

PROCESS VALIDATION OF DRY POWDER INHALERS (GENERALIZED APPROACH, THEORY AND PRACTICES): A REVIEW

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ABSTRACT

Drugs can be delivered to the lungs by inhalation, oral, parenteral routes. Different types of devices such as pressurised metered dose inhalers (p-MDI's), nebulizers or dry powder inhalers (DPI's) are used for the pulmonary delivery of drugs. This present review article focus on the process validation of dry powder inhalers. Dry powder inhaler is a device that deliver medication to the lungs in the form of dry powder. Validation of dry powder inhaler is done to ensure that a specific manufacturing process will consistently produce a product meeting its pre-determined specifications and quality attributes. Validation is defined as the collection and evaluation of data, from the process design stages through commercial production, which establishes scientific evidences that a process is capable of consistently delivering quality product. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. Three consecutive batches of dry powder inhaler shall be taken up for process validation. Based on the results of all the 3 batches, suitable conclusions will be drawn with respect to the suitability of proposed method for powder for inhalation. Once the validation process is complete a Batch Manufacturing Record (BMR) can be written. Any changes in BMR can be made in accordance with change control procedure.

KEYWORDS: Validation, Dry powder Inhalers, Consistently, Consecutive, Batch Manufacturing Record, Inhalation.

INTRODUCTION

In Pharmaceutical organizations, validation is a fundamental segment that supports a company commitment to quality assurance. Validation is a tool of quality assurance which provides confirmation of the quality in equipment systems, manufacturing processes, software and testing methods¹. Validation is defined as the collection and evaluation of data, from the process design stages through commercial production, which establishes scientific evidences that a process is capable of consistently delivering quality product. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it^{2,3}. The review focus on the need for Pharmaceutical validation, the various approaches and general steps involved in process validation of dry powder inhalers(DPIs). Most DPIs formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways. When a DPI is actuated, the formulation is fluidized and enters the patient's airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. If the cohesive forces acting on the powder are too strong, the shear of the airflow may not be sufficient to separate the drug from the carrier particles, which results in low deposition efficiency. The formulation typically consists of micronized drug blended with larger carrier particles, dispensed by a metering system. An active or passive dispersion system entrains the particles into the patient's airways, where drug particles separate from the carrier particles and are carried into the lung.(Fig-1)⁴ The foremost priority of regulatory agencies is to ensure the safety of general public health. The bioavailability of drugs is greatly influenced by the dosage form characteristics and its imperative to ensure the consistent performance of the product from batch to batch. In order to check final quality of product, a series control test has been devised. It's understood that the central role of these final stage tests limited to measure the attributes of product produced before releasing into

market^{5,6}. Quality control tests are tools to ensure not assure the quality of product. It has always been known that facilities and processes involved in pharmaceutical production impact significantly quality of products. Processes controls are mandatory in Good Manufacturing Practices (GMP). Pharmaceutical industries are concerned about validation for the assurance of quality, for cost reduction, Government regulation.

Process validation is establishing documented evidence, which provide a high degree of assurance that a specific process will consistently produce a product meeting its predefined specifications and quality characteristics^{7,8}.

Dry Powder Inhalers (DPI'S)

A dry powder inhaler (DPI's) is a device that deliver medication to the lungs in the form of dry powder. DPI's are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema & COPD. The medication is held either in a capsule for manual loading or a proprietary form inside the inhaler. DPI's capsule should not be swallowed.

DPI's don't contain CFC or HFA but some contain amount of lactose.

Types Of DPI'S

DPI's comes into two main types

- Multidose device which contain up to 200 doses.
- Single dose device which require you to place a capsule in the device immediately before each treatment.

How To Use DPI's

- Remove the cap for single use device, load a capsule into the device as directed.
- Breathe out slowly and completely (not into mouth piece).
- Place mouthpiece between the front teeth and seal the lips around it.
- Breathe in through the mouth quickly & deeply over 2-3 seconds.
- Remove the inhaler from mouth. Hold your breath for as long as possible (4-10) seconds.
- Breathe out slowly.

Advantages Of Dry Powder Inhalers

1. Easy to use than MDI (metered dose inhalers).
2. Cause fewer irritant effects.
3. Direct delivery of drug into lungs.

4. With DPIs you don't need to co-ordination squeezing the canister and inhalers.
5. Propellant free
6. Portable and compact
7. In DPI issue of 'hand-lung' co-ordination was resolved.
8. Introduction of dry powder inhalers was growing environmental concern that the chlorofluorocarbon (CFC) propellants used in metered dose inhalers (MDIs) were causing damage to the ozone layer in atmosphere while DPI is free of this.

Formulation Considerations Of DPI'S

Main ingredients used in formulation of dry powder inhaler^{9,10}.

Ingredients	Purpose
Drug	Active Constituent
Lactose	Carrier
Isopropyl alcohol	Solvent
Purified water	Solvent

Methodology/General Procedure

In a suitable stainless steel container take X kg of Isopropyl alcohol and X kg of purified water, add and dissolve X g of drug with continuous stirring to make drug solution. Now sift the lactose monohydrate through mesh no.≠ 60 and transfer it to Fluid bed processor (FBP) top spray bowl. Start process and spray previously prepared drug solution on lactose monohydrate. Once the drug solution is completely sprayed, dry the granules. After completion of drying collect the samples and check for loss on drying. Sift the dried granules through mesh no.≠ 40. Now proceed for the micronization of granules. Blend the granules and proceed for filling in empty capsule by keep in mind all critical parameters in each and every step.

Types Of Process Validation

1. Prospective Validation

This approach to validation is normally undertaken whenever the process for new formula must be validated before routine pharmaceutical production commences.

2. Retrospective Validation

It deals with performing the validation after production is already in market place.

It's based upon existing & historical process data.

3. Concurrent Validation

It's nothing more than requalifying, revalidating or even recertification an ongoing process in response to a significant change in product components manufacturing, equipment, facilities, batch size or manufacturing procedure.

4. Revalidation

It means repeating the original validation effort or any part of it and includes investigation review of existing performance data.

Need Of Process Validation

- To reduce batch to batch variation.
- To achieve reproducible products of same quality, purity & strength.
- To assure safety & efficacy & to minimize hazardous effect.
- To reduce chances of product recall from market.

Validation Should Be Considered In The Following Situation

- Totally new process.
- New equipment.
- Process and equipment which have been altered to suit changing priorities.
- Process where the end- product test is poor and an unreliable indication of product quality.

Pre-Requisites For Process Validation

- The facilities and equipment in which the process validation is to be conducted meet Good Manufacturing Practices (GMP) requirements.
- The operators and supervising personnel who will be running the

validation batches have an understanding of the process and its requirements.

- The design, selection and optimization of the formula have been completed.
- The qualification trials using (10xsize) pilot-laboratory batches have been completed.
- Finally, at least one qualification trial of a pilot-production(100 x size) batch has been made and shown, upon scale-up, that there were no significant deviations from the expected performance of the process¹¹⁻¹³.

Stages Of Process Validation

The three stages of process validation are shown in **Table-1**

Stage 1 – process design or process pre-qualification: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control^{14,15}.

Process Validation Protocol For DPI'S

- Protocol Approval Sheet
- Table of contents
- Scope and objective
- Validation term and responsibility
- Steps for validation and acceptance criteria
- Process flow chart
- Procedure
- For Review of raw material/packing material
- Evaluation of active raw material
- Evaluation of inactive raw material
- Qualification of equipment
- Test instrument calibration
- Revalidation criteria
- Reference document
- Product details
- Raw material for bulk manufacturing and their function
- Packing material detail
- Equipment detail
- Manufacturing process flow chart
- Critical process parameters
- In process specification
- Sampling procedure and testing plan
- Re validation criteria
- Change control
- Stability
- Deviations
- Incidence
- Conclusion
- Report and Approval

Validation Master Plan

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as

well as re-validation. The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, Standard Operating procedures (SOPs) and validation protocols and reports¹⁶⁻²⁰.

CONCLUSION

From the complied data of three batches it was concluded that the process of manufacturing for dry powder for inhalation meets the acceptance criteria for its designed parameters and quality attributes and hence concluded that the process followed confirms its capability of producing the product in consistent manner.

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Table-1 Three stages of Process validation

STAGE 1: PROCESS PREQUALIFICATION	STAGE 2: PROCESS QUALIFICATION	STAGE 3: LIFE CYCLE QUALIFICATION
Parameter risk assessment	At least 3 consecutive runs at scale	Statistical process Control
Range studies		Change control
Critical parameter determination		Re-validation

Table-2 Critical process parameters

Sr. No.	Process stage	Specifications
1.	Environment condition (a) %Relative humidity (b) Temperature	Below 45% Below 25°C
2.	Preparation of Drug solution	Clear solution
3.	Top spray granulation (a) Product temperature (b) Loss on drying	30±10°C Not more than 0.30%w/w
4.	Micronization of granules	4-7microns
5.	Micronization of lactose monohydrate	15-30 minutes
6.	Sifting	Through sieve#40

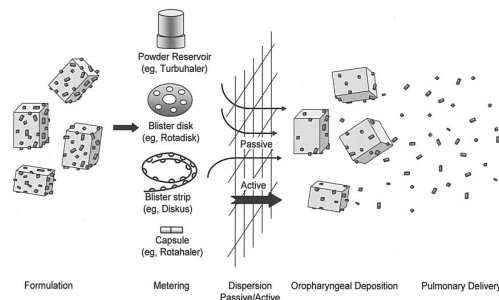
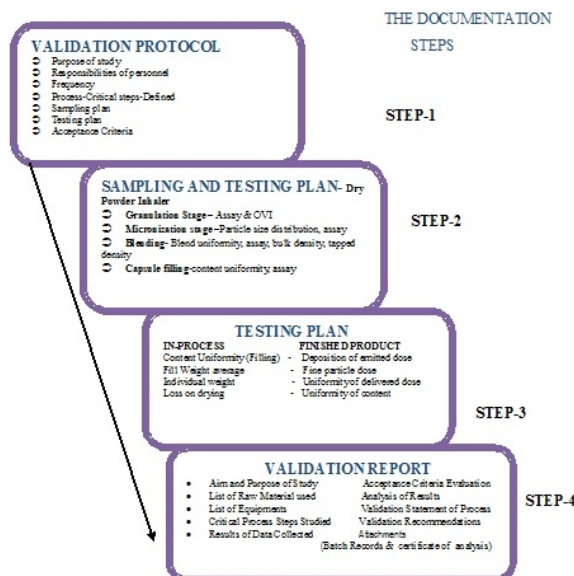
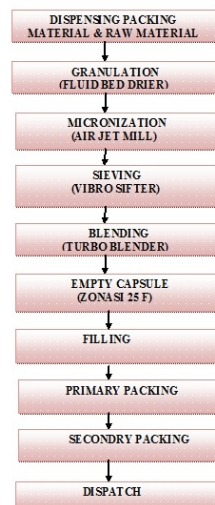


Fig. 1 Principle of dry powder inhaler design



PROCESS VALIDATION MASTER PLAN



General Flow diagram of manufacturing process of dry powder inhalers.