2: Different department and their responsibility in Process Validation in Pharmaceutical industry.

Department /Designation	**Responsibility**
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples Collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering Support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

Conclusion:

Validation has been proven assurance for then process efficiency sand sturdiness and it is the fully fledged quality attributing tool for the pharmaceutical industries. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry.

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