International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 4 Issue 7, July 2017

ISSN: 2394-4404

Process Validation Of Antidiabitic Drug: Gliclazide 30mg Prolonged Release Tablet

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Abstract: ***Validation is very crucial step involved in achieving and maintaining the quality of any drug products. The main objective of my research is to study the process validation of gliclazide 30mg. The study untaken here provides the assurance that the manufacturing procedure is suitable for intended purpose and the product consistently meets predetermined specification and quality attributes, as per specified master formula record. It give the detailed information of various steps involved in the validation like sifting, mixing, granulation, sizing, compression and analyses of final finished products. During this process all the critical control parameters are observed such as uniformity in blend, Bulk density, tapped density, flow property, uniformity of content, uniformity of dosage unit, average weight, thickness, hardness, friability, disintegration time , dissolution test, and assay. After all the result and discussion it can be said that this manufacturing process is capable of producing the product consistently of its quality attributes and meeting its predetermined specification, hence the process is validated and can be use for routine manufacturing of gliclazide 30mg tablet.***

Keywords: Gliclazide, validation, Process validation, Prospective validation, Concurrent validation, Retrospective validation, Revalidation.

I. INTRODUCTION

Development of the drug product is a long process which covers drug discovery, laboratory testing, preclinical studies in animals, clinical trials in human, regulatory registration and approval. Facilities involved and processes handled during drug development impact the quality significantly. Hence even after regulatory approval, to further improve the safety and efficacy of the drug product, regulatory agencies necessitate the manufacturer to test its drug product for identity, strength, quality, purity and stability before release the drug product for commercial use. To implement the requirements, pharmaceutical validation becomes significant. The concept of validation had its first formal appearance in United States in 1978. However; the origin of validation in the healthcare industry is from the terminal sterilization process failures in the early 1970s.

II. VALIDATION

Validation is an extremely diverse and a complex area of regulatory concern, impacting all area of pharmaceutical,

medical devices, and biologic research, manufacturing, and clinical testing

DEFINITIONS OF VALIDATION

In 2011, "A process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products".

TYPES OF VALIDATION

There are different types of validation:

ANALYTICAL VALIDATION

The Code of Federal Regulations (CFR) explicitly states that "the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."

EQUIPMENT VALIDATION

Validation of equipment's is known as Qualification. Equipment Validation is divided into Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ).

COMPUTER SYSTEM VALIDATION

It encompasses computers, which directly control process or system or collect data. It includes the qualification of all software and hardware, which has an impact, directly or indirectly, on the quality of product. The validation approach to programmable logic controller (PLC) hardware and personal computers (PCs) is similar, both to one another and to the general overall approach top validation in that the end user should define each requirement.

CLEANING VALIDATION

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations.

PROCESS VALIDATION

"It is an established documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".

Process validation is divided into different types as follows:

- ✓ Prospective validation.
- ✓ Concurrent validation
- ✓ Retrospective validation
- ✓ Re-validation

ELEMENTS OF VALIDATION

The validation activities are performed in accordance with pre-approved written protocols. The facility, utilities, major manufacturing equipment and laboratory instruments should be qualified by performing Design Qualification (DQ)/Installation Qualification (IQ)/Operational Qualification (OQ)/Performance Qualification (PQ) as per the approved protocols.

Design Qualification (DQ)

The DQ is aimed to specify that the equipment, system or facility is designed in accordance with the requirements of the user and Good Manufacturing Practice (GMP) guidelines. A protocol should be made for design requirements/technical specifications with consultation of the supplier and a report is documented for the same.

Installation Qualification (IQ)

Upon arrival of the equipment in the plant, it is first checked to ensure that the equipment is supplied as per the design requirements/technical specifications. The Engineering Department verify that the equipment and components are supplied in accordance with the specifications mentioned in (DQ)

Operational Qualification (OQ)

During Operational Qualification documented evidence are made to establish that all parts of the equipment work within their specifications and operational parameters.

Performance Qualification (PQ)

Performance qualification is the final stage of qualification, which demonstrates that how the equipment/ system will perform when challenged under simulated or actual production conditions. A series of tests are designed to demonstrate that the equipment / system is capable to perform consistently and meet required specifications under routine production operations.

PROCESS VALIDATION DEFINITION

ACCORDING TO US FDA

In 1987, "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".

In 2008, "Process Validation is defined as the collection and evaluation of data, from the process design stage

throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products".

In 2011, "The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entities "Pharmaceuticals CGMPs for the 21st century –A Risk-Based Approach," particularly with regards to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality tools and concepts".

TYPES OF PROCESS VALIDATION

PROSPECTIVE VALIDATION

It is defined as the establishment of documented evidence that a system does what it purports to do based on preplanned 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.

A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol. All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

It is generally considered acceptable that three consecutive batches will runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. It is a confirmation on the commercial three batches before marketing. Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the batch manufacturing and packaging record or into appropriate standard operating procedures.

Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified. It may be possible and acceptable in particular circumstances for a manufacturer that uses the same process for several related products to develop a scientifically sound validation plan for that process rather than different plans for each product manufactured by that process.

RETROSPECTIVE VALIDATION

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified. Prior to undertaking retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities and subsystems used in connection with the manufacturing process must be qualified in conformance with cGMP requirements.

The basis for retrospective validation is stated in 21CFR 211.110(b): "Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate."

Using either data-based computer systems or manual methods, retrospective validation may be conducted in the following manner:

- ✓ Gather the numerical data from the completed batch record and include assay values, end-product test results, and in-process data.
- ✓ Organize these data in a chronological sequence according to batch manufacturing data, using a spreadsheet format.
- ✓ Include data from at least the last 20–30 manufactured batches for analysis. If the number of batches is less than20, then include all manufactured batches and commit to obtain the required number for analysis.
- ✓ Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.
- ✓ Subject the resultant data to statistical analysis and evaluation.
- ✓ Draw conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.
- ✓ Issue a report of your findings (documented evidence).

CONCURRENT VALIDATION

In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process is in a state of control. Is similar to prospective, except the operating firm will 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. Retrospective validation is only acceptable for well-established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility.

The source of data for retrospective validation should include amongst others, batch documents, process control charts, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results. For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum often consecutive batches produced be utilized.

When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control. In such cases the study should be supplemented with data generated with concurrent or prospective validation. Some of the essential elements for retrospective validation are:

- ✓ Batches manufactured for a defined period (minimum of10 last consecutive batches).
- ✓ Number of lots released per year.
- ✓ Batch size/strength/manufacturer/year/period.
- ✓ Master manufacturing/packaging documents.
- ✓ Current specifications for active materials/finished products.
- ✓ List of process deviations, corrective actions and changes to manufacturing documents.
- ✓ Data for stability testing for several batches.
- ✓ Trend analyses including those for quality related complaints.

REVALIDATION

Almost all GMP texts recommend that whenever there are significant changes in the facility, equipment or process, revalidation should be carried out. The FDA process validation guidelines refer to a quality assurance system in place that requires revalidation whenever there are changes in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics. Conditions requiring revalidation study and documentation are listed as follows:

- ✓ Change in a critical component (usually refers to raw materials).
- ✓ Change or replacement in a critical piece of modular (capital) equipment.
- ✓ Change in a facility and/or plant (usually location or site).
- ✓ Significant (usually order of magnitude) increase or decrease in batch size
- ✓ Sequential batches that fail to meet product and process specifications.

ADVANTAGES OF PROCESS VALIDATION

- ✓ Increased throughput
- ✓ Reduction in rejections and reworks
- ✓ Reduction in utility costs
- ✓ Avoidance of capital expenditures
- ✓ Fewer complaints about process related failures
- ✓ Reduced testing in process and finished goods
- ✓ More rapid and accurate investigations into process deviations
- ✓ More rapid and reliable start-up of new equipment
- ✓ Easier scale-up from development work
- ✓ Easier maintenance of the equipment
- ✓ Improved employee awareness of processes
- ✓ More rapid automation

REASON FOR PROCESS VALIDATION

The possible reason of performing process validation may include:

- ✓ New product or existing products as per SUPAC changes.
- ✓ Change in site of manufacturing.
- ✓ Change in batch size.
- ✓ Change in equipment.
- ✓ Change in process existing products.
- ✓ Change in composition or components.
- ✓ Change in the critical control parameters.
- ✓ Change in vendor of API or critical excipient.
- ✓ Change in specification on input material.
- ✓ Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
- ✓ Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

III. STAGES INVOLVED IN PROCESS VALIDATION

Process validation involves a series of activities taking place over the lifecycle of the product and process. The activities relating to validation studies may be classified into three stages:

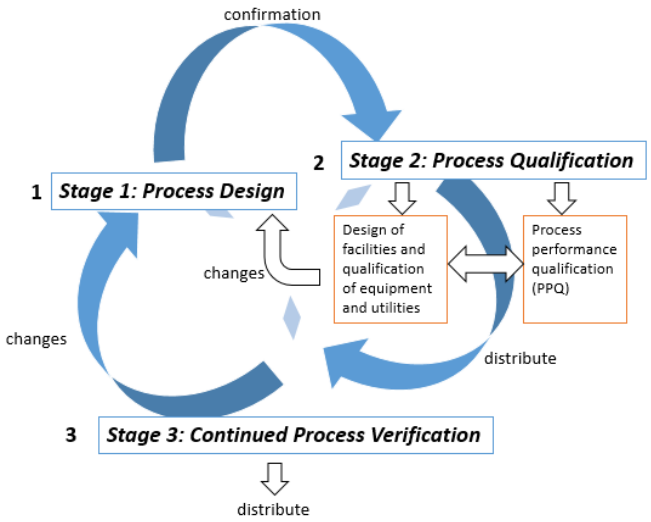

Figure 1: Three model of process validation according to FDA Guidance for Industry – Process Validation

STAGE 1 – PROCESS DESIGN

Constructing and Apprehending Process Knowledge and Understanding:

- ✓ The functionality and limits of commercial manufacturing equipment should be considered in the process design.
- ✓ Design of experiments (DOE) studies can help to develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs and the resulting outputs.
- ✓ Risk analysis tools can be used to display possible variables for DOE studies.

APPROACH FOR PROCESS CONTROL

- ✓ Controls and consist of material analysis and equipment monitoring at significant.
- ✓ The controlled records are established in the Master formula records and control processing points.
- ✓ The calculated commercial production and control records should be carried forward to the next stage for confirmation.

STAGE 2 – PROCESS QUALIFICATION

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under "worst case" conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product. There are two aspect of process qualification:

DESIGN OF FACILITIES AND QUALIFICATION OF EQUIPMENT AND UTILITIES

- ✓ Proper design of manufacturing facility is desired under 21 CFR part 211, subpart C, of the cGMP regulation on buildings and facilities.
- ✓ Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

PROCESS PERFORMANCE QUALIFICATION(PPQ)

"Criteria and process performance indicators that allow for a science and risk-based decision about the ability of the process to consistently produce quality products".

- ✓ Part of the planning for stage 2 involves defining performance criteria and deciding what data to collect when, how much data, and appropriate analysis of the data.
- ✓ Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and trial product attributes.
- ✓ Manufacturer must scientifically determine suitable criteria and justify it.
- ✓ Objective measures, where possible.
- ✓ May be possible to leverage earlier study data if relevant to the commercial scale.

PPQ REPORT

- ✓ This PPQ report states a clear conclusion as to whether the data indicates the process meets the conditions established in the protocol. If not the report should state what should be accomplished before such a conclusion can be reached.
- ✓ This conclusion should be based on entire compilation of knowledge and information gained from the design stage through the PPQ stage.

STAGE 3 – CONTINUED PROCESS VERIFICATION

Ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires 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. A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation.

IV. MANUFACTURING PROCESS IN BRIEF

A. RAW MATERIAL SIFTING

Sift Gliclazide & lactose monohydrate incrementally scoop through 40# then sift maize starch, hypromellose (Methocel K 4M) & hypromellose (Methocel K 15M premium) through 40# using vibratory sifter.

B. BINDER PREPARATION

Take 25.00 lit of purified water (Temp: 30$\pm$ 10^{o} C). Dissolve 4.800 kg providone (PVPK30) in above purified water under continuous stirring.

C. DRY MIXING

Load the sifted raw materials into RMG and Mix it for approx 15 minutes at slow speed impeller with chopper off.

D. WET MIXING

Binder solution divided into 3 equal part, add 1stpart of binder solution into RMG blow having a dry mix blend for about approx. 3 min at impeller slow and chopper off. Stop mixer and scrap the sides of impeller, chopper and inner side of mixer and lid. Then mix for further approx 3 min with impeller at slow speed and chopper off with addition of 2nd part of binder solution, stop the mixer & scrap the sides of impeller, chopper & inner side of mixer and lid.

Continue mixing by addition of 3rd part of binder solution for approx, 4 min impeller slow chopper off. Stop the mixer and scrap the sides of impeller, chopper & inner chopper slow. Stop the mixer and scrap the sides of impeller, chopper and inner side of mixer and lid. If required extra purified water (temperature 30$\pm$ 10 ^{o}C can be added in incremental lots (of about 100ml) and mix for approx. 2min impeller fast & chopper off, or till the granulation end point is achieved at the same setting & discharge the granules on same setting.

V. DETERMINATION OF END POINT

A. BANANA BREAKING TEST

Precaution: Use hand gloves for this test.

Procedure: Take one handful of wet mass in the palm and press to form a lump. Open the palm and break the lump by pressing the thumb at the center of the lump.

Observation: The lump shall break into small pieces.

At the end point of granulation,

- ✓ Impeller: 27 Ampere
- ✓ Chopper: 9 Ampere

B. WET MASS MILLING

Pass the wet mass through suitable mill/co-mill using 8.0mm screen at slow speed or directly through co-mill attached with RMG without screen.

C. DRYING

Air dry the wet granules for approx. 5 min then dry at 50-60^{0}C inlet air temperature in 2 part in FBD till the loss on drying (LOD) of the granules is achieved between 1.5-4.0%w/w (best result between 2-3 %w/w) (check the LOD at 105^{0}C temperature on IR moisture analyser till constant weight is observed)

If LOD is not within the limit, re dry the granules to achieve the LOD within the limit.

D. SIFTING & SIZING OF DRIED GRANULES

Pass the dried granules through 30# and retention mill through 1.0 mm screen using oscillating granulator.

E. LUBRICANTS SIFTING

Sift the required quantity of colloidal anhydrous silica (areosil-200) with equal amount of fines from sized granules through 40#. Sift required quantity of magnesium stearate (vegetable grade) separately through 40# using vibratory sifter.

F. LUBRICATION

Load the sized granules into octagonal blender and mix for approx. 5 min at 14 RPM check the loss on drying (LOD) of the mixed granules at 105^{0}C on IR moisture balance up to constant weight (limit: 1.5- 4.0 %w/w).

Load the sifted colloidal anhydrous silica (aerosol-200) to octagonal blender and mix for approx. 10 min at 14 RPM.

Add magnesium stearate into the octagonal blender and mix for approx. 2min at14 RPM

Check LOD of the lubricated granules.

G. COMPRESSION

Compress the tablet at the average weight 116.0 mg $\pm$ 3% using single/double rotary compression machine.

MACHINERIES

Vibratory Sifter (30 inch) (Wintech Pharmachem), Rapid Mixer Granulator (Sainath Boiler), Binder preparation vessel (Wintech Pharmachem), Fluid bed dryer (Allience), Oscillating granulator (Kanath Eng.), Bin blender (R. P. Product), Tablet Compression Machine (Cadmach), Tablet Deduster (Omega Pharma), Tablet Deduster (Omega Pharma), Metal Detector (Technofore), Metal Detector (Technofore).

UTILITIES

HVAC System (ABB), HVAC System (ABB), Compressed air System (Ingersollrand), Purified water System (Christnisotec).

INSTRUMENTS USED FOR ANALYSIS

HPLC (Waters), Weighing Balance (Mettler), Disintegration Apparatus (Electro Lab), Disintegration Apparatus (Electro Lab), UV Spectrophotometer (Perkin Elmer), Sieve Shaker (Elactron Pharma), Tap Density Tester (Electrolab), Weighing Balance (Mettler Toledo), Friability Apparatus (Electrolab), Hardness Test Apparatus (Pharmatron).

Sr. No.	Raw Material	Function
Granulation Ingredients:		
1.	Gliclazide	Active pharmaceutical ingredient
2.	Lactose Monohydrate	Diluent
3.	Maize Starch	Glidant and binder
4.	Hypromellose (methocel K 4M	Disintegrant
5	Hyprmellose (methocel K 15M premium)	Colourant
7	Povidone CPVPK30	Disintegrant
8	Purified Water*	Solvent
Lubricants:		
9	Colloidal anhydrous silica (aerosol-200)	Disintegrant
10.	Magnesium stearate (vegetable grade)	Lubricant

Table 1: List of Raw Materials and their Functions

Process stages, control variables and measuring response / justifications

Following process parameters will be monitored during the manufacturing process

Process	Critical process parameter	Quality attributes
Sifting	Mesh	Lump Free Material
Dry Mixing	Dry Mixing Time	Blend Uniformity
Wet Granulation	Quality Of Binder Solution Binder Addition Rate Impeller Speed Chopper Speed Impeller Amperage	Nature Of Granules, Agglomeration Or Wet Mass LOD

Wet Milling & Drying	Inlet And Outlet Temperature, Time Of Drying	LOD
Milling	Mesh, Mill Type Speed, Screen Size.	Granules Particle Size Distribution, Bulk Density.
Lubrication	Final Blend Mixing Time With Lubricant, Blender Rpm Blender Type	Blend Uniformity, Particle Size, LOD, BD, TD, Compressibility Factor.
Compression	Compression Speed Press Type & Number Of Station, Pre- Compression Force, Fill Depth, Run Time.	Appearance, Average Weight, Dissolution, Assay, Thickness, Hardness, Friability.

Table 2: Critical Control Parameter

SAMPLING PLAN

During the manufacturing process of propranolol hydrochloride 10 mg tablets various samples were collected to perform various tests.

Process Step	Equipment	Sampling Plan	Monitoring/ Evaluation parameter
Dry Mixing	RMG	-	Blend homogeneity
Wet Mixing	RMG	-	Appearance of wet mass
			Ampere reading at the end of granulation end point
Wet Milling	Corn mill or Vibratory Sifter	-	Size of sieve used Size of screen used
Drying	FBD	Collect 5 sample From different locations of FBD as mentioned in the sampling plan	Loss of drying
			Inlet and outlet temperature
			Total drying time
Sifting & Sizing	Vibratory Sifter & corn mill		Size of sieve used
			Total sizing time
Lubrication	Octagonal blender	Collect approximately 1 to 3 times unit dose sample quality require for analysis from 10 location of the octagonal blender using sampling device on completion of lubrication process.	Blend homogeneity.
		Composite sample of approximately 20 g from all the 10 sampling point.	LOD /sieve analysis. Bulk density. Granules flow properties
Compression	Compression Machine	Collect tablets from LHS & RHS at low, optimum and high speed of compression machine for following test.	-
		10 tablets (Minimum Optimum and Maximum Speed)	Thickness
		10 Tablets (Minimum Optimum and Maximum Speed)	Friability
		10 Tablets (Minimum Optimum and Maximum Speed)	Hardness
		20 Tablets (Minimum Optimum and Maximum Speed)	Average Weight
		80 Tablets (Minimum Optimum and Maximum Speed)	Uniformity of Weight
		6 Tablets (Minimum Optimum and Maximum Speed)	Disintegration time
Compression machine		Collect tablets 150 Tablets from each side at Initial, Middle and End Stage of compression.	-
		30 Tablets (Initial, Middle and End)	Assay and Dissolution. rate in QC
		10 Tablets (Initial, Middle and End)	Thickness
		10 Tablets (Initial, Middle and End)	Friability
		10 Tablets (Initial, Middle and End)	Hardness
		20 Tablets (Initial, Middle and End)	Average Weight
		80 Tablets (Initial, Middle and End)	Uniformity of height
		6 Tablets (Initial, Middle and End)	Disintegration time
		Approximately 50 Tablets (Composite Sample)	Complete analysis in QC.

Table 3: Sampling plan

VI. RESULTS AND DISCUSSION

Test parameter	Acceptance criteria	Batch 1	Batch 2	Batch 3
Description	White to off white, capsule shaped,bioconex, uncoated tablets debossed with C12 on one side plain on other side.	White to off white, capsule shaped,bi oconex, uncoated tablets debossed with C12 on one side plain	White to off white, capsule shaped,bi oconex, uncoated tablets debossed with C12 on one side plain	White to off white, capsule shaped,bi oconex, uncoated tablets debossed with C12 on one side plain

			on other side	on other side	on other side
Average weight	116.0 mg ± 3.0%(112.52-119.48 mg)		115.05 mg	117.04%	116.85%
Identification	By IR		Complies	Complies	Complies
	By HPLC		Complies	Complies	Complies
Assay	95.0-105.0 %		100.1 %	100.4 %	99.3 %
Uniformity of dosage unit (By content unifomity)	Confirms as per ph.Eur (acceptance value AV ≤ 15.0) .		3.2	3.9	4.0
Dissolution (By UV) <711>	NLT 85% (Qty. of the labeled amount of Gliclazide is dissolved in 12 hours)	Min.	91 %	93 %	106 %
		Max.	107 %	111 %	111 %
		Avg	101 %	101 %	108 %
Related substances	Impurity F	NMT 0.1 %	Not detected	Not detected	Not detected
	Any other secondary impurity	NMT 0.20 %	Not detected	Not detected	Not detected
	Sum of all impurities	NMT O.30%	Not detected	Not detected	Not detected
Hardness	40-80 N		48 N	62 N	55 N
Thickness	2.30mm + 2.90 mm	Min.	2.63 mm	2.63 mm	2.64 mm
		Max	2.74 mm	2.76 mm	2.75 mm
Loss on drying (at 105^{0}C on IR balance up to constant weight	NMT 4.0% w/w		3.12% w/w	3.27% w/w	3.39% w/w

Table 4: Observations and Acceptance Finished Product Testing of Gliclazide Tablet 30 mg

Batch No.	A	B	C
Yield	96.56 %	97.75 %	97.54 %

Table 5: Batch yield of compressed tablets

Sr. No.	Sampling Point	Batch No. and Results (%)		
		Batch-1	Batch-2	Batch-3
		Gliclazide %	Gliclazide %	Gliclazide %
1	Top left	99.6%	95.0%	96.9%
2	Top right	100.8%	94.2%	98.1%
3	Top front	97.4%	94.8%	99.2%
4	Top rear	95.6%	94.4%	96.0%
5	Middle left	97.5%	94.8%	99.1%
6	Middle right	97.0%	94.1%	98.2%
7	Bottom left	96.7%	93.6%	97.0%
8	Bottom right	97.9%	94.6%	96.8%
9	Bottom front	97.0%	94.5%	96.9%
10	Bottom rear	99.1%	94.7%	97.4%
Mean		97.8%	94.5%	97.6%
% RSD		1.6	0.4	1.0

Table 6: Results of Dry Mixing (Blend uniformity)

Limit: Mean assay between90.0% - 110.0 % of labelled amount of Gliclazide and RSD NMT 5.0 %. Mean of individual test result: 95.0%-105.0%

DRYING

Sr. no	Sampling location	Batch 1		Batch 2		Batch 3	
		LOT A	LOT B	LOT A	LOT B	LOT A	LOT B
1.	Left	2.79 %	2.71 %	2.25 %	2.02 %	2.56 %	2.54 %
2.	Right	2.73 %	2.69 %	2.20 %	2.08 %	2.51 %	2.51 %
3.	Centre	2.79 %	2.72 %	2.26 %	2.22 %	2.56 %	2.59 %
4.	Front	2.74 %	2.74 %	2.27 %	2.10 %	2.59 %	2.58 %
5.	Back	2.77 %	2.68 %	2.24 %	2.06 %	2.57 %	2.55 %
6.	Composite	2.70 %	2.71 %	2.25 %	2.06 %	2.53 %	2.59 %

Table 7: Results of LOD for Drying

Limit: 1.0 – 3.0 % w/w at 90° C for 10 min.

Batch No.	A	B	C
Yield	98.61 %	98.71 %	98.58 %

Table 8: Batch yield of lubricated granules:

PRE-LUBRICATION

Sr. No.	Sampling location	Batch 1	Batch 2	Batch 3
1.	Top (Left)	96.1%	104.5%	98.8%
2.	Middle (Left)	94.2%	104.5%	101.2%
3.	Bottom (Left)	97.2%	106.3%	99.8%
4.	Top (Rear)	95.1%	104.5%	99.0%
5.	Bottom (Rear)	94.4%	105.3%	100.3%
6.	Top (Front)	96.2%	104.0%	99.1%
7.	Bottom (Front)	96.5%	102.3%	100.4%
8.	Top (Right)	94.2%	106.2%	100.8%
9.	Middle (Right)	98.7%	103.9%	101.1%
10.	Bottom (Right)	95.9%	105.6%	99.8%
	AVERAGE	95.9%	104.7%	100.8%
	% RSD (NMT 5.0 %)	1.4	1.1	0.8

Table 9: Results of Blend Uniformity for Pre-Lubrication

Limit: (% LC) (by HPLC) 90.0 % - 110.0 % of label amount, RSD: NMT 5.0 % Mean of individual test result: 95.0 % - 105.0 %

LUBRICATION

Sr. No	Sampling location	Batch 1	Batch 2	Batch 3
1.	Top (Left)	98.2 %	97.2 %	98.7 %
2.	Middle (Left)	99.1 %	99.1 %	97.1 %
3.	Bottom (Left)	98.7 %	99.2 %	97.3 %
4.	Top (Rear)	97.4 %	99.4 %	98.0 %
5.	Bottom (Rear)	99.1 %	98.4 %	99.8 %
6.	Top (Front)	97.2 %	99.8 %	101.6 %
7.	Bottom (Front)	97.7 %	99.7 %	100.1 %

8.	Top (Right)	99.2 %	98.4 %	99.2 %
9.	Middle (Right)	98.4 %	99.4 %	98.8 %
10.	Bottom (Right)	98.7 %	97.9 %	97.2 %
	AVERAGE	98.4 %	98.9 %	98.8 %
	% RSD (NMT 5.0 %)	0.7 %	0.9 %	1.5 %

Table 10: Results of Blend Uniformity of Lubrication Stage

Limit: (% LC) (by HPLC) 90.0%-110.0 % of label amount, RSD: NMT 5.0 % Mean of individual test result: 95.0 %-105.0 %

Sieve Analysis	**% Passed through**		
	Batch 1	Batch 2	Batch 3
Mesh 40	100.0%	100.0%	100.0%
Mesh 60	66.79%	66.79%	68.24%
Mesh 80	66.79%	66.79%	68.24%
Mesh 100	64.49%	64.52%	64.14%
Sieve Analysis	**% Retained**		
	Batch 1	Batch 2	Batch 3
Mesh 60 (250 µ)	33.21%	33.21%	31.76%
Mesh 100 (150 µ)	35.51%	35.48%	35.86%

Table 11: Sieve Analysis on Composite Sample

Batch No.	A	B	C
P – bulk density g/ml (untapped)	0.62 g/ml	0.62 g/ml	0.58 g/ml
Pt – bulk density g/ml (tapped)	0.83 g/ml	0.83 g/ml	0.83 g/ml
LOD (1.5-4.0 % w/ w)	3.20 %	3.31 %	3.44 %

Table 12: Bulk density and LOD

Batch No.	A	B	C
Hausner's ratio (Pt / P)	1.33	1.33	1.41

Table 13: Hausner's ratio

Batch No.	A	B	C
% Compressibility $=\frac{(pt-p)}{pt} * 100$	25	25	29.41

Table 14: % Compressibility

VII. CONCLUSION

On the basis of data generated from the three batches (Batch-1, Batch-2, Batch-3), it is concluded that the manufacturing process of Gliclazide tablet 30mg tablets capable of producing a product meeting its quality attributes and predetermined specification.

The results of all stages were found within the standard specification and acceptance criteria mentioned in the process validation protocol and finished product specification.

Hence manufacturing process of Propranolol HCl USP 10 mg tablet is considered validated and approved for routine production.

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