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PROCESS VALIDATION OF PIROXICAM DISPERSIBLE TABLETS

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ABSTRACT

The purpose of the research investigation was to study prospective process validation of Dispersible tablet dosage form. Quality cannot be adequately assured by in process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. Therefore building of quality requires careful attention to a number of factors, such as the selection of materials, product and process design, control variables in process Control and finished product testing. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower and upper release specifications. Three initial process validation batches of same size, method, equipment & validation criteria were taken. The critical parameter involved in sifting, dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication & compression stages were identified and evaluated as per validation plan.

KEY WORDS: prospective process validation, dispersible tablets, Control varibles.

INTRODUCTION

VALIDATION

Concept of validation

Validation is an act of demonstrating and documenting that any procedure, process, and activity were consistently lead to the expected results.

OR

According to FDA

It is documented evidence which provide a high degree of assurance that a specific product were consistently produce a product meeting its predetermined specification and quality attributes**.**

OR

According to European Commission

Action of proving in accordance with the principle of Good Manufacturing Practice that any procedure, process, equipment, material and system actually lead to the expected result.

Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials. Validation is therefore one element of quality assurance associated with a particular process, as the process differs so widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have developed general non-mandatory guidelines. Then word validation simply means, 'assessment of validity' or 'action of proving effectiveness'[1-4].

History of Validation

The concept of validation is first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995). It is proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes. U.S.F.D.A. is the pioneer in advocating the concept of Process Validation. But till 29th Sept., 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. No cGMP regulations talked anything about process validation.

There have been a number of incidents involving biological products that have killed, harmed or placed at risk people who have received products from processes that were not effectively validated. The contamination of biological with viruses provides examples of instances where inadequate control of raw materials or insufficient viral clearance during processing led to contaminated products.

A number of products derived from human blood or plasma have been tainted with human immunodeficiency virus (HIV) and hepatitis B virus (HBV). Just when the term "process validation" is first used is debatable, as the concepts underlying the term are quite old and the use of synonyms such as "verification" and" confirmation" appears to predate the use of "validation."

The term now here appeared in the U.S.F.D.A. documentation. This was not defined in law. It is only in a F.D.A. Compliance programmed entitled "Drug Process Inspections" issued in

June 1978 (before publication of the revised cGMP Regulations) "A validated manufacturing process is one, which has been proved to do what it purports to or is represented to do. The proof of validation was obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continued through into the production phase, Validation necessarily includes process qualification (the qualification of materials, equipment, system, buildings, personnel), but it also includes the control of the entire process for repeated batches or runs" [5]. This particular definition did not appear in any of the yearly revision of that particular compliance programmed. But until March 29, 1983 it is the only official definition of process validation. On March 29, 1983 draft on guidelines entitled **"Guidelines on General Principles of Process Validation"** is made available and the same is finalized in May, 1987.

The finalized definition is as "A documented Programme, which provides a high degree of assurance that a specific process were consistently produce, a product meeting its predetermined specifications and quality attributes". The first drafts of the May 1987 contained a similar definition, which has frequently been used in FDA speeches since1978, and is still used to day [6].

Benefits of Validation

1. Assurance of Quality

➢ Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality.

➢ Without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are

1. Very limited sample size.
2. The limited number of tests performed on a sample.
3. The limited sensitivity of the test.

2. Cost reduction

Quality costs are divided in to four categories:

a) Preventive costs.

b) Appraisal costs.

c) Internal failure costs.

d) External failure costs.

E.g.: of internal failure costs: Any validated and controlled process were result in fewer internal failures like

1. Fewer rejects
2. Reworks
3. Re-tests
4. Re-inspection

Process validation makes it possible to do the job right the first time. Also, a scientifically studied and controlled process makes it unlikely that defective products were dispatched to market thus no recalls or market complaints [7, 8].

3. Process Optimization

The optimization of a process for maximum efficiency, while maintaining quality standards, was a consequence of validation. Literal meaning of word to optimize was "To make as effective, perfect or useful as possible" [9].

4. Safety

Validation can also result in increased operation safety. e.g.: gauges used on equipment that designed to operate at certain temperature and pressures must be reliable i.e. they must be calibrated [10].

Analytical Validation

Analytical validation was the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised.

Types of Qualification:

The validation of a process requires the qualification of each of the important elements of the process. Some of the elements are as below,

1. Design Qualification(DQ)

The documented verification that the proposed design of the facility, system and equipment is suitable for the intended purpose.

2. Installation Qualification (IQ)

Establishing confidence that process, equipment and ancillary systems are capable of consistently operating or within established limits and tolerance.

It is a documented verification that the facility, system and equipment as installed or modified comply with the approved design and the manufacturer's recommendation.

3. Operational Qualification (OQ)

The documented verification that the facilities, systems and equipments as installed or modified, perform as intended throughout the anticipated operating ranges.

4. Performance Qualification (PQ)

The documented verification that the facilities, system and equipment as connected together to perform effectively and reproducibly based on approved process method and product specification [11, 12, 13, 14].

PROCESS VALIDATION

Definition: "Establishing documented evidence which provides a high degree of assurance that a specific process were consistently produce a product meeting its pre-determined specifications and quality attributes" FDA Guideline, 1987. The FDA in its new guidelines had made some changes in the aspects of process validation and defined it as "The collection andevaluation of data, from the design stage throughout production, which The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality [15].

Validation is defined as "Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled".

Validation is the overall expression for a sequence of activities in order to demonstrate and document that a specific product can be reliably manufactured by the designed processes, usually, depending on the complexity of today's pharmaceutical products, the manufacturer must ensure that the products were be consistently of a quality appropriate to their intended use. To achieve this with confidence, only in process control and finished product testing

alone are not sufficient to assure product quality; but all factors including the services which could affect product quality must be correctly designed, demonstrated to work effectively, Consistently and their performance is also regularly conformed so that consistent quality product is obtained. The compliance to their working rules defines a validated manufacturing process as "one has been proven to do what it purport or it represented to do."

The word "validation" simply means assessment of validity or action of proving effectiveness. Validation is a proof that a process works and this must be done using scientific and statically principles.

Process validation is not just an FDA or a U.S. requirement. Similar requirements are included in the World Health Organization (WHO), the Pharmaceutical Inspection Co-operation Scheme (PIC/S), and the European Union (EU) requirements, along with those of Australia, Canada, Japan, and other international authorities [16, 17, 18].

Why to Validate the Processes?

There are many reasons, in addition to theregulatory requirements, for validating processes. A manufacturer can assure through careful design of the device and packaging, careful design and validation of processes, and process controls, that there is a high probability that all manufactured units were meet specifications and have uniformquality. The dependence on intensive in-process and finished device testing can be reduced. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process were yield little scrap or rework, resulting in increased output [19, 20].

What Processes Should Be Validated?

Where process results cannot be fully verifiedduring routine production by inspection and test,the process must be validated according toestablished procedures. Process validationis the only practical means for assuring thatprocesses were consistently produce devices thatmeet their predetermined specifications:

1. Routine end-product tests have insufficientsensitivity to verify the desired safety andefficacy of the finished devices;Clinical or destructive testing would be requiredto show that the manufacturing process hasproduced the desired result or product.

2. Routine end-product tests do not reveal allvariations in safety and efficacy that may occur inthe finished devices.The process capability was unknown, or it wassuspected that the process is barely capable ofmeeting the device specifications [21, 22].

Steps in Validating a Process

1. Develop validation protocol
2. Conduct installation qualification
3. Conduct operational qualification
4. Conduct performance qualification
5. Analyze results and reach conclusions
6. Monitor and control process

Purpose: to ensure process remains within established parameters under anticipated conditions

1. Investigate deviations from established parameters
2. Take corrective action
3. Consider whether revalidation was necessary
4. Changes in process or product

   Evaluate changes in process, product, procedures, equipment, personnel, environment, etc. to determine effect of change.

Types of Process Validation

Process validation is divided into different types as follows:

1. Prospective Validation: It is defined as the establishment of documented evidence that a system does what it purports to do based on pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences. 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. During prospective validation, critical parameters that may affect the quality of the finished product are assessed. Sequence of trial should be designed to determine the

criticality of these factors. All equipment, production environment and the analytical testing methods to be used should be fully validated. Preparations of Master batch documentation were be initiated after identification of critical parameters, machine settings, component specifications and environmental conditions of the process. Using this well-defined process, a series of batches (generally considered acceptable that three consecutive batches/runs within the finally agreed parameters) should be produced which would give desired quality product and constitute a proper process validation. Detailed testing should also be done on the final product in its package. After review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production which should be included in the batch manufacturing and packaging record.

Following Details Are Included:

1. Short description of process
2. Summary of critical processing step to be investigated
3. Finished product specification for release
4. List of analytical method
5. Proposed in –process controls with acceptance criteria
6. Additional testing to be carried out with acceptance criteria and analytical validation
7. Sampling plan
8. Method for recording and evaluating result
9. Function and Responsibilities
10. Proposed time table
11. A series of batches of the final product may be produced under routine condition
12. Batch made for process validation should be same size as the intended industrial scale.

2. Concurrent Validation: similar to prospective; except the operating firm were sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing.

Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:

1. When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site.
2. Where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients.

3. When the number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control.
4. When the numbers of batches produced are limited (e.g. orphan drugs).

The justification for conducting concurrent validation must be documented and the protocol must be approved by the Validation Team. A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process [23, 24].

3. Retrospective Validation: It is defined as the establishment of documented evidence that a system does what it purports to do based on review and analysis of historical data. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Data from batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results acts as a source for retrospective validation. Data from a minimum of ten consecutive batches produced were be acceptable for retrospective validation. In case if there are less than ten batches, which is not sufficient to demonstrate retrospectively then the retrospective validation should be supplemented with data generated with concurrent or prospective validation [25].

4. Revalidation: It is the repetition of a validation process or a specific part of it. Thisis carried out when there is any change or replacement in formulation, equipment, plant or site location, batch size and in the case of sequential batches that do not meet product and process specifications and is also carried out at specific time intervals in case of no changes. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Possible reasons for starting the revalidation process include:

1. The transfer of a product from one plant to another.
2. Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.
3. Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc., that may affect the process or product).
4. Changes in the source of active raw material manufacturer.
5. Changes in packaging material (primary container/closure system).
6. Changes in the process (e.g., mixing time, drying temperatures and batch size)
7. Changes in the equipment (e.g. addition of automatic detection system).
8. The necessity of periodic checking of the validation results.
9. Significant (usually order of magnitude) increase or decrease in batch size.
10. Sequential batches that fail to meet product and process specifications.
11. Variations revealed by trend analysis (e.g. process drifts).

5. Validation: Cleaning Validation should be perform in order to confirm effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents and microbial contamination should be logically based of the material involved the limits should be achievable and verifiable.

Phases of Process Validation

Phase 1

Pre-Validation Phase or the Qualification Phase

which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment Qualification, master production documents, Process Capability.

Phase 2

Process Validation Phase (Process Qualification phase)

Designed to verify that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Phase 3

Validation Maintenance Phase: requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations,

failures, modifications to the production process, and that all SOPs have been followed, including Change Control Procedures [26].

Documentation

The main objective of documentation is to establish, monitor and record "Quality" for all aspects of Good Laboratory Practices and Quality Control". Documentation system should provide for a periodic review & revision if necessary, and such revised versions shall also be approved by the authorized persons. The most important documents in the pharmaceutical industry considering validation are the SOP (Standard operating procedure), Validation Master Plan and Validation Protocol.

1. SOP (Standard Operating Procedure)

Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work instructions, appropriate specifications and required records. These outline procedures, must be followed to claim compliance with GMP principles or other statutory rules and regulations. The general aspects covered under the SOPs are the Preparation and maintenance of work area like ishing and sterilization, decontamination and testing area. Even the work done in the laboratory were documented, for eg., the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labeling and storage, test procedures, reference material, identification, handling, storage, use deviation. Even the details of the equipments and their maintenance were also involved.

2. Validation Master Plan

An approved written plan of objectives and actions stating how and when companies were achieve compliance with the GMP requirements regarding validation. VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of its being the list/ inventory of the items to, relevant to product and process controls within a firm should be included in the validation master plan. It even holds the calibration and qualification of equipment's, summary and conditions of Validation Protocol.

3. Validation Protocol

A written plan of actions stating how process validation were be conducted, it were specify who were conduct the various tasks and define testing parameters, sampling plans, testing

methods and specifications, were specify product characteristics, and equipment to be used. It must be specify the minimum number of batches to be used for validation studies, it must specify the acceptance criteria and who were sign \ approve \ disapprove the conclusions derived from such a scientific study. The validation protocol should contain the following elements,

1. Short description of the process
2. Summary of critical processing steps to be investigated
3. In process, finished product specification for release
4. Sampling plans
5. Departmental responsibility
6. Proposed timetable
7. Approval of protocol.

Experimental Work

Prospective process validation was performed on the three batches of Piroxicamdispersible Tablets. The three consecutive batches were labeled as (Batch X, Batch Y, Batch Z).The protocol includes list of raw materials, list of equipments used, process flow diagram, critical process parameters, standard specification and acceptance criteria & sampling plan as given below. During the manufacturing process samples were collected and sent to for analysis to Q.C. department.

3.1 Responsible Authorities for Validation

Table 1: Responsibilities of multi-functional Validation team

Sr. No	Department	Responsibility
1	**Process Development**	Preparation and review of process validation protocol and report. Monitoring of the manufacturing process as per the protocol and batch record
2	**Production**	To review of process validation protocol andreport. Execution of process as defined in the batchrecord& process validation protocol and relevant operating procedures. Investigation of any deviations from definedmanufacturing process and process validationprotocol.

Sr. No	Department	Responsibility
3	**Regulatory Affairs**	To review of process validation protocol and report To review the impact on regulatory submission and for necessary regulatory update if required.
4	**Engineering**	To provide necessary utility as per the product requirement. To ensure the calibration of measuring devices available on process equipment and utilities. To ensure maintenance of processing equipment and utilities.
5	**Quality Assurance**	To ensure the pre-requisite requirements are completed before proceeding for processdevelopment. To review and approve process validation Protocol and report. To with draw samples as per sampling plan defined in the process validation protocol. To review and approve the investigations and corrective / preventive actions for deviations fromdefined manufacturing process and protocol.

2.2 MATERIAL AND METHOD

2.2.1 List of Equipment & Calibration

Table 2: Shows list of Equipment and Status:

Sr.No.	Equipment	Make	Capacity	Equipment ID No.	Instruments Calibration Status
1.	Weighing balance	Axpert	220gm	BA – 54	Must be Calibrated
2.	Digital Analytical Balance	Mettlar Toledo	220gm	BA – 53	Must be Calibrated
3.	Moisture Analyzer	Sartorius	45 gm	QC- 077	Must be Calibrated
4.	DT Apparatus	Electro lab	NA	QC – 073	Must be Calibrated
5.	Friability Tester	Electro lab	NA	QC – 059	Must be Calibrated
6.	Hardness Tester	Electro lab	NA	QC – 085	Must be Calibrated
7.	VernierCalipers	Mitutoyo	6 inch	VC – 102	Must be Calibrated
8.	Dissolution apparatus	Electro lab	NA	QC – 011	Must be Calibrated
9.	UV Spectroscopy	Shimadzu	NA	QC – 083	Must be Calibrated

2.3 Manufacturing Process

Table 3: Shows list of Ingredient

Sr. No	Ingredients	Category	Quantity
1	Pyroxicam IP	Active ingredients	18.000 Kg
2	Lactose IP	Diluents	337.500 Kg
3	Microcrystalline Cellulose IP	Diluents	117.000 Kg
4	Hydroxy Propyl Cellulose	Thickening & stabilizing agent	18.000 Kg
5	Sodium StearylFumarate	Lubricant	4.500 Kg

2.3.1 MANUFACTURINGPROCEDURE

1. Brief Description of Manufacturing Process

The steps in the manufacturing process were followed as per the approved batch manufacturing record. Process parameters during each unit operation were monitored to demonstrate that product meets the acceptance criteria. The processing of Piroxicam dispersible tablets comprises of following stages.

2. **Dispensing:**

Raw material was dispensed as per the standard operating procedure.

1. Sifting

Sizing of the materials i.e. piroxicam IP and Diluents were sifted through x mesh S.S. sieve Fitted to Vibratory sifter and collected it in OGB.

2. Dry mixing

Dry mix material for x minutes and at x rpm speed with addition of binder and dilutions in OGB.

3. Drying

Collect the mixed material in FBD and dry until the desired LOD achieved.

4. Milling

Multi-mill is used to reduce large particle in required range particle.

5. Blending and Lubrication

1. Sifting Of Extracellular Materials

Disintegrant, Glidant & Diluents were sifted through the S.S. sieve using vibratory sifter and collected it in the polybags.

2. Sifting of Lubricant

The Lubricant was sifted through given S.S. sieve using vibratory sifter and collected it in the polybags.

3. Blending

The sized granules of Piroxicam were mixed for y minutes in Octagonal blender at appropriate RPM and the sifted extra granular materials was added and it was mixed for y minutes in Octagonal blenderat stated RPM.

4. Lubrication

Sifted Lubricant was added into Octagonal blender containing sized granules and extra granular materials and mixed it.

1. **Compression-**Compression was performed on compression machine as per parameters given in BMR

2. Inspection

Compressed tablets were inspected through tablet inspection machine for removing defected tablet.

Sampling Location Diagram

- **Sampling plan diagrams of Octagonal Blender:** Eleven samples were collected from ten different parts of the Octagonal Blender Bin. One set was taken for analysis other set kept as reserved sample. And also one pooled sample was taken after blend unloading.

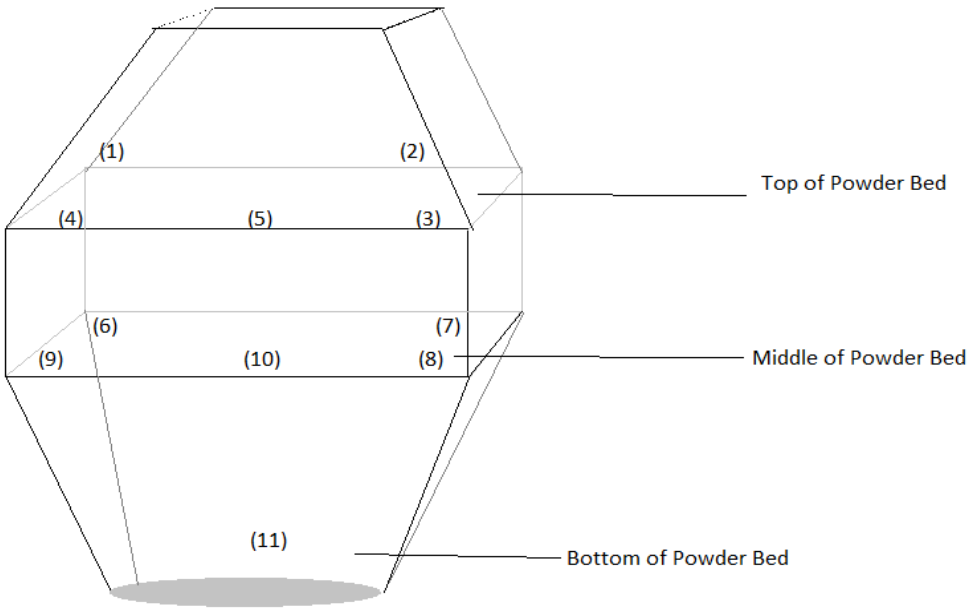


Figure No. 4 Sampling Plan Diagrams of Octagonal Blender.

2.4 Process Flow Chart and Critical Parameter

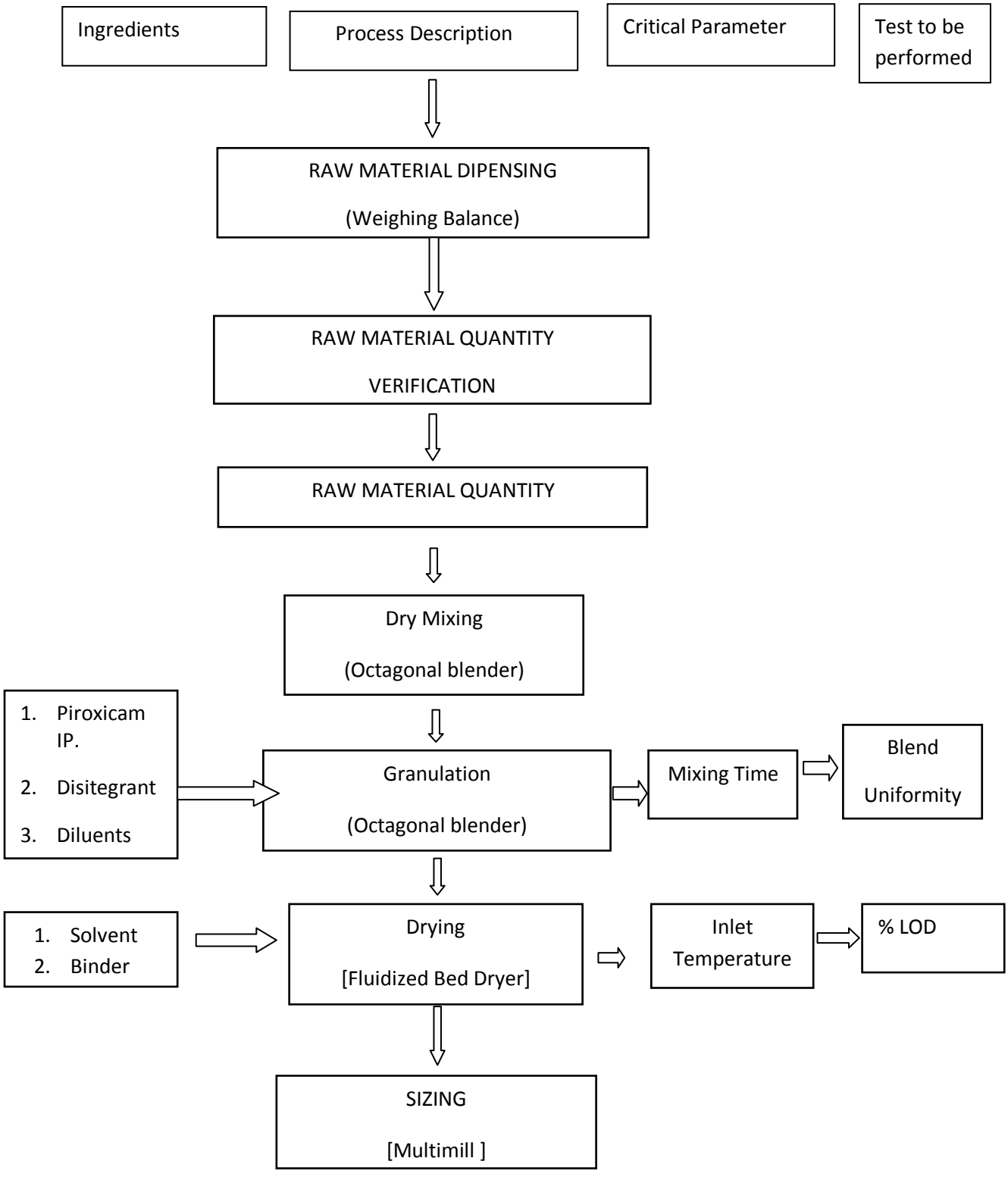


Figure: 1 Process Flow Chart for Granulation, Drying & Sizing

Assessment of Critical Process Parameter

Table: 4Shows Assessment of Critical Process Parameter

Process Steps	Critical variables	Rational	Critical Parameters
Sifting	ifter sieve size integrity of Sifter Sieve	Secure sifting	orrect sieve number, Sieve integrity before and after use.
Dry Mixing	lixing Time Mixing npeller Speed	To ensure proper mixing	peed of impeller lixing Time
Granulation	Binder addition rate Speed of granulator Granulation time Mixing time	To ensure uniform binder addition To obtain uniform granules	Quantity of binder solution added Speed of granulator Granulation time Amperage reading
Drying	rying temp. rying time	To get the granules of desired Moisture Content (MC) / Loss On Drying (LOD).	Drying time Inlet temperature utlet temperature LOD
Process Steps	**Critical variables**	**Rational**	**Critical Parameters**
Milling	article size distribution ulk density	To obtain the desired granule profile for blending and compression	creen integrity orrectness of creen number Rate of size reduction irection of blade
Blending & Lubrication	lending time (pre-lubrication) lending time (with lubricant)	To obtain final blend uniformity for compression	lending time Speed of blender Assay Bulk / Tap density Sieve analysis Blend uniformity
Compression	lachine speed (Tab/min)	To meet the desired product specification during compression	M/C Speed Average weight Description Physical Appearance Weight Variation Thickness Hardness Friability Disintegration test

Tests Which Has To Be Performed

1. Description
2. Average weight
3. Uniformity of weight
4. Thickness
5. Content Uniformity (By UV)
6. Dissolution (By UV)
7. Assay (By UV)
8. Hardness

Sampling Plan and Testing Plan

Table 5: Shows Sampling Plan and Testing Plan

STAGE	SAMPLE LOCATION	SAMPLE SIZE	TEST
Dry mixing	Three samples of approx.1g each from top,middle,and bottom of octagonal blender after 30 min of blending.	Approx. 300 mg /each location	Blend uniformity Assay
Drying	Samples of dried granules shall be withdrawn from 5 sampling points comprising left, right, center, front, back layer of FBD bowl.	Approx. 5.0 g /each location	Loss on Drying
Lubrication	Unit dose samples shall be withdrawn from 11 different location of the blender comprising of upper,middle,lower layer and bottom layer after 3 minutes mixing with Lubricant in Octagonal blender.	Approx. 1100 mg.	Blend uniformity
	Approximately 300 g of lubricated bulk blend to be sampled for physical characteristic evaluation.	Approx. 300 g	Physical characteristics Description Bulk density Tapped density Angle of repose Particle size analysis Assay Sieve analysis.
Compression Minimum speed Optimum speed Maximum speed	During compression, samples to be collected & mixed from both sides of press(RHS and LHS) at initial, middle and atthe end of compression operation	150 Tablets at each stage	Description Average weight uniformity of Weight Disintegration time Friability Hardness Thickness Dissolution Content uniformity Assay

Compression	Tablets to be collected as a composite sample during operation	200 tablets	Description Average weight Uniformity of Weight Disintegration time Friability Hardness Thickness Dissolution Content uniformity . Assay

Specifications

Table 6: Shows Specifications

Stage	Test	Specification
Dry mixing	Content Uniformity	a] 95.0 to 105 % w/w of mean value b] RSD of the sample NMT 5.0%
Drying Dried granule	Loss on drying	2.5% w/w (at 105^0 C on moisture Analyzer)
Lubrication	Blend uniformity	Mean Individual sample should be within : 95.0-105.0 % of labeled claim. RSD: NMT 5.0 %
	Description	Whitecoloredpowder blend.
	Compressibility index	5 – 15(excellent – Free)
	Assay	Between 97.0% - 105.0% RSD not more than 5.0%
	Loss on drying	Between 2.0 – 3.0 %w/w
Compression	Description	White to off-white, oblong tablet with a break line and "DOL 20" engraved on one the same side and plain on the other.
	Average Weight	560.0 mg ± 2.0%
	Uniformity of Weight	Not more than two of individual weights deviates from average weight by more than 7.5% and none deviate by more than 15%
	Disintegration Time	Not more than 2 Minutes
	Friability	Not more than 0.8 % w/w
	Hardness	NMT 100 to 120N
	Thickness	4.30 mm to 4.70 mm
	Assay	97.0% – 105.0%
	Dissolution	Not less than 70 % (Q) dissolved in 45 min.

RESULT & DISCUSSION

OVERVIEW

Purpose & Scope: The purpose of this report was to provide documentary evidence that the manufacturing process of Piroxicam Dispersible Tablets 20 mgwith batch size of 2,60,000,

was capable to produce the product meeting the predefined specification and quality attributes.

PRODUCT DETAILS

Product Name

Dispersible Tablets 20 mg

Label Claim

Each tablet contains……

Piroxicam IP…… 20 mg.

DESCRIPTION OF TABLET

White to off white coloured, oblong tablet with a break line and "DOL 20" engraved on one the same side and plain on other.

Batch Details

Table 7: Shows Batch Detail of Batch X, Y, and Z

Batch No.	Mfg. Date	Expiry Date	Batch Qty.
BATCH X	JULY.2013	JUNE.2016	2,60,000
BATCH Y	JULY.2013	JUNE.2016	2,60,000
BATCH Z	JULY.2013	JUNE.2016	2,60,000

3.6 Analytical Data for Dry Mix

3.6.1 Dry Mixing: Dry mixing was carried out in Rapid Mixer Granulator for 15 minutes and samples were collected from eleven different locations (11-points) to test the Blend Uniformity. Once pooled Sample was collected, content uniformity, test were performed on it**.** The results are as follows:

3.6.1.1 Content Uniformity of Dry mix (for 5 min)

Table 9: Shows Results of Content Uniformity of Dry Mix:

Sr. No.	Sampling layer &	Acceptance Criteria	Content Uniformity (%)		
			BATCH X	BATCH Y	BATCH Z
1	Top Left	Not less than 95.0% and not more than 105.0% of the labeled amount of Piroxicam	101.9	101.5	98.6
2	Top Right		101.6	99.8	101.8
3	Top Right		101.3	100.6	100.4
4	Top Left		100.2	98.4	98.4

5	Top Middle	with	99.5	99.9	99.9
6	Middle Left	RSD NMT 5.0%.	97.4	100.8	99.5
7	Middle Right		99.4	97.6	98.2
8	Middle Right		99.1	99.5	101.5
9	Middle Left		98.1	100.6	99.7
10	Middle		100.4	99.8	100.1
11	Bottom		100.6	102.1	100.1
Minimum			97.4	97.6	98.2
Maximum			101.9	102.1	101.8
Mean			100.0	100.1	99.8
SD			1.4208	1.2902	1.1613
RSD (%)			1.42	1.29	1.16

3.6.1.2 Content Uniformity of Dry mix (10 min)

Table 10: Shows Results of Content Uniformity of Dry Mix

Sr. No.	Sampling layer & Location	Acceptance Criteria	Content Uniformity (%)		
			BATCH X	BATCH Y	BATCH Z
1	Top Left Back	Not less than 95.0% and not more than 105.0% of the labeled amount of Piroxicam with RSD NMT 5.0%.	101.5	102.1	101.2
2	Top Right Back		101.4	99.5	101.2
3	Top Right Front		100.1	101.2	100.4
4	Top Left Front		99.4	99.8	99.5
5	Top Middle		99.2	101.2	99.6
6	Middle Left Back		101.9	101.2	100.1
7	Middle Right Back		100.4	99.1	101.1
8	Middle Right Front		101.0	101.0	100.1
9	Middle Left Front		100.6	101.1	102.5
10	Middle Middle		102.3	100.8	100.7
11	Bottom Middle		101.2	99.5	102.2
Minimum			99.2	99.1	99.5
Maximum			102.3	102.1	102.5
Mean			100.8	100.6	100.7
SD			0.9857	0.9534	0.9668
RSD (%)			0.98	0.95	0.96

3.6.1.3 Content Uniformity of Dry mix (15 min)

Table 11: Shows Results of Content Uniformity of Dry Mix

Sr. No.	Sampling layer & Location	Acceptance Criteria	Content Uniformity (%)		
			BATCH X	BATCH Y	BATCH Z
1	Top Left Back	Not less than 95.0% and not	101.3	101.4	101.4
2	Top Right Back		102.5	100.1	102.1

3	Top Right Front	more than 105.0% of the labeled amount of Piroxicam with RSD NMT 5.0%.	100.4	100	101.4
4	Top Left Front		102.5	102.6	99.5
5	Top Middle		100.9	101.5	101.4
6	Middle Left Back		100.2	102.1	101.7
7	Middle Right Back		99.9	100.5	100.9
8	Middle Right Front		102.4	101.2	101.8
9	Middle Left Front		102.1	102.9	100.5
10	Middle Middle		101.8	102.4	103.1
11	Bottom Middle		101.2	101.4	102.4
Minimum			99.9	100	99.5
Maximum			102.5	102.9	103.1
Mean			101.4	101.5	101.5
SD			0.9516	0.9821	0.9613
RSD (%)			0.94	0.97	0.95

Evaluation

% RSD of Piroxicam Dispersible Tablet for all three validation batches were within the range 1.42-0.94. Which were found within the specification? Based on % RSD data of Piroxicam Dispersible Tablets of three validation batches, it was evident that the dry mixing throughout the sampling locations.

3.6.3 Analytical Data for Lubricated Blend

3.6.3.1 Blend: Blending was carried out in Octagonal Blender for 13 minutes and samples were collected from 11 different locations (11-points) to test the Blend Uniformity. Once pooled Sample was collected, blend uniformity, Assay and loss on drying, and physical properties determination tests were performed on it. The results are as follows:

3.6.3.2 Content Uniformity of Lubricated Blend (13 MIN)

Table 12: Shows Result of Content Uniformity of Lubricated Blend

Sr. No.	Sampling layer & location	Content Uniformity (95.0 % to 105.0 %)		
	Batch No.-->	BATCH X	BATCH Y	BATCH Z
1	Top Left Back	104.0	103.2	105.0
2	Top Right Back	103.1	101.5	103.5
3	Top Right Front	103.5	104.2	101.4
4	Top Left Front	101.6	101.6	101.9
5	Top Middle	102.9	103.4	103.2
6	Middle Left Back	98.9	102.4	104.2
7	Middle Right Back	101.1	101.7	99.9
8	Middle Right Front	103.9	102.4	100.5
9	Middle Left Front	100.3	104.1	101.8
10	Middle Middle	104.0	99.8	101.7
11	Bottom Middle	101.3	101.1	103.2
11	Minimum	98.9	98.8	99.9

12	Maximum	104.0	104.2	105.0
13	Average	102.2	102.3	102.4
14	SD	1.7095	1.3442	1.5805
15	RSD (%)	1.67	1.31	1.54

Acceptance Criteria

1. Individual samples result: 102.2% - 102.4% of mean value
2. Mean of individual samples should be within 95.0% -105.0% for Piroxicam Dispersible Tablets of labeled claim respectively
3. RSD: NMT 5.0 %

Evaluation

% RSD of Piroxicam Dispersible Tablets for all three validation batches were within the range 1.31-1.67, which were found within the acceptance criteria.

% RSD of Piroxicam Dispersible Tablets for all three validation batches, it was evident that there was no segregation or demixing occurs in the blender and mixing is homogeneous throughout the sampling locations.

3.7.3.1.2 Assay of Lubricated Blend

Table 13: Shows Results of Assay of Lubricated Blend

Description	Batch No.→ Limit	BATCH X	BATCH Y	BATCH Z
Assay (Composite Blend)	97.0 % to 105.0%	100.2	101.1	100.9

Evaluation

Assay of Piroxicam Dispersible Tablet for three validation batches was within the specification.

3.7.3.1.3 Physical Characteristics of Lubricated Blend

Table 14: Shows Physical Characteristic of Lubricated Blend

Sr. No.	Parameter	Batch		
		Batch X	Batch Y	Batch Z
1	Description	White Colored Powder Blend	White Colored Powder Blend	White Colored Powder Blend
2	Bulk density gm/ml	0.69	0.68	0.69
3	Tapped density gm/ml (500taps)	0.76	0.75	0.76
4	Compressibility Index (%) (considering TD-500 Taps)	9.21	9.33	9.21

5	Angle of Repose	1.28	1.27	1.28
6	**Particle Size Distribution**	**Cumulative Retention (%)**	**Cumulative Retention (%)**	**Cumulative Retention (%)**
	Above 20#	98.24	98.12	98.24
	Above 60#	58.39	57.9	58.40
	Above 80#	27.44	27.26	27.40
	Above 100#	20.80	20.70	20.75
	Below 100#	19.42	19.52	19.47

Evaluation

The physical parameter such as description, bulk density, tapped density, compressibility index, and particle size distribution for three validation batches were satisfactory and found consistent. No significant observation related to the flow of the blend was observed throughout the compression activity.

3.7.4 Analytical Data for Compressed Tablet

3.7.4.1 Compression: During compression, samples from compression machine at minimum speed, optimum speed, maximum speed were collected only from first batch while at the initial, middle, end and composite of compression from all the three consecutive batches, samples were collected to test various in-process checks i.e. description, average weight, Uniformity of weights, thickness, hardness, friability, and disintegration test. Assay, dissolution test performed.

3.7.4.1.1 In-process checks tablet compression

Table 15: Shows Results of In-process Check of three Batches at Minimum, optimum andmaximum Speed.

Sr No.	Parameters	Limit	Batch No.	MINIMUM SPEED	OPTIMUM SPEED	MAXIMUMSPEED
1	Description	White to off white, oblong tablet with a break line and “DOL 20” engraved on one the same side and plain on	X	Complies	Complies	Complies
			Y	Complies	Complies	Complies
			Z	Complies	Complies	Complies
2	Average weight (mg)	550.0 ± 5% 550.0-560.0mg.	X	552.1	551.0	558.2
			Y	553.2	557.1	557.2
			Z	556.0	555.0	556.2
3	Uniformity of weight (mg)	550.0±5 % of Average	X	Complies	Complies	Complies
			Y	Complies	Complies	Complies

		weight	Z	Complies		Complies	Complies
4	Thickness(mm)	4.30-4.70 mm	X	Min	4.14	4.13	4.14
				Max	4.23	4.24	4.23
				Avg.	4.18	4.20	4.20
			Y	Min	4.13	4.14	4.15
				Max	4.22	4.25	4.25
				Avg.	4.20	4.19	4.20
			Z	Min	4.14	4.15	4.14
				Max	4.22	4.21	4.24
				Avg.	4.20	4.19	4.18
5	Friability (%)	NMT 0.8 w/w	X	0.19		0.14	0.16
			Y	0.17		0.16	0.14
			Z	0.15		0.18	0.18
6	Disintegration time (minutes)	NMT 2 minutes	X	50 sec.		42 sec.	52 sec.
			Y	42 sec.		55 sec.	35 sec.
			Z	44 sec.		44 sec.	40 sec.

Sr. No.	Parameters	Limit	Batch No.		Observation		
					MINIMUM SPEED	OPTIMUM SPEED	MAXIMUM SPEED
7	Diameter	12.80-13.20mm	X	Min	13.01	13.03	13.03
				Max	13.06	13.07	13.05
				Avg.	13.04	13.05	13.04
			Y	Min	13.03	13.04	13.03
				Max	13.05	13.06	13.07
				Avg.	13.04	13.05	13.06
			Z	Min	13.02	13.02	13.01
				Max	13.06	13.06	13.06
				Avg.	13.04	13.04	13.04
8	Hardness	100-220N	X	Min	140.9	140.3	152.1
				Max	148.6	156.2	146.8
				Avg.	135.2	142.2	164.2
			Y	Min	120.1	156.2	142.3
				Max	126.3	178.2	156.1
				Avg.	124.3	166.2	163.9
			Z	Min	120.3	145.3	142.5
				Max	155.9	149.3	164.1
				Avg.	143.2	185.2	152.5

Evaluation

Physical parameter of Piroxicam Dispersible tablet at Minimum, Optimum, Maximum, speed of compression for three validation batches X, Y, Z were found in the range within the acceptance criteria.

Table 16: Shows Results of In-process Check of three Batches atoptimum Speed.

Sr No	Parameters	Limit	Batch	Observation				
				INITIAL		MIDDLE	END	COMPOS
1	Description	White to off white coloured,oblong tablet with a break line and "DOL20"	X	Complies		Complies	Complies	Complies
			Y	Complies		Complies	Complies	Complies
			Z	Complies		Complies	Complies	Complies
2	Average weight (mg)	550.0 ± 5% 550-560mg.	X	551.6		554.3	553.2	559.2
			Y	552.2		554.2	555.4	566.3
			Z	550.5		553.1	556.4	556.4
3	Uniformity of weight (mg)	550.0±5 % of Average weight	X	Complies		Complies	Complies	Complies
			Y	Complies		Complies	Complies	Complies
			Z	Complies		Complies	Complies	Complies
4	Thickness (mm)	4.30-4.70 mm	X	Min	4.13	4.14	4.15	4.13
				Max	4.24	4.24	4.23	4.24
				Avg.	4.19	4.20	4.20	4.19
			Y	Min	4.15	4.14	4.14	4.14
				Max	4.23	4.24	4.26	4.26
				Avg.	4.20	4.19	4.20	4.21
			Z	Min	4.11	4.15	4.12	4.13
				Max	4.24	4.26	4.25	4.23
				Avg.	4.20	4.19	4.18	4.20
5	Diameter (mm)	12.80 -13.20 mm	X	Min	Min	13.01	13.03	13.03
				Max	Ma	13.06	13.07	13.05
				Avg.	Avg	13.04	13.05	13.04
			Y	Min	Min	13.03	13.04	13.03
				Max	Ma	13.05	13.06	13.07
				Avg.	Avg	13.04	13.05	13.06
			Z	Min	Min	13.02	13.02	13.01
				Max	Ma	13.06	13.06	13.06
				Avg.	Avg	13.04	13.04	13.04
6	Hardness	100-220 N	X	Min	Min	195.6	164.5	155.2
				Max	Ma	168.6	166.2	156.8
				Avg.	Avg	165.2	152.2	164.2
			Y	Min	Min	165.2	166.9	156.3
				Max	Ma	159.3	168.2	166.1
				Avg.	Avg	165.3	156.2	153.9
			Z	Min	Min	165.8	166.8	155.1
				Max	Ma	185.9	169.3	160.1
				Avg.	Avg	173.2	165.2	142.5

Sr.No.	Parameters	Limit	Batch No.	Observation			
				INITIAL	MIDDLE	END	COMPOSITE
7	Friability	NLT 0.8 % W/W	X	0.19	0.14	0.16	0.15
			Y	0.17	0.16	0.14	0.14
			Z	0.15	0.18	0.18	0.19
8	Disintegration	NMT 2 min.	X	50 sec.	42 sec.	52 sec.	40 sec.
			Y	42 sec.	55 sec.	33 sec.	30 sec.
			Z	44 sec.	44 sec.	40 Sec.	41 sec.

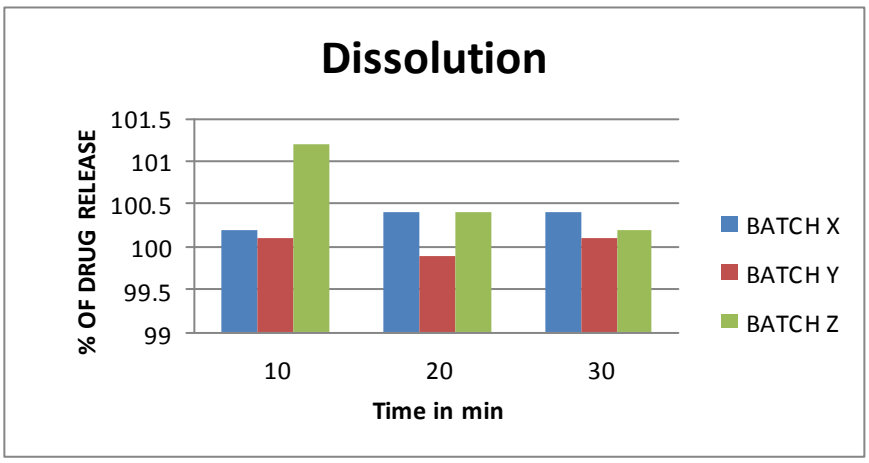
Evaluation

Physical parameter of Piroxicam Dispersible Tablets at Optimum speed of compression for three validation batches X, Y, Z were found in the range within the acceptance criteria.

3.7.4.1.2 Dissolution during Compression:

Table 17: Results of Dissolution Test of **Three Batches at optimum speed.**

Parameter	Batch		Observation			
			NLT70 % OF DISSOLVED IN 40 MIN.			
			INITIAL	MIDDLE	END	COMPOSI
Dissolution (%)	X	Min	98.9	98.4	98.6	98.7
		Max	101.5	102.4	102.4	101.5
		Avg.	100.2	100.4	100.4	100.0
	Y	Min	98.7	98.2	99.2	98.9
		Max	101.3	100.6	101.2	100.6
		Avg.	100.1	99.9	100.1	99.8
	Z	Min	98.8	98.5	99.1	99.2
		Max	100.8	101.5	101.2	101.6
		Avg.	101.2	100.4	100.2	100.1



Graph 1: Dissolution of Tablet

Evaluation

% dissolution of Dispersible Tablets at Optimum speed of compression for three validation batches X, Y, Z were found in the range 100.0-100.4, 99.8-100.1, 100.1- 101.2 respectively, which were within the acceptance criteria.

3.7.4.1.3 Assay of Compressed Tablet

Table 18: Results of Assay of Compressed Tablet

Parameter	Active	Batch		Observation			
				Piroxicam. (95.0% - 105.0%)			
				INITIAL	**MIDDLE**	**END**	**COMPOSI**
Assay	Piroxicam (95.0% -105.0)	**X**	Min	98.7	98.4	98.6	98.4
			Max	103.0	102.4	102.8	102.5
			Avg	100.7	100.1	100.2	100.4
		Y	Min	98.6	98.3	98.6	98.7
			Max	102.8	102.4	102.1	102.4
			Avg	100.4	100.1	100.3	100.4
		Z	Min	98.4	98.9	98.6	98.4
			Max	102.9	102.4	102.1	102..4
			Avg	100.8	100.5	100.2	100.8

Evaluation

Assay of Dispersible Tablets at initial, middle, end and composite stage of compression at optimum were found within the specification.

CONCLUSION

Based on the validation test result, reviews, assessment & evaluation, it was concluded that the manufacturing process ofPiroxicam Dispersible Tablet was validated as per CGMP guideline for the predetermined acceptance criteria.

REFERENCE

1. Christine O, Lazar S, "Process validation from the viewpoint of the FDA", http://www.gmp-publishing.com/en/gmp-products.html, February 2012.
2. Manohar A.P. In Pharmaceutical quality assurance; Nirali Prakashan, 2nd Edn, 2009; 8.2-8.20.
3. WHO expert committee on specifications for pharmaceutical preparations. WHO technical report, series no. 863 – 34th report, Annex 6 – GMP: Guidelines on the validation of manufacturing processes, 4-7.
4. Sofer G., Zabriskie D. In Biopharmaceutical Process Validation; Informa Healthcare, Marcel Dekker, New York, 2000; 11–100.

5. U.S. Food & Drug Administration, Guidelines on General Principles of Process Validation; Division of Manufacturing and Product Quality, CDER, FDA, Rockville, MD, May 1987.
6. Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029). 2009; 2-13.
7. Guidelines on General Principles of Process Validation, Food and Drug Administration, Maryland, 1993; 60-74.
8. Manoher A Potder, Pharmaceutical Quality Assurance, Nirali Prakashan 8.1-8.15.
9. Guideline on Process Validation; the European Agency for the Evaluation of Medicinal Products, March 2001.
10. ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 33.
11. Guidance for Industry on general principles and practices of process validation; US department of health and human services Food and Drug Administration, 2011; 7-9.
12. www.pharmaturor.org/articles/pharmaceutical-process-validation-cgmp-concept
13. Guidance for Industry: General principles and practices of process validation; Center for Drug Evaluation and research, center for Biologics Evaluation and Research and U.S. food and Drug Administration, 2008; 1-16.
14. U.S. Food & Drug Administration, Guidelines on General Principles of Process Validation; Division of Manufacturing and Product Quality, CDER, FDA, Rockville, MD, May 1987.
15. Christine O, Lazar S, "Process validation from the viewpoint of the FDA", http://www.gmp-publishing.com/en/gmp-products.html, February 2012.
16. Validation Guidelines for Pharmaceutical dosage form; Health products and Food branch Inspectorate, Canada, 8-13, December 2009.
17. Thaduvai Raveendranath, Jeybaskaran M. " Process Validation of Pantoprazole 40mg Tablets''The Pharma.Innov. 2012; (5): 48.
18. Chapman KG. In a history of validation in the United States; Part I, Pharm. Tech. 1991; 79-290.
19. Loftus BT. In The regulatory basis for process validation; vol.3; Marcel Dekker, New York, 1984; 1–7.
20. U.S. Food & Drug Administration, Guidelines on General Principles of Process Validation; Division of Manufacturing and Product Quality, CDER, FDA, Rockville, MD, May 1987.

21. Christine O, Lazar S, "Process validation from the viewpoint of the FDA", http://www.gmp-publishing.com/en/gmp-products.html, February 2012.
22. Validation Guidelines for Pharmaceutical dosage form; Health products and Food branch Inspectorate, Canada, 8-13, December 2009.
23. www.processvalidation.com
24. Raghunandhan R, "Validation of Pharmaceutical Processes." Pharma Times, 1999 31(11): 61-62.
25. Jena S, "Industrial process validation of solid dosage form – an overview." Int. J. of pharm. Science. 2010; 4(2):145-154.
26. Herber L.A, Leon L, Joseph SB. Pharmaceutical Dosage form Tablets. 2nd ed. New York: Marcel Dekker, 1990; 417-447.