# *Development of a Generic Pharmaceutical Solid Dosage Form Using Quality by Design (QbD)*

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***Abstract* —** *The Pharmaceutical Generic Sector has been growing over the past years and it is expected to surpass brand drugs in sale over next years. The FDA now recommends Quality by Design to develop Generic Drugs. The present work was aim to develop a Generic Version of Polytripcin Immediate Release Tablet (Polytripsin is a given name to protect the identity of the real product) using Quality By Design, equivalent to the Reference Listed Drug (RLD) Brand Polytripcin 600 mg. The physical properties (Flow and Particle Size Distribution) of the Active Substance were evaluated. Two Formulations were proposed based on the physical characteristic of the Active Drug. The formulations were evaluated for blend and tablet physical characterization. Formulation # 2 had a Dissolution Profile Similarity Factor (F2) of 65, indicating similarity to the RLD. A Design of Experiments (DOE) for Process Improvement was also performed to correct flow problems during compression of the blends.*

***Key Terms* —** *Design of Experiment, Generic Drug Pharmaceutical Development, Quality by Design, Reference Listed Drug.*

## INTRODUCTION

Just a few years ago generic drug makers owned just a small portion of the pharmaceutical drug market. Today generics are a large segment of the pharmaceutical industry and are on track to surpass branded drugs in sales value as well as sales volume within a few years, according to industry analysts [1].

In the present work we aim to develop Generic Polytripsin Tablets, 600 mg a generic version of the Reference Listed Drug (RLD), Brand's Polytripsin Tablets, 600 mg. The RLD is an antibiotic, immediate release (IR) tablet indicated for the treatment and prevention of microbial infections. Quality by Design (QBD) is going to be used to demonstrate that Generic Polytripsin Tablets 600 mg are equivalent to Brand Polytripsin Tablets 600 mg.

### Reference Listed Drug (RLD)

The Reference Listed Drug is an approved drug product to which generic versions are compared to show equivalence. A drug company seeking approval by Food and Drug Administration (FDA) to market a generic equivalent must refer to the RLD in its Abbreviated New Drug Application [2].

For Generic Polytripsin Tablets 600mg, the RLD is Brand's Polytripsin Tablets 600mg approved in the United States in 2001 (NDA 12345678). The RLD is an unscored immediate release (IR) tablet with no cosmetic coating. The tablet needs to be swallowed "as is" without any intervention. Thus, the proposed generic product will also be an unscored IR tablet with no cosmetic coating.

### Composition of the RLD

Based on RLD Labeling and Patent Literature the following table shows the composition of Brand Polytripsin Tablets:

**Table 1**
**Composition of the RLD**

| Ingredients | Function | mg per Tablet | Unit (% w/w) |
|---|---|---|---|
| Polytripsin Trihydrate | Active | 630* | 58.33 |
| Pregelatinized Starch | Binder | 65 | 6.02 |
| Dibasic Calcium Phosphate | Diluent | 332 | 30.74 |
| Sodium Starch Glycolate | Disintegrant | 22 | 2.04 |
| Magnesium Stearate | Lubricant | 28 | 2.59 |
| Sodium Lauryl Sulfate | Lubricant | 3 | 0.28 |
| Total | | 1080 | 100 |

*Based on theoretical potency.

### Active Pharmaceutical Ingredient (API)

The active substance of the Generic Polytripsin IR Tablets is Polytripsin Trihydrate USP, an established active substance described in the United States Pharmacopoeia (USP). Polytripsin, USP, as the trihydrate, is a white to off-white crystalline powder.

## LITERATURE REVIEW

### Composition of a Pharmaceutical Solid Dosage (Tablet)

A Pharmaceutical Solid Dosage Form such as a tablet is composed of the Active Pharmaceutical Ingredient and Pharmaceutical Acceptable Excipients. Excipients are inactive substances used as carriers for the active ingredients of a medication. Although technically "inactive" from a therapeutic sense, pharmaceutical excipients are critical and essential components of a modern drug product. They are classified by the functions they perform in a pharmaceutical dosage form [3]. Principal excipient classifications (functions) that are going to be used in the development of Generic Polytripsin IR Tablets 600 mg are the following:

**Diluent**: Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules [4]. For Polytripsin Tablets the preferred diluents are Silicified Microcrystalline Cellulose and Microcrystalline Cellulose.

**Disintegrant:** Excipient used to aid in the breakup of the compacted mass when it is put into a fluid environment [4]. This is important for immediate release products where rapid release of drug substance is required. For Polytripsin Tablets the preferred disintegrant is Crosscarmellose Sodium.

**Glidant:** Used in tablet and capsule formulations to improve flow properties of the powder mixture [4]. For Polytripsin Tablets the preferred glidant is Colloidal Silicon Dioxide.

**Surfactant:** Used to improve solubility properties of a drug product [4]. For Polytripsin Tablets the preferred surfactant is Sodium Lauryl Sulfate.

**Lubricant:** Used To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dies [4]. Prevent sticking to punch faces or product contact equipment parts. For Polytripsin Tablets the preferred lubricants are Magnesium Stearate and Talc.

### Physical Characterization of Pharmaceutical Powders

**Flow Properties**: The physical properties of pharmaceutical powders are of importance in the pharmaceutical industry. The knowledge of their flow properties is of critical significance in operations such as blending, tablet compression, capsule filling, transportation, and in scale-up operations. One way of characterizing flow properties of a powdered material is by bulk-Tapped density measurements.

Bulk Density: It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume [5]

Tap Density: Is the apparent density of a volume of powder obtained when its container is tapped [5].

Carr's Compressibility Index is a simple test to evaluate flowability by comparing both the bulk and Tapped densities and the rate of packing down. Refer to table 2. A useful empirical guide to flow is given by Carr's compressibility index: Compressibility Index(%)=[(tapped density−initial density)/tapped density]×100 [5].

**Table 2**
**Scale of Flowability**

| Compressibility Index (%) | Flow Character |
|---|---|
| ≤10 | Excellent |
| 11–15 | Good |
| 16–20 | Fair |
| 21–25 | Passable |
| 26–31 | Poor |
| 32–37 | Very poor |
| >38 | Very, very poor |

A flow character of at least passable it's recommended for a powder blend to be amenable for a compression process.

**Particle Size Distribution (PSD):** Particle size of a powder can affect the formulation's performance, appearance and stability. With Particle Size measurements you can evaluate the "Processability" of a powder (drug substance, excipient or blend). A PSD analysis is a procedure used to assess the particle size distribution of a granular material.

## Physical Characterization of Pharmaceutical Tablets

**Tablet Hardness:** Measurement of the mechanical integrity of tablets. The force required to cause the tablets to fail (i.e., break) in a specific plane [5]. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture.

**Tablet Friability:** Employed test to study the ability of tablets to withstand mechanical stresses; determines their resistance to chipping and surface abrasion by tumbling them in a rotating cylinder [5].

**Dissolution Testing:** In vitro drug release characterization test where the product is a solid dosage form. Dissolution Testing helps to find the relationship between an in vitro characteristic of a dosage form, and its in vivo performance. Dissolution testing is required for all solid oral Pharmacopeial dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect. The Dissolution Similarity Factor (F2) is used to compare two dissolution profiles of a reference and a test. FDA has set a public standard of F2 value between 50-100 to indicate similarity between two dissolution profiles [6].

## Manufacturing Processes of Pharmaceutical Tablets

Tablet blends may be dry-granulated or wet granulated. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and the chosen excipients, for example particle size, blending, compatibility, density and flow ability.

Wet granulation is the process where a granulating liquid is used to facilitate the agglomeration process. Wet granulation has been and continues to be the most widely used agglomeration process. Typically wet massing of pharmaceutical powder is carried out in the high shear mixture before wet screening. The granules are dried in fluid bed dryer or oven. The advantages of wet granulation include improvement of the cohesiveness and compactability of powders, increase in density, good distribution providing uniform content and prevention of segregation of components [7].

Dry granulation is a process in which granulates are formed by a compaction step that is followed by sizing the compacts into particles that can be processed easily. It is often used to improve flow properties and/ or densify the formulation which can facilitate further manufacturing processes such as tableting, encapsulation and powder filling. In dry granulation a granulating liquid is not used and no drying step is required. [7]

Direct compression is a tableting process in which tablets are compressed directly from powder blends containing an active ingredient. In direct compression, all the ingredients required for tableting, including the active ingredient and processing excipients, are incorporated into a free flowing blend which is then tableted. The active ingredient, excipients, and other substances are blended and then compressed into tablets. Tablets are typically formed by pressure being applied to a material in a tablet press [7].

Pharmaceutical manufacturers prefer the use of direct compression, over wet and dry granulation processes, because of its shorter processing times and cost advantages. However, direct compression is generally limited to those situations in which the active ingredient has physical characteristics suitable for forming pharmaceutically acceptable tablets [7].

For Polytripsin tablets, granulation is desired, with dry granulation being the most preferred process to wet granulation methods because of shorter processing times and cost advantages. Polytripsin, generally, is not considered to be amenable to the production of directly compressible tablets of Polytripsin formulations because of its high active dose.

## METHODOLOGY

### Raw Material Procurement

Polytripsin Trihydrate USP, Silicified Microcrystalline Cellulose, Microcrystalline Cellulose, Talc, Crosscarmellose Sodium, Magnesium Stearate and Sodium Lauryl Sulfate were procured commercially.

### Active Pharmaceutical Ingredient and Final Blend Powder Characterization

The Bulk-Tap Density and Carr's Compressibility Index of the active substance Polytripsin Trihydrate USP and the Final Blends were measured by taking an initial density of a sample in a 250 ml graduated cylinder. The sample was tapped 10, 500 and 1250 times on a Quantachrome Autotap Tap Density Tester and the tapped density of the sample in the 250 ml graduated cylinder was taken. The procedure is described in United States Pharmacopeia (USP) <616> Bulk Density and Tapped Density of Powders.

The Particle Size Distribution of the active substance and final blends was determined by light scattering. In light scattering the particles scatter the light, smaller particles scatter the light at larger angles than bigger particles. The scattered light can be measured by a series of photo-detectors placed at different angles. This is known as the diffraction pattern for the sample. The diffraction pattern can be used to measure the size of the particles. A Malvern MasterSizer 3000 was used for the PSD analyis. The particle size distribution of 90% ( $d_{90}$), 50% ($d_{50}$) and 10% ($d_{10}$) was recorded.

### Preparation of Polytripsin Tablets

The proposed formulations for Polytripsin Immediate Release Tablets are described in the following table:

**Table 3**
**Proposed Formulations**

| Function | Formula 1 Ingredients | Formula 2 Ingredients | mg per tablet |
|---|---|---|---|
| Active | Polytripsin Trihydrate | Polytripsin Trihydrate | 630* |
| Diluent | Silicified Microcrystalline Cellulose | Microcrystalline Cellulose | 225 |
| Glidant | Colloidal Silicon Dioxide | Colloidal Silicon Dioxide | 22 |
| Disintegrant | Croscarmellose Sodium | Croscarmellose Sodium | 45 |
| Lubricant | Talc | Talc | 122 |
| Lubricant | Magnesium Stearate | Magnesium Stearate | 33 |
| Lubricant | Sodium Lauryl Sulfate | Sodium Lauryl Sulfate | 3 |
| Total | -- | -- | 1080 |

***Based on theoretical potency.**

The Polytripsin tablets were prepared by dry granulation method (Roller Compactor). Blends of 2 Kg of each formulation were be prepared. The quantities of the materials are described in table 4.

**Table 4**
**Material Quantities**

| | Qty per tablet Quantity (mg) | Unit (% w/w) | 2 Kg Blend Quantity(Kg) |
|---|---|---|---|
| **Active** | 630.0 | 58.33 | 1.17 |
| **Diluent** | 224.2 | 20.76 | 0.42 |
| **Glidant** | 22.2 | 2.06 | 0.04 |
| **Disintegrant** | 44.5 | 4.12 | 0.08 |
| **Lubricant** | 122.4 | 11.33 | 0.23 |
| | 33.4 | 3.09 | 0.06 |
| | 3.3 | 0.31 | 0.01 |
| **Total** | 1080.0 | 100.00 | 2.00 |

Both Formulations were prepared using the same process. The first step of the process was to combine the Talc with the Colloidal Silicone Dioxide in PK-Blender with a V-Shaped shell of 4 Qt. The materials were mix for 1 minute at 25 rpm. Then the blend was passed thru a Quadro Comil, Model L1A with a round hole screen of 0.457 mm. The blend was collected in a polyethylene bag and weighted.

The second step was the dry granulation mix. A layer of 50% of the Polytripsin was added to a PK Blender with a V-shaped shell of 16 Qt. The

next layer added was the sieved Talc-Colloidal Silicon Dioxide blend, 75% of the Magnesium Stearate, Sodium Lauryl Sulfate, **the Diluent** and 50% of the Crosscarmellose Sodium. The final layer was the remaining Polytripsin. The materials were blended for 2 minutes at 25 rpms. The blend was unloaded into a polyethylene bag.

The blend was then roller compacted using a Vector Corporation TF-Mini Roller Compactor. The parameters of the roller compactor were:

- Roll Pressure: 325 psi
- Roll Speed: 2.0 rpm
- Screw Speed: 8.0 rpm

The Polytripsin compacted sheet of material was collected in a polyethylene bag. The next step was to mill the compacted sheet. The equipment used to mill the compacted sheet into granules was a Quadro Comil, Model L1A with a round hole screen of 0.84 mm. After milling the dry blend was collected in a polyethylene bag.

The dry blend was added back the PK blender with the V-Shaped Shell of 16qt. The amounts of magnesium stearate and crosscarmellose sodium for the final blend were adjusted based on loss of material during the Dry Granulation Process and the theoretical weight of the blend. After the magnesium stearate and crosscarmellose sodium were added, the materials were blended for 1 minute at 25 rpm. This is the final blend.

The final blend was then compressed into tablets in a Riva Piccola Tablet Press of 8 stations with a 0.40" x 0.75" Oval tooling. Four stations of the tablet press were used. The target weight was 1080 (±60) mg. The target Hardness was no less than 10 kp and the target thickness was 7.0 (±0.1) mm.

Tablets were compressed at the following parameters:

- Compression Force Set Point = 5 (24 kN)
- Feeder Set Point = 5
- Turret Set Point = 3 (29 RPM)

**Characterization of Tablets**

**Tablet Hardness:** The tablet crushing strength was measured with a Dr Schleuniger tablet hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break was recorded.

**Tablet Friability:** Tablet strength was tested by Erweka Friability Tester. Pre-weighed tablets were given 200 revolutions in 8 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.

**Tablet Weight:** Twenty (20) tablets were randomly selected from the two (2) formulations. The tablets were weighed individually on electronic balance (Mettler Toledo: Model PG203-S).

**Dissolution Profile:** Drug release profile of the two formulations and the RLD were evaluated in vitro using a dissolution test apparatus 2 (paddle type at 75 rpm) method (TDT-08L, Electrolab) .The dissolution of the Polytripsin tablet is performed into pH 6.0 phosphate buffer, 900mL. Samples (5 ml) were withdrawn at 10 minute intervals for 50 minutes and filtered. The samples were analyzed by a Waters System HPLC (High Performance Liquid Chromatography). A sample of six (6) tablets was taken from each formulation.

**Comparison to the RLD**

**Similarity Factor ($f_2$):** Two profiles are considered identical when $f_2$=100. A public standard of $f_2$ value between 50-100 to indicate similarity between two dissolution profiles [6]. Equation 1 describes the Similarity Factor:

$$f_2 = 50 \cdot \log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\} \quad (1)$$

$R_t$ and $T_t$ are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. The number of time points (n) must be similar between the reference and the test product. The dissolution profiles of the two (2) formulations were compared to the RLD using the similarity factor ($f_2$). The formulation with the highest value of $f_2$ will be chosen as the preferred formulation.

### Process Improvement

During compression erratic flow problems (rathole) were observed in both formulations, although the problems were more noticeable in Formulation # 1. This happens when the powder is too fine and cohesive. This may indicate that a screen with a bigger aperture should be used during milling of the compacted sheet.

A design of experiments was performed to study the effects of the: Screw Speed, Roll Pressure and Mill Screen Size on the flow ability of the blend (compressibility index) of formulation 2 after milling. A two level Full Factorial Design with 3 Factors was used. Samples of each combination were taken and analyzed for flow properties (Carr Index). The combination that gives the best compressibity index is going to be determined. The program used to create and analyze the DOE was Mini Tab 16. The results of the DOE were analyzed using Analysis of Variance (ANOVA) and the main effects plots. The following table 5 summarizes the DOE:

**Table 5**
**Process Improment DOE**

| Factors | Screw Speed | Roll Pressure | Mill Screen Size |
|---|---|---|---|
| Levels | 6.0 rpm | 300 psi | 1.10 mm |
| | 8.5 rpm | 350 psi | 1.65 mm |
| Replicates | 2 | 2 | 2 |
| Response | Carr Index | | |

A blend was prepared at the best combination determined by the DOE. This blend is going to be compressed and analyzed for PSD and Dissolution profile.

## RESULTS AND DISCUSSION

The first step was to analyze data for the Active Pharmaceutical Ingredient Characterization. The results characterization of the flow properties of Polytripsin Trihydrate USP is shown in table 6. Based on the results of the Carr Index, Polytripsin Trihydrate has very poor flowability. For a compression process it is preferred a flow character of passable. This result indicates that a granulation process with good flowing excipients is required to improve flow properties and avoid flow problems in the tablet press.

**Table 6**
**API Flow Properties**

| Sample | Bulk Density (g/mL) | Tap density (g/mL) | Carr Index | Flow Character |
|---|---|---|---|---|
| Polytripsin Trihydrate | 0.183 | 0.277 | 33.818 | Very Poor |

The results of the Particle Size Distribution of the Polytripsin Trihydrate USP are shown in table 7. Based on the results Polytripsin has a median particle size of 9.10 µm. This result indicates that Polytripsin is a very fine powder. Fine powder are cohesive and can lead to sticking and flow problems in manufacturing processes such a Roller Compaction and Compression. To prevent sticking excipients such as talc and magnesium stearate were added to the formulation.

**Table 7**
**API Particle Size Distribution**

| Sample | $D_{90}$ (µm) | $D_{50}$ (µm) | $D_{10}$ (µm) |
|---|---|---|---|
| Polytripsin Trihydrate | 20.6 | 9.10 | 1.82 |

The next step is the characterization of the final blend. This is the blend that is used to compressed tablets. The results characterization of the flow properties of final blend is shown in table 8. Based on the results of the Carr Index, the final blend for both formulations has passable flowability. Formulation 2 has a slightly better flowability than formulation 1. Also these results show how a granulation process can improve flow properties of a powder when you compare the results to the flow properties of the API.

**Table 8**
**Final Blend Flow Properties**

| **Formulation** | **Bulk Density (g/mL)** | **Tap density (g/mL)** | **Carr Index** | **Flow Character** |
|---|---|---|---|---|
| 1 | 0.505 | 0.655 | 22.974 | Passable |
| 2 | 0.533 | 0.67 | 21.052 | Passable |

A flow character of passable is recommended for a powder blend to be suitable for a compression process.

The results of the Particle Size Distribution of the final blend are shown in table 9. Based on the results formulation 2 has a bigger particle size than formulation. The bigger is the particle size, the better are the flow properties. This can be seen on the Carr Index results. Also both formulations have powder fines of less than 10 µm. These powder fines can be the cause of the erratic flow in the tablet press hopper. Also PSD can affect dissolution, the smallest the particle size, the more rapidly is the dissolution. This happens because small particle have a bigger surface contact area than bigger particles.

**Table 9**
**Final Blend Particle Size Distribution**

| Sample | $D_{90}$ (µm) | $D_{50}$ (µm) | $D_{10}$ (µm) |
|---|---|---|---|
| Formulation 1 | 410 | 140 | 8.57 |
| Formulation 2 | 490 | 190 | 9.22 |

The summary of results of the physical characterization of Polytripsin Tablets is shown on Table 10. Based on the result, the tablets for both formulations are within the target values of weight (1080 (±60) mg), thickness (7.00 (±0.1) mm), hardness (no less than 10 kp) and friability (no more than 1% weight loss after 100 revolutions).

**Table 10**
**Polytripsin Tablet Physical Characterization**

| | **Formulation # 1** | | |
|---|---|---|---|
| **20 Tablets** | **Weight (mg)** | **Thickness (mm)** | **Hardness (kp)** |
| **AVG** | **1088.5** | **7.04** | **16.6** |
| **STDEV** | **10.9** | **0.03** | **1.3** |
| **%RSD** | **1.0** | **0.45** | **7.8** |
| **Friability** | **0.21 % weight loss after 200 revolutions** | | |
| | **Formulation # 2** | | |
| **20 Tablets** | **Weight (mg)** | **Thickness (mm)** | **Hardness (kp)** |
| **AVG** | **1072.2** | **6.92** | **17.4** |
| **STDEV** | **12.9** | **0.05** | **2.1** |
| **%RSD** | **1.2** | **0.67** | **12.2** |
| **Friability** | **0.31 % weight loss after 200 revolutions** | | |

The Dissolution Profile results are shown in table 11. A similarity factor (f2) value of 50-100 indicates similarity between two dissolution profiles. The value f2 for both formulations indicates similarity of dissolution profiles between the Polytripsin 600 mg tablets and the Brand Polytripsin Tablets 600 mg. Formulation 2 has a better f2 value and better physical properties over Formulation 1.

**Table 11**
**Polytripsin Tablets Dissolution Profile Results**

| Time (minutes) | Formulation 1 | Formulation 2 | Brand RLD |
|---|---|---|---|
| | % Dissolved | % Dissolved | % Dissolved |
| 10 | 94.72 | 91.09 | 83.75 |
| 20 | 97.68 | 95.68 | 84.73 |
| 30 | 97.90 | 97.65 | 90.40 |
| 40 | 98.55 | 97.81 | 93.02 |
| 50 | 99.42 | 98.30 | 94.30 |
| Similarity Factor $f_2$ | **52** | **57** | |

The next step is to perform process improvement. During the compression stage erratic flow (rathole) was observed in both formulations. Formulation 2 was chosen to perform process improvement due to its highest value of $f_2$ over formulation1.

The DOE results to study the effects of the: Screw Speed, Roll Pressure and Mill Screen Size on the flow ability are shown in table 12.

**Table 12**
**DOE Results**

| **Std Order** | **Screw Speed** | **Roll Pressure** | **Screen Size** | **Carr Index** |
|---|---|---|---|---|
| 1 | 6 | 300 | 1.10 | 17.98 |
| 2 | 6 | 300 | 1.65 | 16.05 |
| 3 | 6 | 350 | 1.10 | 17.86 |
| 4 | 6 | 350 | 1.65 | 17.37 |
| 5 | 8.5 | 300 | 1.10 | 18.23 |
| 6 | 8.5 | 300 | 1.65 | 17.02 |
| 7 | 8.5 | 350 | 1.10 | 18.05 |
| 8 | 8.5 | 350 | 1.65 | 16.20 |
| 9 | 6 | 300 | 1.10 | 19.03 |
| 10 | 6 | 300 | 1.65 | 16.75 |
| 11 | 6 | 350 | 1.10 | 18.98 |
| 12 | 6 | 350 | 1.65 | 17.76 |
| 13 | 8.5 | 300 | 1.10 | 19.48 |
| 14 | 8.5 | 300 | 1.65 | 17.88 |
| 15 | 8.5 | 350 | 1.10 | 18.97 |
| 16 | 8.5 | 350 | 1.65 | 16.51 |

The ANOVA is shown on figure 1 and the main effect plot is shown on figure 2. From the ANOVA results and the main effects plots, the Screen size appears to have a significant effect on the Compressibity of the blend after milling. The bigger the screen size, the compressibility index is lower.

Analysis of Variance for Compressibility Index, using Adjusted SS for Tests

| Source | DF | Seq SS | Adj SS | Adj MS | F | P |
|---|---|---|---|---|---|---|
| Screw Speed | 1 | 0.0196 | 0.0196 | 0.0196 | 0.05 | 0.828 |
| Roll Pressure | 1 | 0.0324 | 0.0324 | 0.0324 | 0.08 | 0.781 |
| Screen Size | 1 | 10.6276 | 10.6276 | 10.6276 | 27.23 | 0.001 |
| Screw Speed*Roll Pressure | 1 | 1.5876 | 1.5876 | 1.5876 | 4.07 | 0.078 |
| Screw Speed*Screen Size | 1 | 0.0900 | 0.0900 | 0.0900 | 0.23 | 0.644 |
| Roll Pressure*Screen Size | 1 | 0.0625 | 0.0625 | 0.0625 | 0.16 | 0.699 |
| Screw Speed*Roll Pressure* Screen Size | 1 | 1.0000 | 1.0000 | 1.0000 | 2.56 | 0.148 |
| Error | 8 | 3.1218 | 3.1218 | 0.3902 | | |
| Total | 15 | 16.5415 | | | | |

**Figure 1**
**DOE Analysis of Variance (ANOVA) Results**

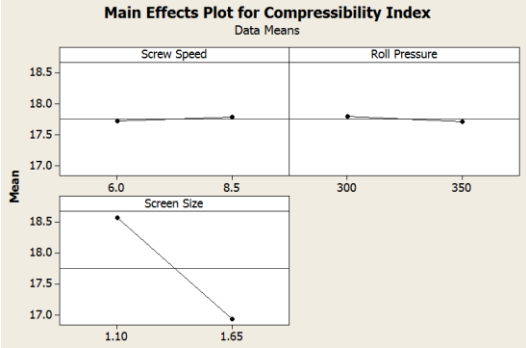


**Figure 2**
**Main Effects Plot**

According to the DOE results the best combination of parameters that gives the flow properties is a screw speed of 6.0 rpm, roll pressure of 350 psi and a screen size of 1.65 mm. Nevertheless in the blend samples taken after milling with the bigger screen (1.65 mm), noticeable size segregation was observed. No segregation was observed from the samples taken after milling with the 1.1 mm screen. In the pharmaceutical industry such segregation is often of major concern when handling formulation blends prior to compressing tablets or capsules. The result can be unacceptable variations in tablet weights and/or assays. Size segregation can also lead to tablet capping. For this reason the combination of parameters that are going to be used for the roller compactor-milling process will be screw speed of 6.0 rpm, roll pressure of 350 psi and a screen size of 1.1 mm. The 1.65 mm screen is not going to be used to avoid segregation problems.

The next step was to produce tablets with the new Roller Compactor- Milling parameters determined by the process DOE. During compression no erratic flow problems (rathole) were observed The tablets were compressed at the same parameters for the Tablet press as the previous trials. The summary of the physical characterization of the Tablets is shown on table 13. Based on the result, the tablets are within the target values of weight (1080 (±60) mg), thickness (7.00 (±0.1) mm), hardness (no less than 10 kp) and friability (no more than 1% weight loss after 100 revolutions).

**Table 13**
**Tablets Characterization after DOE process improvement**

| | Formulation # 2 | | |
|---|---|---|---|
| **20 Tablets** | **Weight (mg)** | **Thickness (mm)** | **Hardness (kp)** |
| **AVG** | **1073.7** | **7.01** | **19.2** |
| **STDEV** | **3.8** | **0.03** | **1.6** |
| **%RSD** | **0.35** | **0.48** | **8.4** |
| **Friability** | **0.35 % weight loss after 200 revolutions** | | |

A sample of the final blend was taken to be analyzed for PSD. Table 14 shows the result for PSD for the final blend after the DOE process improvement. Based on these results we can see that the particle size of the final blend was increase with the new roller compactor-milling parameters. The effect of this increase was observed in the improved flow properties of the blend. No erratic flow problems were observed in the product hopper

**Table 14**
**Final Blend PSD after DOE process improvement**

| Sample | $D_{90}$ (µm) | $D_{50}$ (µm) | $D_{10}$ (µm) |
|---|---|---|---|
| Formulation 2 | 590 | 230 | 10.57 |

The dissolution profile results of the tablets after process improvement DOE are shown in table 15. In the result the effect of the increase in particle size in the dissolution profile can be observed. PSD can affect dissolution, the bigger the particle size, the dissolution will be slower. This happens because small particle have a bigger surface contact area than bigger particles. The value of the Similarity Factor ($f_2$) of the formulation also improved after the process improvement DOE. The dissolution profile of the formulation was more similar to the dissolution profile of Brand' Polytripsin. A Dissolution Profile Comparison graph between Formulation 2 and the RLD is shown on Figure 3.

**Table 15**
**Tablets Dissolution Profile Results after DOE**

| Time (minutes) | Formulation 2 | Brand RLD |
|---|---|---|
| | % Dissolved | % Dissolved |
| 10 | 88.34 | 83.75 |
| 20 | 93.88 | 84.73 |
| 30 | 94.19 | 90.40 |
| 40 | 95.27 | 93.02 |
| 50 | 95.56 | 94.30 |
| Similarity Factor $f_2$ | **65** | |

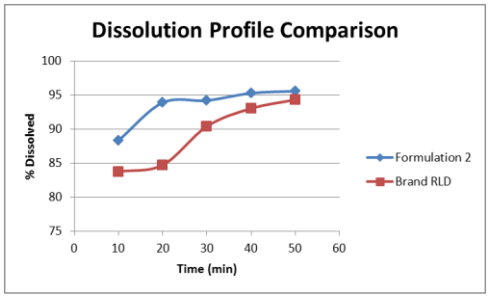


**Figure 3**
**Dissolution Profile Comparison**

## CONCLUSION

The purpose of this study was the development of Generic Version of Brand's Polytripsin Tablets 600 mg (RLD). The physical characteristic of the Active Drug Ingredient were evaluated and it was found that had very poor flowability and it was cohesive. A dry granulation manufacturing process and two (2) formulations were proposed.

Physical characterization of the final blend and tablets from both formulations was performed. In addition the dissolution profile of tablet from both formulations was performed and compared to the dissolution profile of the RLD, Brand's Polytripsin Tablets.

Formulation 2 showed better flow properties and had a higher Similarity Factor ($f_2$) value than formulation 1. Formulation 2 was more similar to the RLD than formulation 1.

During compression erratic flow was observed in the tablet press product hopper. It is important to identify these kinds of problems before going to a scale up process. A process improvement DOE was performed to identify the best parameter combination for the Roller Compaction-Milling process that gave the best flow properties and PSD.

The DOE was performed, the optimum parameters for the Roller Compaction-Milling process were identify and the erratic flow problem in the compression stage was addressed and resolved. In addition the Similarity Factor ($f_2$) also improved after the process improvement DOE.

Based on the results of this study it can be concluded that Formulation 2 is similar to the RLD and the improved dry granulation process is amenable for a scale up process, to manufacture a generic version of Brand's Polytripsin Tablets 600 mg.

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