INDUSTRIAL PROCESS VALIDATION OF SOLID DOSAGE FORMS – AN OVERVIEW

Satyabrata Jena*, G. Arjun, N. V. Anil Kumar Ravipati, D.Satish kumar, Vinod.K.R, David Banji
Department of pharmaceutics, Nalanda College of pharmacy, Nalgonda, Andhra Pradesh. Pin-508 001, India.
***Email:** sbjena2007@gmail.com

ABSTRACT

Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated we can assure that the final product is of the best quality. Validation of the individual steps of the processes is called the process validation. Different dosage forms have different validation protocols. Here this article concentrates on the process validation of solid dosage forms, protocol preparation and regulatory basis for process validation with special emphasis on tablets in industry. It gives in detail the validation of each step of the manufacturing process through wet granulation.

Keywords: Process validation, Solid dosage forms, Tablets, Regulatory basis, Protocol.

INTRODUCTION

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation[1].

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 systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[3]

USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics."[5]

Solid dosage forms include tablets and capsules. The manufacturing of solid dosage forms involves extensive powder handling. The powder must be blended for uniformity and converted into the dosage form either through compression or encapsulation. Typical requirements include weighing, blending, mixing/granulation areas, compression/encapsulation areas, and coating areas. [2]

Despite the ongoing development of more sophisticated solid drug delivery systems, 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 (and problems) encountered when validating actual production operations.

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipients can include binders, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.[7]

TYPES OF PROCESS VALIDATION: [10, 13, 15]

1. Prospective Process Validation. Where an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put to commercial use. Most validation efforts require some degree of prospective experimentation in order to generate validation support data.

2. Concurrent Process Validation. Establishing documented evidence that the process is in a state of control during the actual implementation of the process. This is normally performed by conducting in-process testing and/or monitoring of critical operations during the manufacture of each production batch.

3. Retrospective Process Validation. Where historic data taken from the records of the completed production batches are used to provide documented evidence that the process has been in a state of control prior to the request for such evidence.

THE REGULATORY BASIS FOR PROCESS VALIDATION [3, 6, 8, 9]

The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations.

In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one of its basic tenets the assurance that approved validation protocols and schedules were being generated and that comprehensive development, scale-up, and biobatch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit. There are several important reasons for validating a product and/or process.

First, manufacturers are required by law to conform to cGMP regulations. Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality.

Although the original focus of validation was directed towards prescription drugs, the FDA Modernization Act of 1997 expanded the agency's authority to inspect establishments manufacturing over-the-counter (OTC) drugs to ensure compliance with cGMP.

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with cGMP.

The cGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

STRATEGY FOR INDUSTRIAL PROCESS VALIDATION OF SOLID DOSAGE FORMS. [3, 6]

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.

GUIDELINES FOR PROCESS VALIDATION OF SOLID DOSAGE FORMS [3, 5]

Numerous factors should be considered when developing and validating solid dosage forms. As a means of providing a broad overview of these validation criteria, the following checklist/guideline as in Table 1, is provided for tablets and dry-filled capsules for inclusion in an in-depth validation program. Some of these unit operations will not be applicable for every solid dosage form (e.g., direct compression tablets and uncoated tablets).

PROTOCOL FOR PROCESS VALIDATION.

The protocol for process validation is given from the tables 2, 3, 4 & 5 as follows:

STEPS FOR VALIDATION AND ACCEPTANCE CRITERIA

The following steps (Table 6) are used in industry for validation of tablets in wet granulation process.

INDUSTRIAL PROCESS EVALUATION AND SELECTION FOR TABLETS [3, 14, 16, 18]

Determine the unit operations needed to manufacture the tablets.

1. Mixing or Blending

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.

Parameters to consider:

- *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.

- *Mixing or blending speed*: Determine the intensity (low/high shear) and/or speed (low/high/optimal shear) (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 overmixed, 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).
- *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 overhandling, 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.
- *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).
  - *Color*: 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.

Table 1: Check list of Validation and Control Documentation

Sr. No.	Selection of cGMP	Validation and control documentation
1	Introduction	Establishing of QA & PV functions
2	Organization and personnel.	Establishment and facility installation and qualification
3	Buildings and facilities	Plant and facility installation qualification Maintenance and sanitation Microbial and pest control
4	Equipment	Installation and qualification cleaning methods.
5	Air and water quality	Water treatment and steam systems air, heat, and vacuum handling.
6	Control of raw material, in-process material, product	Incoming components Manufacturing non-sterile products
7	Production and process controls	Process control systems (instruments and computers)
8	Packing and labeling controls	Depyrogenation, sterile packing, filling, and closing.
9	Holding and distribution	Facilities
10	Laboratory controls	Analytical methods
11	Records and reports	Computer systems
12	Returned and salvage drug products	Batch processing

Table 2: Protocol for title page in industry

Name of the company	
Process validation protocol	
Product:	Page No. : 1 of .....
Protocol No. :	Version No. :
Product name :	
Label claim :	
Master Formula Record (MFR) No. :	
Batch Manufacturing Record (BMR) No. :	
Effective Date :	

Table 3: Protocol approval

	Prepared By	Checked By			Approved By
Signature					
Date					
Name					
Department	Quality Assurance (QA)/Research and development (R&D)	R & D	Production	Quality Control	Head – QA

Table 4: Table of contents

Sr. No.	Title	Page No.
1.	Protocol Approval Sheet	
2.	Table of contents	
3.	Objective	
4.	Scope	
5.	Validation term and responsibility	
6.	Steps for validation and acceptance criteria	
7.	Process flow chart	
8.	Procedure	
9.	Form – A : Review of raw material/packing material	
10.	Form – B : Evaluation of active raw material	
11.	Form – C : Evaluation of inactive raw material	
12.	Form – D : Qualification of equipment	
13.	Form – E : Test instrument calibration	
14.	Form – F : Dry mixing	
15.	Sampling point diagram of RMG	
16.	Form – G : Wet mixing	
17.	Form – H : Drying	
18.	Sampling point diagram of FBD	
19.	Form – I : Lubrication	
20.	Sampling point diagram of RMG	
21.	Form – J : Compression	
22.	Form – K : Coating	
23.	Form – L : Bulk packing	
24.	Re validation criteria	
25.	Change control	
26.	Stability	
27.	Deviations	
28.	Conclusion	
29.	Report and Approval	

Table 5: Validation team and Responsibilities

Department	Designation	Responsibility
Research and development (R&D)	Executive/Officer	To coordinate the entire validation process by scheduling meetings and discussions with production, quality control and quality assurance. Preparation of preliminary validation protocol, master formula record, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review the preliminary validation documents.
Quality assurance	Officer	To coordinate the entire validation process by scheduling meetings and discussions with the team. Preparation of validation protocol, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review of validation documents.
Production	Officer	To participate in performing the validation steps during manufacturing processes. To assist in collection of data.
Quality control	Officer	To test and report the test results
Quality assurance	General manager Quality assurance	To approve the process validation protocol and report. To review of validation documents. To approve the process.

Table 6: Steps for validation and acceptance criteria in wet granulation process

Sr. No.	Steps	Control Variable	Critical Parameters to be checked	Acceptance criteria
1	Dry mixing	Time Impeller speed	Mixing time and speed	Mixing time: .....min. Impeller speed: (slow/medium/high)±5RPM. Content uniformity :90%-110% RSD : ±5%
2	Binder preparation and addition.	Time Temperature, solvent used	Mode and time of addition	Depending up on the formulation.
3	Kneading	Time Impeller speed & chopper speed	Mixing time and speed	Impeller speed : (slow/medium/high) Chopper speed: (slow/medium/high) Depending up on the formulation.
4	Drying	Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time	Initial drying:.....^{0}C Drying time: .....min. Final drying : .....^{0}C±5^{0}C Loss on drying : .....% below 3% or depending on formulation
5	Lubrication	Time Blender/granulator speed	Mixing time and speed	Mixing time: .....min. Speed: slow.....rpm. Content uniformity : Physical parameters – for information.
6	Compression	Pressure and turret speed	Machine speed and compression pressure	Average weight: mg±5%,7.5%,10%. Uniformity of weight mg : Thickness : .....mm Hardness : .....KN or Kg/cm^2 Disintegration time: NMT.....min. Friability : NMT.....%w/w Assay : As per the label claim Dissolution:.....%
7	Coating	Pan speed and spray rate	Pan speed Inlet & outlet temperature Spray rate	Average weight : .....mg±5% Weight of 20 tablets :.....mg Thickness : .....mm Disintegration time: NMT.....min. Assay : As per the label claim Dissolution: .....%

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:

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

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

- *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 (evaporation rate).
- *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.

- *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.
- *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:

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

6. Lubrication

Selection of lubricant: what kind of lubricant should be used? Grade of the lubricant used. Compatibility with other ingredients.

Amount of lubricant added: How much lubricant is required? Too much lubricant will form hydrophobic layer on the tablet resulting in dissolution problems.

Mixing time: How long should the material is mixed to ensure proper formation? Should mixing stop after the addition of the lubricant or should additional mixing be required? If not mixed long enough form problems like chipping, capping, etc.

7. 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:

- *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.
- *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?
- *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 should be examined during the compression stage:

1. Appearance
2. Hardness
3. Tablet weight
4. Friability
5. Disintegration
6. Weight uniformity

8. Tablet Coating

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:

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

- *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.
- *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.
- *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.
- *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.
- *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:

1. Cracking or peeling of the coating
2. Intagliation fill-in
3. Surface roughness
4. Color uniformity
5. Coating efficiency should be determined for the coating operation. The efficiency will determine the amount of coating solution overage that may be required.

9. In-process tests

1. *Moisture content of "dried granulation"*
2. *Granulation particle size distribution*
3. *Blend uniformity*
4. *Individual tablet/capsule weight*
5. *Tablet hardness*
6. *Tablet thickness*
7. *Disintegration*
8. *Impurity profile*

10. Finished product tests

1. *Appearance*
2. *Assay*
3. *Content uniformity*
4. *Tablet hardness*
5. *Tablet friability*
6. Impurity profile
7. *Dissolution*

These key test parameters are the yardsticks by which the major processing variables in solid dosage forms are evaluated. Some processing variables are:

- Mixing time and speed in blenders and granulators
- Solvent addition rates in granulators
- Time, temperature, and airflow conditions in dryers and coaters
- Screen size, feed rate, and milling speed in mills
- Machine speed and compression force in tablet presses

Process validation testing is generally done on the **first three batches** of product made in production-size equipment. Revalidation testing is only done when a "significant" change has occurred. A significant change is one that will alter the in-process or final product specification established during the validation program or a change in formula, process, or equipment.

CHANGE CONTROL [3, 17]

Process validation of a solid dosage form should include an SOP to reassess a process whenever there are significant changes in the process, equipment, facilities, reactants, process materials, systems, and so on that may affect the *critical* quality attributes and specifications of the solid dosage forms. Such changes should be documented and approved in accordance with the scope of the change control SOP.

The change control SOP should consist of the following elements:

- Documentation that describes the procedure, review, approval, and basis for formal revalidation studies
- Identification of the change and assessment of its likely implication
- Requirements for monitoring change and testing needs
- Assessment of information and justification for the change
- Review and formal approval to proceed
- Identification of changes made to the physical and chemical composition of the solid dosage forms.
- Possible regulatory action and customer notification

DOCUMENTATION [6, 11, 12, 13]

Documentation at each stage of the process validation lifecycle is essential for effective communication in solid dosage form projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle.

In addition to being a fundamental tenet of following the scientific method, information transparency and accessibility are essential so that organizational units responsible and accountable for the process can make informed, science-based decisions that ultimately support the release of a product to commercial scale. The degree and type of documentation required by CGMP is greatest during process qualification, and continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (21 CFR 211.22 and 211.100).

CONCLUSION

Solid dosage form validation should be part of a comprehensive validation program within an industry. The multidisciplinary validation team must identify the product and process characteristics that must be studied and incorporate specific validation tests to ensure that that product will meet all quality, manufacturing, and regulatory requirements. The total program should begin with validation of the active pharmaceutical ingredient (API) characteristics so that this material will be uniform batch after batch, providing a solid footing upon which the dosage form will be built. Scientific information obtained during the preformulation stage can form the basis for a well-designed and comprehensive validation program. The parameters chosen must be relevant indicators of a controlled process. It is not sufficient merely to devise a test and set specifications for it; rather, it is desirable to show a cause and effect relationship between the parameter tested and control of the quality and/or process output. Continued awareness of validation requirements and a diligent application of validation principles will thus help to ensure that pharmaceutical products will be able to be developed and produced with the quality and reproducibility required from regulatory agencies across the world.

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