

**PROCESS VALIDATION OF SOLID DOSAGE FORM**

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**ABSTRACT**

The goal of quality system is to consistently produce products that are suitable for their intended use. Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. It is establishing documented evidence that a process does what it purports to do, base on information generated during actual implementation of the process. In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation. Validation is the art of designing and practicing the designed steps alongside with the documentation.

Solid dosage forms include tablets and capsules. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials. Despite the ongoing development of more sophisticated solid drug delivery system, tablets are still by far the most prevalent solid dosage form. Additionally a view of validation against the quality assurance, drug development and manufacturing process has been discussed.

**KEY WORDS:** Quality, process validation, quality assurance, consistency.

**INTRODUCTION** <sup>[1,2,3]</sup>

Process is a series of inter related functions and activities using a variety of specified actions and equipment which is designed to produce a defined result. To validate the reproducibility and consistency of a process, the full defined process is carried out using validated equipment, under the established procedure usually at least 3 times. The process must successfully and consistently meet all acceptance criteria each time, to be considered a

validated process. In many cases, "worst case" conditions are used for the validation to ensure that the process is acceptable in the extreme case. Sometimes worst case conditions for systems can only really be tested over time and hence must be evaluated using a rigorous long term monitoring programme.

Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation which is a systemic approach to identifying, evaluating, measuring, documenting and reevaluating a series of critical steps in the manufacturing process that require control to ensure reproducible final product.

USFDA defines process validation as establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

Solid dosage forms include tablets and capsules. The manufacturing of solid dosage form involves extensive powder handling. The powder must be blended for uniformity and converted into dosage form either through compression or encapsulation. Typical requirements include weighing, blending, granulation areas, compression or encapsulation areas, and coating areas.

Despite the ongoing development of more sophisticated solid drug delivery system, tablets are still by far the most prevalent solid dosage form. The emphasis will be on the practical inspectional requirement, rather than on a theoretical approach that does not reflect the practicalities encountered when validation actual production operations. A tablet is a pharmaceutical dosage form it comprises a mixture of active substances and excipient can include binders, glidants, and lubricants to ensure efficient tableting, disintegrants to promote tablet break-up in the digestive tract sweeteners or flavors to enhance the taste and pigments to make the tablet visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow to control the release rate of active ingredients to make it more resistant to the environment to enhance the tablets appearance.

**DEFINITION OF PROCESS VALIDATION** <sup>[3,4,5]</sup>**As per U.S. Food and Drug Administration (FDA)**

“Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics.” The definition is very well thought out and each word has a special significance:

**Documented Evidence**

Validation requires a through documentation everything that is not documented is considered incomplete.

**High degree of Assurance**

The assurance is that a large software package as used in complex computerized systems is rarely free of errors. Frequently there is a perception that validation means ‘error free’. This assumption is wrong. During the validation process everything realistically possible should be done to reduce errors to a high degree.

**Specific process**

Same subparts of validation such as qualification. (Installation, Operation, Performance) are product specific and have to be done for each system

**Consistently**

Validation is not a one-time event. The performance of equipment has to be controlled during the entire life of product.

**Predetermined Specifications**

Validation activities start with the definition of specifications. The performance of equipment is then verified against these specifications. Acceptance Criteria must be defined prior to testing.

**As per ICH**

“Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of Repeatedly and Reliably producing a finished product of the required quality.”

**As per WHO**

“Validation studies are essential part of GMP and should be conducted in according with predefined protocols. A written report summarizing results and conclusions should be recorded, prepared and stored. Processes and procedures should be established based upon the validation study and undergo periodic revalidation to ensure that they remain capable of achieve the intended results. Particular attention should be accorded to the validation of processing, testing, and cleaning procedures. Critical process should be validated, prospectively or retrospectively. When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its stability for routine processing. The defined process, using the materials and equipments specified, should be shown to yield a product consistently of the require quality. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the responsibility of the process, should be validated.”

Process validation is a requirement of the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals. Process validation is a key element in assuring that quality assurance quality is met. It is thorough careful design and validation of both the process and process controls that a manufacturer can establish a high degree of assurance that all manufactured units from successive lots will meet the reset standards.

**WHY IS VALIDATION REQUIRED?** <sup>[5,6,7]</sup>

1. It would not be feasible to use the equipment's without knowing whether it will produce the product we wanted or not.
2. The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
3. The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, and recalls, complaints are the significant parts of the total production cost.
4. Detailed study and control of the manufacturing process- validation is necessary if failure to be reduced and productivity improved.

**The main reasons for validation are****1 Assurance of quality**

Validation and process control are the heart of GMPs. Without Validated and controlled process it is impossible to achieve quality products. Hence validation is a key element in

assuring the quality of the product. The basic principles of quality assurance, that are quality, safety, and effectiveness must be designed and built in to the product. Quality cannot be inspected or tested in the finished products. So, each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. Validation checks the accuracy and reliability of a system or a process to meet the predetermined criteria. A successful validation provides high degree of assurance that a consistent level of quality is maintained in each unit of the finished product from one batch to another batch. The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance functions; nevertheless it is fair to say that process validation is a quality assurance tool because it establishes a quality standard for the specific process.

## **2 Cost reduction (Economics)**

Due to successful validation, there is a decrease in the sampling and testing procedures and there are less number of product rejections and retesting. This lead to cost-saving benefits.

## **3 Compliance**

For compliance to current good manufacturing practices cGMPs, validation is essential.

## **4 Government regulation.**

## **5 Process Optimization**

The optimization of the facility, equipment system and closures etc results in a product that meets quality requirements at the lowest costs. Trained, qualified people are the key elements in process optimization that results in improving efficiency and productivity.

## **6 Safety**

Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges used to reduce accident and results in safety.

## **7 Better Customer Quality**

Through Proper validation, Market recall is avoided which result in better customer care and quality of the product.

## **OBJECTIVES OF PROCESS VALIDATION<sup>[8]</sup>**

1 The manufacturing process, in addition to the individual equipment, must be validated.

- 2 The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
- 3 A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a performance qualification section.
- 4 Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation. In the end, process validation will ensure a robust product that is highly reproducible over time.
- 5 In the end, process validation will ensure a robust product that is highly reproducible over time.

#### **ADVANTAGES OF PROCESS VALIDATION<sup>[8]</sup>**

- 1 Expanded real time monitoring and adjustment of process.
- 2 Enhanced ability to statistically evaluate process performance and product variables. e.g., individuals; mean; range; control limits.
- 3 Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
- 4 Improved ability to set target parameters and control limits for routine production, correlating with validation results.
- 5 Enhanced reporting capability.

#### **PROCESS VALIDATION STAGES<sup>[9]</sup>**

**The Process validation activities can be described in three stages.**

##### **Stage 1 – Process Design**

The commercial process is defined during this stage based on 100 knowledge gained through development and scale-up activities.

##### **Stage 2 – Process Qualification**

During this stage, the process design is confirmed as 103 being capable of reproducible commercial manufacturing.

##### **Stage 3 – Continued Process Verification**

Ongoing assurance is gained during routine production that the process remains in a state of control.

## PHASES OF PROCESS VALIDATION<sup>[9]</sup>

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, scaleup 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.

## TYPES OF PROCESS VALIDATION<sup>[3,10]</sup>

### (1) Prospective validation

- 1 Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. Validation conducted prior to the distribution of either a new product or product made under a revised manufacturing process.
- 2 This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. This is a preplanned scientific approach and includes initial stages of equipment validation. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.
- 3 Prospective validation includes those considerations that should be made before an entirely new product is introduced by a firm or when there is a change in the

manufacturing process which may affect the product's characteristics, such as uniformity and identity.

- 4 The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials.
- 5 It is generally considered acceptable that three consecutive batches\runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process.
- 6 It is preferred that the validation batches made should be of the same size as the intended production scale batches. When this is not practical, a reduced batch size corresponding to at least 10% of the intended batch size for full-scale production can be considered.
- 7 The following are considered as key elements of prospective validation.

### **1 Equipment and process**

- 1 Equipment: Installation qualification (DQ, IQ, OQ and PQ)
- 2 Process: Performance qualification
- 3 Product: Performance qualification

### **2 System to assure timely revalidation**

### **3 Documentation**

## **Equipment and Process**

The equipment and processes should be designed and/or selected so that product specifications are consistently achieved. This should be done with the participation of all appropriate groups that are concerned with assuring a quality product, e.g., engineering design, production operations, and quality assurance personnel.

## **Equipment**

### **Installation Qualification**

- 1 Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process. This phase of validation includes examination of equipment design; determination of calibration, maintenance, and adjustment requirements; and identifying critical equipment features that could affect the process and product.

Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and control.

- 2 In assessing the suitability of a given piece of equipment, it is usually insufficient to rely solely upon the representations of the equipment supplier, or upon experience in producing some other product. Sound theoretical and practical engineering principles and considerations are a first step in the assessment.
- 3 It is important that equipment qualification simulate actual production conditions, including those which are "worst case" situations.
- 4 Tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results. All acceptance criteria must be met during the test or challenge. If any test or challenge shows that the equipment does not perform within its specifications, an evaluation should be performed to identify the cause of the failure. Corrections should be made and additional test runs performed, as needed, to verify that the equipment performs within specifications. The observed variability of the equipment between and within runs can be used as a basis for determining the total number of trials selected for the subsequent performance qualification studies of the process.
- 5 Once the equipment configuration and performance characteristics are established and qualified, they should be documented. The installation qualification should include a review of pertinent maintenance procedures, repair parts lists, and calibration methods for each piece of equipment. The objective is to assure that all repairs can be performed in such a way that will not affect the characteristics of material processed after the repair. In addition, special post-repair cleaning and calibration requirements should be developed to prevent inadvertent manufacture of non-conforming product. Planning during the qualification phase can prevent confusion during emergency repairs which could lead to use of the wrong replacement part.

## **Process**

### **Performance Qualification**

- 1 The purpose of performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. In entering the performance qualification phase of validation, it is understood that the process specifications have been established and essentially proven acceptable through laboratory or other trial methods and that the equipment has been judged acceptable on the basis of suitable installation studies.

- 2 Each process should be defined and described with sufficient specificity so that employees understand what is required. Parts of the process which may vary so as to affect important product quality should be challenged. In challenging a process to assess its adequacy, it is important that challenge conditions simulate those that will be encountered during actual production, including "worst case" conditions. The challenges should be repeated enough times to assure that the results are meaningful and consistent.
- 3 Each specific manufacturing process should be appropriately qualified and validated. There is an inherent danger in relying on what are perceived to be similarities between products, processes, and equipment without appropriate challenge.

## **Product**

### **Performance Qualification**

- 1 For purposes of this guideline, product performance qualification activities apply only to medical devices. These steps should be viewed as pre-production quality assurance activities.
- 2 Before reaching the conclusion that a process has been successfully validated, it is necessary to demonstrate that the specified process has not adversely affected the finished product. Where possible, product performance qualification testing should include performance testing under conditions that simulate actual use. Product performance qualification testing should be conducted using product manufactured from the same type of production equipment, methods and procedures that will be used for routine production. Otherwise, the qualified product may not be representative of production units and cannot be used as evidence that the manufacturing process will produce a product that meets the predetermined specifications and quality attributes.
- 3 After actual production units have successfully passed product performance qualification, a formal technical review should be conducted and should include: Comparison of the approved product specifications and the actual qualified product.
- 4 Determination of the validity of test methods used to determine compliance with the approved specifications
- 5 Determination of the adequacy of the specification change control program.

### **System to assure timely revalidation**

- 1 There should be a quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact

on product effectiveness or product characteristics, and whenever there are changes in product characteristics. Furthermore, when a change is made in raw material supplier, the manufacturer should consider subtle, potentially adverse differences in the raw material characteristics. A determination of adverse differences in raw material indicates a need to revalidate the process.

- 2 One way of detecting the kind of changes that should initiate revalidation is the use of tests and methods of analysis which are capable of measuring characteristics which may vary. Such tests and methods usually yield specific results which go beyond the mere pass/fail basis, thereby detecting variations within product and process specifications and allowing determination of whether a process is slipping out of control.
- 3 The quality assurance procedures should establish the circumstances under which revalidation is required. These may be based upon equipment, process, and product performance observed during the initial validation challenge studies. It is desirable to designate individuals who have the responsibility to review product, process, equipment and personnel changes to determine if and when revalidation is warranted.
- 4 The extent of revalidation will depend upon the nature of the changes and how they impact upon different aspects of production that had previously been validated. It may not be necessary to revalidate a process from scratch merely because a given circumstance has changed. However, it is important to carefully assess the nature of the change to determine potential ripple effects and what needs to be considered as part of revalidation.

### **Documentation**

- 1 It is essential that the validation program is documented and that the documentation is properly maintained. Approval and release of the process for use in routine manufacturing should be based upon a review of all the validation documentation, including data from the equipment qualification, process performance qualification, and product/package testing to ensure compatibility with the process.
- 2 For routine production, it is important to adequately record process details (e.g., time, temperature, equipment used) and to record any changes which have occurred. A maintenance log can be useful in performing failure investigations concerning a specific manufacturing lot. Validation data (along with specific test data) may also determine expected variance in product or equipment characteristics.

### Retrospective Validation

- 1 It is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information.
- 2 Validation of a process for a product already in distribution based upon accumulated production, testing and control data.
- 3 Retrospective Validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analyzed to determine the limits of process parameters.
- 4 A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.
- 5 Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Retrospective validation may then be useful in establishing the priorities for the validation program. If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule. For tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form.
- 6 The retrospective validation option is chosen for established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified. Prior to undertaking retrospective validation, where in the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities and subsystems used in connection with the manufacturing process must be qualified in conformance with cGMP requirements. The basis for retrospective validation is stated in 21CFR 211.110(b): "Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate."

- 7 Using either data-based computer systems or manual methods, retrospective validation may be conducted in the following manner:
  - 1 Gather the numerical data from the completed batch record and include assay values, end-product test results, and in-process data.
  - 2 Organize these data in a chronological sequence according to batch manufacturing data, using a spreadsheet format.
  - 3 Include data from at least the last 20–30 manufactured batches for analysis. If the number of batches is less than 20, then include all manufactured batches and commit to obtain the required number for analysis.
  - 4 Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.
  - 5 Subject the resultant data to statistical analysis and evaluation.
  - 6 Draw conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.
  - 8 Issue a report of your findings (documented evidence).

### **Concurrent Validation**

- 1 It is establishing documented evidence that a process does what it purports to do, based on information generated during actual implementation of the process. In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation. It may be practical approach under certain circumstances.
- 2 Examples of these may be as follows:
  - 1 When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
  - 2 Where product is a different strength of a previously validated product with same ratio of active ingredients.
  - 3 When number of lots evaluated under retrospective validation was not sufficient to obtain a high degree of assurance demonstrating that process is fully under control.
  - 4 When number of batches produced are limited.
- 5 It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. 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.

- 6 The decision to carry out concurrent validation must be justified, documented approved by authorized person.

### Re-Validation

- 1 Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Revalidation provide an assurance that changes in the process/equipment introduced intentionally/ unintentionally; is in accordance with change control procedures do not adversely affect process characteristics and product quality.
- 2 Possible reasons for starting the revalidation process include:
  - 1 The transfer of a product from one plant to another
  - 2 Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality
  - 3 The necessity of periodic checking of the validation results
  - 4 Significant (usually order of magnitude) increase or decrease in batch size.
  - 5 Sequential batches that fail to meet product and process specifications.
  - 6 The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.
  - 7 Changes in source of active raw material manufacturers
  - 8 Changes in raw materials
  - 9 Changes in packaging materials
  - 10 Changes in process e.g., mixing time, drying temperature, and batch size etc.
  - 11 Changes in equipment
  - 12 Changes in plant facility
  - 13 Monitoring of equipment capabilities over a period of time.

### THREE LOT CONTROVERSY<sup>[3]</sup>

During 1983-1984, representatives of FDA and industry debated over the value of poisoning three consecutive commercial sized lots as pivotal evidence of process validation industry agreed that FDAs argument for three lots might be suitable device, but agreed successful that it was not appreciate for pharmaceutical processes for several reasons.

- 1 Unnecessarily costly and risky to perform to regulatory submission.
- 2 Limited statistical benefit for three lots.

- 3 Establishing critical process parameter ranges and probable adverse consequences of exceeding ranging limits represents better investment of resources and contributes more to process robustness and reliability while the three lot requirement can detract from such efforts.

In 1990, when FDA launched its Pre-approval inspection (PAI) program, the three-lot again arose. PAI chief architects (Richard Davis and Joseph Philips, FDA neqark district directors) announced they could require evidence if three consecutive successful lots of commercial size prior to shipment of a new product across state lines (NDA) approvable letter.

The industry did not protest the requirements several reasons made requirement logical.

- 1 Three commercial lots add some degree of assurance that the process made 1 the requirement logical action of reproducibility.
- 2 Three lots can be made in practical a period of time compared with number of lots require to gather statistical evidence of responsibility.
- 3 The overall approach forces of validation emphasis on process development measures that occur earlier in the lifecycle.

Since 1990, most firms have found pre-distribution three-lot requirement practical and useful. Some have made the mistake of believing that critical parameters should be varied during the three runs in order develop validation evidence, usually of the kind that can be developed in the laboratory or pilot plant more economically and less risk of failure.

### **REQUIREMENTS TO INITIATE PROCESS VALIDATION** <sup>[5,6,7,12]</sup>

This project intends to review the current practices followed in the process validation for a tablet dosage form.

#### **Operations involved in tablet manufacturing**

The manufacture of oral solid dosage forms such as tablets is a complex multi-stage process under which the starting materials change their physical characteristics, a number of times before the final dosage form is produced.

The following operations are involved in tablet manufacturing:

#### **Process overview of tablet manufacturing**

- 1 Dispensing
- 2 Sifting

- 3 Dry mixing
- 4 Granulation
- 5 Drying
- 6 Milling
- 7 Blending
- 8 Compression
- 9 Packaging

### **DISPENSING (Weighing & Measuring)**

- 1 Dispensing is the first step in any pharmaceutical manufacturing process.
- 2 Dispensing is one of the most critical steps in pharmaceutical manufacturing; as during this step, the weight of each ingredient in the mixture is determined according to dose.
- 3 Dispensing can be done by purely manual by hand scooping from primary containers and weighing each ingredient by hand on a weigh scale on mechanical devices according to BMR specification.
- 4 Issues like weighing accuracy, dusting control (laminar air flow booths, glove boxes), during manual handling lot control of each ingredient, material movement into and out of dispensary should be considered during dispensing.
- 5 There should be no due for calibration of the balance and zero error must be ensured in the balance.
- 6 Ensure the expiry date of material is later than that of the batch expiry date and retest date is older than day of dispensing.
- 7 Ensure all the materials are issued as per BMR.

### **SIFTING**

Size plays an important role in the homogeneity of the final product. When large differences exist between the active ingredient and excipients, demixing effects can occur making thorough mixing difficult during the subsequent processing steps. Size can also be a factor in the stability. Fine materials are relatively more open to attack from atmospheric oxygen, heat, light, humidity and interacting excipients than coarse materials. Because of these significant roles it is important to decide on a desired size range, and hence to maintain and control it.

- 1 Factors to be considered during sifting:
- 2 Check and record the temperature and relative humidity in process area. Temperature should be  $25 \pm 2^{\circ}\text{C}$  and RH  $50 \pm 5\%$ .

- 3 Check and ensure visually all the equipments and equipment parts are cleaned, record remarks if any.
- 4 Check and record the integrity of the sieves before and after sifting through out the processing activity.

### **DRY MIXING**

Mixing is defined as the process that tends to result in the randomization of dissimilar particles within a system. Dry mixing is generally carried out in a rapid mixer granulator. Dry mixing involves the mixing of ingredients before adding the granulation or binder solution.

### **GRANULATION**

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. Granulation method can be broadly classified into two types.

- 1 Wet granulation
- 2 Dry granulation

### **5) DRYING**

Drying is defined as the removal of a liquid from a material by the application of heat and is accomplished by the transfer of a liquid from a surface into an unsaturated vapor phase.

#### **Steps followed in drying**

- 1 Check and ensure the integrity of the FBD bag.
- 2 Initially dry the wet granules with air for 10 minutes, till the odor of IPA is eliminated.
- 3 Dry the granules as per BMR instructions.
- 4 Check the LOD of granules.
- 5 Check and ensure that the dried granules are not stored above 25°C before the milling is started.
- 6 Check the integrity of the sieves before and after sieving.
- 7 Collect the weight of sifted and dried granules.

#### **Factor to be considered during drying**

##### **Loss on Drying:**

LOD, is an expression of moisture content on a wet- weight bases, which is calculated As

$$\% \text{ LOD} = \frac{\text{Weight of water in sample}}{\text{Total weight of wet sample}} \times 100$$

The moisture in a solid can be expressed on a wet – weight or dry – weight basis. On wet – weight basis, the water content of a material is calculated as the percentage of the weight of the wet solid, whereas on dry – weight basis, the water is expressed as a percentage of the weight of the dry solid.

### Moisture Content

Measurement of the moisture in wet a solid is calculated on a dry – weight basis.

$$\% \text{ M.C} = \frac{\text{Weight of water in sample}}{\text{Weight of dry sample}} \times 100$$

### 6) MILLING

Milling is the mechanical process of reducing the particle size of solids. Milling equipment is usually classified as

1. Coarse : 20 #
2. Intermediate : 20 -200 #
3. Fine milling : < 200 #

### Pharmaceutical Applications

- 1 The control of particle size and specific surface affects the therapeutic efficiency of medical compounds.
- 2 The drying of wet masses may be facilitated by milling, which increases the surface area and reduces the distance; the moisture must travel within the particle to reach the outer surface.
- 3 Milling enables the free flow of powder to produce tablets of uniform weight.
- 4 The mixing and blending of several solid ingredients of a pharmaceutical is easier and more uniform if the ingredients are approximately of the same size.

### DRY GRANULATION

In the granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granule. Two methods are used for dry granulation. The most widely used method is slugging. Where the powder is pre-compressed and the resulting tablet or slug is milled to yield the granules. The other method is to pre-compress the powder with pressure rolls using a machine such as chilsonator.

## **BLENDING**

The powder/granules blending are involved at stage of pregranulation and/or post granulation stage of tablet manufacturing. Each process of mixing has optimum mixing time and so prolonged mixing may result in an undesired product. So, the optimum mixing time and mixing speed are to be evaluated. Blending step prior to compression is normally achieved in a simple tumble blender. The blender may be mixed blender into which the powder are charged, blended and discharged. In special cases of mixing a lubricant, over mixing should be particularly monitored. The various blenders used include double cone blender, 'V' blender, octagonal blender, container blender, tumbling blender, agitated powder blender, etc.

## **TABLET COMPRESSION**

After the preparation of granules (in case of wet granulation) or slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to the final product. There are a number of types of tablet presses or tableting machines, each varying in productivity but similar in basic function and operation. They all compress a tablet formulation within a steel die cavity by the pressure exerted by the movement of two steel punches, lower punch and an upper punch. It 'squeezes' the ingredient into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet. The operation of a single punch describes the basic mechanical process. Stages occurring during compression:

### **Stage 1**

Top punch is withdrawn from the die by the upper cam. Bottom punch is low in the die so the powder falls in through the hole and fills the die.

### **Stage 2**

Bottom punch moves up to adjust the powder weight it raises and expels some powder.

### **Stage 3**

Top punch is driven into the die by upper cam. Bottom punch is raised by lower cam. Both punch heads pass between heavy rollers to compress the powder.

### **Stage 4**

The upper cam withdraws top punch. Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface-by-surface plate.

**Stage 5**

Return to stage 1. Rotary tablet machines equipped with multiple punches and operate through the continuous rotating movement of the punches. A single rotary press with 16 stations (16 sets of punches and dies) may produce up to 1150 tablets per minutes. Double rotary tablet presses with 27, 33, 37, 41, or 49 sets of punches and dies are capable of producing 2 tablets for each data.

**Factors to be considered during compression:**

- 1 Check and ensure the temperature and relative humidity of the compression room is not more than 25°C and RH not more than 50%.
- 2 Check and ensure the compression machine is cleaned as per BMR.
- 3 Collect tablets and inspect for appearance, weight, thickness, friability and hardness at regular interval as per BMR.
- 4 Tablet weight variation shall be in mg, hardness shall be in kg/cm<sup>2</sup> and thickness shall be in mm (As per BMR).
- 5 Collect tablets by “Bracketing” i.e., by increasing this speed of the compression machine from the target speed and by reducing the speed by 4 rpm.
- 6 Collect tablets during initial, middle and end of the compression process and subjective it to analysis for assay.

**PACKAGING**

Pharmaceutical manufacturers have to pack their medicines before they can be sent out for distribution. The type of packaging will depend on the formulation of the medicine. ‘Blister packing’ is a common form of packing used for a wide variety of products. They are safe and easy to use and they allow the consumer to see the contents without opening the pack. Many pharmaceutical companies use a standard size of blister pack. This saves the cost of different tools and to change the production machinery between products. Sometimes the pack may be perforated so that individual tablets can be detached. This means that the expiry date and the name of the product have to be printed on each part of the package. The blister pack itself must remain absolutely flat as it travels through the packaging processes, especially when it is inserted into a carton.

**Factors to be considered during packing**

- 1 Check and record the temperature at the heating roller and sealing roller are as per BPR.

- 2 Check and record that the over printing instructions on labels and cartons as per instructions of BPR.
- 3 Check and verify that the price overprinted on label and carton is as per current price list.
- 4 After ensuring the proper labeling of tablets, check for correctness of cartons packing for the same.

## **VALIDATION OF SOLID DOSAGE FORMS** <sup>[3,13]</sup>

There are numerous factors that should be considered when developing and validating solid dosage forms.

### **1 Compressed tablets**

#### **1.1 Tablet Composition**

Provide the reason for the presence of each ingredient in the formula.

#### **1.2 Process Evaluation and Selection**

1. Determination of the optimal blending time
2. Demixing and segregation of components
3. Content uniformity
4. Distribution of active ingredient in the overall mix. E.g. direct compression of formulations, the type of blender, length of blending operation and the intensity of shear during the blending operation will be different depending upon the 'objective'.
5. Possible interaction between the process and its effects on tablet (core) compression. E.g.: rpm of compression machine.
6. Characteristics of blend
7. Bulk density
8. Particle size distribution
9. Moisture, if applicable
10. Any ingredient in the formulation affecting the density of the final blend to a greater extent than any other ingredient
11. Colour uniformity
12. Different sized loads in the blender.

#### **1.3 Wet Granulation**

##### **1) Evaluation of blender depends on**

Binder concentration

Solubility in granulation solution

Behavior during the drying step

## **2) Evaluation of Mixed granulation**

1. Compare density of wet granulation versus dry powder mix.
2. Determine the optimum density powder flow & tablet formulation.
3. Amount of granulating solution required for optimum granulation.
4. Compactability of granulation.
5. Optimal mixing time.

## **3) Evaluation of drying step and dried granules**

1. Determine the optimal moisture content of the dried granules.
2. Particle size distribution of dried granules.
3. Density of dried granules.
4. Equipment and/or instrument conditions required promoting drug.
  1. Airflow
  2. Inlet temperature
  3. Outlet temperature
  4. Dryer efficiency
  5. Load to be dried.
  - 6.

### **1.4 Milling operation for the dried granules**

1. Particle size distribution
2. Dissolution (if applicable)
3. Granule disintegration

### **1.5 Tablet (core) Compression**

1. Appearance
2. Color uniformity
3. Stability
4. Moisture pick up versus percent relative humidity
5. Powder flow from hopper
6. Separation or uniformity in feed frame
7. Special requirements needed. E.g. Screen to delump powder
8. Optimal speed of tablet press

9. Tablet parameters at varying speeds of compression machine.

## CONCLUSION

Quality is the first intention to any industry and its products manufactured. Thus to obtain such qualities are the current interest in every pharmaceutical industry. It is establishing documented evidence that a process does what it purports to do, base on information generated during actual implementation of the process. In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation. Validation is the art of designing and practicing the designed steps alongside with the documentation. Solid dosage forms include tablets and capsules. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials. Despite the ongoing development of more sophisticated solid drug delivery system, tablets are still by far the most prevalent solid dosage form.

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