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Research Article

Process Validation of Benazepril HCl 5 mg Tablet

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ABSTRACT
The purpose of research was to study prospective process validation Benazepril HCl 5 mg tablet dosage formulation. The critical process parameter was identified with the help of process capability and evaluated by challenging its lower & upper release specification. One initial process validation batches size, method, equipment & validation criteria were taken. The critical parameter involved in sifting, Blending ,compression stages were identified and evaluated as per validation master plan. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes.
Key words: process validation parameters, Quality assurance, Tablet dosage form.

INTRODUCTION

According to Indian GMP validation study is essential part of GMP. Those required to be done as per predetermined protocols. Prospective process validation is carried out during the development stage by means of risk analysis of the production process which is broken down into individual steps[1]. Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. Validation as it is known today has developed from the need to maintain quality, consistency, and above all public safety. Validation is a rapidly growing and evolving concept. This evolution stems from technology's growth rate. It is responsible for providing higher degree of assurance for the product. The foundation of validation, the methodology behind validation, and the need for validation will likely remain a key aspect of the industry. The present project reflects the current trends and serves as an educational tool in our progressive industry. Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

Definition of Validation[1-3]

As per ISO 17025 Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.
As per USFDA (1987) "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacturing of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics."
As per USFDA (2008) "Process validation is the collection and evaluation of data, from the process design stage throughout the production, which establish scientific evidence that a process is capable of consistently delivering quality products."
The definition is very well thought out and each word has a special significance

Principle Elements of Validation:

Documented Evidence:
Validation requires a through documentation everything that is not documented is considered incomplete.
High degree of Assurance:
The assurance is that a large software package as used in complex computerized systems is rarely free of errors. Frequently there is a perception that validation means "error free". This assumption is wrong. During the validation process everything realistically possible should be done to reduce errors to a high degree.
Specific process:
Same subparts of validation such as qualification. (Installation, Operation, Performance) are product specific and have to be done for each system.
Consistently:

Validation is not a one-time event. The performance of equipment has to be controlled during the entire life of product.

Predetermined Specifications:

Validation activities start with the definition of specifications. The performance of equipment is then verified against these specifications. Acceptance Criteria must be defined prior to testing.

Reasons for Validation[4]

The three basic and most important reasons for validation are quality assurance,

Quality assurance:

Product quality cannot be assured for a process by routine quality control testing because of the limitation of statistical sampling and the limited sensitivity of finished product testing. Quality variations among units within a batch or among different batches are seldom detected by testing of finished product samples. Validation changes the adequacy and reliability of a system or process to meet predetermined criteria.

Economics:

The direct economic benefit of validation is a reduction in the cost associated with process monitoring, sampling and testing. Analysis of multiple samples would not be required in order to slow homogeneity for a validated blending process. The consistency and reliability of a validated process to produce a quality product provide direct cost savings resulting from a decrease or elimination of product rejections, reworks and retesting. Final release of the batch would be expedited and freed of delays and complications caused by lengthy investigations of process, or analytical related variances. In addition product quality complaints and potential product recalls would be minimized.

Compliance:

GMP requires that written procedures and process controls be established to assure that the drug products have the "identity, strength, quality and purity they purport or are represented to possess."

Regulatory Requirements:

Fourth, and certainly foremost, among the reasons for validation is that it is a regulatory requirement for virtually every process in the global health care industry-for pharmaceuticals, biologics, and medical devices. Regulatory agencies across the world expect firms to validate their processes. The continuing trend toward harmonization of requirements will eventually result in a common level of expectation for validations worldwide. Utility for validation beyond compliance is certainly available. The emphasis placed on compliance as a rationale has reduced the visibility of the other advantages a firm gleans from having a sound validation program.

Benefits of Validation:

Reduction of Quality Cost:

Through proper validation, the cost of the following process can be optimized.

1) Preventive costs are costs incurred in order to prevent failures and reduce appraisal costs
2) Appraisal costs of inspection, testing and quality evaluation.
3) Internal failure costs
4) External failure costs that associated with a non-conformance condition after the product has left the company's ownership.

Process Optimization:

The optimization of the facility, equipment system and closures etc. results in a product that meets quality requirements at the lowest costs. Trained, qualified people are the key elements in process optimization that results in improving efficiency and productivity.

Assurance of Quality:

Validation and process control are the heart of GMPs. Without Validated and controlled process it is impossible to achieve quality products. Hence validation is a key element in assuring the quality of the product.

Safety:

Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges used to reduce accident and results in safety.

Better Customer Quality:

Through Proper validation, Market recall is avoided which result in better customer care and quality of the product.

Elements of Validation[5, 6]

Design Qualification (DQ):

It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

1. GMPs and regulatory requirements
2. Performance criteria
3. Facility air flow, movement flow & pressure regimes
4. Reliability& efficiency
5. Commissioning requirements
6. Construct ability & installation of equipment
7. Maintenance& access to critical equipment & instrumentation
8. Safety& environment impact

Installation Qualification (IQ):

It is documented verification that all aspects of a facility, utility or equipment that can affect product

quality adhere to approved specifications and are correctly installed. Important IQ considerations are:

1. Installation conditions (wiring, utilities, and functionality)
2. Calibration, preventative maintenance, cleaning schedules
3. Safety features
4. Supplier documentation, prints, drawings and manuals
5. Software documentation
6. Spare parts list
7. Environmental conditions (such as clean room requirements, temperature and Humidity)
8. Equipment design features (i.e. materials of construction clean ability)

Operational Qualification (OQ):

It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intend throughout all anticipated ranges. OQ considerations include:

1. Process control limits (time, temperature, pressure, line speed and setup conditions)
2. Software parameters
3. Raw material specifications
4. Process operating procedures
5. Material handling requirements
6. Process change control
7. Training
8. Short term stability and capability of the process.
9. Potential failure modes, action levels and worst-case conditions.

Performance Qualification (PQ):

It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

PQ considerations include:

1. Actual product and process parameters and procedures established in OQ
2. Acceptability of the product
3. Assurance of process capability as established in OQ
4. Process repeatability, long term process stability

Types of Validation[7]

Prospective Validation

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. This is a preplanned scientific approach and includes initial stages of equipment validation. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

Prospective validation includes those considerations that should be made before an entirely new product is introduced by a firm or when there is a change in the manufacturing process which may affect the product's characteristics, such as uniformity and identity.

The following are considered as key elements of prospective validation.

Equipment and Process

a. Equipment: Installation Qualification
b. Process: Performance Qualification
c. Product: Performance Qualification:

Retrospective Validation

Retrospective Validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analyzed to determine the limits of process parameters. Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Retrospective validation may then be useful in establishing the priorities for the validation program. If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule. For tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form.

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

1. Gather the numerical data from the completed batch record and include assay values, End product test results and in-process data.
2. Organize these data in a chronological sequence according to batch manufacturing data, using a spread sheet format.
3. Include data from at least the last 20–30 manufactured batches for analysis. If the number of batches is less than 20, then include all manufactured batches and commit to obtain the required number for analysis.

4. Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.
5. Subject the resultant data to statistical analysis and evaluation.
6. Draw conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.
7. Issue a report of your findings (documented evidence).

Concurrent Validation:

It is establishing documented evidence that a process does what it purports to do, based On information generated during actual implementation of the process. It may be Practical Approach under certain circumstances. Examples of these may be as follows

- When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
- Where product is a different strength of a previously validated product with same ratio of active ingredients.
- When number of lots evaluated under retrospective validation was not sufficient to obtain a high degree of assurance demonstrating that process is fully under control.

Revalidation

Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. 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:

- The transfer of a product from one plant to another
- Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality
- The necessity of periodic checking of the validation results
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.
- Changes in source of active Raw material Manufacturers
- Changes in Raw Materials
- Changes in Packaging Materials
- Changes in process e.g. Mixing Time, Drying Temperature, and Batch Size etc.
- Changes in Equipment
- Changes in Plant Facility

RESULTS AND DISCUSSION

Formulation

Ingredients	Use of Ingredients	Quantity required/ Tablet (mg)	Quantity required/Batch (mg)
Blending			
Benazepril Hydrochloride	Active Ingredient	5.000	1.000
Lactose monohydrate	Diluent	149.000	29.800
Microcrystalline Cellulose	Diluent	25.000	5.000
Pregelatinised Starch	Disintegrating agent	5.000	1.000
Crospovidone	Disintegrating agent	3.000	0.600
Colloidal Hydrated Silica Syloid 244 FP	Glidant	8.000	1.600
Lubrication			
Talc	Glidant	2.000	0.400
Hydrogenated Castor Oil	Lubricant	5.000	1.000
Film Coating			
Hypromellose E5	Film former, polymer	3.600	0.936
Polysorbate 80	Plasticizer	0.600	0.156
Titanium dioxide	Opacifier, Pigment	0.900	0.234

Talc	Glidant	0.870	0.226
Ferric oxide yellow	Pigment	0.030	7.800 g
Purified Water	Solvent	q.s	14.000
TOTAL		208.000	-----

BLENDING

Tests	**Results**	**Acceptance criteria**
After adding Co-Sifted Benazepril Hydrochloride (DMF), Lactose Monohydrate (DCL 11), Microcrystalline Cellulose (Avicel PH 112), Pregelatinised Starch (Starch 1500), Crospovidone (PolyplasdoneXL-10), Colloidal Hydrated Silica Syloid 244 FP		
RPM of blender	16	16 ± 1 RPM
Mixing time	20 minutes	20 minutes
After adding Co-Sifted Talc & Hydrogenated Castor Oil		
RPM of blender	16	16 ± 1 RPM
Mixing time	5 minutes	5 minutes
Sieve analysis		
Above 30 #	0.00 %	To be recorded
Above 40 #	0.00 %	To be recorded
Above 60 #	1.45 %	To be recorded
Above 100 #	18.95 %	To be recorded
Untapped BD	0.59 g/ml	To be recorded
Tapped BD	0.78 g/ml	To be recorded

Blending stage yield reconciliation		
% Yield of blend (Practical)	100.04 %	To be recorded

Compression Process

The blend obtained was run on the 55 station DR compression machine. The Speed of compression in RPM was optimized and the tablets was tested for various parameters like description, average weight, uniformity of weight, thickness, hardness, friability, disintegration time and dissolution to assure the reproducibility of the compressed tablets.

	Observations	**Description**
Upper punch	8.0 mm , standard concave, Round embossed with '5'	8.0 mm , standard concave, Round embossed with '5'
Lower punch	8.0 mm , standard concave, Round Plain	8.0 mm , standard concave, Round Plain
Dies	8.0 mm, round	8.0 mm, round
Tooling	B Type	B Type
No. of Upper punches	55	To be recorded
No. of lower punches	55	To be recorded
No. of dies	55	To be recorded
Compression machine	CPD IV 55 B (Cadmach)	To be recorded

Machine speed challenge study

Following table represent the summarized details of process parameters for machine speed challenge

Process parameters

Parameters	**Observations**	**Acceptance Criteria**
	Minimum speed challenge:	
Machine speed in RPM	12 RPM	To be recorded
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.
Average weight (in mg)	LHS: 200.2 RHS: 199.5	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Uniformity of weight (in mg)	LHS RHS Min. : 197.8 196.4 Max.: 202.6 201.6	202.0 mg ± 7.5% (186.9 mg to 217.1 mg)
Breaking force (Hardness)	LHS RHS Min. : 85 73 Max.: 104 106	25N-150N(Target 110N)
Thickness (mm)	LHS RHS Min. : 3.69 3.68 Max.: 3.72 3.73	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)
Friability (% w/w)	LHS RHS 0.01% NIL	NMT 1.0 % w/w (Weight: around 6.5 g)
Disintegration time (minutes)	LHS RHS Min. : 1'20" 1'25" Max.: 1'40" 1'40"	NMT 15 minutes
Uniformity of dosage units (by content uniformity)	The acceptance value of the first 10 tablets should be 3.3	The acceptance value of the first 10 tablets should be less than or equal to 15.0. If the acceptance value is greater than 15.0, test next 20 tablets and calculate the acceptance value. The final acceptance value of the 30 tablets should be less than or equal to 15.0 and no individual content of the dosage unit should be less than (1-25.0x0.01)M or more than (1+25.0x0.01)M.

Machine speed challenge study

Parameters	**Observations** **Maximum speed challenge:**	**Acceptance Criteria**
Machine speed in RPM	60 RPM	To be recorded
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.
Average weight (in mg)	LHS: 201.3 RHS: 200.4	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Uniformity of weight (in mg)	LHS RHS Min. : 198.7 198.0 Max.: 204.6 203.0	202.0 mg ± 7.5% (186.9 mg to 217.1 mg)
Breaking force (Hardness)	LHS RHS Min. : 93 92 Max.: 120 106	25N-150N(Target 110N)*
Thickness (mm)	LHS RHS Min. : 3.67 3.67 Max.: 3.80 3.81	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)*
Friability (% w/w)	LHS RHS NIL 0.02%	NMT 1.0 % w/w (Weight: around 6.5 g)
Disintegration time (minutes)	LHS RHS Min. : 1'17" 1'27" Max.: 1'39" 1'40"	NMT 15 minutes
Uniformity of dosage units (by content uniformity)	The acceptance value of the first 10 tablets should be 3.3	The acceptance value of the first 10 tablets should be less than or equal to 15.0. If the acceptance value is greater than 15.0, test next 20 tablets and calculate the acceptance value. The final acceptance value of the 30 tablets should be less than or equal to 15.0 and no individual content of the dosage unit should be less than (1-25.0x0.01)M or more than (1+25.0x0.01)M.

Hardness challenge study
Following table represent the summarized details of process parameters for machine speed challenge

Process parameters

Parameters	**Observations** **Minimum Hardness challenge:**	**Acceptance Criteria**
Machine speed in RPM	30 RPM	To be recorded
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.
Average weight (in mg)	LHS RHS 199.6 201.4	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Uniformity of weight (in mg)	LHS RHS Min. : 197.2 199.5 Max.: 201.8 205.1	202.0 mg ± 7.5% (186.9 mg to 217.1 mg)
Breaking force (Hardness)	LHS RHS Min. : 31 32 Max.: 40 41	25N-150N(Target 110N)*
Thickness (mm)	LHS RHS Min. : 3.98 3.99 Max.: 4.02 4.03	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)*
Friability (% w/w)	LHS RHS 0.20 % 0.12 %	NMT 1.0 % w/w (Weight: around 6.5 g)
Disintegration time (minutes)	LHS RHS Min. : 0'17" 0'14" Max.: 0'21" 0'23"	NMT 15 minutes
Dissolution	Min. : 86 % Max.: 91 % Avg.: 88 %	Not less than 80% (Q) in 30 minutes.

Hardness challenge study

Parameters	**Observation** **Maximum Hardness challenge:**	**Acceptance Criteria**
Machine speed in RPM	30 RPM	To be recorded
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.

Average weight (in mg)	LHS RHS 200.1 204.1	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Uniformity of weight (in mg)	LHS RHS Min. : 196.6 200.1 Max.: 202.8 208.2	202.0 mg ± 7.5% (186.9 mg to 217.1 mg)
Breaking force (Hardness)	LHS RHS Min. : 133 148 Max.: 164 167	25N-150N(Target 110N)*
Thickness (mm)	LHS RHS Min. : 3.55 3.59 Max.: 3.61 3.65	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)*
Friability (% w/w)	LHS RHS 0.04 % 0.03 %	NMT 1.0 % w/w (Weight: around 6.5 g)
Disintegration time (minutes)	LHS RHS Min. : 4'17" 4'20" Max.: 4'49" 4'47"	NMT 15 minutes
Dissolution	Min. : 87 % Max.: 96 % Avg.: 91 %	Not less than 80% (Q) in 30 minutes.

DIFFERENT STAGES OF THE COMPRESSION PROCESS

Following table represent the summarized details of process parameter for different stages of compression process in the manufacturing of Pre- Process validation batches.

Parameters	**Observations**			**Acceptance Criteria**
	Initial stage	**Middle stage**	**End stage**	
Machine speed in	30 RPM	30 RPM	30 RPM	To be recorded
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on
Average weight (in mg)	LHS RHS 203.3 200.8	LHS RHS 202.5 203.3	LHS RHS 201.0 202.6	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Uniformity of weight (in mg)	LHS RHS Min.: 146.5 196.5 Max. 206.6 206.7	LHS RHS Min.:198.3 199.1 Max.:206.7 206.2	LHS RHS Min: 193.0 197.9 Max: 204.7 205.6	202.0 mg ± 7.5% (186.9 mg to 217.1 mg)
Hardness (N)	LHS RHS Min. : 93 85 Max.: 130 109	LHS RHS Min. : 103 105 Max.: 119 130	LHS RHS Min. : 75 68 Max.: 94 90	25N-150N(Target 110N)*

Thickness (mm)	LHS RHS Min. : 3.66 3.69 Max.: 3.74 3.78	LHS RHS Min. : 3.70 3.69 Max.: 3.79 3.75	LHS RHS Min: 3.66 3.74 Max:3.72 3.78	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)*
Disintegration time (minutes)	LHS RHS Min. :1'30" 1'26" Max.:1'44" 1'40"	LHS RHS Min. :1'30" 1'26" Max.:1'44" 1'40"	LHS RHS Min:1'27" 1'30" Max:1'40" 1'40"	NMT 15 minutes
Friability (% w/w)	LHS RHS 0.02% NIL	LHS RHS NIL NIL	LHS RHS NIL NIL	NMT 1.0 % w/w (Weight: around 6.5 g)
Dissolution (%)	Min. : 93 % Max.: 95 % Avg.: 94 %	Min. : 88 % Max.: 95 % Avg.: 91 %	Min. : 91 % Max.: 96 % Avg.: 95 %	Not less than 80% (Q) in 30 minute

compression stage yield reconciliation		
% Yield of compression (Practical)	92.64 %	To be recorded

COMPOSITE SAMPLE AFTER COMPLETION OF COMPRESSION PROCESS:
Following table represent the summarized results of composite sample analysis.

Parameters	**Observations**	**Acceptance Criteria**
Description	White, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.	White to off white, round, biconvex uncoated tablets debossed with '5' on one side and plain on other side.
Average weight (in mg)	201.8	202.0 mg ± 5.0% (191.9 mg to 212.1 mg)
Friability (% w/w)	NIL	NMT 1.0 % w/w (Weight: around 6.5 g)
Tablet breaking force Hardness (N)*	Min: 63 Max: 78	25 N to 150 N
Uniformity of dosage units (by content uniformity)	The acceptance value of the first 10 tablets should be 5.3	The acceptance value of the first 10 tablets should be less than or equal to 15.0. If the acceptance value is greater than 15.0, test next 20 tablets and calculate the acceptance value. The final acceptance value of the 30 tablets should be less than or equal to 15.0 and no individual content of the dosage unit should be less than (1-25.0x0.01)M or more than (1+25.0x0.01)M.
Assay	100.1%	95.0% to 105.0% of label claim

COATING
Coating solution preparation

Following table represent the summarized details of process parameter for samples of coating solution in the manufacturing of Pre-Process validation batches.

Parameters	**Observations**		**Acceptance Criteria**
	Initial	After 48 hrs	
Stirring time	10 Minutes	10 Minutes	To be recorded
Description	Light yellow viscous solution	Light yellow viscous solution	To be recorded
Viscosity	102 cp	105 cp	To be recorded
Weight/mL	0.92 g/ml	0.94 g/ml	To be recorded
Bioburden	TAMC: 60 CFU/g TYMC: <10 CFU/g	TAMC: 45 CFU/g TYMC: < 10 CFU/g	To be recorded

Coating stage
Following table represent the summarized details of process parameter for coating stage in the manufacturing of Pre-Process validation batches.

Parameters	**Observations**	**Acceptance criteria**
No.of Guns@	2	2
Inlet air temperature@	Min: 62.5°C Max: 65.0°C	60°C $\pm$ 5°C
Exhaust air temperature@	40°C	40°C $\pm$ 5°C
Product bed temperature@	Min: 36.5°C Max: 40°C	35°C $\pm$ 5°C
Atomizing air pressure@	0.4 Mpa	0.4 $\pm$ 0.1 Mpa
Pan RPM@	Min: 1.3 Max: 3.5	3.0 – 14.0
Peristaltic pump RPM@	Min: 6 Max: 8	To be recorded
Spray rate of solution@	Min: 78.1 ml/min. Max: 104.8 ml/min.	To be recorded
Coating Time	1 hr 29 minute	To be recorded
Gun to bed distance	8”	6-10’’
Qty. of Coating solution consumed	22.32 kg	To be recorded
Target Coat weight build up	3.04 %	Approx. 2.97% (1.97% to 3.97% w/w)
Description	Light yellow colored, round biconvex, film coated tablets debossed with ‘5’on one side and plain on other side.	Light yellow colored, round biconvex, film coated tablets debossed with ‘5’on one side and plain on other side.
Average Weight in mg.	208.32	208.0 mg $\pm$ 5% (197.6 mg to 218.4 mg).
Yield (%) of Coated Tablets	100 %	To be recorded

FINISHED PRODUCT ANALYSIS

Tests	**Observations**	**Acceptance Criteria**
Description	Light yellow colored, round biconvex, film coated tablets debossed with '5'on one side and plain on other side.	Light yellow colored, round biconvex, film coated tablets debossed with '5'on one side and plain on other side.
Average weight of tablets (mg)	208.8	208.0 mg ± 5% (197.6 mg to 218.4 mg).
Identification	A) By TLC: The Rf value of the principle spot obtained from the test solution under test corresponds to that obtained from the standard solution. B) By HPLC: The retention time of the major peak in the chromatogram of the assay preparation should correspond to that in the chromatogram of the standard preparation as obtained in the assay.	A) By TLC: The Rf value of the principle spot obtained from the test solution under test corresponds to that obtained from the standard solution. B) By HPLC: The retention time of the major peak in the chromatogram of the assay preparation should correspond to that in the chromatogram of the standard preparation as obtained in the assay.
Tablet breaking force (Hardness)	110	25 to 150 N
Loss on drying	1.2 %	Not more than 5.0%
Uniformity of dosage units (By Content Uniformity)	The acceptance value of the first 10 tablets should be less than or equal to 4.4	The acceptance value of the first 10 tablets should be less than or equal to 15.0. If the acceptance value is greater than 15.0, test next 20 tablets and calculate the acceptance value. The final acceptance value of the 30 tablets should be less than or equal to 15.0 and no individual content of the dosage unit should be less than (1-25.0x0.01)M or more than (1+25.0x0.01)M.
Dissolution	Min. : 95 % Max. : 101 % Mean.: 98 %	Not less than 80% (Q) in 30 minutes.
Assay (By HPLC)	101.3 %	95.0 % to 105.0% of label claim.

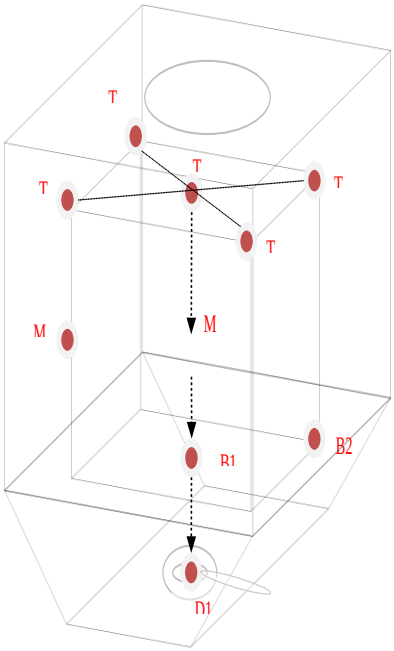
Tests	**Observations**	**Acceptance Criteria**
Microbial examination A) Microbial enumeration tests i) Total Aerobic microbial count ii) Total combined Yeasts / Moulds count B) Test for specified microorganism i) Escherichia coli	 2.5 CFU/g Less than 10 CFU/g Absent	 Not more than 10^3 cfu /g Not more than 10^2 cfu /g Should be absent
Related compound (By HPLC) Related compound E Related compound F Related compound C Related compound B Related compound D Related compound G Single maximum unknown impurity Total impurities (Excluding Related compound C)	 Below Quantification limit ND 0.07 % 0.06 % Below Quantification limit 0.1% 0.07 % 0.3 %	 Not more than 1.0% Not more than 1.0% Not more than 3.0% Not more than 1.0% Not more than 1.0% Not more than 1.0% Not more than 0.2% Not more than 2.0%
Residual solvents**	Meet USP <467>	Meet USP <467> option-1 requirements.

Table.1 Process Variables

Processing Stage	**Equipment**	**Process Variables**	**Quality Attributes**
Sifting	Vibro sifter	Sieve Size	Particle size
Blending	Blender	Load Mixing time Mixing Speed	Untapped Bulk Density
Compression	Compression Machine	Compression Speed Compression Force	➢ Description ➢ Average Wt. of 20 tablets ➢ Uniformity of Wt. ➢ Hardness ➢ Thickness ➢ Disintegration time ➢ Friability ➢ Dissolution ➢ Uniformity of dosage units (By content Uniformity) ➢ Assay

Coating Solution	Stirrer	Time Stirrer speed	➢ Description ➢ Viscosity ➢ Weight/ml ➢ Bio burden
Coating	Auto Coater	➢ Coating ➢ Pan load (kg) ➢ No. of guns ➢ Distance of guns from bed pan speed ➢ Peristaltic pump speed ➢ Inlet air temperature ➢ Exhaust air temperature ➢ Atomization air pressure ➢ Tablet bed temperature ➢ Coating time ➢ Coating solution	➢ Description ➢ Average Wt. of 20 tablets ➢ LOD ➢ Uniformity of weight

Figure.1 sampling location from Blender Bin after Blending



SUMMARY

Process validation is a fundamental concept of cGMP. Benazepril Hydrochloride 5 mg used in treatment of hypertension. The main objective of presented work was to carry out Prospective Pre-process validation of one batch of having same batch size 200,000 Tablets and same manufacturing process and formula. The entire manufacturing and sampling procedure was done with the approved validation protocol and sampling plan. The Critical process parameters was studied for validation of

one batch were validation of Sifting, blending & lubrication, compression, film coating and finished product testing was done.

Validation of sifting process
The Vibrosifter 36" & Vibrosifter 20" was used for the process set with different process parameters such as Particle size, sieve size. Sifting process was carried out as per BPCR and 40# sieves used. And observe that No Materials should be retained.

Validation of Blending
The lubrication was done in cage bin by adding the lubricants and blending it at 16 RPM for 20 minutes followed by 5 minutes after addition of Talc & Hydrogenated Castor Oil. The variables studied after lubrication was blend uniformity, composite assay and % LOD.

- Results for Blend uniformity: 97.8 % to 102.0 % (Limit: 95.00 % to 105.00 % of the target value (i.e. label claim) of active ingredient.)
- RSD value for was found between 1.5 % (Limit: NMT 5 %)
- Assay: 101.4 % (Limit: 95.0 % – 105.0 % of labeled amount)
- % LOD: 1.08 % w/w (Limit: Not more than 4.0%w/w at 105ºC)
- % Yield: 100.04 % (Limit: To be recorded).

Validation of Compression:
The blend obtained was run on the 55 station DR compression machine. The Speed of compression in RPM was optimized and the tablets was tested for various parameters like description, average weight, uniformity of weight, thickness, hardness, friability, disintegration time and dissolution to assure the reproducibility of the compressed tablets.

- Average weight: 198.0 – 204.6 mg (Limit: 191.9 mg – 212.0 mg)
- Thickness: 3.55 mm – 4.03 mm (Limit: 3.60 mm – 4.00 mm)
- Hardness: 7-8 (Limit: 25N – 150 N)
- Friability: 0.01 % – 0.20 %(Limit: NMT 1.0 % w/w)
- Disintegration time: 0 minute, 14 sec – 4 minute, 49 sec (Limit: NMT 10 minutes)
- Dissolution: 86 % – 96 % (Limit: NLT 80 (Q) % 30 minutes)
- Assay: 100.1 % (Limit: 95.0 % – 105.0 % of labeled amount)
- % Yield: 92.64 % (Limit: To be recorded)

Validation of Film Coating
The Automatic Coating Machine used for the process was set with different process parameters such as pan speed, inlet air temperature, outlet air temperature, tablet bed temperature, compressed air pressure, peristaltic pump speed, coating time and spray rate. After completion of coating, coated tablet were tested for various parameters like description, average weight, uniformity of weight, disintegration time, and % LOD to assure the reproducibility of the coated tablets.

- Speed of pan: 1.3 – 3.5 RPM (Limit: 3.0 – 14.0 RPM)
- Inlet air temperature: 62.5ºC – 65.0ºC (Limit: 60ºC + 5 ºC)
- Exhaust air temperature: 40ºC (Limit: 40ºC + 5 ºC)
- Product bed temperature: 36.5ºC – 40ºC (Limit: 35ºC + 5 ºC)
- Peristaltic pump speed: 6 - 8 RPM (To be recorded)
- Atomizing air pressure: 0.4 Mpa (Limit: 0.4 + 0.1Mpa)
- Spray rate: 78.1 – 104.8 ml/min. (To be recorded)
- Coating Time: 89 min. (To be recorded)
- Average weight: 208.32 mg (Limit: 208.0 mg + 5%)
- % Yield: 100.0 % (To be recorded)
- Quantity of Coating solution consumed: 22.32 kg (To be recorded)

Validation of Finished Product

- Average weight: 208.8 mg (Limit: 208.0 mg + 5%)
- Assay: 101.3% (Limit: 95.0 % – 105.0 % of labeled amount)
- Dissolution: 95 % – 101 % (Limit: NLT 80 (Q) % in 30 minutes)
- % LOD: 1.2 % (Limit: NMT 5.0 %)
- Hardness: 110 N (Limit: 25N – 150 N)

Based on the data, various physicochemical test parameters it was summarized that the process, parameters, specifications and controls have been adequate to show the total conformance of the product to specifications. So presented study show that the set process parameters of the Benazepril Hydrochloride 5 mg could be reproduced during the process resulting in the product meeting the specifications.

CONCLUSION

Process validation study on one Batch of Benazepril Hydrochloride Tablet 5 mg having batch size of 200,000 tablets was successfully completed and the manufacturing critical process parameters were validated in this process validation study.

Based on the review of critical process parameters and analytical results as detailed in this summary

report, for critical process parameters are specified below in this Process Validation Summary Report for "BENAZEPRIL HYDROCHLORIDE TABLET 5 mg" having batch size of 200,000 tablets.

The manufacturing critical process parameters for "BENAZEPRIL HYDROCHLORIDE TABLET 5 mg" having batch size of 200,000 tablets mentioned in process validation protocol.

The data presented in this validated summary report indicates that the manufacturing process with above recommended limit(s)/range(s) of critical process parameters for "Benazepril Hydrochloride Tablet 5 mg" as described in batch manufacturing record having batch size of 200,000 tablets is validated and consistently produce the finished product of "Benazepril Hydrochloride Tablet 5 mg" meeting all pre-determine specification and quality attributes.

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