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THE PHARMA INNOVATION

Process Validation of Pantoprazole 40mg Tablets

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Renata P. Raffin, Have done Sodium Pantoprazole-Loaded Enteric Micro particles Prepared by Spray Drying: Effect of the Scale of Production and Process Validation. Pantoprazole is a prodrug used in the treatment of acid related disorders and Helicobacter pylori infections. The purpose of this study was to investigate the physical characteristics of enteric pantoprazole-loaded micro particles prepared by spray drying using a blend of Eudragit and HPMC. At pilot scale, among the four sets of micro particles prepared varying the atomization and the air pressure, in three of them free micro particles were obtained. The micro particles prepared with rotating disc atomizer or two fluid atomizer and mixed flow presented either crystals on the particle surface or very high polydispersity, respectively. Using two fluid nozzle and air pressure of 49 kPa (N1-microparticles) the product obtained was not adequate because it presented strings in the powder. Using the same atomizer but air pressure of 196 kPa (N2-microparticles) the micro particles presented high encapsulation efficiency and the highest stabilization of formulation in acid medium. N2-microparticles were chosen for the pilot scale evaluation. The three batches of pantoprazole-loaded micro particles prepared to validate the process showed reproducible diameter, polydispersity, densities, encapsulation efficiency and gastro-resistance profile. T. Scholten, G. Gatz, Once-Daily Pantoprazole 40 mg and Esomeprazole 40 mg Have Equivalent Overall Efficacy in Relieving GERD-Related Symptoms.

*Keyword:*Process validation, Absolute validation, Validation protocol, Analytical method validation.

1. Introduction:

The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications. Process validation is a key element in assuring that these principles and goals are met.

The **basic principles** for validation may be stated as follows:

- Establish that the process equipment has the capability of operating within required parameters;
- Demonstrate that controlling, monitoring, and measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;
- Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and

- Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.

1.1 FDA Definition:

Process Validation:

"Establishing Documented Evidence, Which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

Steps in Validating a Process:

- Develop validation protocol
- Conduct installation qualification
- Conduct operational qualification
- Conduct performance qualification
- Analyze results and reach conclusions
- Monitor and control process
- Purpose: to ensure process remains within established parameters under anticipated conditions
- Investigate deviations from established parameters
- Take corrective action
- Consider whether revalidation is necessary
- Changes in process or product

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

Why to Validate the Processes:

There are many reasons, in addition to the regulatory 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 will meet specifications and have uniform quality. 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 will yield little scrap or rework, resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process.

What Processes Should Be Validated:

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures. When any of the conditions listed below exist, process validation is the only practical means for assuring that processes will consistently produce devices that meet their predetermined specifications:

Routine end-product tests have insufficient sensitivity to verify the desired safety and efficacy of the finished devices;

Clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product.

Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices.

The process capability is unknown, or it is suspected that the process is barely capable of meeting the device specifications.

Validation Responsibilities

- Colleagues to administer program - e.g. Technical Services or Site Validation Committee (SVC)
- Develop site master validation plan.
- Prepare/execute/approve validation studies.
- Manufacturing Operations prepares the batches as though they are Routine production batches.
- QA ensures compliance and that documentation and proceduresare in place. Approves protocols and reports.
- QC Laboratories - performs testing or contracts validation testing. Reviews protocols and reports as needed.

- SVC - Technology Group (lead), Manufacturing Operations, QA/QC, Engineering,
- Computer Systems

1.2 Validation Protocol:

Definition: A document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

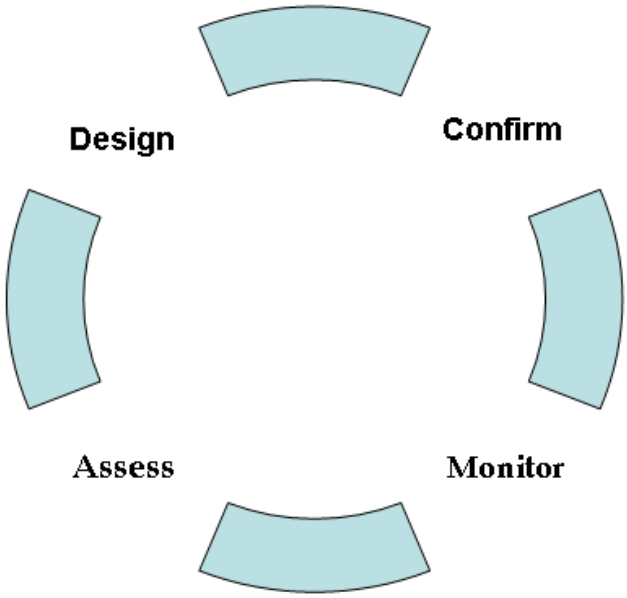
Contents of validation Protocol:

1. General information
2. Objective
3. Background/Prevalidation Activities, Summary of development and tech transfer (from R&D or another Site) activities to justify in-process testing and controls; any Previous validations.
4. List of equipment and their qualification status
5. Facilities qualification
6. Process flow charts
7. Manufacturing procedure narrative
8. List of critical processing parameters and critical excipients
9. Sampling, tests and specifications
10. Acceptance criteria

Validation- Related Issues

- Approach to validation
- SOPs
- Calibration
- Environmental monitoring
- Preventive maintenance
- Training
- Raw material sampling and qualification programs
- Change control
- Facilities/systems
- Manufacturing/packaging methods
- Formulations
- Raw materials & Suppliers

Process Validation Lifecycle:



Design:

GMP requirements for Process Design

- Design of Facility
- Design of Equipment
- Design of Production and Control Procedures
- Design of Laboratory Controls
- Propose process steps (unit operations) and process variables (operating parameters) that need to be studied.
- Identify sources of variability each unit operation is likely to encounter.
- Consider possible range of variability for each input into the operation.
- Evaluate process steps and variables for potential criticality.
- Select process steps and variables for test in representative models.
- Development studies to identify critical operation parameters and operating ranges
- Designed experiments
- Lab scale, pilot scale and/or full scale experimental batches to gain process understanding
- Establish mechanisms to limit or control variability based on experimental data
- Aim for a “robust process”, i.e., one that can tolerate input variability and still produce consistent acceptable output.

Confirm:

- Transfer developmental knowledge to Production, i.e., technology transfer.
- Batch record and operating SOPs in place, equipment and facilities equivalency established.
- Raw materials approved.
- Measurement systems qualified (QC lab as well as production floor test instrumentation).
- Personnel training completed.
- Environment controlled as necessary.
- Execution of Conformance Batches with appropriate sampling points and sampling level.
- First evidence that process can function at commercial scale by Production personnel.
- Demonstrates reproducibility.
- Reasonable measure of protection to consumer.
- Full sample and data analysis
- Data may confirm process as-is, point to major process design change(s) or suggest process improvement(s).
- Implement changes via approved change control procedures.
- Assess need for additional conformance batch(es) or limited testing. Amount/degree of additional work commensurate with the significance of the change and its impact on product quality

Monitor:

Routine Commercial Manufacturing

- Monitor critical operating and performance parameters
- Utilize appropriate tools, e.g., Statistical Process Control
- Monitor product characteristics (e.g., stability, product specifications)
- Monitor state of personnel training and material, facility/equipment and SOP changes
- Investigate OOS for root cause and implement corrective action.

Assess:

- Analyze Monitoring Data
- -Trend data: e.g., Real time, Monthly, Quarterly review
- -Evaluate need to increase level of monitoring/sampling, or decreased monitoring based on accumulated data
- Periodic evaluation (at least annually) per 21 CFR 211.180(e)
- To determine the need for changes in drug product specifications or manufacturing and control procedures
- Study OOS and OOT (out of trend) data in the aggregate.
- Assess impact of process and product changes made over time.
- Feed back into design stage for significant process shifts or changes

1.3 Types of Process Validation

Process validation may be conducted at different points during the life cycle of a product. The types of process validation are defined in terms of when they occur in relation to product design, transfer to production and release of the product for distribution.

1.4 Prospective Validation

Prospective validation is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics, before a product made under a revised manufacturing process is released for distribution.

1.5 Concurrent Validation

Concurrent validation is a subset of prospective validation and is conducted with the intention of ultimately distributing product manufactured during the validation study. Concurrent validation is feasible when nondestructive testing is adequate to verify that products meet predetermined specifications and quality attributes. If concurrent validation is being conducted as the initial validation of a new process or a process which has been modified, product should be withheld from distribution until all data and results of the validation study have

been reviewed, and it has been determined that the process has been adequately validated.
Concurrent validation may be conducted on a previously validated process to confirm that the process is validated. If there have been no changes to the process and no indications that the process is not operating in a state of control, product could be released for distribution before revalidation of the process is completed.

1.6 Retrospective Validation

Retrospective validation is the validation of a process based on accumulated historical production, testing, control, and other information for a product already in production and distribution. This type of validation makes use of historical data and information which may be found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports. Historical data must contain enough information to provide an in-depth picture of how the process has been operating and whether the product has consistently met its specifications. Retrospective validation may not be feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis.

1.7 Revalidation

When changes or process deviations occur, the process must be reviewed and evaluated, and revalidation must be performed where appropriate. Review, evaluation, and revalidation activities must be documented.
Revalidation may be divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals.

a) ***Revalidation after changes***. Revalidation must be performed on introduction of any changes affecting a manufacturing or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, steam, etc.).
Some typical changes which require revalidation include the following:

b) **Changes in the starting material(s)**. Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.

c) **Changes in the packaging material,** e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.

d) **Changes in the process,** e.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.

e) **Changes in equipment**, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.

f) **Changes in the production area** and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process.

g) ***Periodic revalidation***. It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based essentially on a review of historical data, i.e. data generated during in-

process and finished product testing after the latest validation, aimed at verifying that the process is under control. During the review of such historical data, any trend in the data collected should be evaluated.

2. Materials and Methods:

2.1 Drug Profile:

a. Pantoprazole

Commonly used brand name (s): Zovanta 40, Pantoloc; Protonix; &Protonix I.V

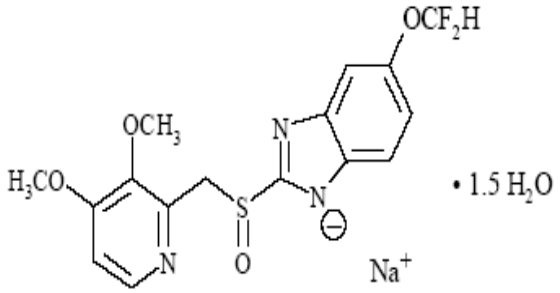
Category:

Gastric acid pump inhibitor

Antiulcer agent

2.1.2 Description

Pantoprazole sodium Tablets are substituted,Benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3, 4-dimethoxy-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole Sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C16H14F2N3NaO4S x 1.5 H2O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

2.1.3 Label Claim:

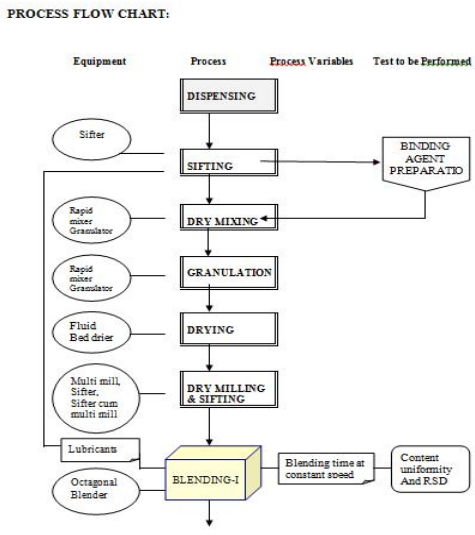
Each enteric coated tablet contains;
Pantoprazole sodium sesquihydrate equivalent to Pantoprazole 40 mg.
Colours: Yellow oxide of iron and titanium dioxide

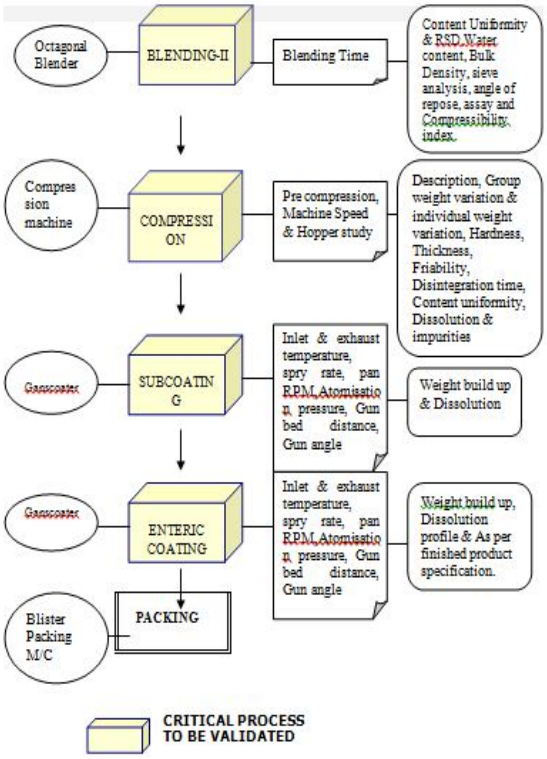
2.1.4 Manufacturing Formula:

Core Materials:

Item	Function
Pantoprazole sodium sesquihydrate	Active
Mannitol	Diluent
Anhydrous sodium carbonate	Stabilizer
Hypromellose	Binder
Crospovidone	Disintegrate
Calcium stearate	Lubricant
Hypromellose	Film former
Povidone	Plasticizer
Titanium dioxide	Anti-taking agent
Propylene glycol	Opacifier
Iso propyl alcohol	Vehicle
Methacrylic acid copolymer	Film former
Sodium hydroxide	Neutralizing agent
Purified water	Vehicle
Macrogols	Plasticizer
Purified talc	Glident
Titanium dioxide	Opaquent/Colourant
Ferric oxide	Colourant

2.1.5 Process Flow Chart:





2.1.6 Description of Work:

Pantoprazole 40 tablets are validated to improve the dissolution properties. It is proposed to reduce the quantity of Calcium stearate from 3.20mg per tablet to 1.60mg per tablet and to compensate the quantity with Crospovidone is increased from 10.0mg to 11.60 mg per tablet .Since this change is at blending stage, subsequent impact to be studied further stages also, So the process needs to be validated for blending, compression and coating stages. Dry mixing, granulation, drying stages remains same.

Most widely used lubricants are of the hydrophobic category. Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations. Many also have both anti- adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds.

Calcium stearates have long been recognized in the art of pharmaceutical compounding as lubricants and are probably the most common pharmaceutical lubricants in use at the present time. These substances, however, in spite of their wide acceptance in the pharmaceutical arts as lubricants have certain disadvantages.

Determining the level of lubricants to use and the manner in which they are incorporated into a batch is critical. If concentrations are **too low**, or distribution and mixing times are inadequate, problems can arise.

Some examples are as follows:

- Punch filming
- Picking
- Sticking
- Capping
- Binding in the die cavity

If concentrations are **too high**, or distribution and mixing times are too great, potential problems include:

- Decrease in tablet hardness
- Inability to compress into tablets
- Increase in tablet disintegration times (DTs)
- Decrease in rate of dissolution

The primary disadvantage to the use of calcium stearate as pharmaceutical lubricants lies in the fact that they are extremely hydrophobic. This hydrophobicity hinders dissolution and disintegration time of solid dosage forms containing magnesium and calcium stearates. Another factor which acts to hinder dissolution and disintegration time of solid dosage forms containing magnesium or calcium stearate is their electrostatic attraction with therapeutically active substances and other excipients. This electrostatic attraction is particularly pronounced when calcium and magnesium stearate are utilized in finely divided particulate form, i.e., an average particle size in the range of from 1 to 15 microns. This disadvantage of magnesium and calcium stearates is not uncommon, however, as there are in the literature numerous reports of other common pharmaceutical excipients inhibiting the dispersion of particles of active drug in the gastric media as a result of hydrophobicity. Other commonly utilized pharmaceutical compounding excipients act to impede dissolution in various ways in addition to being hydrophobic such as, for example, by forming an insoluble film around

the active drug particle or by chemically complexing the active drug particles.
Failures in the dissolution properties are due to Hydrophobicity of calcium stearate. Problems caused by the hydrophobicity of Calcium stearate can be prevented by the reduction of 50% quantity of calcium stearate (lubricant) and the reduced amount is compensated by crospovidone (disintegrant).

2.2 Rationale for Selection of Critical Steps and Its Process Parameters for Validation:

Blending:

This step involves mixing of granules with other blending material. The purpose of blending is to get a uniform distribution of pantoprazole sodium sesquihydrate.This is followed by mixing of the blend with calcium stearate (Lubrication to get good flow and anti-adhesion property of the blend.
Mixing speed and time are critical variables in this process. Since speed of the blender is constant, proper mixing time shall be determined. Mixing is a critical as less blending will result in non-uniform distribution of drug and poor flow whereas more blending will result in de-mixing leading to non-uniform distribution of drug and increase in disintegration time. Proper blending shall be established by checking content uniformity of drug at all the time intervals mentioned in protocol. In addition to this following tests shall be carried out for information purpose. This shall be carried out on final time interval samples only.

A) Water content
B) Bulk density
C) Sieve analysis
D) Compressibility index
E) Content uniformity & RSD
F) Angle of Repose
G) Assay

2.2.1 Compression:

This step involvesConversions of blended material into tablets as per specifications. Speed of machine, tablet thickness and hopper level are the major variables.
So, following parameters are to be checked to establish the above-mentioned variables at regular intervals

A) Description
B) Weight variation (group and individual)
C) Hardness
D) Thickness
E) Friability
F) Disintegration time
G) Dissolution time
H) Content uniformity and
I) Impurities

2.2.2 Coating:

The coating step involves the covering of tablet surface with a polymer film. The pan RPM, Inlet and Exhaust temperatures, Spray rate, gun distance and air pressure are critical process variables. These parameters affect the coating and final appearance of the tablets.

a) **Pan RPM:**If the RPM of coating pan is not within the specified limit then uneven distribution of the coating solution on tablet take place.
b) **Inlet/Exhaust temperature:** If the temperature of coating pan is not within the specified limit then the drying will be insufficient which results twining and sticking of tablets or rough surface and cracking of the film.
c) **Spray rate:** If the spray rate is not proper then the coating will not be uniform.
d) **Gun to bed distance:** If gun to bed distance is not adequate, it results in rough surface or over wetting during coating.
e) **Air pressure:** If the compressed air pressure (Main and Atomization) is not adequate, it peeling or rough surface of tablets.

2.2.3 Validation Procedure:

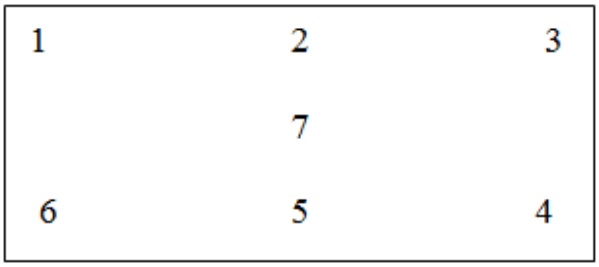
1. Three batches of **0.225 Million Tablets** batch size to be manufactured as described in the Batch manufacturing record.
2. Current version of standard operating procedures to be followed.
3. Record the yield after blending, Compression, Coating and Inspection.

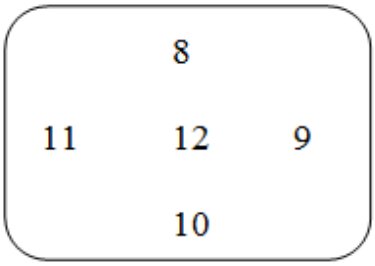
2.3 Sampling Procedure at Different Stages:

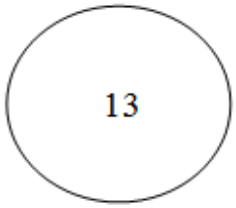
2.3.1 Blending: Load sifted materials into the Octagonal Blender except Calcium stearate.Start the blender in inch mode and check for any

leakage of material. On ensuring that there is no leakage, blend for 18 minutes.Samples to be drawn from 13 locations of the blender as shown in figrure.Contnuue the blending for another 2 minutes and collect the sample from 13 locations as shown the figure.Collect samples as per the below diagram using sampling rod. The sample quantity should be between 15.3mg to 460.2mg.Bag blend Calcium stearate along with equal quantity of blend from Octagonal Blender in double polythene bags for 2minand load into Octagonal Blender and blend for 3 minutes and collect the sample from 13 locations as shown in the figure. The sample size after 3 minutes lubrication shall be between 155mg to 465mg.All samples shall be collected in butter paper. Collect samples in two sets. One set of sample is taken for analysis and other set is kept as a reserve sample. In case of failure results of one set use the reserve sample set for analysis, otherwise, discard the reserved sample set.

Octagonal blender sampling location:







Send the sample for analysis with proper label to QC along with Analytical request form.

Labels shall contain following details.

1) Date of sampling
2) Stages
3) Location No.
4) Sample no.
5) Sampled by

Compression: Compression to be carried not as per batch manufacturing record using 8.0mm normal concave plain lower and upper punches and 8.0mmdies.Set the machine at three different speeds of 15,25 & 35 RPM.

No. of stations: 37

Type of tooling 'D' type

Carry out the testing of physical parameters as mentioned in the below table.

S.No	Parameter	Standard	Number of Tablets to be taken from each side for testing
1	Description	White to off white coloured round uncoated biconvex tablet plain surface on both sides.	100 Tablets
2	Group Weight variation	3.1 g ± 2% (3.038 g-3.162 g)	20 Tablets
3	Individual Weight variation	155 mg ± 4% (148.8 mg -161.2 mg)	40 Tablets
4	Hardness	NLT 2.5 Kg/cm 2	6 Tablets
5	Thickness	3mm±0.2mm(2.80mm-3.20mm)	40 Tablets
6	Disintegration time	NMT 12min	6 Tablets
7	Friability	NMT 0.8 % w/w	20 Tablets

Set the compression machine at desired parameter and collect the sample for pre-compression studies.
Set the compression machine at lower and higher thickness and collect samples for dissolution.
Divide the total compression time into three equal cycles. Run the compression machine at three different speeds in three cycles respectively and withdraw samples for content uniformity, dissolution and impurity at each speed. And check the physical parameters at each speed.
Hopper study: To evaluate effect of vibrations during compression on blend uniformity, hopper study shall be carried out. Fill the hopper completely and run the compression machine.
Collect tablets when powder level in the hopper is full approximately middle of the hopper and when it is near the end of the hopper. Check the Physical parameters and testing of Content Uniformity at full, middle and near end of the hopper at optimum machine speed.
Coating: Coating to be carried out as per Batch Manufacturing Record.
Before starting sub coating and enteric coating record the average weight of core tablets and sub coated tablets respectively .Check the appearance and weight gain during coating. After completion of coating check for Description, weight variation and moisture content. Make one pooled sample for checking as per current finished product specification
Dissolution profile: Check the dissolution profile on 12 tablets at 15 min20 min, 30 min, 45 min, and 60 min from the pooled sample after the completion of enteric coating

Table: Acceptance criteria for critical in process controls and sampling plan:

Stage	Process variables	Sampling frequencies	Testes to be performed	Approximate sample size	Acceptance criteria
Blending	Blending time	18 and 20 min	uniformity of content and RSD	3X13 samples at each time interval between 153.4 mg to 460.2mg in butter paper	100±15% RSD NMT
		23min	uniformity of content and RSD	3X13 samples at each between 155mg to 465mg in butter paper	
			Bulk density ,sieve analysis, compressibility index , angle of repose, water content, and assay	100g from the blender in poly bags	for information
compression	precompression studies at optimum speed	At lower and higher thickness	Dissolution	3X12 tablets	As per current finished product specifications
	At three different machine speeds	At different speeds	Description	40 Tablets	White to off white coloured round uncoated biconvex tablet plain surface on both sides.
			Group Weight variation	20 Tablets	3.1 g ± 2% (3.038 g-3.162 g)
			Individual Weight variation	40 Tablets	155 mg ± 4% (148.8 mg -161.2 mg)
			Hardness	6 Tablets	NLT 2.5 Kg/cm 2
			Thickness	40 Tablets	3mm±0.2mm(2.80mm-3.20mm)
			Disintegration time	6 Tablets	NMT 12min
			Friability	20 Tablets	NMT 0.8 % w/w
			Dissolution	3X12 tablets	

			Impurity	At high speed	
	Hopper study at max speed	Full hopper approximately middle hopper and near end hopper	Individual Weight variation	40 Tablets	155 mg ± 4% (148.8 mg -161.2 mg)
			Hardness	6 Tablets	NLT 2.5 Kg/cm 2
			Thickness	40 Tablets	3mm±0.2mm(2.80mm-3.20mm)
			Disintegration time	6 Tablets	NMT 12min
			Friability	20 Tablets	NMT 0.8 % w/w
			Content uniformity	3X12 tablets	100±15%RSD; NMT 6.0%

3. Results and Discussion

3.1 Blending:

Fixed Parameters

Blender RPM : 6 RPM

Blender load : 34.875 kg

Variables Considerable For Study : Blending Time

Time Intervals Studied : 18, 20 & 23 Min

Acceptance Criteria : 100±15% (RsdNmt 6.0%)

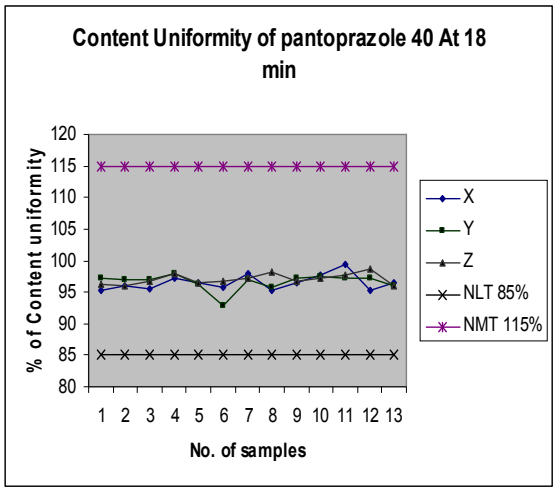
Measured Response : Content Uniformity AndRsd

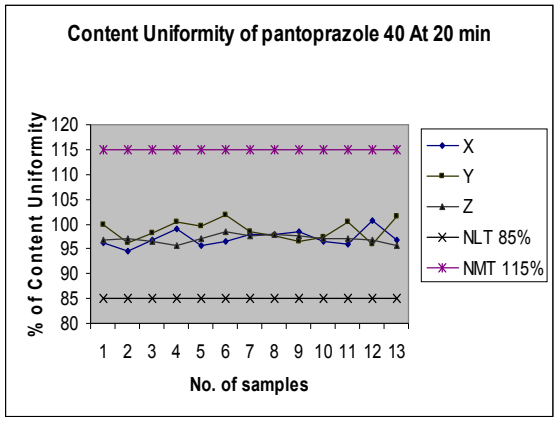
Batches Taken For Study : X, Y & Z

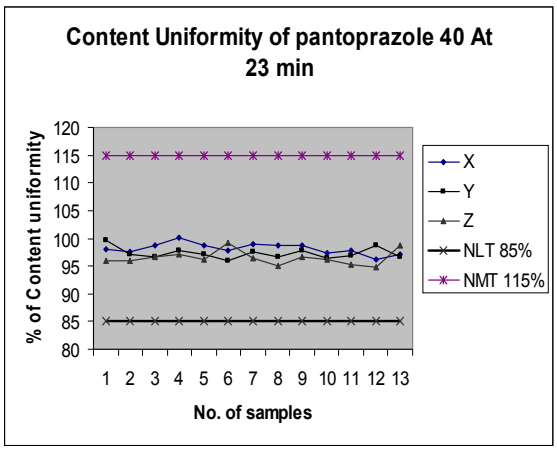
Sub-coating	Inlet temp, exhaust temp, pan speed , atomization pressure, gun distance and spray rate	Weight build up and dissolution	pooled sample 50 tablets	for information
Enteric coating	Inlet temp, exhaust temp, pan speed , atomization pressure, gun distance and spray rate	As per current finished product specifications	pooled sample	As per current finished product specifications
		Dissolution profile at 15,20,30,45and 60min (collect form pool sample at the end)	pooled sample	for information

Table: The content uniformity results of Pantoprazole in the blend after 18, 20 and 23 minutes of blending Batches batch no. X, Y & Z

Batch no.	% of Pantoprazole								
	X			Y			Z		
Blending time	18 min	20 min	23 min	18 min	20 min	23 min	18 min	20 min	23 min
1	95.2	96.2	98.1	97.2	99.9	99.7	96.3	96.7	96
2	95.9	94.5	97.5	97	96.1	97	95.9	97.2	95.9
3	95.5	96.7	98.7	96.9	98.1	96.6	96.7	96.5	96.7
4	97.3	99	100.2	97.9	100.5	97.9	98	95.8	97.1
5	96.4	95.6	98.8	96.3	99.5	97.1	96.5	97	96.2
6	95.7	96.6	97.8	92.8	101.8	96	96.7	98.6	99.2
7	97.9	97.9	98.9	97	98.6	97.6	97.3	97.6	96.5
8	95.2	97.8	98.8	95.8	97.6	96.7	98.1	97.9	95
9	96.6	98.5	98.8	97.2	96.4	97.8	96.7	97.6	96.6
10	97.7	96.4	97.3	97.4	97.3	96.5	97.2	97.1	96.1
11	99.3	96	97.7	97.3	100.5	96.9	97.8	97.2	95.2
12	95.3	100.6	96.2	97.3	95.9	98.7	98.6	96.8	94.9
13	96.4	96.7	97.2	96	101.5	96.7	96	95.8	98.7
Min	**95.2**	**94.5**	**96.2**	**92.8**	**95.9**	**96**	**95.9**	**95.8**	**94.9**
Max	**99.3**	**100.6**	**100.2**	**97.9**	**101.8**	**99.7**	**98.6**	**98.6**	**99.2**
Avg.	**96.42**	**97.11**	**98.28**	**96.62**	**98.76**	**97.32**	**97.06**	**97.06**	**96.47**
RSD	**1.32**	**1.64**	**1.01**	**1.34**	**2.07**	**1.04**	**0.87**	**0.8**	**1.34**







Observations: The distribution of Pantoprazole is well acceptable as per the predetermined specification at all the intervals of blending as shown by the samples analyzed , after 23 minutes results show more closer homogeneity of pantoprazole distribution with other excipent of blend.

The blending time of 23 minutes is concluded validated blending time at blender 6 RPM for Pantoprazole 40 blending, when the process is performed in 150 liters capacity Octagonal blender for a batch size of 34.875 kg. Bulk density and Particle size distribution of the lubricated blend was uniform among three batches indicates that the granulation, milling and blending process has proved to be consistent among the batches.

Compression

VARIABLES CONSIDERED FOR STUDY **:** Compression speed
COMPRESSION MACHINE **:** 37 stations
SPEEDS STUDIED **:** 1110, 1850 & 2220 Tablets/Minutes (15, 25&30 RPM)
MEASURED RESPONSE **:** Description, Group Weight variation,

The physical parameters of the blend for three batches are as follows:

Parameter	X	Y	Z
Particle size distribution			
% retains on #20	0.10%	0.06%	0.00%
% retains on # 40	24.83%	20.90%	23.17%
% retains on #60	50.40%	36.36%	42.63%
% retains on #80	64.53%	47.80%	55.17%
% retains on #100	69.71%	53.12%	60.08%
% Passing through #100	29.43%	46.74%	39.22%
Untapped Density g/ml	0.625 g/ml	0.625 g/ml	0.610 g/ml
Tapped Density g/ml	0.676 g/ml	0.833 g/ml	0.893 g/ml
Compressibility Index	7.50%	25.00 %	31.70%
Angle of repose	Fair	Green zone	Yellow zone fair
LOD	3.43% w/w	2.87% w/w	2.58% w/w
Assay	39.77mg	39.25mg	39.37mg

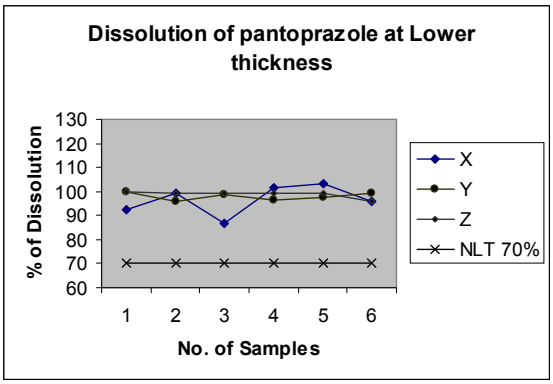
Observations:particle size distribution untapped, Tapped density & angle of repose of batches are similar, Moisture content and Assay values of all three batches are also within the acceptance criteria.
Individual Weight variation, Hardness, Thickness, Disintegration time & Friability

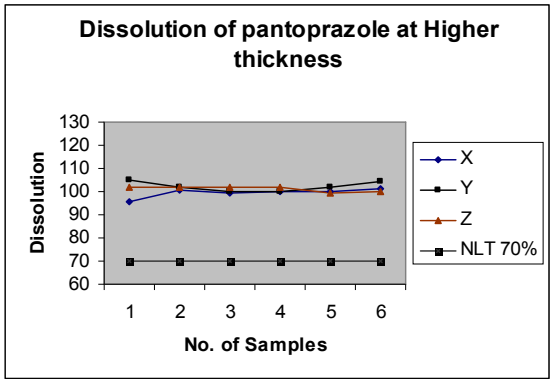
Table : Batches Taken for Study**:** X, Y & Z

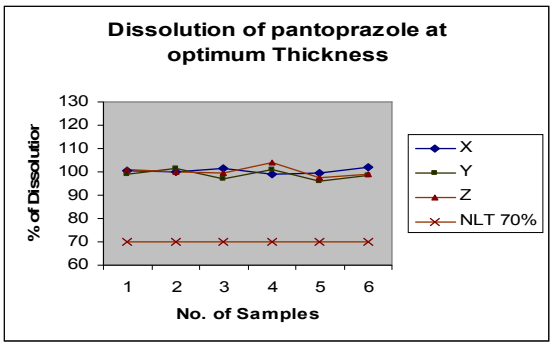
PARAMETER	STANDARD
Appearance	White to off white coloured circular tablets with plain surfaces on both sides
Group weight variation(g)	3.1 g ± 2% (3.038 g-3.162 g)
Individual weight variation(mg)	155 mg ± 4% (148.8 mg -161.2 mg)
Thickness(mm)	3mm±0.2mm(2.80mm-3.20mm)
Hardness(kg/cm 2)	NLT 2.5 Kg/cm 2
Friability(%w/w)	NMT 0.8 % w/w
Disintegration time(min)	NMT 12min
Content Uniformity RSD	100 ± 15% NMT 6.0 %
Dissolution	NLT 70 % in 45 min

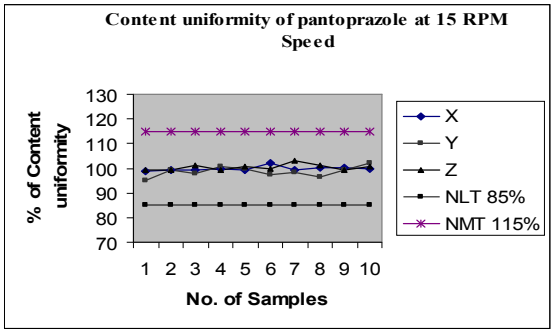
Table : Dissolution of pantoprazole 40 in the Lower, optimum & higher Thickness of compressed tablet batch no. X Y & Z:

	% of Pantoprazole								
Batch No.	**X**			Y			Z		
M/C Speed (RPM)	**Lower**	**Optimum**	**Higher**	**Lower**	**Optimum**	**Higher**	**Lower**	**Optimum**	**Higher**
1	92.6	100.4	95.5	99.8	99.1	104.8	100.1	101.2	101.6
2	99.1	100	100.8	95.8	101.4	101.9	99.5	100	101.8
3	86.9	101.6	99.6	98.6	97	99.9	99.2	99.6	101.9
4	101.3	99.2	100.3	96.3	101.2	99.9	99.2	103.8	102
5	103.2	99.3	99.7	97.6	96.1	101.9	99.1	97.7	99.2
6	96.1	101.8	101.1	99.3	98.5	104.4	95.9	99.1	100.3
Min.	**86.9**	**99.2**	**95.5**	**95.8**	**96.1**	**99.9**	**95.9**	**97.7**	**99.2**
Max.	**103.2**	**101.8**	**101.1**	**99.8**	**101.4**	**104.9**	**100.1**	**103.8**	**102**
Avg.	**96.53**	**100.38**	**99.5**	**97.9**	**98.88**	**102.63**	**98.83**	**100.23**	**101.13**

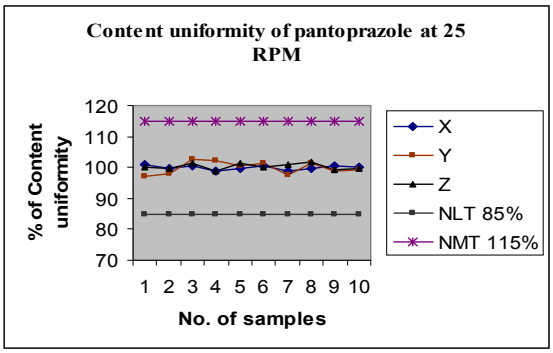








Observations: Pre compression dissolution at lower, optimum and higher thickness complies with acceptance criteria



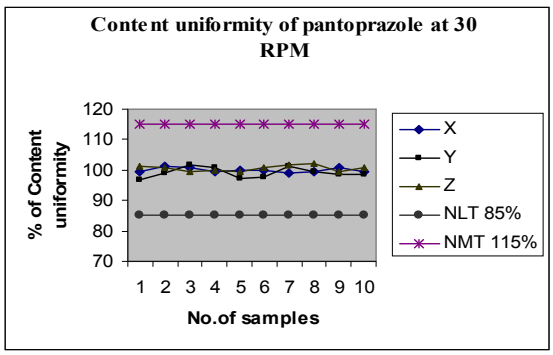


Table : Content uniformity of pantoprazole 40 tablets compressed at different speeds 15, 25, 30 RPM for the batch no. X Y & Z:

	% of Pantoprazole								
Batch No.	**X**			**Y**			**Z**		
M/C Speed (RPM)	15	25	30	15	25	30	15	25	30
1	98.9	101.1	99.5	95.1	97.1	97	99.2	100	101.2
2	99.2	99.6	101.2	99.1	97.9	99.1	99.1	99.6	100.6
3	99.5	100.6	100.7	97.8	102.8	101.7	101	101.4	99.6
4	100	99	99.4	100.5	102.2	100.7	99.1	99	99.7
5	99.4	99.8	100	100	100.3	97.2	100.9	101.2	99.3
6	102	100.4	100.1	97.5	101.5	97.9	99.9	100.2	100.6
7	99.2	98.7	99.1	98.2	97.5	101.4	103.1	100.9	101.7
8	100.1	99.8	99.3	96.6	101.5	99.5	101.2	101.9	102.2
9	100.3	100.6	100.7	99.1	98.7	98.4	99.4	99.4	99.6
10	99.6	100.2	99.5	102	99.4	98.4	100.5	99.6	100.8
Min	98.9	98.7	99.1	95.1	97.1	97	99.1	99	99.3
Max	102	101.1	101.2	102	102.8	101.7	103.1	101.9	102.2
Avg.	99.82	99.99	99.95	98.59	99.89	99.13	99.87	100.23	100.17

Table : Dissolution of pantoprazole tablets compressed at different speeds 15, 25, 30 RPM for the batch no. X, Y & Z

	% of Pantoprazole								
Batch No.	**X**			**Y**			**Z**		
M/C Speed (RPM)	15	25	30	15	25	30	15	25	30
1	95.9	97.2	101	100.9	98.5	102.9	98.3	99.8	99
2	94.5	97.2	100.2	98.6	98.4	100.6	98.8	99.2	98.5
3	97.2	96.9	98.9	102.3	100.2	99.3	98.7	101.1	102
4	94.5	96.9	99.1	99.8	99.9	99.9	97.8	99.3	98.6
5	100.5	97.1	96.3	99.8	100.3	101.2	100.2	99.3	99.8

6	101	96.6	99.7	100.4	98.9	98	98.7	98.1	100.6
Min.	**94.5**	**96.6**	**96.3**	**98.6**	**98.4**	**98**	**97.8**	**98.1**	**98.5**
Max.	**101**	**97.2**	**101**	**102.3**	**100.3**	**102.9**	**100.2**	**101.1**	**102**
Avg.	**97.16**	**96.98**	**99.2**	**100.3**	**99.37**	**100.32**	**98.75**	**99.47**	**99.75**

3. Conclusion

Process validation of pantoprazole 40mg tablets was conducted for a batch size of 2, 25,000 tablets, which included the validation of critical steps of manufacturing such as blending, compression and coating.

3.1 Blending:

The blending was performed and the samples at the designated locations were drawn after 18,20and23 min of blending for determination of the content uniformity and RSD values of pontoprazole. The RSD the values meet the acceptance criteria at the all the 3 blending intervals. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous.

3.2 Compression:

The compression was carried out between the speed limits and physical parameters of the tablets were studied at this speed. The parameters checked included appearance, individual weight variation, group weight variation, thickness of tablets, hardness of tablet, tablet friability and tablet disintegration time.

The parameters are well within the limits of acceptance criteria at the speed s studied. Hence the compression stage of pantoprazole 40is consistent and reproducible when the compression was carried out at the speeds of 15, 25, 30 rpm of the turret.

Content uniformity and dissolution of compressed tablets of all three speeds of compression stage are found to be uniform and well within the limits of acceptance criteria. Hopper study was carried out for full hopper, half hopper and near end hopper to establish the segregation of the blend during compression.

3.3 Sub coating:

The sub coating validation was carried out for a batch size of 37.125 kg and found that all the physical and chemical parameters of subcaoted tablets are well within the limits of acceptance criteria when coating is performed with the recommended coating parameters dissolution data of sub coated tablets well within the limits. The weight build up is 9 mg to 12 mg.

3.4 Enteric coating:

The enteric coating validation for the three batches was carried out in ganscoater for a lot size of 40.50 kg and found that all the physical chemical parameters of coated tablet are well within the limits of acceptance criteria. Dissolution profile of coated tablet are well within the limits of acceptance criteria the weight build up is 10mg to 13mg. over all 3mg per tablet of extra enteric coating material are taken to achieve above enteric weight buildup.

Process of pantoprazole has been validated according to the standard operating procedures, all the Experimental Results were within the specified limits. So it is possible to improve the dissolution properties only by reducing the 50% quantity of calcium stearate and the reduced quantity is compensated by crospovidone.

4. Reference:

1. www.fda.gov/cdrh/qsr/04valid.html
2. http://www3.interscience .wilel.com/journal/118880168/abstract
3. http://www.medscape .com/veiwarticle/463165
4. www.accessmlibrary.com/coms2/summary_0286-34272780_ITM
5. pharmaceuticalvalidation.blogspot.com/2008/01/types-of-process-validation.html
6. http://www.drugs.com/mmx/pantoprazole-sodium-sesquihydrate.html
7. http://www.fda.gov/cder/whatsnew.htm
8. http://www.asian guidelines.com
9. http://www.who guidelines.com
10. Basic Principles of Validation by k. kiran& k. kathiresen

11. In house specifications, Dr.Reddy'sLaborateries Limited, Hyderabad.
12. Pharmaceutical Master Validation by Syed ImtiazHaider, Pg.no: 14 – 23
13. Pharmaceutical process validation by Nash and Berry, pg.no: 432 - 434
14. Handbook of Pharmaceutical Manufacturing Formulations by sarfarajniazi pg.no: 32 – 34.