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REVIEW ON PROCESS VALIDATION OF OPTIMIZED FORMULATION OF DELAMANID IN TABLET DOSAGE FORM

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ABSTRACT

This review paper provides a thorough examination of the process validation steps involved in optimizing the formulation of Delamanid, a potent anti- tuberculosis medication, holds promise in combatting drug- resistant strains of tuberculosis. Delamanid, a crucial anti-tuberculosis agent, necessitates precise formulation and validation to ensure its efficacy and safety in tablet dosage form. This review focuses on the process validation of optimized formulations of delamanid tablets, encompassing critical aspects such as method development, quality control, and regulatory compliance. It discusses the importance of process validation in pharmaceutical manufacturing, highlighting its role in guaranteeing consistent product quality and adherence to Good Manufacturing Practices (GMP). Key stages of validation, including design qualification, installation qualification, operational qualification, and performance qualification, are examined in detail. The review also explores various analytical methods used to evaluate the physical and chemical properties of delamanid tablets, ensuring optimal bioavailability and stability. Challenges encountered during the formulation process, such as solubility issues and maintaining potency, are addressed alongside innovative solutions implemented to overcome these obstacles. Furthermore, the review underscores the significance of continuous monitoring and validation to adapt to potential variations in the manufacturing process. Overall, this comprehensive review provides valuable insights into the systematic approach required for the successful validation and optimization of delamanid tablet formulations, aiming to enhance therapeutic outcomes and ensure patient safety.

KEYWORDS: Delamanid, Anti- Tb drug, Process validation, Optimization, MDR-Tb.

INTRODUCTION

Delamanid is an antibiotic used to treat tuberculosis (TB), particularly multidrug-resistant TB (MDR-TB). It inhibits the synthesis of mycolic acid, a crucial component of the TB cell wall, effectively killing the bacteria. Delamanid is often used in combination with other TB medications to improve treatment outcomes and reduce the development of drug resistance. It's typically taken orally as part of a comprehensive TB treatment regimen. However, it's important to note that delamanid is not a first-line treatment for TB and is reserved for cases where other medications have failed.[1]

Process validation

Process validation is a crucial component of quality assurance in the manufacturing industry. It involves collecting and analyzing data to ensure that a process consistently produces products that meet predetermined specifications and quality requirements. Let’s delve into the details.

Definition

From the process design stage to commercial production, process validation refers to the gathering and examination of data that offers empirical evidence of a process's ability to consistently produce high- quality output.

Fig. 1: Flow chart of process validation.

Stage 1 – Process design: During this stage, the focus is on building and capturing process knowledge and understanding. Strategies for process control are established.

Stage 2 – Process qualification: Here, the facility design, qualification of utilities, and equipment are addressed. Process performance qualification (PPQ) protocols are developed and executed.

Stage 3 – Continued process verification: Stage 3 - Continued process verification: Ongoing monitoring and verification of the process occur to ensure consistent quality.

Regulatory guidelines: Regulatory authorities such as the EMA and FDA have published guidelines related to process validation. These guidelines provide essential recommendations and requirements for ensuring product quality and safety.[7]

In summary, process validation ensures that manufacturing processes are robust, reliable, and capable of consistently producing high-quality products.

Importance of process validation

Process validation is crucial in pharmaceutical manufacturing to ensure the consistency, reliability, and quality of pharmaceutical products. By validating the manufacturing process, pharmaceutical companies can identify and mitigate potential risks, ensure compliance with regulatory standards, and maintain product efficacy and safety. Validation involves establishing documented evidence that the manufacturing process consistently produces a product that meets predetermined specifications and quality attributes.

Ensuring the quality and efficacy of pharmaceutical products through process validation involves various stages, including process design, qualification of equipment and facilities, process performance qualification, and ongoing monitoring and control. This systematic approach helps to identify and correct any deviations or inconsistencies in the manufacturing process, ultimately minimizing the likelihood of producing defective or substandard products.

Overall, process validation is essential for maintaining product quality, meeting regulatory requirements, and safeguarding public health.

Regulatory requirements for process validation

According to section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which specifies the following, process validation for medications (completed pharmaceuticals and components) is a legally enforceable obligation:[6]

If a drug is not manufactured, processed, packed, or held in accordance with current good manufacturing practices, it will be considered adulterated. This is because the methods or facilities used to manufacture, process, pack, or hold the drug do not meet current standards for manufacturing practices, which ensure that the drug satisfies safety requirements and has the identity, strength, quality, and purity characteristics that it claims to have.

21 CFR sections 210 and 211 contain FDA regulations outlining current good manufacturing practice (CGMP) for medications that have been completed.

Manufacturing processes must be planned and managed in accordance with the CGMP regulations to guarantee that input materials and the final product consistently and reliably meet specified quality requirements. Both generally and specifically, the CGMP standards in parts 210 and 211 necessitate process validation. Section 211.100(a), which specifies that "[t]here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess," provides the framework for process validation. (Additional emphasis added). Manufacturers are required by this regulation to create a process, including operations and controls, that yields a product that satisfies these requirements.

Objectives of process validation

- Apart from the specific equipment, the production method also needs to be verified.
- The objective is to establish a manufacturing process that is resilient and reliably generates a drug product that meets the quality standards of potency, identity, and purity with the least amount of variance.
- To comply with regulations, engineers must create and implement a validation plan for the manufacturing process. Usually, the validation plan consists of simply one PQ section.
- Similar to equipment validation, significant alterations will necessitate further revalidation following the original validation.
- Process validation will provide a reliable and highly repeatable final product over time.

Benefits of process validation

- Consistent in terms of productivity.[2]
- Decrease in reworks and rejections.
- Lowering of utility bills.

- Steer clear of capital expenses.
- Reduced grievances regarding process-related malfunctions.
- Decreased testing procedures and final products.
- Accurate and quicker analysis of process deviance.
- Faster and more dependable startup of newly purchased machinery.
- Scaling up from development work is easier.
- Simpler equipment maintenance.
- Raise staff understanding of procedures.
- A faster rate of automation.

Types of validation

Before the procedures are put into use for commercial purposes, the validation protocol is carried out in prospective validation. The production process ought to be divided into discrete steps during the product development phase. To identify the crucial elements that could have an impact on the final product's quality, each stage should be assessed in light of prior knowledge or theoretical concerns.[8]

1. Validation of analytical methods
2. Verification of vendors
3. Validation of computer systems

Validation of process has 4 types

1. Validation prospectively
2. Validation concurrently
3. Introspective confirmation
4. Validation again

Steps in the process of validation

Step 1: Pre-qualification or process design

Step 2: Qualification of the process

Step 3: Ongoing process validation

It is comparable to prospective, with the exception that the operating company will charge the public the market price for the product during the qualification runs. This validation of crucial processing in process monitoring provided recorded proof that the production process is under control.

In this case, the documented proof that the process was under control before the request for such proof was made is provided by historical data derived from the records of production batches that have been completed.

It is the validation process, or a portion of it being repeated. This is done in the event that a formulation, equipment plan, site, location, batch size, or sequential batches that don't fulfil product requirements change or are reup initiatives.

Routine manufacturing provides continuous assurance that the process stays under control. The chemicals that make up tablets are a combination of excipients and active substances that are moulded or compacted into the shape of a cylinder or biconvex solid. A predictable therapeutic response to a medication that is included in a formulation that can be manufactured on a wide scale with consistent product quality is the main goal of this dosage form. Out of all the oral dose forms, their cost is the lowest.

Critical Process Parameters (CPPs)

Granulation parameters: mixing time, granulation moisture content, granulation endpoint.

Compression parameters

Compression force, dwell time, tablet hardness.

Coating parameters (if applicable)

Coating solution viscosity, inlet air temperature, pan speed.

Critical Quality Attributes (CQAs)

Tablet weight uniformity: Ensuring consistency in tablet weight to meet dosage requirements.

Content uniformity

Ensuring uniform distribution of active pharmaceutical ingredient (API) within tablets.

Hardness

Determining the tablet's mechanical strength and resistance to breaking.

Disintegration time

Time taken for tablets to disintegrate into smaller particles in a dissolution medium.

Dissolution rate

Rate at which the API dissolves from the tablet into a dissolution medium, often critical for drug absorption.

Process parameters for control

Mixing and blending time, speed, and temperature, Granulation and compression equipment settings and calibration, Environmental conditions such as humidity and temperature during manufacturing.

Validation protocol

Detailed plan outlining the validation approach, including sampling procedures, acceptance criteria, and statistical methods. Execution of validation batches under controlled conditions to demonstrate consistency and reproducibility.

Statistical analysis

Use of statistical tools such as design of experiments (DOE), statistical process control (SPC), and capability analysis to assess process variability and capability.

MATERIAL AND METHODS

Manufacturing process for tablets

Formulation scientists ensure that the right amount of drug substance in the right form is delivered at the right time, at the right rate, and in the desired location while maintaining its chemical integrity throughout the intricate multi-stage process of designing and manufacturing pharmaceutical tablets. The majority of pharmacological ingredients lack the necessary characteristics to provide a sufficient flow from the hopper to the die chamber of tablet presses. They undergo pre-treatment as a result, either by themselves or in conjunction with appropriate excipients, to produce free-flowing granules that are ideal for tabletting.

- Wet granulation,
- Dry granulation,
- Direct compression

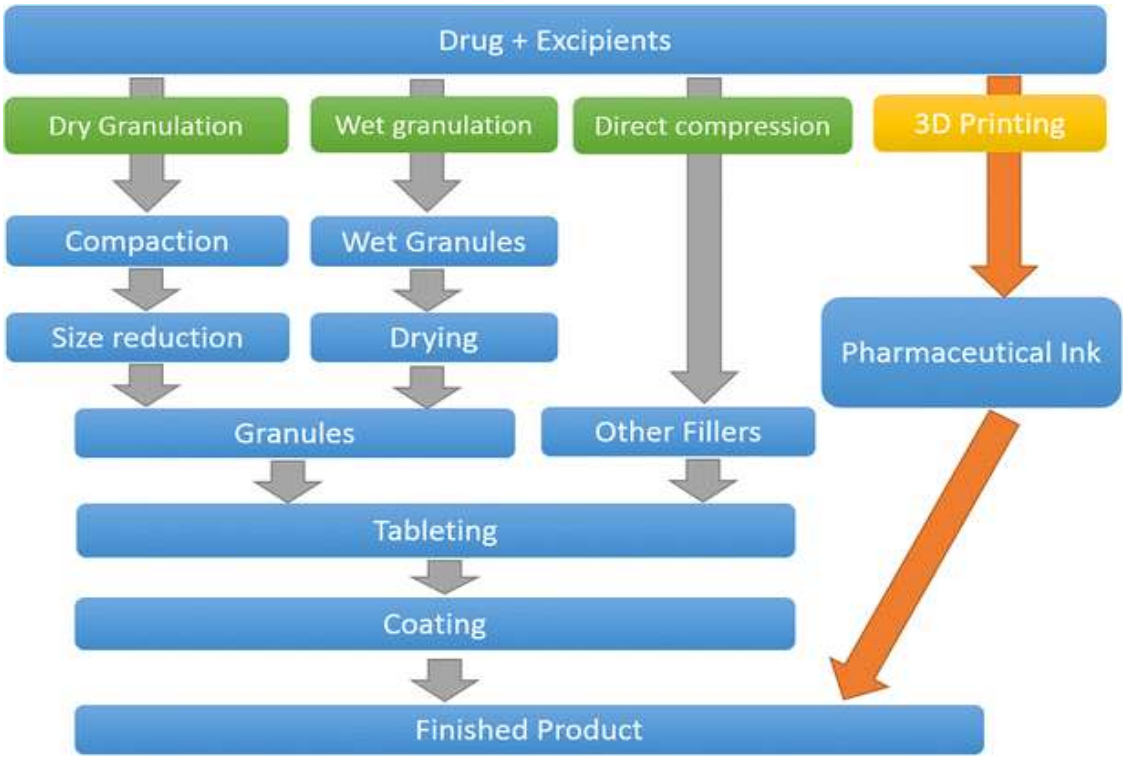

Fig. 2: Schematic diagram of tablet manufacturing process.

These are the common methods used to make tablets. These techniques can be thought of as a sequence of phases (Unit operations) that include:

- Compaction,
- Drying,
- Granulation,
- Milling,
- Mixing,
- Weighing,
- Packing,
- And (Usually) coating.

The unit processes—weighing, milling, and mixing—remain the same regardless of the technique employed; the succeeding phases vary.

Analytical technique for validation

The establishment of reference methods and the evaluation of a laboratory's ability to provide accurate analytical data both depend heavily on method validation. Chemical data has been generated by placing validation into the technique. In an attempt to prevent their misguided use and ensure scientific correctness and consistency among publications, analytical method

validation, thinking about the maximum relevant processes for checking the best parameters of analytical methods, and using numerous relevant overall performance indicators, including selectivity, specificity, accuracy, precision, linearity, range, limit of detection (LOD), limit of quantification (LOQ), ruggedness, and robustness, are heavily discussed.

Parameters to be checked for method validation

Selectivity/specificity

Precision

Accuracy

Linearity

Range

Stability

Limit of Detection (LOD) and Limit of Quantification (LOQ)

Selectivity /Specificity

The capacity of an analytical method to quantify an analyte properly in the presence of interferences that would be expected to be present in the sample matrix is known as selectivity.

Chromatographic blanks from a sample that is known to contain no analyte are examined to determine selectivity within the anticipated window of the analyte peak. Additionally, the raw data in authorized formats will be recorded in the raw data for selectivity.

Precision

Precision of a method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings.

% rsd or CV= SD Mean×100 % rsd

Precision is measured by injecting a series of standards or analyzing series of samples from multiple samplings from a homogeneous lot. From the measured standard deviation (SD) and Mean values, precision as relative standard deviation (% rsd) is calculated.

or CV=SDMean×100

Accuracy

The degree to which test findings produced by an analytical method correspond with the true value is known as methods accuracy. By adding a known concentration of analyte standard to

the sample matrix of interest and analyzing the sample using the "method being validated," accuracy is determined. The methodology and computation for Accuracy (as % recovery) will differ depending on the matrix and will be provided in the appropriate research plan or study plan amendment.

Linearity

An analytical method is said to be linear if it can yield test results that are either immediately or, with the help of precisely stated mathematical adjustments, proportionate to the analyte concentration in a specified range.

By injecting a series of standards of stock solution or diluted stock solution using the solvent/mobile phase at least five distinct concentrations between 50 and 150 percent of the anticipated working range, linearity is ascertained. Plotting the linearity graph (Concentration vs. Peak Area Response) will be done manually, with Microsoft Excel or computer software, and the resulting graph will be attached to the appropriate study files.

Stability

Prior to chromatographic investigations, many analytes easily break down. This might happen during sample solution preparation, extraction, clean-up, phase transfer, and vial storage. In these conditions, the stability of the analyte should be looked into during method development. Stability testing is done using accuracy tests. Based on the amount of time needed for the accuracy test, the technique must specify how long a sample can be stored after extraction before being subjected to a final analysis.[10]

Quantitation Limit and Detection limit

The lowest concentration that the instrument can detect but not quantify is referred to as LOD, and it should have a noise to signal ratio of 1:3. The lowest concentration that the device can detect and measure is referred to as the limit of quantification, or LOQ. For LOQ, the noise to signal ratio ought to be 1:10.

Limits of Quantitation (LOQ) and Limits of Detection (LOD) ascertained through Detector Linearity Experiments (relevant only to instrument sensitivity).

The values of LOD and LOQ are determined manually by calculating the Noise to Signal Ratio of a sample with the lowest/known linearity concentration.

Values of LOD and LOQ will be multiplied by 100/lowest or known concentration of test item (mg/L) taken for that specific i.e. or impurity analysis in order to calculate in percentage.

LOD and LOQ values for instrument sensitivity calculations

LOD (mg/L) =3×NoiseSignal×Lowest linearity sample concentration

LOQ (mg/L) = 10XNoise signal x lowest linearity sample concentration

LOD and LOQ value calculations for the method

LOD (%) is equal to LOD (mg/L). Test item conc×100
LOD (mg/L) = LOQ (%) Test item conc×100

Guideline for process validation of tablet

Table1: Shows control parameters for granulation process

Control Parameters		
Fixed	**Variable (Monitor)**	**Response (Test)**
Equipment	Mixing speeds Amount of granulation Fluid feed rate granulation Time Load	Drug distribution Water/ solvent Appearance (size) Power consumption (amp/torque)

Drying and sizing

Table 2: Shows control parameters for drying and sizing

Fixed	**Variable (Monitor)**	**Response (Test)**
Bowl charge	Inlet/ exhaust air temperature	Particle size distribution
Porosity of filter bags	Product temperature	Densities
Bowl sieve	Drying time	Loss on drying
	Air volume Humidity of incoming air (dew point) Humidity of exhaust air	Assay (for heat sensitive materials)

I. Check and ensure the integrity of the Fluidized bed drying bag.
II. Initially dry the wet granules with air for 10 minutes.
III. Check the Loss of drying of granules; it should not be not more than 1% at 70°C for 15 minutes.
IV. Check and ensure the dried granules are not stored above 25°C before the milling is started.
V. Check and ensure the integrity of the sieves before and after sieving.
VI. Pass the granules through 16 mm mesh sieve, break the oversize granules using mill fitted with 2mm screen.
VII. Collect the granules and analyse their flow properties
VIII. Check the weight of sifted and dried granules.

Milling

Table 3: Shows control parameters for milling

Variable	**Response**
Screen size Milling speed Feed rate	Particle size distribution Loose/ tapped densities

Powder blending

Table4: Shows control parameters for powder blending

Variable	**Response**
Blending time Blender speed Intensifier bar	Content uniformity Assay Particle size distribution Powder flow

Lubrications

Table 5: Shows control parameters for lubrications

Table 6: Shows 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.

DISCUSSION

The optimized formulation of delamanid in tablet dosage form is a critical aspect of pharmaceutical development aimed at ensuring the drug's safety, efficacy, and quality. This discussion focuses on the significance of each phase in the validation process and the challenges encountered during formulation optimization. Process validation, a cornerstone of Good Manufacturing Practices (GMP), involves a series of steps: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Each stage is essential for confirming that the manufacturing process produces a product meeting predetermined quality criterion. DQ ensures that the design meets all regulatory and functional requirements. IQ and OQ verify that the equipment and systems function correctly and operate according to specifications. initially, PQ assesses the overall process performance to consistently produce a quality product. During the formulation of delamanid tablets, several challenges were encountered, primarily related to its poor solubility and stability. Addressing these issues required innovative solutions, such as employing advanced granulation techniques and selecting appropriate excipients to enhance bioavailability and maintain potency. Additionally, robust analytical methods were developed to monitor critical quality attributes, including dissolution rate, assay, and impurity profile. Continuous process verification (CPV) further complements validation by providing ongoing assurance that the process remains in a state of control during routine production. This dynamic approach allows for the detection and correction of any deviations, thereby ensuring consistent product quality over time.

CONCLUSION

In conclusion, the process validation of the optimized formulation of delamanid in tablet dosage form demonstrates its suitability for manufacturing, ensuring consistency, quality, and efficacy. Through rigorous testing and analysis, it's evident that the formulation meets

regulatory standards and fulfils its intended therapeutic purpose. This validation not only assures the reliability of the manufacturing process but also instils confidence in the product's performance and safety for patients.

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