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Review Article

Basic Aspects of Process Validation of Solid Oral Dosage Forms

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Validation of the manufacturing process is performed in order to ensure that the manufacturing process does what it purported to do. Pharmaceutical validation guarantees the reliability and reproducibility of the manufacturing process. Validation is the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation), if it is not possible, it may be necessary to validate processes during routine production(concurrent validation) and processes in use some time should also be validated(retrospective validation).this article examines the need for pharmaceutical validation, the various approaches, processing stage and control variables and sampling plan related to tablets dosage form.

Key word: Validation, Process validation, Control variables, tablets dosage form, reproducibility

INTRODUCTION

The documented act of demonstrating that any process and activity will consistently lead to the expected results. It also includes the qualification of systems and equipment[1]. Manufacturer should plan validation in a manner that will ensure regulatory compliance and ensuring that the product quality, safety and consistency are not compromised.[2] Validation itself does not improve processes but confirms that the processes have been properly developed and are under control. Different agencies defined the validation as follows:

FDA:[3]

Validation is defined as "The collection and the evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

European Commission (EC):[4]

Validation is defined as "Action providing in accordance with principles of GMP (Good Manufacturing Practice), that any procedure, process, equipment, material, activity or system actually lead to the expected results".

World Health Organization (WHO):[5]

Validation is defined as "Action providing that any procedure, process, equipment,

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material, activity or system actually lead to the expected results".

Importance of Validation [6]

First, and certainly foremost, among the reasons for validation is that it is a regulatory requirement for virtually every process in the global health care industry- for pharmaceuticals, biologics, and medical devices. Regulatory agencies across the world expect firms to validate their processes. The continuing trend toward harmonization of requirements will eventually result in a common level of expectation for validations worldwide. Utility for validation beyond compliance is certainly available. The emphasis placed on compliance as a rationale has reduced the visibility of the other advantages a firm gleans from having a sound validation program.

Benefits of Validation

- Quality
- Customer – patient satisfaction.
- It has been built into the product.

Types of Process Validation[7]

Prospective Validation:

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 broken down 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. Minimum three consecutive batches of the product shall be considered for the prospective validation study. This type of validation activity is normally completed prior to the distribution and scale of the drug product. 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. It is preferred that the validation batches made should be of the same size as the intended production scale batches.

Concurrent Validation:

Establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

Retrospective Validation:

This type of validation is acceptable only for well-established processes, without any change in the composition of the product, operating procedure and equipments. The sours of data for these type of validation

may include batch documents process control charts, maintenance logbook, process capability studies, finished product data, including trend data, and stability data.

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. Documentation requirements will be the same as for the initial validation of the process.

Government regulations

Validation is considered to be integral part of GMPs essentially worldwide, compliances with validation requirements is necessary for obtaining approval to manufacture and to introduce new products. The FDA's cGMP refer to the concepts of the validation in both sections. They state that such control procedure shall be established to monitor out put and to validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process materials and drug materials. The Accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented. A generally stated requirement for process validation is contained in the medicinal device GMP regulations. Where deviations from device specification could occur as result of manufacturing process itself. There shall be written procedures describing any process controls necessary to assure conformance to specifications.

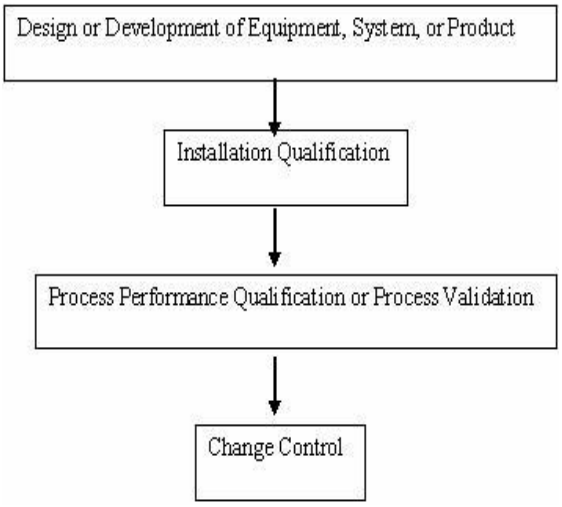

Figure 1: Phases in Process validation

How validation is done

The principle is characterized by harmony between the results obtained and requirements. This supposes Specific requirements and objectives

- Available means
- Choices, which are justified in relation to objectives
- Each stage should begin when the
- previous stage is over

Certain depositions should be defined

- How norms should be dealt with
- How modifications should be dealt with controlling evaluation will involve
- Set data for decision making

- Evaluation before decision making
- Justifying the decision
- Follow-up.

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

Strategy for Industrial Process Validation of Solid Dosage Forms.[7, 8]

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[9]

Protocols should specify the following in detail:

a) A clear and precise definition of process equipment system or subsystem, which is to be the subject of study with details of performance characteristics;
b) Installation and qualification requirement for new equipment;
c) Any upgrading requirement for

existing equipment with justification for the change(s) and statement of qualification requirement;

d) Detailed stepwise statement of actions to be taken in performing the study (or studies);
e) Assignment of responsibility for performing the study;
f) Statement on all test methodology to be employed with a precise statement of the test equipment and/or materials to be used;
g) Test equipment calibration requirements;
h) References to any relevant standard operating procedures (SOP);
i) Requirement for the current format of the report on the study;
j) Acceptance criteria against which the success (or otherwise) of the study is to be evaluated; and
k) The personnel responsible for evaluating and certifying the acceptability of each stage in the study and for the final evaluation and certification of the process as a whole, as measured against the pre-defined criteria.

All personnel involved in conducting the studies should be properly trained and qualified. All information or data generated as a result of the study protocol should be evaluated by qualified individuals against protocol criteria and judged as meeting or failing the requirements. Written evidence supporting the evaluation and conclusion should be available. If such an evaluation shows that protocol criteria have not been met, the study should be considered as having failed to demonstrate acceptability and the reasons should be investigated and documented. Any failure to follow the procedure as laid down in the protocol must be considered as potentially compromising the validity of the study itself and requires critical evaluation of all the impact on the study.

Table 2: Protocol for title page in industry

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

The final certification of the validation study should specify the pre-determined acceptance criteria against which success or failure was evaluated.

Industrial Process Evaluation [8, 10, 11, 12]

Determine the unit operations needed to manufacture the tablets.

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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

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.

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.

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. 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).

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.

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

i. ***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 low dissolution due to excessive lubricant in some tablets.

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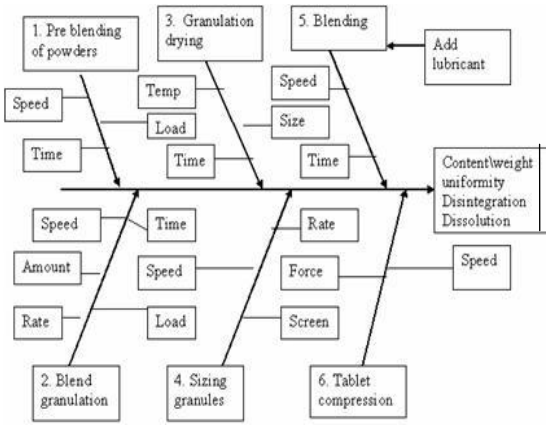

Figure 2: Schematic diagram of processing steps and respective in-process variables during tablet manufacture

ii. ***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.

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.

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 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)?

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).

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

(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 (evaporization 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.

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

Screen size: A smaller screen size will produce a smaller particle size and a greater number of fines.

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.

6. Lubrication

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.

Table 4: Table of contents

S. 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	

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: 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: 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.

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Table 5: Validation team and Responsibilities

Department	Designation	Responsibility
Research and Develop-ment (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.

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 and 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.

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:……..0C Drying time: ……min. Final drying : ……0C±50C 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: …….%

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 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*

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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