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Industrial Application of Process Validation in the Development & Scale-Up of Pharmaceutical Tablet Dosage Form of a Low Dose Containing Drug and a High Dose Containing Drug

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Abstract:

Aim of the study is the Application of Process Validation approach in the Development and Scale-Up of pharmaceutical tablet dosage form of a low dose containing drug Diazepam tablet IP[2] (5 mg) and a high dose-containing drug Paracetamol tablet IP [3](650 mg). Application of Process validation showsgreat advancement from the trial and error method or serendipity of development of Drug Delivery Systems. Although Diazepam Tablet IP (5 mg) as a low dose containing dosage form and Paracetamol Tablet IP (650 mg) as a high dose containing dosage form, will be taken as a model for the purpose of development, scale-up & validation in this thesis, the same approach of validation can be adopted for any Pharmaceutical Tablet dosage form containing low dose and high dose of active ingredients. Critical parameters of major processes of manufacturing of tablet dosage form will be identified and validated. Process variables will be optimized by updated Statistical tools[4]like Sampling Plan, Process Capability Studies, Analysis of Variance, Regression Analysis, t-test[5], Control Chart[6], Histograms, Pareto Charts[8]and Design of Experiments. Based on those statistical analysis and interpretation the developed validated process will be sufficiently robust to produce products with pre-determined quality attributes consistently over time which will also lead to Cost reduction, Productivity improvement, Cycle time reduction,Defect reduction, and also result in fewer complaints and recalls & reduces the cost of inspection and Testing and also it will lead to quality improvement of products as well as help pharmaceutical industry to increase productivity, profit and customer satisfaction. This thesis will be immensely beneficial for industry and customers as well. Therefore, process validation of tablet dosage form of a low dose containing drug and a high dose-containing drug is taken up as a project in this present work.

Keywords: *FDA: United State Food & Drug Administration. ; CGMP: Current Good Manufacturing Practice R&D: Research and Development. ; WHO: World Health Organization.*

INTRODUCTION:

The U.S. Food & Drug Administration (FDA) [1] & WHO under the authority of CGMP Regulations guidelines and directives consider process validation necessary because it makes good engineering sense. The basic concept has long been applied in other industries often without formal reorganization that such a concept was being used. But today under FDA's pre approval inspection (PAI) program, the watchword is to provide scientifically sound justifications (including Qualification and Validation, Documentation) for everything that comes out of the pharmaceutical R&D functions. FDA compliance programme on drug process inspections provide the following definition of Validation :

A validated manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing through the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, personnel), but it also includes the control on the entire process for repeated batches or runs.

Assurance of the product quality is derived from careful and systematic attention to a number of important factors including selection of quality components and materials, adequate product and process design and statistical control of the process through the in-process and end- product testing. Thus it is through careful design and validation of the processes and it's control system, a high degree of confidence can be established that all individual manufacturing units of a given batch or succession of batches that meet specifications will be acceptable. Keeping above background in mind, attempts will be made on the present

thesis on the validation of tablet dosage forms containing a low and a high dose of drug.

Proposed plan of research work:

1. Strategies of Process Validation to be planned [9,10,]
2. Steps in Process Validation to be outlined [11]
3. Formulation design and development of tablet dosage form of low dose drug Diazepam (5 mg) & high dose drug Paracetamol (650 mg) as model at laboratory scale.[12]
4. Pilot – Scale-up and Process Validation of critical parameters of major processes at pilot scale studies.[13]
5. Technology transfer from R&D to Production and Prospective Process Validation of process variables of major processes.
6. Providing feedback / validation report with necessary suggestion/modification.
7. Concurrent Validation[14]
8. Retrospective Validation[14]
9. Re-validation of the process if required[14]

METHOD:

1. Strategies of Process Validation[15, 16]

The strategy selected for process validation should be simple and straightforward.

The following few points need to be considered:

1. The use of different lots of raw materials should be included i.e. active drug substance and major excipient.
2. Batches should be run in succession and in different days and shifts.
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 operations.
5. Failure to meet the requirements of the validation protocol with respect to process input and output control should be subjected to process re-qualification and subsequent revalidation following a through analysis of process data.

2. Steps in Process Validation

a) Step 1: Identification of critical parameters of major processes to be validated (refer table 1).

b) Step 2: Identify the methodology, processes, and piece of equipment that will be used in the manufacture of the products.

c) Step 3: Identify the potentially relevant and critical process variables. (refer table 1).

d) Step 4: Conduct process validation experiments.

e) Step 5: Review product performance against the proposed specification. After describing the quality features, which must be achieved in the product and the minimum acceptable values of each feature, the specifications developed for the product should be reviewed.

f) Step 6: Monitor and review the results of the validation experiments. Validation report will be prepared. Optimized values of process variables will be assigned based on those validations experiments for subsequent running production which will give the confidence that the each unit operations/sub processes will lead to produce products of pre-defined quality consistently over time.

3. Formulation design[18] and development of tablet dosage form of low dose drug Diazepam (5 mg) & high dose drug Paracetamol (650 mg) as model at laboratory scale.

No validation process will be entirely fruitful unless validation process begins from formulation design stage. This is because if a product is defective in the design stage, a robust method of manufacturing and process control, good quality raw materials and best analytical methods will not produce validated product. Therefore, process validation activities will be started from the formulation design phase in the R&D.

Laboratory Batch: The first step in the scale – up process is the selection of suitable preliminary formula for more critical study and testing based on certain agreed-upon initial

design criteria, requirements and / or specifications. The work is performed for development in the laboratory. The
formula selected is designated as the (1 X) laboratory batch.

4. Pilot – Scale-up and Process Validation of critical parameters of major processes at pilot scale studies

The pilot program is defined as the scale-up operation conducted subsequent to the product and it's
process leaving the development laboratory and prior to it's acceptance by the full production manufacturing units. For the pilot program to be successful, elements of process validation (i.e., product and process qualification studies) must be included and completed during the developmental or pilot –laboratory phase of the work. Thus product and process scale-up should proceed in graduated steps with elements of process validation (such as qualification) incorporated at each stage of piloting program.
After the (1 X) laboratory batch is determined to be both physically and chemically stable based on
accelerated, elevated temperature testing, the next step is the scale- up process is the preparation of (10 X) laboratory – pilot batch. The (10 X) laboratory –pilot batch represents the first replicated scale-up of the designated formula. It is usually prepared in small size, pilot equipment within a designated CGMP approved area of the development laboratory. The number and actual size of the laboratory-pilot batches may vary in response to one or more of the following factors: a) Equipment availability b)
Active drug substance availability c) Cost of raw materials. Process qualification or capability studies are usually started in this important second stage of the pilot program. Such qualification or capability studies consist of process ranging, process characterization and process optimization as a prerequisite to the more formal validation program that follows later in the piloting sequence.

5. Technology transfer from R&D to Production and Prospective Process Validation of process variables of major processes.

Pilot Production: The pilot- production phase may be carried out either as a shared responsibility between the development laboratories and it's appropriate manufacturing counterpart. Technology and know-how of manufacturing the dosage form as developed by Laboratory Batch trials and Laboratory –Pilot Batch trials in R & D department is transferred to production department.
The objective of the pilot – production batch is to scale the product and process by another order to magnitude (100 X). For most drug products this represents a full production batch in standard production equipment. Again the actual batch size of the pilot-production (100 x) batch may vary due to equipment and raw material availability. The need for additional pilot- production batches ultimately depends on the successful completion of a first pilot batch and it's process validation program. Usually three successfully completed pilot-production batches are required for validation processes.
Three batches are subjected to Prospective Process Validation studies to optimize the process variables as outlined in table 1. In summary, process capability studies start in the development laboratories and / or during product and process development continue in well-defined stages until the process is validated in the pilot plant and / or pharmaceutical production.

6. Providing feedback / validation report with necessary suggestion/modification

Results of the validation experiments will be monitored and reviewed. Validation report will beprepared. Optimized values of process variables will be assigned based on those validation experiments for subsequent running production which will give the confidence that the each unit operations/sub processes will lead to produce products of pre-defined quality consistently over time. Scope of further modification and improvement of processes will also be suggested.

7. Concurrent Validation

Concurrent validation will be reviewed where current production batches are used to monitor the processing parameters. It gives assurances of the present batches being studied and offers the limited assurance regarding consistency of quality from batch to batch. This is generally carried out after several batches are manufactured with the prospectively validated process.

8. Retrospective Validation

Retrospective validation will be reviewed for a product being marketed and is based on extensive data accumulated over several lots and over time.

9. Re-validation of the process if required

Revalidation will be carried out only if there is introduction of any changes affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics.

Such changes may include those in starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems.

RESULT AND DISCUSSION :

Application of process validation approach in the development and scale up of Diazepam Tablet IP (5 mg) as a low dose containing dosage form and Paracetamol Tablet IP (650 mg) as a high dose containing dosage form, is

Table 1: Process Variables of Major Processes to be Validated

Unit operation	*Purpose*	*Process variables*	*Test parameters*	*Instruments Used (for process control)*
Screening	Ensure a set particle size of raw material[17]	➢ Screen size (mesh size)	1. Mesh analysis, 2. Bulk volume	Oscillating granulator using 12 & 40 mesh SS sieve
Dry Mixing (Preblending)	Homogenous mixture	➢ Mixing time ➢ Mixing speed (rpm) ➢ Load size ➢ Order of addition	1.Assay for mixing uniformity (Chemical content uniformity) 2. Mesh Analysis, 3. Yield reconciliation	Saizoner (Mixer cum Granulator)
Wet Mixing & Wet-Granulation	Convert powders to granules having suitable flow and compressive properties	➢ Granulating time ➢ Granulator speed ➢ Load size ➢ Liquid addition rate ➢ Amount of liquid	1. Weight per subpart 2. Amount of granulating agent per subpart 3. End-point by wattmeter /ampere reading	Saizoner (Mixer cum Granulator)
Drying	Reduce moisture content to proper level for compression	➢ Drying time ➢ Inlet temperature ➢ Steam pressure ➢ Load size	1. Moisture content analysis 2. Yield reconciliation	Fluid bed Dryer
Dry granulation (Size reduction)	Convert powders to desired granules size distribution	➢ Type of Granulating machine ➢ Screen size ➢ Feed rate	1. Particle size distribution	Multimill using a circular sieve of 2.5 mm diameter pores
Final mixing (Blending with lubricants)	Convert powders to required for suitable flow and compressive properties	➢ Load size ➢ Mixing speed (rpm) ➢ Blending time	1. Assay for mixing 2. Uniformity 3. Particle size distribution 4. Flow characteristics	Planetary Mixer
Compression of tablets	Manufacture of compressed tablets	➢ Type of compression machine ➢ Compression rate ➢ Granulate feed rate ➢ Compression force	1.Dose uniformity, 2. Weight uniformity 3. Average wt. 4.Hardness, 5. Thickness 6. Dissolution time 7. Disintegration time	Single Rotary 20 station tableting machine

taken as a model for the purpose of development, scale-up & validation in this thesis, the same approach of validation can be adopted for any Pharmaceutical Tablet dosage form containing low dose and high dose of active ingredients. The research work will provide frame-work and necessary important guidelines for the development, scale-up & process validation of tablet dosage form of low and high dose containing active ingredient(s). There are lot of products in the market for which well-controlled process validation studies are not conducted and there are many new molecules are in the pipelines for which development of pharmaceutical dosage forms are in progress in the Formulation & Development of pharmaceutical industry. Application of process validation approach in the development and scale up of those drugs, which would be lucidly described in the thesis, will be immensely beneficial for the pharmaceutical industry. Application of Process Validation will culminate the era of trial and error method or serendipity of development of Drug Delivery Systems and will begin the era of development and scale-up of Drug Delivery Systems on the basis of systematic application of scientific, technological and statistical knowledge through well thought of controlled experimentations, documentation and interpretation to produce products with optimized, validated robust processes. Such processes will be sufficiently robust to produce products with pre-determined quality attributes consistently over time.

Benefits of process validation Cost reduction, Productivity improvement, Cycle time reduction, Defect reduction, fewer complaints and recalls & reduction of cost of inspection and testing will also be achieved for dosage from of other drugs also. This approach of process validation in the development and scale-up will revolutionize the pharmaceutical industry with change in Culture and also lead Market share growth & Customer retention and growth. Validated process will lead to quality improvement of products as well as help pharmaceutical industry to increase productivity, profit and customer satisfaction.

CONCLUSION :

The present research work in will give a good guidance for pharmaceutical industry in the area of development and scale- up products using a systematic and scientific approach of process validation.

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