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# PROCESS VALIDATION OF SOTALOL HYDROCHLORIDE TABLETS

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## ABSTRACT

Process Validation is a very common term in the pharmaceutical industry. But it involves series of activities carried out in order to have the assurance that the desired quality products are manufactured. The manufacturing process need to be controlled and for this one should have sound knowledge and understanding regarding the process as well as the product. Each and every step should be scientifically planned and conducted and documented appropriately in order to have an effective and efficient program. So here we discuss the Prospective Process validation of the Sotalol Hydrochloride 40 mg tablets, the critical process parameters involved in the manufacturing process and the consistency in the results of the three consecutive batches.

**INTRODUCTION:** As per the FDA's November 2008 draft version of Process Validation Guidance for Industry, Process validation is defined as collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that the process is capable of consistently delivering quality products.

It involves series of activities taking place over the lifecycle of product and process which are divided into 3 stages [1].

- Stage 1- Process Design
- Stage 2- Process qualification
- Stage 3- Continued Process Verification

Types of Process validation [2]:

1) Prospective validation - Normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

2) Concurrent validation - Documenting the evidence that a process does what it purports to do base on information generated during actual implementation of the process.

3) Retrospective validation - Achieving validation by documenting all the historical information (e.g., release data) for existing products and using that data to support the position that the process is under control.

4) Revalidation - Indicates that the process must be validated once again, may not necessarily mean that the original program must be repeated however.

Process Validation has been widely discussed by the pharmaceutical industry during the past 20-30 years. An effective Process Validation contributes significantly to assuring the drug quality. But the advantages and

disadvantages of Process Validation have never been systematically evaluated and Process Validation is frequently performed without real understanding of work involved. There is also much confusion as to what constitutes Process Validation and what does not.

The Pharmaceutical Process Validation has always been understood in one of the two ways- either as total validation activity in pharmaceutical manufacturing site from development, qualification of equipments to final validation of three consecutive batches of the final product or as final production scale validation of a pharmaceutical preparation only.

John R. Sharp, Principal Medicines Inspector at Department of Health in UK, said that Process Validation is nothing more than common sense – it is simply proving that a process does what it is designed to do.

The major challenge for the pharmaceutical industry is to streamline and/or simplify validation without sacrificing the product quality.

So here we are trying to build in quality in Sotalol Hydrochloride 40 mg tablets manufactured under specified environmental conditions by performing Prospective Process Validation and identifying various Critical Process Parameters (**Table 3**) which needs to be validated in order to have the desired quality products.

Sotalol Hydrochloride is a beta-adrenoceptor antagonist; class II and class III antiarrythmic. It is white or almost white powder. It is freely soluble in water, soluble in alcohol, practically insoluble in methylene chloride. pH is 4-5 and should be stored protected from light [3].

It is not metabolized and excreted unchanged in urine. Its half life is 8±3 hrs. Minimum dose is 80 – 160 mg in two divided doses per day. Complication ranges from nausea, fatigue to torsades de pointes [4].

**MATERIALS AND METHOD**: Materials used in the manufacturing of tablets are shown in **Table 1** and the equipments used in the production are mentioned in **Table 2**.

**TABLE 1: CONTENTS OF FORMULATION**

| STAGE | INGREDIENTS | QUANTITY (mg/tab) |
|---|---|---|
| DRY MIXING | Sotalol Hydrochloride | 40 |
| | Maize Starch | 10.45 |
| | Calcium hydrogen phosphate dihydrate | 17.50 |
| BINDER SOLUTION | Povidone K-30 | 2 |
| | Purified water | 3.96 L |
| LUBRICATION | Sodium starch glycollate | 2 |
| | Talc | 2.25 |
| | Magnesium stearate | 1.75 |

**TABLE 2: EQUIPMENTS USED IN THE PRODUCTION.**

| STAGE | EQUIPMENT | CAPACITY |
|---|---|---|
| Sifting | Vibrosifter | -- |
| Dry mixing/Granulation | Rapid Mixer Granulator | 400 L |
| Binder preparation | Paste Kettle | 20 L |
| Drying | Fluidized Bed Drier | 60 kg |
| Sizing | Multimill | -- |
| Lubrication | Cage Blender | 350 L |
| Compression | Compressing machine | 31 station |
| | De duster | -- |

## Methodology:

- After dispensing Sotalol Hydrochloride, Maize Starch, Calcium hydrogen phosphate dihydrate, these are sifted using Vibrosifter having 20# mesh.
- These are then dry mixed together in the RMG, at interval of 5 min for 15 min.
- Samples are taken at each interval in order to see the uniformity of mixing. Based on the results the appropriate mixing time will be considered for the next two validation batches. Locations for sampling are shown in **Fig. 1**. The amount taken from each location is three times that of the standard average weight of the tablet, and composite sample of 5 gm from all the different locations.
- Then binder solution is prepared by using the paste kettle for granulating the dry mixture.
- This binder solution is then sprayed over the dry mix with the help of peristaltic pump at 30 rpm and the impeller of RMG moving at 75 rpm.
- As the granulation proceeds, there is increase in the amperage and the end point amperage is determined when the desired granules are obtained.
- The entire granulation process takes place for about 30 min.

- After that the granules are discharged from the RMG and collected in the FBD trolley.
- These are then dried in the FBD with the inlet temperature between 40 – 45 °C.
- Drying takes place for 10 min or until the specified LOD is obtained.
- Samples are taken from different locations which are shown in **Fig. 2**, and LOD is determined. The sample quantity is three times that of the standard average weight of the tablet, and composite sample of 5 gm from all the different locations.
- These dried granules are then sifted using vibrosifter having 50# mesh.
- The oversized granules are then sized using the Multimill having 0.5 mm screen.
- All these retained and passed granules are then taken for blending with talc and sodium starch glycollate. These are mixed in Cage Blender for 15 min.
- After this, magnesium stearate is added and mixed for 5 min.
- Samples are taken from different locations as shown in **Fig. 3**, in order to see the uniformity in mixing and also to measure the bulk and tapped density. The sample quantity of composite sample is 25 gm.
- After this the final lubricated blend is compressed into tablets using the 31 station compression machine.
- For the first batch we are compressing the blend at different rpm, in order to select an appropriate rpm for compressing the remaining first batch and second and third batch.
- Samples are taken at different hopper level in order to verify there is uniformity in the blend throughout the hopper fill.
- Samples taken at the start, middle, end of the compression of all the three batches are tested for various physical and IPQC parameters.
- These tablets are then stored at specified environment prior to packing.

**TABLE 3: THE CRITICAL PROCESS PARAMETERS IDENTIFIED**

| Process stage | Critical process parameters | Measured response | Acceptance criteria |
|---|---|---|---|
| Sifting | -- | Sieve integrity (before and after) | Complies |
| Dry Mixing | Speed of mixer blade, Load size, Time of mixing | Content Uniformity | Assay: 565.12 – 612.21 mg/gm (96-104%) |
| Granulation | Chopper speed, Impeller speed, Binder Quantity, Binder addition rate, End point amperage, Total granulation time | Binder quantity, Amperage | As per requirement 14 – 18 A |
| Drying | Outlet temperature, Inlet temperature, Drying load, Total drying time | LOD | 3 – 5 % |
| Lubrication | Speed of mixer, Time of mixing, Blend load | Blend Uniformity, Tapped density, Bulk density | Assay: 512.0 – 554.67 mg/gm (96-104%) |
| Compression | Temperature of area, Humidity of area, Compression force, Filling depth, Hopper fill Compressing speed | Appearance, Weight of 20 tablets, Average weight, Uniformity of weight, Thickness Hardness, Diameter, Friability Disintegration, Dissolution, Assay | *, 1.5 gm ± 4%, 75 mg ± 4%, ± 7.5% of avg.wt, 5.9 – 6.1 mm, 30 – 80 N, 1.9 – 2.9 mm, NMT 1%, NMT 10 min, NLT 70%, 96 – 104% (38.4 – 41.6 mg/tab) |

*Appearance: Round white to off white flat bevel edged tablet with break line on one side and SOT 40 imprinted on other side

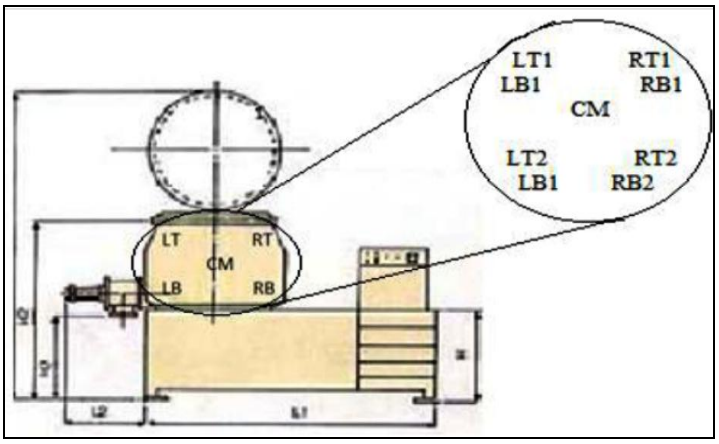


**FIG. 1: RAPID MIXER GRANULATOR SAMPLING LOCATIONS**

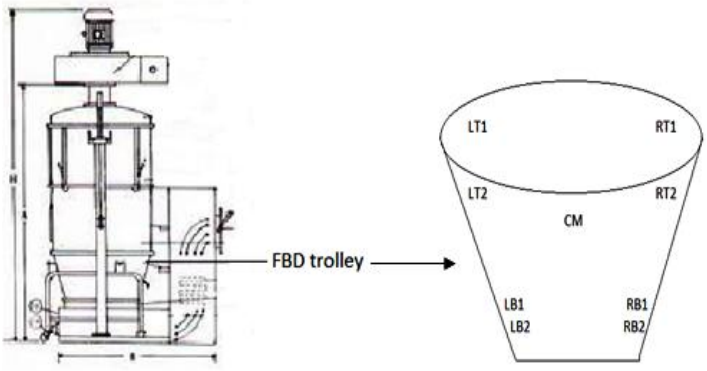


**FIG. 2: FBD TROLLEY SAMPLING LOCATIONS**

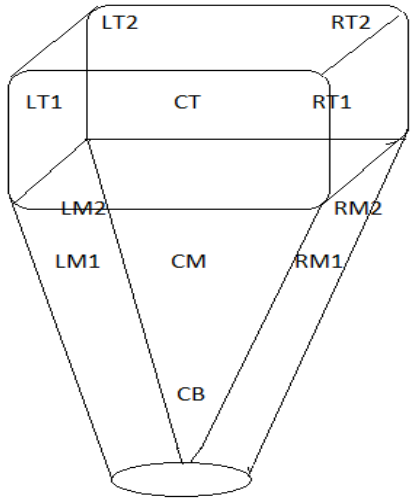


**FIG. 3: CAGE BLENDER SAMPLING LOCATIONS**

**TABLE 4: ABBREVATIONS OF SAMPLING LOCATIONS**

| | |
|---|---|
| **RT** | Right Top |
| **RB** | Right Bottom |
| **RM** | Right Middle |
| **LT** | Left Top |
| **LB** | Left Bottom |
| **LM** | Left Middle |
| **CT** | Centre Top |
| **CB** | Centre Bottom |
| **CM** | Centre Middle |

**RESULTS AND DISCUSSION**: The first batch is experimented for various parameters. Based on the results obtained, the second and third batch is operated at the selected, appropriate parameter in order to see the consistency in the results.

**For Batch 1:**

**Dry mixing:** The first batch is dry mixed at 5, 10, 15 min interval. The results are shown in **Table 5**.

**TABLE 5: DRY MIXING RESULT FOR FIRST BATCH**

| Location | Assay results (%) | | |
|---|---|---|---|
| | 5 min | 10 min | 15 min |
| Right Top1 | 102.6509 | 103.553 | 102.0733 |
| Right Bottom1 | 96.67978 | 102.887 | 102.0971 |
| Left Top1 | 103.7194 | 102.391 | 102.002 |
| Left Bottom1 | 103.7041 | 103.0841 | 101.9901 |
| Right Top2 | 103.7551 | 101.9459 | 102.267 |
| Right Bottom2 | 99.95159 | 103.8536 | 103.3202 |
| Left Top2 | 103.6906 | 103.3236 | 102.4624 |
| Left Bottom2 | 96.47592 | 96.18544 | 102.7342 |
| Centre Middle | 103.7228 | 103.6549 | 102.9261 |
| Composite | 103.4867 | 102.1345 | 103.3508 |
| **SD** | **2.980481** | **2.245378** | **0.530842** |
| **%RSD** | **2.92825** | **2.194868** | **0.517782** |

So as the 15 min mixture showed the %RSD within the specification [6], 15 min time period for dry mixing was considered to be optimum and the following second and third batch will be dry mixed for15 min.

**Drying:** The batch was dried into two portions for 10 min. Whether further drying is required or not is determined from the LOD results shown in **Table 6**. LOD should be within 3 – 5 %

**TABLE 6: DRYING RESULTS FOR FIRST BATCH**

| Location | LOD (Trolley 1) | LOD (Trolley 2) |
|---|---|---|
| Right Top | 3.18 % | 3.02 % |
| Right Bottom | 3.32 % | 3.11 % |
| Left Top | 3.35 % | 3.14 % |
| Left Bottom | 3.88 % | 3.24 % |
| Center Middle | 3.31 % | 3.44 % |
| Composite | 3.40 % | 3.16 % |

As the results were within limit, the 10 min drying time was selected and the next two batches will be dried for this period.

**Lubrication**: Lubricating the blend with Magnesium Stearate for 5 min. The samples are then assayed in order to see the uniformity of blend. Results are shown in **Table 7** (limit: 96 – 104 %).

**TABLE 7: LUBRICATION RESULTS FOR FIRST BATCH.**

| Location | Assay |
|---|---|
| Right Top1 | 101.2253 % |
| Right Top2 | 101.7822 % |
| Right Middle1 | 101.4016 % |
| Right Middle2 | 102.8041 % |
| Left Top1 | 102.8059 % |
| Left Top2 | 102.5059 % |
| Left Middle1 | 101.7916 % |
| Left Middle2 | 101.2759 % |
| Centre Top | 101.8309 % |
| Centre Middle | 101.7128 % |
| Centre Bottom | 101.2797 % |
| Composite | 102.5509 % |
| SD | 0.600751 |
| %RSD | 0.589469 |

The blend showed uniformity and so the following batches will be lubricated for the same time period.

**Compression at different speed and different hopper level**: The blend is compressed at different rpm and based on the results obtained (shown in **Table 8**); particular rpm will be selected for further compression. The results of compressing the blend at different hopper levels are shown in **Table 9**.

From the results given below; we have fixed the critical process parameters and the second and third batch were operated at these parameters in order to see the consistency in results.

By fixing the challenging variables mentioned above, the remaining batches are continued to process at these fixed parameters and are analysed for consistency in the product manufactured.

15 min dry mixing time is fixed and the assay results of the batches shown in **Table 10** indicates it to be sufficient enough to have a uniform mixture. All the batches dried for 10 min showed LOD results within the acceptable limit. Results are shown in **Table 11**.

All three batches were lubricated with Magnesium stearate. **Table 12** dictates the uniformity in content.

This blend when was compressed into tablets, tablets with desired properties were manufactured and the results are shown in **Table 13 – 15**.

**TABLE 8: COMPRESSION RESULTS OF FIRST BATCH AT DIFFERENT RPM**

| | 22 rpm | 25 rpm | 28 rpm |
|---|---|---|---|
| **Weight of 20 tab** | 1.539 g | 1.526 g | 1.529 g |
| **Avg. wt** | 76.9 mg | 76.45 mg | 76.3 mg |
| **Uniformity of wt** | ± 5.76 % | ± 5.73 % | ± 5.72 % |
| **Minimum deviation** | 0% (75 mg) | 1.33% (74 mg) | 1.33 % (74 mg) |
| **Maximum deviation** | 5.33 % (79 mg) | 4 % (78 mg) | 5.33 % (79 mg) |
| **Thickness** | 2.02 – 2.09 mm | 2.02 – 2.13 mm | 2.05 – 2.10 mm |
| **Diameter** | 5.99 – 6.04 mm | 6.01 – 6.03 mm | 6.00 – 6.02 mm |
| **Hardness** | 30 – 45 N | 33 – 46 N | 32 – 51 N |
| **Disintegration Time** | 5 min 18 sec | 4 min 56 sec | 5 min 15 sec |
| **Friability** | 0.16 % | 0.168 % | 0.3604 % |

Results of 25 rpm were more desirable and so 25 rpm was selected for compressing.

**TABLE 9: COMPRESSION RESULTS OF FIRST BATCH AT DIFFERENT HOPPER LEVEL**

| | 99% hopper level | 66% hopper level | 33% hopper level |
|---|---|---|---|
| **Weight of 20 tab** | 1.526 g | 1.541 g | 1.522 g |
| **Avg. wt** | 76.45 mg | 77.2 mg | 79.9 mg |
| **Uniformity of wt** | ± 5.67 % | ± 5.79 % | ± 5.99 % |
| **Minimum deviation** | 1.33 % (74 mg) | 0 % (75 mg) | 2.66 % (73 mg) |
| **Maximum deviation** | 4 % (78 mg) | 4 % (78 mg) | 4 % (78 mg) |
| **Thickness** | 2.0 – 2.08 mm | 2.01 – 2.13 mm | 2.04 – 2.09 mm |
| **Diameter** | 6.01 – 6.04 mm | 6.01 – 6.04 mm | 6.01– 6.04 mm |
| **Hardness** | 32– 45 N | 33 – 46 N | 32 – 44 N |
| **Disintegration Time** | 5min 17 sec | 4min 56 sec | 5 min 01 sec |
| **Friability** | 0.147 % | 0.168 % | 0.39 % |
| **Assay** | 101.185 % | 103.26 % | 102.15 % |

The results were within the desired specifications and so we can say that the blend was homogeneous throughout the compression process

**TABLE 10: RESULTS OF DRY MIXING AT 15 MIN.**

| Location | Assay results (%) | | |
|---|---|---|---|
| | Batch 1 | Batch 2 | Batch 3 |
| Right Top1 | 102.0733 | 103.2862 | 102.3978 |
| Right Bottom1 | 102.0971 | 102.9312 | 103.1181 |
| Left Top1 | 102.002 | 103.0331 | 102.7732 |
| Left Bottom1 | 101.9901 | 102.5558 | 102.4199 |
| Right Top2 | 102.267 | 102.9227 | 102.0428 |
| Right Bottom2 | 103.3202 | 101.9408 | 103.2455 |
| Left Top2 | 102.4624 | 102.2279 | 103.13 |
| Left Bottom2 | 102.7342 | 103.0824 | 103.1724 |
| Centre Middle | 102.9261 | 102.7138 | 102.7155 |
| Composite | 103.3508 | 102.7953 | 103.1215 |
| **SD** | **0.530842** | **0.409509** | **0.413147** |
| **%RSD** | **0.517782** | **0.398553** | **0.401841** |

All the batches showed uniformity in content

**TABLE 11: RESULTS OF DRYING FOR 10 MIN.**

| Location | LOD results (%) | | | | | |
|---|---|---|---|---|---|---|
| | Batch 1 | | Batch 2 | | Batch 3 | |
| | Trolley 1 | Trolley 2 | Trolley 1 | Trolley 2 | Trolley 1 | Trolley 2 |
| Right Top | 3.18 | 3.02 | 3.06 | 3.07 | 3.05 | 3.04 |
| Right Bottom | 3.32 | 3.11 | 3.04 | 3.02 | 3.03 | 3.07 |
| Left Top | 3.35 | 3.14 | 3.04 | 3.05 | 3.05 | 3.05 |
| Left Bottom | 3.88 | 3.24 | 3.03 | 3.05 | 3.03 | 3.05 |
| Center | 3.31 | 3.44 | 3.05 | 3.03 | 3.04 | 3.06 |
| Middle | | | | | | |
| Composite | 3.40 | 3.16 | 3.02 | 3.04 | 3.04 | 3.05 |

All the batches were within the desired LOD range

**TABLE 12: RESULTS OF LUBRICATION**

| Location | Assay results (%) | | |
|---|---|---|---|
| | Batch 1 | Batch 2 | Batch 3 |
| Right Top1 | 101.2253 | 101.0603 | 102.6297 |
| Right Top2 | 101.7822 | 102.6803 | 102.8078 |
| Right Middle1 | 101.4016 | 102.0897 | 101.7822 |
| Right Middle2 | 102.8041 | 102.5341 | 101.7634 |
| Left Top1 | 102.8059 | 102.1328 | 101.7147 |
| Left Top2 | 102.5059 | 102.4084 | 102.4853 |
| Left Middle1 | 101.7916 | 102.9559 | 102.6616 |
| Left Middle2 | 101.2759 | 102.5078 | 101.2422 |
| Centre Top | 101.8309 | 102.9991 | 102.8678 |
| Centre Middle | 101.7128 | 101.8028 | 101.9753 |
| Centre Bottom | 101.2797 | 101.8647 | 102.7647 |
| Composite | 102.5509 | 102.4647 | 102.6766 |
| **SD** | **0.600751** | **0.543163** | **0.55024** |
| **%RSD** | **0.589469** | **0.530994** | **0.53797** |

All the batches showed blend uniformity.

## Results of Compression:

**TABLE 13: FIRST BATCH COMPRESSION RESULTS**

| | Start | Middle | End |
|---|---|---|---|
| **Weight of 20 tab** | 1.519 g | 1.507 g | 1.516 g |
| **Avg. wt** | 75.9 mg | 75.35 mg | 75.8 mg |
| **Uniformity of wt** | ± 5.69 % | ± 5.65 % | ± 5.685 % |
| **Minimum deviation** | 1.33 % (74 mg) | 0 % (75 mg) | 1.33 % (74 mg) |
| **Maximum deviation** | 4 % (78 mg) | 5.33 % (79 mg) | 1.33 % (76 mg) |
| **Thickness** | 2.03 – 2.08 mm | 2.02 – 2.07 mm | 2.04 – 2.09 mm |
| **Hardness** | 35– 49 N | 40 – 50 N | 32 – 43 N |
| **Disintegration Time** | 4 min 13 sec | 4 min 11 sec | 5 min 01 sec |
| **Friability** | 0.168% | 0.147 % | 0.16 % |
| **Assay** | 101.57 % | 100.2% | 102.57% |
| **Dissolution** | 99.89 % | 101.67 % | 99.18 % |

**TABLE 14: SECOND BATCH COMPRESSION RESULTS.**

| | Start | Middle | End |
|---|---|---|---|
| **Weight of 20 tab** | 1.514 g | 1.513 g | 1.508 g |
| **Avg. wt** | 75.7 mg | 75.7 mg | 75.45 mg |
| **Uniformity of wt** | ± 5.677 | ± 5.677 | ± 5.658 |
| **Minimum deviation** | 0 % (75 mg) | 1.33 % (74 mg) | 1.33 % (74 mg) |
| **Maximum deviation** | 4% (78 mg) | 4 % (78 mg) | 2.66 % (77 mg) |
| **Thickness** | 2.0 – 2.07 mm | 2.01 – 2.07 mm | 2.02 – 2.06 mm |
| **Hardness** | 30– 42 N | 33 – 55 N | 38 – 45 N |
| **Disintegration Time** | 4 min 57 sec | 5 min 19 sec | 5 min 26 sec |
| **Friability** | 0.305 % | 0.306 % | 0.261 % |
| **Assay** | 99.62% | 99.57% | 99.25% |
| **Dissolution** | 99.54 % | 100.32 % | 99.01 % |

**TABLE 15: THIRD BATCH COMPRESSION RESULTS.**

| | Start | Middle | End |
|---|---|---|---|
| **Weight of 20 tab** | 1.508 g | 1.510 g | 1.498 g |
| **Avg. wt** | 75.40 mg | 75.5 mg | 74.85 mg |
| **Uniformity of wt** | ± 5.655 % | ± 5.662 % | ± 5.613 % |
| **Minimum deviation** | 1.33 % (74 mg) | 1.33 % (74 mg) | 1.33 % (74 mg) |
| **Maximum deviation** | 4 % (78 mg) | 2.66 % (77 mg) | 2.66 % (77 mg) |
| **Thickness** | 2.04 – 2.09 mm | 2.02 – 2.10 mm | 2.00 – 2.07 mm |
| **Hardness** | 34– 45 N | 32 – 51 N | 38 – 53 N |
| **Disintegration Time** | 4 min 13 sec | 4 min 01 sec | 4 min 11 sec |
| **Friability** | 0.289 % | 0.227 % | 0.23 % |
| **Assay** | 99.60% | 99.60% | 99.57 % |
| **Dissolution** | 99.78 % | 101.32 % | 99.9 % |

All the three batches were within the acceptance criteria limit.

**CONCLUSION**: Based on the results obtained, it was concluded that three validation batches comply with the approved In-process and finished specifications defined for the product.

The overall review of results shows consistency and reproducibility within and between batches.

These results demonstrate that the manufacturing process was under control throughout all stages, within and between batches.

Hence it was concluded that the manufacturing process and the equipments adopted were robust enough and produce product meeting predetermined standards and quality attributes.

Therefore the Process stands Validated.

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