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A REVIEW ON PROCESS VALIDATION OF SOLID DOSAGE FORM (CAPSULE)

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Abstract

Every time a product is taken into consideration, quality is an absolute requirement. Drug production must therefore be of the greatest caliber. A productive production process is essential for incorporating quality into the goods, and validation is a component of the quality assurance programme. Process validation is the validation of a process's constituent steps. Validating a process is gathering and analyzing data from the process design stage through production to generate scientific proof that a method is able to reliably produce a high-quality medicinal material. The validation's aim is to make sure that quality is incorporated throughout the system rather than merely evaluated for at the end. It entails the gathering and assessment of data that establishes scientific proof that a process is capable of reliably producing a high-quality pharmacological ingredient, starting with the process design stage and continuing through production. According to cGMP, process validation is a crucial component of quality assurance. Together, validation and quality control will guarantee the items' thorough quality. As a result, emphasis is placed on reviews that provide a thorough summary of validation.Validation studies must be carried out in accordance with established methods, as per GMP. Different validation procedures apply to various dose types. With particular reference to the requirements set forth by the US Food and Drug Administration (FDA) for Solids (capsules), Liquids, and Semisolids, the work's goal is to give an introduction and basic overview on process validation of pharmaceutical manufacturing process.

Keywords: Quality; Validation; Dosages form; CGMP

1. INTRODUCTION

The main goal of any pharmaceutical plant is to produce products of required quality consistently, at the lowest cost possible.[1,2] Validation has been an important process in pharmaceutical industries for a long time but it has gained greater emphasis in recent years due to industry's greater interest on assurance ofquality and productivity improvement. For an efficient production operation, there is a greater need of an efficient validation team.[3,4] The concept of validation was first proposedby two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, inthe mid 1970's in order to improve the quality of pharmaceuticals. The prime focus of validation is on ensuring if the quality is built into the

system at every step, and not just tested for at the end. Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.[5,6,7]

1.1 Process Validation

Process validation provides the flexibility and constraints inthe production process controls in the achievement of desirable qualities in the drug product while preventing undesirableattributes. USFDA defined process validation as "establishingdocumented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."[8,9,10]

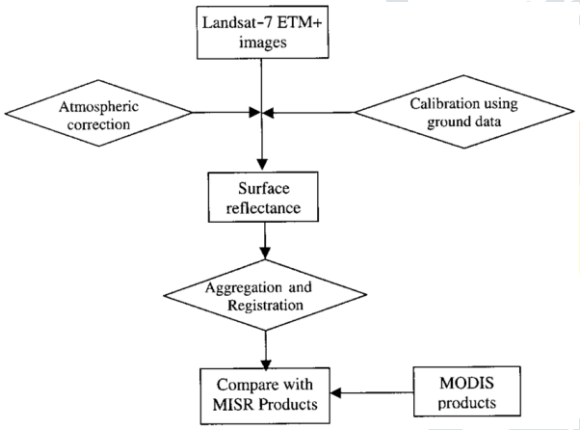

Figure 1. validation process

1.2 Types of Process Validation

a) Prospective Process Validation: In prospective processvalidation, the experimental plan known as validation protocolis preparedbefore the process is used for commercial use. In order to produce support data for validation there is requirement of some degree of prospective experimentation.[11,12]

b) Concurrent Process Validation: The concurrent processvalidation establishes documented evidence that the process isin a state of control during the actual execution of the process.The in-process testing and/or monitoring of critical operationsduring the manufacture of each production batch is done forconcurrent process validation.

c) Retrospective Process Validation: When validationis based on the historic data taken from the records of thecompleted production batches and used as documented evidence for stating that the process has been in a state of control comes under retrospective process validation.

d) Revalidation: Revalidation ensures that changes inthe process and/or in the processing environment, whetherintentional or unintentional, do not negatively affect processcharacteristics and product quality attributes.[13,14,15]

Revalidation can be sub-divided into two categories:

i. Revalidation after any change having abearing on productquality.

ii. Periodic revalidation carried out at scheduled intervals.[16,17]

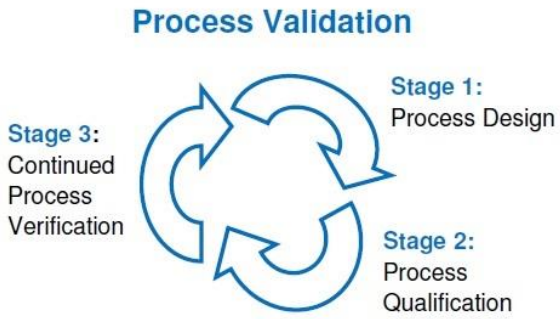

Figure 2. process validation stages

1.3 Importance of Process Validation

a) Quality of product is assured

b) Optimization of the process

c) The cost of Quality of products is reduced

d) The market recalls of products is minimized.

e) The process is under control and detailed study is possible.[18,19]

1.4 Documents Used in Validation

i. Validation master plan

ii. Validation protocol

iii. Validation report

iv. SOPs

i. Validation Master Plan: A validation master plan isa summary of entire philosophy, intentions and approaches tobe used for establishing performance adequacy of the company.The management must agree upon the validation master plan.The validation master plan provides an outlook of the overallvalidation operation, its organizational structure, its content and planning.[20,21]

ii. Validation Protocol: Validation protocol is a plan of actions stating how process validation will be done,it specifies who will conduct the various tasks and definesthe testing parameters, sampling plans, testing methods andspecifications. It also specifies product characteristics andequipment to be used. It must state the minimum number of batches that can be used for validation studies, it must specify the acceptance criteria and who will sign \ approve \ disapprove the conclusions obtained from such a study.The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

I. Title
II. Objective & Scope
III. Responsibility
IV. Protocol Approval
V. Validation Team
VI. Product Composition
VII. Process Flow Chart
VIII. Manufacturing Process
IX. Review of Equipment / Utilities
X. Review of Raw Materials and Packing Materials Review of Analytical and Batch Manufacturing Records
XI. Review of Batch Quantities for Validation (Raw Materials)
XII. Review of Batch Quantities for Validation (PackingMaterials)
XIII. HSE Requirements
XIV. Review of Process Parameters Validation Procedure
XV. Sampling Location
XVI. Documentation
XVII. Acceptance Criteria
XVIII. Summary
XIX. Conclusion
XX. Validation Report [22,23,24]

Standard format of validation report

a) Executive summary
b) Discussion
c) Conclusions & recommendation
d) List of attachment

The above topics should be represented in the series in which they appear in the protocol and if the protocol is deviated it shouldbe explained with justification. The report must be signed & datedby designated representatives of each unit.[25,26]

iv. SOP (Standard Operating Procedure)

The general format of the SOPs involves:

A. Title
B. Code
C. Objective
D. Scope
E. Definitions
F. Description
G. Safety
H. Documentation
I. Effective date, review date, version number.
J. Footer: Prepared By, Reviewed By, Approved By,Authorized By.

K. References[27,28]

1.5 Process validation of capsules

Capsules are the solid dosage form in which the drug or the mixture of drug are enclosed in Hard Gelatine Capsule Shells, in soft, soluble shells of gelatine, or in hard or soft shells of any other suitable material, of various shape and capacities. They usually contain a single dose of active ingredients and are intended for oral administration.

They are basically of two types:

a) Hard Gelatin Capsules: It is a solid dosage form in whichmedications are encapsulated in a two-part empty hard gelatin

capsule shell. The upper and small part is called 'CAP' and theremaining large part is called 'BODY'. There are 8 different sizes

of capsule shell with different fill volume.[29,30,31]

Normally 0 and 2 sized shells are widely used. The shell of hard gelatin capsules basically consists of gelatin, plasticizers and water. Modern day shells may, in addition, consist ofpreservatives, colours, pacifying agents, flavours, sugars, acids,enteric materials etc.[32,33]

b) Soft Gelatin Capsules: A soft gel (or a soft gelatincapsule) is a solid capsule (outer shell) surrounding a liquidor semi-solid centre (inner fill). An active ingredient can be incorporated into the outer shell, the inner fill, or both. Theyprocess of manufacturing of hard gelatine capsules is same as that of tablets, the only difference is that instead of compressingthe granules they are filled in the capsule shell. So the validationprocess is also the same.In encapsulation process following additional parameters need to bevalidated:

A. Capsule Shell Contentsa) Establish the compatibility of the capsule shell and thecapsule contents.

b) Determine the hygroscopic nature of the capsuleformulation

For example: A hygroscopic formulation (API /excipients) can pull water from the capsule shell, which could affect the API stability.[34,35,36]

B. Encapsulation Speed: The formulation should be encapsulated at a wide range of speeds to determine the operating range of the encapsulation.

C. Encapsulation: Encapsulation is a critical step in theproduction of capsules, similar to the compression for tabletdosage forms, The materials to be encapsulated will need tohave good flow properties and a consistent density.[37,38]

1.6 Drug categories suitable forcapsules

1. Drugs with Poor bioavailability: The bioavailability of the poorly water-soluble drugs can be significantly enhanced when formulated as a liquid in a hard gelatin capsule.

2. Drugs with Low melting point: Materials having low melting points or are liquid at room temperature have some problems when formulating as dry powders, often requiring high concentrations of excipient to avoid processing problems.

3. Potent drugs: Drugs in this category present two main challenges; content uniformity and cross-contamination and worker protection.

4. Sustained release drug candidates: By choosing an appropriate excipient the release rate of an active ingredient can be modified. E.g., soybean oil and glyceryl monostearate. [39,40,41]

1.7 Compatibility of Fill Materials

The properties of the API which shows whether it is a good candidate for liquid filling or not. The suitable excipients are evaluated by considering that neither the API nor the excipients should cause the gelatin shell to gain or lose excessive moisture, which can cause the shell to lose its mechanical strength. All substances must also be chemically compatible with gelatin. To maintain flexibility, the capsule shell should have the moisture content ranging 13-16%. Below that range capsules become brittle and are prone to breakage. Above that range the capsules may deform. To measure the moisture exchange between the fill material and the shell, fill the capsules with the product and store them at different levels of relative humidity (RH) (i.e., 2.5, 10, 30, 50 and 60%) for 2 weeks. During that period, the moisture exchange across the range of RHs should not exceed ±2%.[42,43] Fill materials that exchange more than ±2% moisture compared to empty shells stored under the same conditions as liquid filling. The capsule's mechanical resistance must be checked with relation to moisture content. This involves storing the filled capsules for 1week at different RHs and then testing them for resistance to breakage and deformation. The chemical compatibility of the fill material with the gelatin shell is also important. If there is a cross linking between fill material and the protein chains of the gelatin may causes delay in dissolution. One method of monitoring cross- linking is to first store the fill material inside the hard gelatin capsules under ICH accelerated storage conditions (40°C at 75% RH) and then substitute the fill material with acetaminophen. And then conduct a dissolution test according to USP guidelines to compare the dissolution profiles of filled and unfilled capsules stored at the accelerated conditions.[44,45,46]

1.8 Capsule filling

Capsugels are capsule especially designed for liquid and semi-solid fillings. This capsule is longer than standard capsules, so that when the capsule body and cap are fully joined, the top of the capsule body's wall contacts the interior of the cap. This provides the primary barrier to prevent the liquid fill from escaping. As it is essential to keep the area of the cap-body interface uncontaminated by fill material, otherwise it is virtually impossible to seal the capsule. To further prevent or reduce leakage and contamination at the cap-body interface, the capsule has no side air vents, which are of typical capsules used in highspeed powder filling. The capsule is normally filled to no more than 90% of its volume to minimize the chance of the liquid fill contaminating the cap-body interface.[47,48,49]

1.8.1 Specifications for filling liquids into hard gelatin capsules

1. Temperature of fill material: Max 700C
2. Viscosity: 0.1 – 1Pa s
3. Particle size of suspended particle: <50µm
4. Visco properties: clean break from dosing nozzle

1.8.2 Sealing methods:

Once closed, the capsule must be sealed to avoid leaks and tampering. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing. This fusion procedure starts with an application of less than 50 microliters of sealing solution to the cap-body interface. The solution enters the overlapping cap and body by capillary action while a vacuum removes excess sealing fluid from the capsule. Next is the gentle

application of warm (40° to 60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution. The complete procedure takes less than 1 minute and converts the two-piece hard capsule into a leak-free dosage unit. Once sealed, the capsule meets tamper-evidence guidelines since it cannot be opened without visibly altering it.[50,51,52]

Another method involves banding the cap-body interface with a thin film of gelatin. Banding involves several added tasks compared with hydroalcoholic sealing. First prepare the gelatin bath and its viscosity must be checked continuously. Care should be taken as there is a risk of microbiological contamination associated with warm liquid gelatin. Furthermore, the gelatin band can cause physical defects in the capsule such as bubbles may form in the gelatin band or the capsules may take on a "banana" shape. The deformation usually occurs when the warm band of gelatin cools and the capsules are subjected to a long drying cycle.[53,54,55]

2. Conclusion

Validation is a proven assurance of the process efficiency and sturdiness and it is the full-fledged quality control tool forthe pharmaceutical industries. It eliminates the chances of batch failures as the products are manufactured as per pre optimization of each manufacturing steps. The conventional process of testing at last stage created much problems in maintain uniformity of each batch but with the introduction of concept of validation, it has been easy to maintain the batch uniformity of the product along with imparting quality in them. This paper summarizes the process validation stages of solids, liquids and semisolids which are the most common pharmaceutical dosages form in use.[56,57,58]

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