5. EXPERIMENTAL STUDY
5.1. Characterization of drug substance and preformulation studies

5.1.1. Solubility of Pantoprazole sodium sesquihydrate

Saturated solubility was performed with the addition of excess drug substance in solvent. It was anticipated that decomposed Pantoprazole sodium sesquihydrate (PTZ) could be replaced with the intact substance during experiment (Kristl et al., 2000).

Excess of the substance was tested for solubility in water using agitation method, in 100 ml flasks at temperature of 25°C ± 0.1°C in a water shaking bath for 48 h, with shaking amplitude of 66. Different concentrations were prepared diluting the standard stock solution with water and quantified.

In order to assure working in the sink conditions solubility of PTZ was also determined at 37°C in 0.1N HCl, 0.01N HCl (pH 2.0), pH 4.5 acetate buffer, pH 6.8 Phosphate buffer, FaSSGF (Fasted-State Simulated Gastric Fluid) (pH 1.6), FaSSIF (Fasted-State Simulated Intestinal Fluid) (pH 6.5) using the same procedure.

5.1.2. Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra of pantoprazole was obtained using PerkinElmer FTIR spectrophotometer (Waltham, Massachusetts, USA) using diffuse reflectance technique (KBr disc technique) as a part of qualitative analysis by comparing it with the spectra of pantoprazole sodium phosphate USP standard. Samples of pantoprazole powder and pantoprazole USP standard were previously ground and mixed with KBr and scan in the mid-infrared regions of the spectrum form 4000 – 400 cm\(^{-1}\) at resolution of 1 cm\(^{-1}\).

5.1.3. Differential-scanning calorimetry (DSC)

The samples (2.5 – 5.0 mg) were placed in aluminium sample pans with holes, 50 µm, sealed and scanned from 60°C up to 220°C/300°C (40°C above the determined signal) with different heating rates in a Perkin Elmer Pyris 1 DSC/Diamond DSC, in order to see the effect of scanning rate on the thermal behavior of the studied substance.

5.1.4. Powder X-ray diffractometry

XRD was performed with an Siemens, Model D 5005, X-ray diffractometer over
5-60° range at a scan rate of 1°/min (Zhang et al., 2007).

5.1.5. **Particle size measurement**

Appropriate method for determination of particle size distribution by laser diffraction is conducted as follows. Dry powder laser diffraction method was proposed by the producer of the substance which is in some cases more appropriate for determination of PSD. PSD distribution measurement has been performed on Mastersizer 2000 (Malvern Instruments) using dry powder feeder unit Scirocco 2000.

Dry powder laser diffraction has been conducted with optical characteristics of particle refraction index 1.500, absorption 0.001. Vibration feed rate was set to 50% and dispersion medium pressure (air pressure) was set to 2 bars.

Optical characteristics were set to particle refraction index 2.500 with the absorption 0.1. An obscuration value in the range of 1-10% in all measurements as obtained (2.9%). Vibration feed rate was set to 50% with air as dispersion medium, with pressure of 2 bars.

5.1.6. **Bulk and tapped density**

Bulk (poured) density and tapped density was measured using automated tapper (Stav, J. Engelsmann, Ludwigshafen, Germany). 100 g mass of sample, giving the volume 250 ml, was poured into the graduated cylinder. The volume noted, without any tapping of the cylinder, is the bulk volume. After fitting, cylinder was tapped 500 times and the volume was noted. Sample was further tapped until 1250 times and again the volume was checked. If the difference between the volume after 500 and 1250 taps was higher than 2 ml sample was tapped 1250 times more, giving the volume after 2500 times of tapping. The relative bulk density (ρ_{bulk}) and relative tapped density (ρ_{tapped}) were calculated as ratio of volume and mass used for determination, respectively.

Hausner ratio (R) and Carr’s index (CI) were calculated using the Equation 4.1 and Equation 4.2:

\[
H = \frac{\rho_{tapped}}{\rho_{bulk}} \tag{6.1}
\]
\[
\frac{(\rho_{\text{tapped}} - \rho_{\text{bulk}})}{\rho_{\text{tapped}}} \times 100
\]

Where, \(H\) = Hausner ratio
\(\rho_{\text{bulk}}\) = Bulk density (g/cm\(^3\))
\(\rho_{\text{tapped}}\) = Tapped density (g/cm\(^3\))
CI = Carr Index (%)

### 5.1.7. Scanning electron microscopy

Scanning electron microscopy (SEM) pictures of PTZ powder were sputtered with gold palladium and then observed with a SEM Philips ESEM XL 30 FEG at a voltage of 10 KV, using magnification of 300, 3000 and 10000. SEM pictures of neutral pellets were obtained after a neutral pellet and cross section of pellet was sputtered with gold palladium and then observed with a SEM Philips ESEM XL 30 FEG at a voltage of 5 and 10 KV, using magnification of 100, 300, 1000 and 3000.

### 5.1.8. Excipient compatibility study

Excipient compatibility performed to know the chemical compatibility of excipients with drug substance. The physical mixture of excipient and drug substance passed through 40 mesh screen and mixed in polybag for uniform mixing. Added approx 1 gm mixture (mentioned in Table 4.1) in transparent glass vials and charge at 25°C ± 2°C/60% RH ± 5% RH and 40°C ± 2°C/75% RH ± 5% RH for 1 month. After withdrawal, noted the physical observation and performed related substance test. One set of vials preserved at 5°C ± 3°C as control samples.

### Table 5.1 List of excipients and drug substance-excipient ratio

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTZ</td>
<td>-</td>
</tr>
<tr>
<td>PTZ : Sugar spheres (Pharma-a-Spheres)</td>
<td>1:5</td>
</tr>
<tr>
<td>PTZ : MCC pellets (Ceolus CP-203)</td>
<td>1:5</td>
</tr>
<tr>
<td>PTZ : Povidone (PVP K30)</td>
<td>1:5</td>
</tr>
<tr>
<td>PTZ : Sodium Carbonate, anhydrous</td>
<td>1:0.25</td>
</tr>
<tr>
<td>PTZ : Sodium Carbonate, anhydrous</td>
<td>1:0.5</td>
</tr>
</tbody>
</table>
Optimization of stabilizer level

Mixed PTZ and sodium carbonate anhydrous well, sifted through 40 mesh sieve and made thick paste using 0.1N HCl. Take PTZ and sodium carbonate anhydrous in the ratio of 1:0.10, 1:0.25, 1:0.50 and 1:1. Charge suspension in petri plate at 30º C ± 2º C/75 % RH ± 5 % RH for 1, 3 and 7 days and record the observations.

5.2. Characterization of pellets and MUPS tablets

Pantoprazole Sodium Delayed Release Tablets are official in USP. Chemical test performed comparable with USP-NF 37 and physical test as per pharmacopieal general chapters.
5.2.1. Scanning electron microscopy
SEM pictures of pellets and broken tablets were performed as per method mentioned in 5.1.7.

5.2.2. Coating efficiency
Coating efficiency is the way to calculate the actual coating level which is calculated as per the below formula.

\[
\text{Coating efficiency} = \left( \frac{\text{Theoretical coating quantity} - \text{Actual coating quantity}}{\text{Theoretical coating quantity}} \right) \times 100
\]

5.2.3. Hardness of tablet
Tablet hardness measured the force required to crush the tablets using a tablet hardness Tester (Erweka TBH200, Germany). Mean of 5 Tablets were observed and reported.

5.2.4. Friability of tablet
Friability of tablets was determined using Friabilator (Electrolab, India). Tablet (or split tablet) weights were not less than 6.5gm. Tablets dropped form at 25 rpm for 4 min.

\[
\text{Friability} = \left( \frac{W - Wo}{W} \right) \times 100
\]

Where, 
Wo = Weight of the tablets before the test
W = Weight of the tablet after the test.

5.2.5. Disintegration test
In vitro disintegration time for oro-dispersible tablet (ODT) was measured using USP General Chapter. A disintegration tester (EF-2W, Electrolab, India) filled with 800ml distilled water. Mean disintegration time of 6 tablets was observed and reported.

5.2.6. Loss on drying
Accurately weighed pellets (1.5 to 2 gm) were placed on tare aluminium plate of moisture balance (Mettler Toledo HR83P). The test was performed at a temperature 105°C till a constant weight was achieved. The reading displayed on the screen was noted as the LOD of the sample.
5.2.7. Dissolution studies
Dissolution test of tablets were performed as per Pantoprazole Sodium Delayed-Release Tablets USP monograph (USP37-NF32).

Acid stage
Acid stage medium: 0.1 N hydrochloric acid; 1000 mL
Apparatus: 2
Rotations: 75 rpm
Time: 120 min

Buffer stage
Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL
Apparatus: 2
Rotation: 75 rpm
Time: 60 min

5.2.8. Assay
Stationary phase: (4.6mm X 25CM) 5H C12, (Hypersil BDS)
Mobile phase: buffer: acetonitrile (40:60), SpH 7.4 with KOH solution.
Flow rate: 1ml/min
Control temp: Room temperature
Detector: 280 nm
Injection volume: 20 micro liters

Preparation of buffer -
Dissolve 2.72 g of KH2PO4 & 0.525 g of K2HPO4 and volume makeup up to 10000 ml by purified water

Preparation of standard -
40.4 mg of pantoprazole sodium sesquihydrate dissolved in 20 ml of methanol from this 2ml of solution dilute. And volume makes up to 50 ml by using mobile phase Preparation of sample – weight equivalent to 40 mg pantoprazole sodium into 20 ml volumetric flask then add 15 ml methanol and sonicated it. Passed through 0.45 micrometer filter take 2 ml of filtrate add volume make up to 50mL.

5.2.9. Tablet breakability
Took sufficient quantity of sample required for performing the subtests mentioned below (Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation guideline, USFDA, 2013).
a. **Loss of mass:**
Tablet splitability at both ends of the proposed hardness range (low and high) demonstrated as followed. Tested 15 tablets to ensure a loss of mass of less than 3.0 percent between the individual segments (30 for bisected tablets) when compared to the whole tablet. Took 30 tablets at random and weighed each tablet. Recorded the weight. Braked each tablet by hand at the score line(s) and weighed each of the subdivided parts. Loss of mass calculated the for each tablet.

b. **Friability:**
The split tablet portions should also be tested for Friability as per 5.2.4.

c. **Accuracy of subdivision:**
Took 30 tablets at random and braked them by hand at the score line(s). From all the parts obtained from 1 tablet, selected one part and rejected the other part(s). Weighed each of the 30 parts individually and calculated the average mass.

d. **Uniformity of content:**
Performed as per Assay method discussed at 5.2.8.

e. **Dissolution:**
Dissolution performed as per discussed at 5.2.7.

**5.2.10. Stability studies**
Alteration in pharmacological effect was seen due to physical and chemical degradation of the drug molecule. This alteration may cause changed in therapeutic efficacy and some time may produced undesirable effects. As pharmaceutical dosage forms are therapeutically sound they should maintained their quality and safety till used by the patients or up to the expiry date. Decreased in the potency of medicament was observed due to chemical degradation of the compound. Dehydration, hydrolysis or oxidation and sometime photo degradation reactions may take place within the formulated compound which resulted in instability of the dosage forms. If dosage form stored in humid state then moisture get absorbed on the surface of it resulting in alteration in mechanical strength. It is reported in the literature that the excipients which are added in the formulation may impact the release behavior of medicament if dosage form stored for longer period of time.

With the harmony of guiding principles as given by the ICH the study was accomplished. The tablets packed in Alu-Alu blister pack and charge for stability at
25°C ± 2°C/60% RH ± 5% RH, 30°C ± 2°C/75% RH ± 5% RH and 40°C ± 2°C/75% RH ± 5% RH for 24 months, 12 months and 6 months respectively. Sufficient split tablets packed in High-density polyethylene (HDPE) container (without seal and desiccant) and charge for stability at 25°C ± 2°C/60% RH ± 5% RH for 90 days. Assay, dissolution and related substance tests were performed for stability samples.

5.2.11. Content uniformity
Followed the process as per 5.2.8 used for Assay test.

5.2.12. Related substance
The sample preparation performed as per described in Assay. The resolution was NLT 3 between pantoprazole and pantoprazole related compound A. Remaining conditions same as discussed in USP-NF monograph.

5.2.13. Biorelevant dissolution studies
In case of PTZ MUPS tablets, release dissolution test performed in two stages i.e. in acid media to check the acid resistance capacity of PTZ and in buffer media to predict the dissolution profile in intestine. PTZ tablets recommended to take before food so fasted state biorelevant media selected for study. To understand the \textit{in vivo} behaviour of PTZ MUPS, biorelevant dissolution performed in below mentioned (Table 2.2) media.

\textbf{Table 5.2 Biorelevant dissolution conditions}

<table>
<thead>
<tr>
<th>Fasted Stage dissolution condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: USP Type II/ 250ml FaSSGF pH 1.6/ 100 rpm/60 min/ 37°C</td>
</tr>
<tr>
<td>Stage II: USP Type II/ 500ml FaSSIF pH 6.5/ 100 rpm/120 min/ 37°C</td>
</tr>
</tbody>
</table>

Dissolve the ready mix FaSSGF and FaSSIF in purified water to quantity sufficient. Pass the aliquot through filter of 0.45-µm pore size. Biorelevant dissolution studies were performed for prototype formulation and reference product.
5.3. **Quality Target Product Profile**

Quality Target Product Profile (QTPP) was set based on the existing literature and design to be targeted for the research. QTPP gave the guidance to develop the dosage form as per target from the initial stage of the research.

**Table 5.3 Quality target product profile (QTPP) for PTZ MUPS tablets 40mg**

<table>
<thead>
<tr>
<th>QTPP Elements</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Uncoated oro-dispersible tablet</td>
<td>Patient friendly design</td>
</tr>
<tr>
<td>Dosage design</td>
<td>Circular, flat faced beveled edge</td>
<td>Suitable for dosage form</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Most preferred and suitable administration route</td>
</tr>
<tr>
<td>Dosage strength</td>
<td>40mg</td>
<td>Same strength available in market</td>
</tr>
<tr>
<td>Stability</td>
<td>6 months accelerated stability data and 24 months long term</td>
<td>Equivalent or better than reference shelf life</td>
</tr>
<tr>
<td>Drug product Quality</td>
<td>Appearance</td>
<td>Pharmaceutical Equivalence requirement: Must meet the same compendial requirements or other applicable quality standards (i.e., identity, assay, purity and quality)</td>
</tr>
<tr>
<td></td>
<td>taste</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splitability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disintegration time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hardness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Friability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Identification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Content Uniformity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dissolution Profile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impurities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residual Solvents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Water Content</td>
<td></td>
</tr>
<tr>
<td>QTPP Elements</td>
<td>Target</td>
<td>Justification</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pack configuration</td>
<td>Alu-Alu blister</td>
<td>Needed to achieve the target shelf-life and to ensure tablet integrity during shipping</td>
</tr>
<tr>
<td>Storage condition</td>
<td>Preserve in well-closed containers. Store at controlled room temperature.</td>
<td>Similar to USP and reference product. Need to achieve the shelf life.</td>
</tr>
<tr>
<td>Administration</td>
<td>Before food</td>
<td>Same as reference products</td>
</tr>
<tr>
<td>Alternative methods of</td>
<td>Tablet can keep on the tongue or Tablet can be dispersed in tablespoon of water before administration. For 20 mg dose, tablet can be divide into two parts.</td>
<td>Additional benefit over marketed products</td>
</tr>
</tbody>
</table>

5.4. **MUPS Tablets and Design of Dosage Form**

MUPS tablets basically have two components i.e. pellets and extragranular excipients. Pellets manufactured by any process have typical steps. Drug loading step where drug i.e. PTZ, loaded followed by barrier or seal coating to protect degradation of PTZ from acidic enteric coat. So times cushion coating also needed to give increase the elasticity of pellets after compression.

The MUPS tablets dosage form design presented in below figure was best possible design considering the research aim.
5.4.1. Selection of drug loading pellets manufacturing process

5.4.1.1. Suspension loading method

First step of process was drug loading on neutral pellets. Drug loaded pellets were prepared as per below formula mentioned in Table 5.4.

PTZ, povidone, sodium carbonate anhydrous and polysorbate 80 dissolved in purified water (equivalent to 12% w/w solid content) to got lumps free solution followed by LHPC LH-31, followed by aqueous homogenized dispersion of talc and mixed for 30 min using stirrer. Strained the dispersion through 80 mesh screen and loaded on sugar spheres/CP-203 in Wurster (GPCG 1.1, Glatt) at process parameters mentioned in Table 5.5.

Table 5.4 Drug loading formulations by suspension loading process

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL1</td>
</tr>
<tr>
<td>Pantoprazole Sodium Sesquihydrate</td>
<td>45.1</td>
</tr>
<tr>
<td>Povidone (PVP K30)</td>
<td>5.0</td>
</tr>
<tr>
<td>Sodium Carbonate, anhydrous</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Polysorbate 80 | 0.4 | 0.4 | 0.4 | 0.4  
Purified Talc | 4.5 | 4.5 | 4.5 | 4.5  
LHPC LH-31 | 7.5 | 7.5 | 7.5 | 7.5  
Sugar Spheres 212-250 micron | - | - | - | 30.0  
Celpheres CP-203 | 20.0 | 20.0 | 30.0 | -  
Purified Water | q.s | q.s | q.s | q.s  

PTZ is water soluble molecule so trial started with lesser binder (PVP K30) quantity. Sugar spheres and MCC spheres used to selection of neutral pellets.

Table 5.5 Process parameters of suspension loading

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size (Initial load)</td>
<td>500 gm</td>
</tr>
<tr>
<td>Spay nozzle</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-11 g/min</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.1 bar</td>
</tr>
<tr>
<td>Air volume</td>
<td>45-60 cfm</td>
</tr>
<tr>
<td>Product temperature</td>
<td>35-41 °C</td>
</tr>
<tr>
<td>Inlet temperature</td>
<td>37-55 °C</td>
</tr>
</tbody>
</table>

Pellets dried till LOD achieved less than 1.5% w/w at 105°C. Pellets shifted through 40 mesh and 60 mesh. Collected the fraction of 40 mesh and 60 mesh for further processing.

5.4.1.2. Powder loading method

Another approach to prepare drug loaded pellets was by powder loading technology. Pellets prepared as per formulation mentioned in Table 5.6 and process parameters in Table 5.7.

Table 5.6 Drug loading formulations by powder loading process

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PL1</td>
</tr>
<tr>
<td>Starting Load</td>
<td></td>
</tr>
</tbody>
</table>
PVP K30 and polysorbate 80 dissolved in purified water to get clear solution. Separately dissolved sodium carbonate anhydrous in purified to get clear solution. Mixed both the solution and stirred for 15 min. Purified water added to make 3.0 % w/w solid content. PTZ, LHPC LH-31, purified talc (and pulverized sucrose) sifted through 40 mesh sieve and mix in blender for homogeneous mixing. Celpheres CP-203 added in 12-inch spheronizer containing plain bottom plate, powder feeder and binder spray gun assembly using above prepared binder at controlled speed to get spherical pellets. Pellets dried in FBD till LOD achieved NMT 1.5% w/w. Pellets sifted through 30 mesh and 60 mesh. Collect the fraction of 30 mesh and 60 mesh for further processing.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>12-inch Spheronizer</td>
</tr>
<tr>
<td>Batch Size</td>
<td>500 gm</td>
</tr>
<tr>
<td>Spay nozzle</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Binder rate</td>
<td>2-3 g/min</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.2-0.4 bar</td>
</tr>
<tr>
<td>Purging air</td>
<td>3 bar</td>
</tr>
<tr>
<td>Plate speed</td>
<td>80-250 rpm</td>
</tr>
</tbody>
</table>
5.4.1.3. **Extrusion-Spheronization Technology**

Extrusion-Spheronization is the fastest process to manufactured drug loaded pellets among others. Pellets prepared as per formulation mentioned in Table 5.8 and process parameters in Table 5.9.

**Table 5.8 Drug loading formulations by extrusion-spheronization technology**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tab</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES1</td>
<td>ES2</td>
</tr>
<tr>
<td><strong>Dry Mix</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole Sodium Sesquihydrate</td>
<td>45.1</td>
<td>45.1</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel PH 101)</td>
<td>40.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Maize Starch</td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Crospovidone (Kollidone CL-SF)</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Mannitol 25</td>
<td>10.0</td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Binder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Povidone (PVP K30)</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Sodium Carbonate, anhydrous</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

PVP K30 and polysorbate 80 dissolved in purified water to get clear solution. Separately sodium carbonate anhydrous dissolved in purified to get clear solution. Mixed both the solution and stirred for 15 min. Purified water added to make 15.0 % w/w solid content. PTZ, MCC, maize starch, crospovidone and mannitol sifted through 40 mesh sieve and dry mixed for 5 min in RMG. Granulation performed using above binder solution to get suitable wet mass for extrusion.

**Table 5.9 Process parameters of Extrusion-Spheronization technology**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Granulation</strong></td>
<td></td>
</tr>
<tr>
<td>Rapid Mixer Granulator</td>
<td>5 Litre</td>
</tr>
<tr>
<td>Impeller Speed</td>
<td>150 rpm</td>
</tr>
<tr>
<td>Chopper</td>
<td>OFF</td>
</tr>
</tbody>
</table>
Dry mixing time | 5 min
---|---
Granulation Time | 3 min
Batch Size | 500 gm

**Extrusion**

Screen size | 0.8 mm
Extruder screw speed | 50-80 rpm

**Spheronization**

Chequered plate size | 3.25 mm
Plate speed | 150-200 rpm
Purging air | 2-3 bar
Spheronization time | 2.5-3 min

**Drying**

Inlet temperature | 40-60°C
Product temperature | 40-45°C

Extruded the above wet mass as per parameter mentioned in Table 5.9 followed by spheronization. Dry spheroids in FBD to achieved LOD NMT 1.5% at 105°C. Sift the pellets through 14 mesh and 24 mesh. Collect the fraction of 14 mesh and 24 mesh for further processing.

### 5.4.2. Selection of extragranular excipients

There were various excipients required along with functional coated PTZ pellets for cushioning, to avoid rupture of pellets during compression, maintained the oro-dispersible properties and have mean particle size nearer to pellets size to avoid segregation. Existed super-disintegrant has some limitations to maintained disintegrant property for MUPS tablets like particle size not matched with pellets size, can't use in high percentage etc so additional co-processed disintegrant tried.

There are list of ingredients and their application mentioned in Table 5.10.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Application</th>
<th>EG1</th>
<th>EG2</th>
<th>EG3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo pellets</td>
<td>-</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Cushioning agent</td>
<td>-</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 5.10 Tablet formulations of various extragranular excipients percentage
(Ceolus KG 1000) | Disintegrant | 17.5% | 17.5% | -
---|---|---|---|---
Pearlitol Flash | | | |
Microcrystalline Cellulose (Avicel PH 200) | Diluent | 20.0% | 17.5% | 25.0%
Mannitol (Pearlitol DC 400) | Diluent and Cooling effect | 20.0% | 17.5% | 27.5%
Crospovidone (Kollidon CL-SF) | Disintegrant | 10% | 10% | 10%
Neotame | Sweetener | 0.5% | 0.5% | 0.5%
Strawberry flavour | Flavouring agent | 1.0% | 1.0% | 1.0%
Colloidal Silicon Dioxide (Aerosil 200) | Glidant | 0.5% | 0.5% | 0.5%
Magnesium stearate | Lubricant | 0.5% | 0.5% | 0.5%

All extragranular excipients sifted through 40 mesh sieve. Placebo pellets co-sifted with Ceolus through 40 mesh sieve, labeled as co-sift I. Crospovidone, flavour and neotame co-sifted through 40 mesh sieve, labeled as co-sift II. Aerosil co-sifted with 1/4th quantity of Pearlitol DC 400 through 40 mesh sieve, labeled as co-sift III. Pre-sifted Avicel PH 200 added followed by co-sift I, co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol DC 400 in double cone blender for 300 revolutions, and sifted magnesium stearate added, and lubricated for 50 revolutions.

### 5.4.3. Compression of pellets blend

Compression of pellets blend is crucial process in manufacturing of MUPS tablets, required sophisticated compression machine which avoid segregation of pellets on turret and crushing of pellets.

Compression performed on different compression machine using formulation of EG3 to evaluate machine and spare parts in assembly. Below is the machine details mentioned in Table 5.11 for trials.

<table>
<thead>
<tr>
<th>Machine Manufacturer</th>
<th>Karanavati</th>
<th>Fette</th>
<th>Fette</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machine Model</td>
<td>-</td>
<td>102 i</td>
<td>102 i</td>
</tr>
<tr>
<td>Force feeder</td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Feeder rod design</td>
<td>Square</td>
<td>Square</td>
<td>Round</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>2.5-4.0 kN</td>
<td>2.5-4.0 kN</td>
<td>2.5-4.0 kN</td>
</tr>
<tr>
<td>Main Compression force</td>
<td>10-14 kN</td>
<td>10-14 kN</td>
<td>10-14 kN</td>
</tr>
<tr>
<td>Turret Speed</td>
<td>25-30 rpm</td>
<td>25-30 rpm</td>
<td>25-30 rpm</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>0.8-1.5 times of turret speed</td>
<td>0.8-1.5 times of turret speed</td>
<td>0.8-1.5 times of turret speed</td>
</tr>
</tbody>
</table>

### 5.5. Identification of Critical Quality Attributes (CQAs)

Based on QTPP discussed at point 5.3 and the experimentation as per 5.4, below are the list of CQAs for further risk assessment studies.

- ✔ Assay
- ✔ Dissolution
- ✔ Content uniformity (Whole and Split tablet)
- ✔ Splitability

Some in-process CQAs also necessary to consider as dosage forms requirement listed below.

- ✔ Hardness
- ✔ Disintegration time
- ✔ Friability

### 5.6. Formulation component

Initial risk assessment performed at very early stage based on initial experiments. An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product CQAs. The results of the initial formulation risk assessment are presented in Table 5.12 and the justification for the risk prioritization is presented in Table 5.13. Each formulation component that has a high risk to impact the drug product CQAs is further evaluated in subsequent risk assessments to determine which formulation variables need to be studied to reduce the risk.
**Table 5.12 Initial risk assessment of formulation components**

<table>
<thead>
<tr>
<th>Drug Product CQAs</th>
<th>Formulation Component</th>
<th>Drug loaded pellets</th>
<th>Seal coated pellets</th>
<th>Enteric coated pellets</th>
<th>Cushion coated pellets</th>
<th>Extra-granular Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dissolution in Stage I*</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Dissolution in Stage II**</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Splitability</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

* Dissolution in 0.1N HCl
** Dissolution in pH 6.8 Phosphate buffer

**Table 5.13 Justification for the initial risk assessment of formulation components**

<table>
<thead>
<tr>
<th>Formulation Components</th>
<th>Drug Product CQAs</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loaded pellets</td>
<td>Assay</td>
<td>PTZ has no binding property so adherence of drug to neutral pellets is depended on the binder type and level. The risk of impact on tablet assay was high.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
<td>Drug loaded (DL) pellets not contained acid resistance ingredient rather acidic protection was not intention. So acid resistance test was not applicable for drug loaded pellets hence risk was low.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II</td>
<td>Drug loaded pellets contained binder, disintegrant and binder, they governed the release of drug in alkaline media. Higher binder could retarded the release, and lesser binder leads to increased release.</td>
</tr>
<tr>
<td>Process</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Friability of pellets and variation in release profile. Hence the risk of the drug loaded pellets to impact tablet drug release was high.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Pellets and extragranular excipient must have similar PSD and density to avoid failure in blend uniformity ultimately failure of content uniformity. Proper selection of neutral pellets and extent of loading impact the content uniformity, hence the risk was medium.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>Drug loading was the intermediate stage of pellets coating. Hence the risk of drug loaded pellets to impact tablet splitability was low.</td>
<td></td>
</tr>
<tr>
<td>Seal coated Pellets</td>
<td>Assay Assay was mainly determined during the drug loading step. Although attrition of the drug loaded pellets may occur during initial seal coating, the risk of the seal coated (SC) pellets to impact tablet assay was low.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I Seal coated pellets not contained acid resistance ingredient rather acidic protection was not intention. So acid resistance test was not applicable for seal coated pellets hence risk was low.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II Seal coated pellets contained binder which governed the release of drug in alkaline media. Higher binder could retarded the release and lesser binder leads to increased friability of pellets and variation in release profile. Hence the risk of the seal coated pellets to impact tablet drug release was high.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Content uniformity Core pellets size was selected in DL stage and thickness was not significantly increased in SC stage like DL stage. The risk of the SC pellets to impact tablet CU was relatively low.</td>
<td></td>
</tr>
</tbody>
</table>
|                      | Splitability SC was the intermediate stage of pellets coating
<table>
<thead>
<tr>
<th>Enteric coated pellets</th>
<th>Process</th>
<th>Hence the risk of seal coated pellets to impact tablet splitability was low.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Assay</td>
<td>Assay was mainly determined during the drug loading step. Although attrition of the SC pellets may occur during initial enteric coating (EC), the risk of the EC coated pellets to impact tablet assay was low.</td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>EC pellets contained enteric polymer as main ingredient to protect PTZ from acidic environment. The type of polymer and level decide the acidic protection. The risk of EC pellets to impact tablet dissolution stage I was high.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>EC pellets contained enteric coating polymer along with plasticizer, they may governed the strength of EC layer hence alter the drug release in stage II. The risk of EC pellets to impact tablet dissolution stage II was high.</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>After enteric coating, almost all pellets became uniform size so less risk of content uniformity. The risk of the EC pellets to impact tablet CU was relatively low.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>EC was the intermediate stage of pellets coating. Hence the risk of EC pellets to impact tablet splitability was low.</td>
<td></td>
</tr>
<tr>
<td>Cushion coated pellets</td>
<td>Assay</td>
<td>Assay was mainly determined during the drug loading step. The risk of the EC coated pellets to impact tablet assay was low.</td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>Cushion coating was the additional coating over EC to avoid crushing of enteric coat due to compression, hence affect the dissolution in stage I. So the risk of cushion coated pellets to impact tablet dissolution in acidic media was high.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Cushion coating affect the stage I drug release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>hence it would may affect on stage II release. So the risk was medium.</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Percentage of cushion coated pellets in the tablet matters the blend uniformity and ultimately CU. The risk of cushion coated pellets to impact tablet CU was high.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>Number of pellets in blend and distribution of pellets in blend affect the tablet splitability. Hence risk was high.</td>
<td></td>
</tr>
<tr>
<td>Extragranular Excipients</td>
<td>Assay</td>
<td>Extragranular (EG) excipients not contained drug so not affect assay. So the risk of extragranular excipients to impact tablet assay was low.</td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>Major part of Extragranular excipients used as cushioning agent to avoid cleavage of pellets during compression. Percentage of extragranular excipients in tablet affect the drug release in acidic medium. The risk of extragranular excipients to impact tablet release in stage I was high.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>Total drug release was the addition of drug release in stage I and II. If extragranular excipients affect the drug release in stage I so indirectly affect the drug release in stage II. The risk of extragranular excipients to impact tablet release in stage II was medium.</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Ideally, EG Excipients has mean PSD that of cushion coated pellets to avoid de-mixing. Even though EG excipients contents excipient has different functions and mean PSD available. The risk of EG excipients to impact tablet CU was medium.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>EG excipient has various PSD excipients which have different density and compressibility. The risk of EG excipients to impact tablet splitability was</td>
<td></td>
</tr>
</tbody>
</table>
Out of five formulation components (i.e. drug loaded pellets, seal coated pellets, enteric coated pellets, cushion coated pellets and extragranular excipients), enteric coated pellets, cushion coating and extragranular excipients components were more critical.

5.6.1. Drug substance
The tests given in Pantoprazole Sodium (Sesquihydrate) USP monograph taken as drug substance attribute.

Table 5.14 Initial risk assessment of drug substance

<table>
<thead>
<tr>
<th>Drug substance Attributes</th>
<th>Drug Product CQAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assay</td>
</tr>
<tr>
<td>Description</td>
<td>Low</td>
</tr>
<tr>
<td>Solubility</td>
<td>Low</td>
</tr>
<tr>
<td>Identification by IR</td>
<td>Low</td>
</tr>
<tr>
<td>Identification by HPLC</td>
<td>Low</td>
</tr>
<tr>
<td>Heavy metal</td>
<td>Low</td>
</tr>
<tr>
<td>Water content</td>
<td>Low</td>
</tr>
<tr>
<td>Related substance</td>
<td>Low</td>
</tr>
<tr>
<td>Assay</td>
<td>Low</td>
</tr>
<tr>
<td>Particle size</td>
<td>Low</td>
</tr>
<tr>
<td>Packing and storage</td>
<td>Low</td>
</tr>
</tbody>
</table>

Particle size of PTZ could impact on drug release but PTZ used in dissolved form where particle size not affected.
5.6.2. Drug loaded pellets

A drug loading by Wurster process was selected over powder layering process and extrusion-spheronization because drug loaded pellets had smoother surfaces and a narrower particle size distribution. These attributes were important for the subsequent functional coated i.e. enteric coated pellets and tablet compression steps.

Initial risk assessment of drug loaded pellets

The initial risk assessment of the formulation components showed in Table 5.15 where drug release in stage I, stage II and assay indentified CQAs where whole tablets has high risk of failure. This was due to variability in drug loading quality attributes. It was discussed in next section about identification of formulation and process variables leads to impact drug release and assay of pellets.

Table 5.15 Initial risk assessment of the drug loaded pellets

<table>
<thead>
<tr>
<th>Drug loading formulation variables</th>
<th>Drug loaded pellets CQAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assay</td>
</tr>
<tr>
<td>Type of neutral pellets</td>
<td>Medium</td>
</tr>
<tr>
<td>Size of neutral pellet</td>
<td>Low</td>
</tr>
<tr>
<td>Binder type/grade</td>
<td>High</td>
</tr>
<tr>
<td>Drug substance/binder ratio</td>
<td>High</td>
</tr>
<tr>
<td>Level of stabilizer</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 5.16 Justification for the initial risk assessment of the drug loaded pellets

<table>
<thead>
<tr>
<th>Formulation variables</th>
<th>Drug loaded pellets CQAs</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of neutral pellets</td>
<td>Assay</td>
<td>The pellets are the substrate for drug loading and ingredients of neutral pellets affect the physical attributes of the final pellets like attrition which have impact on assay. Thus, the risk of pellets type to impact drug loaded pellets assay was medium.</td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>Different type of neutral pellets has different physical parameters like friability. The risk of</td>
<td></td>
</tr>
</tbody>
</table>
pellet selection to impact drug release from the drug loaded pellets was medium.

<table>
<thead>
<tr>
<th>Size of neutral pellet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolution in Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness of drug loaded layer was depend on the size of neutral pellets. Larger size neutral pellets has lesser surface area than smaller which governed the thickness of drug loaded layer. The risk of pellet size to impact drug loaded pellet dissolution was medium.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binder type/grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolution in Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder type and grade may impact the solid state physical stability of the drug substance and, therefore, the dissolution rate of the drug substance in the drug layer. However, the solubility and intrinsic dissolution rate of the drug substance was high. The risk of impact on drug release from the drug loaded pellets was medium.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug substance/binder ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolution in Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ratio of drug substance to binder may impact the physical stability of drug loaded pellets and excessive binder may retard the release of drug substance from the drug layer. The risk of impact on drug release from the layered beads was high.</td>
</tr>
</tbody>
</table>
Drug loading trials performed as per formulations discussed at point 5.4.1.1. In which selection of neutral pellets, binder quantity optimization involved. Formulation # DL3 finalized for next optimization of next coat i.e. seal coat.

5.6.3. Seal coated pellets
Seal coat or barrier coat was applied before enteric coat to avoid degradation of PTZ due to acidic enteric coat. Generally, seal coat applied up to 50 micron is enough as barrier. Film former polymers like HPMC, HPC suitable for seal coat for pellets. Mostly 'E' or 'F' chemistry HPMC is used due to low viscosity at high solid content. HPMC VLV was newly launched 'F' chemistry HPMC polymer used as binder and film former and can be used up to 20% compared to 10% of HPMC E5.

Table 5.17 Initial risk assessment of seal coated pellets

<table>
<thead>
<tr>
<th>Seal coating formulation variables</th>
<th>Seal coated pellets CQAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder grade</td>
<td>Medium</td>
</tr>
<tr>
<td>Binder level</td>
<td>High</td>
</tr>
<tr>
<td>Viscosity of SC suspension</td>
<td>Low</td>
</tr>
</tbody>
</table>

Dissolution in Stage II

Table 5.18 Justification of initial risk assessment of seal coated pellets

<table>
<thead>
<tr>
<th>Formulation variables</th>
<th>Seal coated pellets CQA</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder grade</td>
<td>Dissolution in Stage II</td>
<td>Higher viscosity polymer grade may retard the drug release in stage II. The risk of the binder grade to impact seal coated (SC) pellet dissolution in Stage II was medium.</td>
</tr>
<tr>
<td>Binder level</td>
<td>Dissolution in Stage II</td>
<td>The level of binder in SC governed the release in stage II. Binder level above optimum can retard the</td>
</tr>
</tbody>
</table>
drug release. The risk of the binder level to impact SC pellet dissolution in Stage II was high.

<table>
<thead>
<tr>
<th>Viscosity of SC suspension</th>
<th>Dissolution in Stage II</th>
<th>SC suspension diluted with purified water independent of binder grade and level for easy sprayable which not affect the dissolution in stage II, hence risk was low.</th>
</tr>
</thead>
</table>

Typically, seal coat contains film coating polymer and anti-tacking agent to reduce polymer tackiness during process. Seal coat 5 to 10% of drug loaded pellets is enough for efficient barrier. In this study, smaller size neutral pellets used which has larger surface are hence 10% seal coat targeted. Below are the seal coating formulations with various HPMC grade of different viscosity to study effect on dissolution.

**Table 5.19 Seal coating formulations**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tab</th>
<th>SC1</th>
<th>SC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loaded pellets (Formulation #DL3)</td>
<td>105.0</td>
<td>105.0</td>
<td></td>
</tr>
<tr>
<td>HPMC E5</td>
<td>10.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HPMC VLV</td>
<td>-</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>3.2</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s</td>
<td>q.s</td>
<td></td>
</tr>
</tbody>
</table>

HPMC dissolved in purified water to get lump free solution followed by aqueous homogenize (Ultra-turrex®, IKA, Germany) dispersion of talc and stirred for 30 min using stirrer (Remi Elektrotechnik Ltd, India). Strained the dispersion through 80 mesh screen. Purified water added to make HPMC content 18% w/w. Load the seal coating suspension on drug loaded pellets in Wurster (GPCG 1.1, Glatt) in pre-warm assembly. Performed the seal coating process as per parameters mentioned in Table 5.20.

**Table 5.20 Process parameters for seal coating**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
</tr>
</tbody>
</table>
Batch Size (Initial load) 600 gm
Spray nozzle 1.0 mm
Spray rate 4-10 g/min
Atomization air pressure 0.9-1.1 bar
Air volume 45-60 cfm
Product temperature 36-42 °C
Inlet temperature 38-55 °C

Seal coating trials performed as per formulations discussed at Table 5.20 and formulation # SC2 finalized for next optimization of next coat i.e. Enteric coat.

5.6.4. Enteric coated pellets
Enteric coating was the functional coating for this formulation. In PTZ MUPS tablet, drug needed to protect in upper part of intestine where pH is 1.2-4.5. Methacrylic acid co-polymer are well known for enteric protection in upper part of intestine and practically easy to apply on pellets compared to existing others enteric coating polymer.
Eudragit L30D-55 is the dispersion grade of methacrylic polymer which required additionally -
1) Plasticizer to reduce the glass transition temperature (Tg), and to form a film of polymer e.g. Triethyl citrate (TEC)
2) Anti-tacking agent, to reduced tackiness of polymer and to avoid agglomerate formation of pellets during process e.g. Talc
3) Emulsifying agent, to form homogeneous dispersion e.g. Polysorbate 80.
Talc has tendency to settled down during processing. Nowadays, glycerol monostearate (GMS) used as anti-tacking agent which overcomes all disadvantages of talc. However enteric coating dispersion preparation with GMS is very critical. PlasACRYL HTP20 is the newly launched ready mix dispersion contained plasticizer (TEC), anti-tacking agent (GMS) and emulsifying agent (Polysorbate 80)
### Table 5.21 Initial risk assessment of enteric coated pellets

<table>
<thead>
<tr>
<th>Enteric coated pellets formulation variables</th>
<th>Enteric coated pellets CQAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
</tr>
<tr>
<td>Polymer grade</td>
<td>High</td>
</tr>
<tr>
<td>Polymer level</td>
<td>High</td>
</tr>
<tr>
<td>PlasACRYL HTP20 level</td>
<td>High</td>
</tr>
</tbody>
</table>

### Table 5.22 Justification of initial risk assessment of enteric coated pellets

<table>
<thead>
<tr>
<th>Formulation Variables</th>
<th>Enteric coated pellets CQA</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer grade</td>
<td>Dissolution in Stage I</td>
<td>Various enteric coating polymers has different film forming tendency which withstands the film after compression. Stronger enteric film resist the acid degradation more. So the risk of the polymer grade to impact EC pellet dissolution in Stage I was high.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II</td>
<td>Total drug release was the addition of drug release in Stage I and Stage II. If the drug release was variable in stage I it may affect on release in stage II. The risk of the polymer grade to impact EC pellet dissolution in Stage II was medium.</td>
</tr>
<tr>
<td>Polymer level</td>
<td>Dissolution in Stage I</td>
<td>Polymer level directly linked with drug release in acidic media. Hence, the risk of the polymer level to impact EC pellet dissolution in Stage I was high.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II</td>
<td>Polymer level determined the drug release in acidic media. Variation of drug release in stage I affected the stage II drug release up to some extent. Hence the risk was medium.</td>
</tr>
<tr>
<td>PlasACRYL HTP20 level</td>
<td>Dissolution in Stage I</td>
<td>PlasACRYL HTP20 contained plasticizer, anti-tack agent and wetting agent. Plasticizer quantity altered the film properties which affected the drug release. The risk of the PlasACRYL HTP20 level to impact EC pellets and tablet dissolution in Stage I was high.</td>
</tr>
</tbody>
</table>
dissolution in stage I and II was high.

Table 5.23 Enteric coating formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>EC1</th>
<th>EC2</th>
<th>EC3</th>
<th>EC4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seal coated pellets (Formulation #SC2)</td>
<td>118.7</td>
<td>118.7</td>
<td>118.7</td>
<td>118.7</td>
</tr>
<tr>
<td>Eudragit L30D-55</td>
<td>70</td>
<td>100</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>PlasACRYL HTP20</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

**Blending % (w/w)**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>EC1</th>
<th>EC2</th>
<th>EC3</th>
<th>EC4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric coated pellets</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Ceolus 802)</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Pearlitol Flash</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel PH 200)</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Mannitol (Pearlitol DC 400)</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Neotame</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Strawberry flavour</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide (Aerosil 200)</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Prior to use PlasACRYL HTP20 shaken well in container before use. PlasACRYL HTP20 added in Eudragit L30D-55 dispersion under slow stirring followed by purified water. Stirred the dispersion for 30 min using stirrer and strained through 100 mesh screen. Purified water added to maintain 20% w/w solid content. Seal coated pellets loaded in Wurster (GPCG 1.1, Glatt) and pellets coated using process parameters mentioned in Table 5.24.

All extragranular excipients were sifted through 40 mesh sieves. Cushion coated pellets co-sifted with Ceolus through 30 mesh sieves, labeled as co-sift I. Crospovidone, flavour and neotame were co-sifted through 40 mesh sieves, labeled as co-sift II. Aerosil was co-sift with 1/4th quantity of Pearlitol 400 DC through 40 mesh sieves, labeled as co-sift III. Pre-sifted Avicel PH 200 was mixed with co-sift I followed by co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol 400
DC in double cone blender and rotated for 300 revolutions and then finally added the sifted magnesium stearate and rotated for another 50 revolutions. Compressed the blend using process parameters mentioned in Table 5.24.

**Table 5.24 Process parameters for enteric coating**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size</td>
<td>600 gm</td>
</tr>
<tr>
<td>Spray nozzle</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-10 g/min</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.2 g/min</td>
</tr>
<tr>
<td>Air volume</td>
<td>45-60 cfm</td>
</tr>
<tr>
<td>Product temperature</td>
<td>26-28 °C</td>
</tr>
<tr>
<td>Inlet temperature</td>
<td>26-35 °C</td>
</tr>
<tr>
<td><strong>Compression</strong></td>
<td></td>
</tr>
<tr>
<td>Machine Model</td>
<td>Fette P 2020</td>
</tr>
<tr>
<td>Feeder rod design</td>
<td>Round</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>2.5-4.0 kN</td>
</tr>
<tr>
<td>Main Compression force</td>
<td>10-14 kN</td>
</tr>
<tr>
<td>Turret Speed</td>
<td>25-30 rpm</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>0.8-1.5 times of turret speed</td>
</tr>
</tbody>
</table>

Enteric coating trials performed as per formulations discussed at Table 5.23 and formulation # EC3 was considered for next coat i.e. cushion coat optimization, however systematic optimization study performed in formula optimization section.

**5.6.5. Cushion coated pellets**

After the compression of blend of enteric coated formulation # EC1 to EC4 (30%) and extragranular excipients formula # EG 3 (70%) concluded that enteric coat has less flexibility hence more than 10% drug release in acidic media. Cushion coating was the additional coat required to overcome damage of enteric coat after compression. There are two type of cushion coating materials i.e. water soluble and water insoluble,
however in this research immediate release was targeted in stage II so water soluble cushion coating material used.

Table 5.25 Initial risk assessment of cushion coated pellets

<table>
<thead>
<tr>
<th>Cushion coated pellets formulation variables</th>
<th>Cushion coated pellets CQAs</th>
<th>Splitability</th>
<th>Dissolution in Stage I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushioning agent level</td>
<td>Medium</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Binder grade</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Binder level</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.26 Justification of initial risk assessment of cushion coated pellets

<table>
<thead>
<tr>
<th>Formulation Variables</th>
<th>Cushion coated pellets CQAs</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushioning agent level</td>
<td>Splitability</td>
<td>Cushioning material had tendency to fuse the pellets after compression. Higher level made maximum pellets fusion which lead to non-uniform split of tablet. The risk of the cushioning agent level to impact tablet in splitability was medium.</td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td></td>
<td>Level of cushioning agent decided the cleavage of EC pellets during compression. Hence risk was high.</td>
</tr>
<tr>
<td>Binder grade</td>
<td>Splitability</td>
<td>Binder grade not affected on the tablet splitability. The risk of the binder grade to impact tablet splitability was low.</td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td></td>
<td>Any binder could taken for CC because its role to adhered the cushioning agent and it would easily dissolve in stage I dissolution. The risk of the binder grade to impact EC pellet dissolution in Stage I was low.</td>
</tr>
<tr>
<td>Binder level</td>
<td>Splitability</td>
<td>Binder grade not affected on the tablet splitability. The risk of the binder grade to impact tablet splitability was low.</td>
</tr>
</tbody>
</table>

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The level of binder in CC would not affect the release in stage I. The risk of the binder level to impact CC pellet dissolution in Stage I was low.

Table 5.27 Cushion coating formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC1</td>
</tr>
<tr>
<td>Enteric coated pellets (Formulation # EC3)</td>
<td>267.7</td>
</tr>
<tr>
<td>Polyethylene Glycol 6000</td>
<td>5.35</td>
</tr>
<tr>
<td>HPMC 6cps</td>
<td>0.8</td>
</tr>
<tr>
<td>Neotame</td>
<td>1.0</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0</td>
</tr>
<tr>
<td>Red oxide of Iron</td>
<td>0.1</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s</td>
</tr>
<tr>
<td><strong>Blending</strong></td>
<td></td>
</tr>
<tr>
<td>Enteric coated pellets</td>
<td>30%</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Ceolus 802)</td>
<td>5%</td>
</tr>
<tr>
<td>Pearlitol Flash</td>
<td>17.5%</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel PH 200)</td>
<td>17.5%</td>
</tr>
<tr>
<td>Mannitol (Pearlitol DC 400)</td>
<td>17.5%</td>
</tr>
<tr>
<td>Crospovidone (Kollidon CL-SF)</td>
<td>10%</td>
</tr>
<tr>
<td>Neotame</td>
<td>0.5%</td>
</tr>
<tr>
<td>Strawberry flavour</td>
<td>1.0%</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide (Aerosil 200)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

HPMC, PEG 6000 and neotame dissolved in purified water followed by aqueous homogenize dispersion of talc and colour and mixed for 30 min using stirrer. Strained the dispersion through 80 mesh screen and loaded on enteric coated pellets in Wurster (GPCG 1.1, Glatt) at suitable process parameters. Purified water added to maintained 10% w/w solid content. Seal coated pellets loaded in Wurster (GPCG 1.1, Glatt) and coat pellets using process parameters mentioned in Table 5.28.
All extragranular excipients were sifted through 40 mesh sieves. Cushion coated pellets co-sifted with Ceolus through 30 mesh sieves, labeled as co-sift I. Crospovidone, flavour and neotame were co-sifted through 40 mesh sieves, labeled as co-sift II. Aerosil was co-sift with 1/4th quantity of Pearlitol 400 DC through 40 mesh sieves, labeled as co-sift III. Pre-sifted Avicel PH 200 was mixed with co-sift I followed by co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol 400 DC in double cone blender and rotated for 300 revolutions and then finally added the sifted magnesium stearate and rotated for another 50 revolutions. Compressed the blend using process parameters mentioned in Table 5.28.

### Table 5.28 Process parameters of cushion coating

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size</td>
<td>600 gm</td>
</tr>
<tr>
<td>Spay nozzle</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-10 g/min</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.2 g/min</td>
</tr>
<tr>
<td>Air volume</td>
<td>45-60 cfm</td>
</tr>
<tr>
<td>Product temperature</td>
<td>36-42 °C</td>
</tr>
<tr>
<td>Product temperature</td>
<td>38-55 °C</td>
</tr>
<tr>
<td><strong>Compression</strong></td>
<td></td>
</tr>
<tr>
<td>Machine Model</td>
<td>Fette P 2020</td>
</tr>
<tr>
<td>Feeder rod design</td>
<td>Round</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>2.5-4.0 kN</td>
</tr>
<tr>
<td>Main Compression force</td>
<td>10-14 kN</td>
</tr>
<tr>
<td>Turret Speed</td>
<td>25-30 rpm</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>0.8-1.5 times of turret speed</td>
</tr>
</tbody>
</table>

Cushion coating trials performed as per formulations discussed at Table 5.28 and formulation # CC2 was considered to optimize percentage of extragranular excipients component.
5.6.6. Extragranular excipients

Role of extragranular excipients was equally similar with cushion coating which protect the cleavage of enteric coated pellets during compression. As percentage of extragranular excipient increased, cushioning to enteric coated pellets increased however adversely affect on physical properties of tablets.

Table 5.29 Initial risk assessment of extragranular excipients

<table>
<thead>
<tr>
<th>Extragranular excipients formulation variables</th>
<th>Drug product CQAs</th>
<th>Dissolution in Stage I</th>
<th>Dissolution in Stage II</th>
<th>Content uniformity</th>
<th>Splitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceolus KG 1000 level</td>
<td>High, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Pearlitol Flash level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Avicel PH 200 level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Pearlitol DC 400 level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Crospovidone level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Aerosil level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
<tr>
<td>Magnesium stearate level</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Low, Medium</td>
<td>Low, Medium, Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 5.30 Justification of initial risk assessment of extragranular excipients

<table>
<thead>
<tr>
<th>Formulation Variables</th>
<th>Drug product CQAs</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceolus KG 1000 level</td>
<td>Dissolution in Stage I</td>
<td>Ceolus used as cushioning agent which protected the pellets from cleavage during compression. Hence risk was high.</td>
</tr>
<tr>
<td></td>
<td>Content uniformity</td>
<td>Ceolus is fibrous in nature. It higher concentration, it was acted as good cushioning but hampered the blend flow which affected the blend uniformity (BU) hence content uniformity. Hence risk was medium.</td>
</tr>
<tr>
<td>Avicel PH 200 level</td>
<td>Splitability</td>
<td>Avicel PH 200 used to improve compressibility of blend. If level of Avicel was suboptimal then it was impacted on tablet hardness so impact on tablet</td>
</tr>
</tbody>
</table>
Pearlitol DC 400 level | Content uniformity | Mean PSD of Pearlitol 400 DC was 360 µm. Pearlitol mainly used to overcome blend uniformity issue due to PSD was comparable with CC pellets. Hence risk was medium.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>EE1</th>
<th>EE2</th>
<th>EE3</th>
<th>EE4</th>
<th>EE5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric coated pellets (Formulation #CC2)</td>
<td>30.0</td>
<td>30.0</td>
<td>30.0</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Ceolus KG1000)</td>
<td>0.6 (2*)</td>
<td>1.5 (5*)</td>
<td>3.0 (10*)</td>
<td>1.5 (5*)</td>
<td>1.5 (5*)</td>
</tr>
<tr>
<td>Pearlitol Flash</td>
<td>17.5</td>
<td>17.5</td>
<td>17.5</td>
<td>17.5</td>
<td>-</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel PH 200)</td>
<td>17.5</td>
<td>17.5</td>
<td>17.5</td>
<td>35.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Mannitol (Pearlitol DC 400)</td>
<td>17.5</td>
<td>17.5</td>
<td>17.5</td>
<td>-</td>
<td>17.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Neotame</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Strawberry flavour</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide (Aerosil 200)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Percentage of Ceolus KG1000 wrt pellets

All extragranular excipients were sifted through 40 mesh sieves. Cushion coated pellets co-sifted with Ceolus through 30 mesh sieves, labeled as co-sift I. Crospovidone, flavour and neotame were co-sifted through 40 mesh sieves, labeled as co-sift II. Aerosil was co-sift with 1/4th quantity of Pearlitol 400 DC through 40 mesh sieves, labeled as co-sift III. Pre-sifted Avicel PH 200 was mixed with co-sift I followed by co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol 400 DC in double cone blender and rotated for 300 revolutions and then finally added the sifted magnesium stearate and rotated for another 50 revolutions. Compressed the blend using process parameters mentioned in Table 5.32.
Table 5.32 Compression process parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machine Model</td>
<td>Fette P 2020</td>
</tr>
<tr>
<td>Feeder rod design</td>
<td>Round</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>2.5-4.0 kN</td>
</tr>
<tr>
<td>Main Compression force</td>
<td>10-14 kN</td>
</tr>
<tr>
<td>Turret Speed</td>
<td>25-30 rpm</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>0.8-1.5 times of turret speed</td>
</tr>
</tbody>
</table>

5.7. Formula optimization

Out of four pellets coating step, enteric coating formulation was the critical which optimized. Along with enteric coating formulation, ratio of enteric coating to extragranular excipients altered the CQAs prominently based on the preliminary trials. Along with main drug product CQA i.e. dissolution in stage I and stage II selected in-process CQAs (physical parameters of tablet) also considered important i.e. Hardness, disintegration time and friability, those affected the quality of PTZ MUPS.

The independent variables selected were the quantity of dry polymer ($X_1$), quantity of PlasACRYL HTP20 ($X_2$) and percentage of pellets in tablet ($X_3$). The dependent variables were release in 0.1N HCl at 120min ($Y_1$), release in pH 6.8 at 30min ($Y_2$), hardness ($Y_3$), disintegration time ($Y_4$) and friability ($Y_5$). The concentration ranges of independent variables showed in Table 5.33 along with their low, medium, and high levels, which were selected based on the results from preliminary experimentation.

The quantity of dry polymer ($X_1$), quantity of HTP 20 ($X_2$) and percentage of pellets in tablet ($X_3$) used to prepare the 10 formulations (including 2 centre point formulation) mentioned in Table 5.33.

Table 5.33 $2^3$ Full Factorial Design - factors, levels and successful operating range (DoE 1)

<table>
<thead>
<tr>
<th>Independent variables (Formulation Variables)</th>
<th>Unit</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$ : Quantity of Dry Polymer</td>
<td>mg</td>
<td>80</td>
</tr>
<tr>
<td>$X_2$ : Quantity of HTP20</td>
<td>mg</td>
<td>22</td>
</tr>
</tbody>
</table>
5.8. Manufacturing process development

PTZ MUPS tablet manufacturing had 3 steps, i.e., Pellets coating, blending and compression, presented in Figure 5.2. It also presented how input material attributes and manufacturing process parameters can potentially impact intermediate and finished product quality attributes. The attributes of input raw materials and the process parameters used at the very first unit operation determine the quality attributes of the output material (intermediate) produced at this step. Attributes of the intermediate and processing parameters of the subsequent unit operations in the manufacturing scheme were determined quality attributes of the next intermediate and, eventually, those of the finished drug product. This cycle repeated until the final unit operation where finished product was manufactured and the finished product quality attributes were evaluated.

<table>
<thead>
<tr>
<th>Dependent variables (CQAs)</th>
<th>Unit</th>
<th>Successful operating range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Y_1$: Release in 0.1N HCl (at 120 min)</td>
<td>%</td>
<td>$&lt; 10$</td>
</tr>
<tr>
<td>$Y_2$: Release in pH 6.8 (at 30 min)</td>
<td>%</td>
<td>$70 &lt; Y_2 &lt; 80$</td>
</tr>
<tr>
<td>$Y_3$: Hardness</td>
<td>N</td>
<td>$&gt; 30$</td>
</tr>
<tr>
<td>$Y_4$: Disintegration time</td>
<td>Sec</td>
<td>$&lt; 30$</td>
</tr>
<tr>
<td>$Y_5$: Friability</td>
<td>%</td>
<td>$&lt; 1.0$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X&lt;sub&gt;3&lt;/sub&gt;: Percentage of Pellets in tablet</th>
<th>25</th>
<th>37.5</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material attributes of input materials</td>
<td>Process parameters</td>
<td>Manufacturing process steps</td>
<td>Quality attributes of output materials</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------------</td>
<td>----------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>✓ Drug substance solid state form</td>
<td>✓ Inlet air volume</td>
<td>Drug Loading</td>
<td>Assay</td>
</tr>
<tr>
<td>✓ Drug substance PSD</td>
<td>✓ Inlet air temperature</td>
<td></td>
<td>Uniformity</td>
</tr>
<tr>
<td>✓ Type of neutral pellets</td>
<td>✓ Product temperature</td>
<td></td>
<td>Dissolution</td>
</tr>
<tr>
<td>✓ Neutral pellets size</td>
<td>✓ Spray rate</td>
<td></td>
<td>LOD</td>
</tr>
<tr>
<td>✓ Binder type/grade</td>
<td>✓ Nozzle diameter and number of nozzles</td>
<td>Seal Coating</td>
<td>Coating efficiency</td>
</tr>
<tr>
<td>✓ Binder</td>
<td>✓ Atomization air pressure</td>
<td></td>
<td>After Screened: PSD, Fines/Agglomerates</td>
</tr>
<tr>
<td>✓ Level of Stabilizer</td>
<td>✓ Partition diameter and height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Drug loaded pellets</td>
<td>✓ Capacity utilized</td>
<td>Enteric Coating</td>
<td>Dissolution</td>
</tr>
<tr>
<td>✓ PSD, Assay, LOD and Dissolution</td>
<td>✓ Inlet air dew point</td>
<td></td>
<td>LOD</td>
</tr>
<tr>
<td>✓ Binder grade</td>
<td>✓ Filter type</td>
<td></td>
<td>Coating efficiency</td>
</tr>
<tr>
<td>✓ Binder level</td>
<td>✓ Filter shake</td>
<td></td>
<td>After Screened: PSD, Fines/Agglomerates</td>
</tr>
<tr>
<td>✓ Viscosity of seal coating suspension</td>
<td>interval/duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Holding time</td>
<td>Cusion Coating</td>
<td>Dissolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coating efficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After Screened: PSD, Fines/Agglomerates</td>
</tr>
<tr>
<td>✓ Seal coated pellets</td>
<td>✓ Screen size</td>
<td>Lubricated blend</td>
<td>Lubricated blend</td>
</tr>
<tr>
<td>✓ PSD, Assay, LOD and Dissolution</td>
<td>✓ Screen type</td>
<td></td>
<td>Blend uniformity</td>
</tr>
<tr>
<td>✓ Polymer grade</td>
<td></td>
<td></td>
<td>PSD</td>
</tr>
<tr>
<td>✓ Polymer level</td>
<td></td>
<td></td>
<td>Bulk density</td>
</tr>
<tr>
<td>✓ PlasACRYL HTP20 level</td>
<td></td>
<td></td>
<td>Flowability</td>
</tr>
<tr>
<td>✓ Seal coated pellets</td>
<td></td>
<td></td>
<td>Compressibility/Compactability</td>
</tr>
<tr>
<td>✓ PSD, Assay, LOD and Dissolution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Cushioning agent level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Binder grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Binder level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Seal coated pellets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ PSD, Assay, LOD and Dissolution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Cushion coated pellets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ PSD, Assay, Dissolution, bulk density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Extragranular excipient type/grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Extragranular excipient type/grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Extragranular excipient type/grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Extragranular excipient type/grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Extragranular excipient moisture content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Holding Time</td>
<td></td>
<td>Blending and Lubrication</td>
<td>Compressed Tablets</td>
</tr>
<tr>
<td>✓ Order of Addition</td>
<td></td>
<td></td>
<td>Disintegration test</td>
</tr>
<tr>
<td>✓ Blender Type/Geometry No. of revolutions (time and speed)</td>
<td></td>
<td></td>
<td>Weight Variation</td>
</tr>
<tr>
<td>✓ Capacity utilized</td>
<td></td>
<td></td>
<td>Hardness</td>
</tr>
<tr>
<td>✓ Compression tooling selection</td>
<td></td>
<td></td>
<td>Spiltability</td>
</tr>
<tr>
<td>✓ Pre-compression force</td>
<td></td>
<td></td>
<td>Friability</td>
</tr>
<tr>
<td>✓ Main compression force</td>
<td></td>
<td></td>
<td>Assay</td>
</tr>
<tr>
<td>✓ Force Press speed</td>
<td></td>
<td></td>
<td>Content uniformity - whole and split</td>
</tr>
<tr>
<td>✓ Ejection force</td>
<td></td>
<td></td>
<td>Drug release profile</td>
</tr>
<tr>
<td>✓ Hopper design: Height and vibration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Hopper fill</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.2 MUPS Manufacturing process flow
Initial risk assessment of manufacturing process

A risk assessment of the overall drug product manufacturing process was performed to identify the high risk steps that could affect the final drug product CQAs. Subsequently, the drug product intermediate CQAs that are directly linked to the identified final drug product CQAs were identified. The process variables that could impact the identified drug product intermediate CQAs became the focus of the risk assessment to determine which variables have the highest potential to cause a CQA failure. These variables then needed to be investigated in order to optimize the drug product manufacturing process and reduce the risk of failure. For example, the overall risk assessment of the manufacturing process found assay of the tablets to be at high risk of failure due to the drug loading step. Subsequently, assay of the drug loaded pellets was directly linked to final tablet assay and was identified as the CQA of the drug loaded pellets. Process variables that could directly impact the assay of the drug loaded pellets were assessed to identify which of the variables could have the highest potential to cause a bead assay failure.

In the initial risk assessment of the overall manufacturing process shown in Table 5.34, drug loading, enteric coating, blending, lubrication, and compression were identified as high risk steps. Justification for each risk assignment is presented in Table 5.35.

Table 5.34 Initial risk assessment of manufacturing process for PTZ MUPS tablets

<table>
<thead>
<tr>
<th>Process Component</th>
<th>Drug Product CQAs</th>
<th>Assay</th>
<th>Dissolution in Stage I</th>
<th>Dissolution in Stage II</th>
<th>Content uniformity</th>
<th>Splitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loading</td>
<td></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Sieving I</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Seal coating</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sieving II</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Enteric coating</td>
<td></td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sieving III</td>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Cushion coating</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sieving IV</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Blending and Lubrication</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Compression</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.35 Justification for the initial risk assessment of manufacturing process for PTZ MUPS tablets

<table>
<thead>
<tr>
<th>Process steps</th>
<th>Drug product CQA</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loading Assay</td>
<td>Poor adhesion and/or spray drying had an impact on the potency of the drug-layered pellets. The risk of impact on tablet assay was high.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>Dissolution in stage I was determined for EC pellet formulation and the EC step and was not related to the drug layering step, risk was low.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>Rapid dissolution of the drug loaded pellets was achieved during formulation development. The risk of the drug layering process variables to impact drug release from whole tablets was low.</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Non-uniform fluidization may lead to some pellets receiving more layering than others. The risk of the drug layering process variables to impact the uniformity of the pellets, and therefore the tablet CU, was medium.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>The weight gain was low. Even impact of coating variability on pellet size was minimal and the risk of the drug loading process variables to impact tablet physical attributes was low.</td>
<td></td>
</tr>
<tr>
<td>Seal coating and Cushion Coating Assay</td>
<td>Assay was mainly determined by the drug loading step. Although attrition of the drug loaded and enteric coated pellets may occur during initial seal coating and cushion coating respectively, the risk of the seal coating and cushion coating process variables to impact tablet assay was low.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>Dissolution in stage I is determined for EC pellet formulation and the EC coating step and was not related to the seal coating and cushion coating step, risk was low.</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>There was few possibilities that seal coating and cushion coating ingredients may affect the drug dissolution in stage II and not due to process any ways. Hence risk was low.</td>
<td></td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Drug uniformity of the pellets was mainly determined by the drug layering process step and was unaffected by the SC and CC coating process variables. The risk of the SC and CC coating process variables to impact tablet CU was low.</td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>The weight gain was low. Even impact of coating variability on pellet size was minimal and the risk of the SC and CC process variables to impact tablet physical attributes was low.</td>
<td></td>
</tr>
<tr>
<td>Enteric coating</td>
<td>Assay was mainly determined by the drug loading step. Although attrition of the drug loaded pellets may occurred during initial seal coating and cushion coating, the risk of the seal coating and cushion coating process variables to impact tablet assay was low.</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>Assay was mainly determined by the drug loading step. Although attrition of the drug loaded pellets may occurred during initial seal coating and cushion coating, the risk of the seal coating and cushion coating process variables to impact tablet assay was low.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage I</td>
<td>EC was the functional coating which alter the dissolution in stage I of tablet. The risk of the EC coating process variables to impact drug release in dissolution in stage I from tablets was high.</td>
<td></td>
</tr>
<tr>
<td>Dissolution in Stage II</td>
<td>Total drug release was the addition of drug release in stage I and II. If EC process affected the drug release in stage I significantly so it indirectly affected the drug release in stage II. The risk of extragranular excipients to impact tablet release in stage II was medium.</td>
<td></td>
</tr>
<tr>
<td>Step</td>
<td>Content uniformity</td>
<td>Drug uniformity of the pellets was studied for drug loading process step and was unaffected by the EC coating process variables. The risk of the EC coating process variables to impact tablet CU was low.</td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Splitability</td>
<td>Even weight gain was high, impact of coating variability on pellet size was minimal and the risk of the EC process variables to impact tablet physical attributes was low.</td>
</tr>
<tr>
<td>Sieving I, II, IV</td>
<td>Assay</td>
<td>The main purpose of the sieving I, II and IV step was to screen out agglomerates and fines produced during the drug loading process. The risk of this separation procedure to impact the drug product CQAs was low</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Content uniformity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splitability</td>
<td></td>
</tr>
<tr>
<td>Sieving III</td>
<td>Assay</td>
<td>The main purpose of the sieving III step was to screen out agglomerates and fines produced during the EC coating step. The risk of this separation procedure to impact physical attributes, assay, or content uniformity of the tablets was low</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
<td>There was a possibility of EC coated pellets may be crushed if excessive force is used during sieving III. This might changed the drug release profile. The risk of sieving III to impact the drug release from tablets was medium.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage II</td>
<td>There was less percentage of pellets those polymer film may damaged due to excessive force during sieving III. Hence risk was low.</td>
</tr>
<tr>
<td>Blending and Lubrication</td>
<td>Assay</td>
<td>Blending process variables impacted BU. However, good flowability of the final blend was achieved during formulation development which would</td>
</tr>
<tr>
<td>Process</td>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Stage I</td>
<td>Blending process variables might impacted the distribution of the extragranular excipients and pellets. The risk of impact on tablet drug release was medium.</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Stage II</td>
<td>Incomplete distribution of pellets might possible during blending, lubrication and unloading from blender. If segregation occurred, the CU of the final drug product would be impacted. The risk of impact on tablet CU was high.</td>
</tr>
<tr>
<td>Content uniformity</td>
<td></td>
<td>Due insufficient blending, pellets distribution would be non-uniform in blend hence non-uniform distribution in tablet also. Hence the risk of impact on tablet splitability was medium.</td>
</tr>
<tr>
<td>Compression</td>
<td>Assay</td>
<td>Segregation might occurred during transfer of blend from container to hopper, in the force feeder and on turret which directly impacted the tablet assay. The risk of the compression process variables to impact the tablet splitability was high.</td>
</tr>
<tr>
<td>Content uniformity</td>
<td></td>
<td>Excessive compression force damaged the integrity of the enteric coat and impacted the drug release in stage I. The risk of compression process variables to impact tablet drug release in stage I was high.</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Stage I</td>
<td>If significant drug release occurred in stage I dissolution due to compression process variables then it impacted the dissolution in stage II. The risk of compression process variables to impact tablet drug release in stage II was high.</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Stage II</td>
<td>Score design of punch tooling and compression force applied for tabletting impact the tablet splitability. The risk of the compression process</td>
</tr>
</tbody>
</table>
variables to impact the tablet splitability was high.

Out of number of manufacturing steps of PTZ MUPS tablets; it seems that drug loading, enteric coating, sieving III, blending and lubrication and compression processes were critical for quality product.

5.8.1. Drug loading process development

In the traditional FMEA, the risk priority number (RPN) is used to conduct the risk assessment. Potential failure shows the risk factors as Severity (S), Occurrence (O) and Detection (D). The three factors are all scored from 1 (best) to 10 (worst) on the basis of degree (Stamatis D H, 2003; Xiao N, 2011). RPN is the product of occurrence, detection, and severity, which is expressed as, $RPN = S \times O \times D$, where S, the severity, which is a measure of how severe of an effect a given failure mode would cause; we ranked these as 8-10, severe effect; 4-7, moderate effect; and 1, no effect. The parameter O is the occurrence probability or the likelihood of an event occurring; we ranked these as 8-10, likely to occur; 4-7, 50:50 chance of occurring; and 1, unlikely to occur. The final parameter D is the detectability or the ease that a failure mode can be detected, because the more detectible a failure mode is, the less risk it presents to product quality. For D, we ranked 1-3 as easily detectable, 4-7 as moderately detectable, and 8-10 as hard to detect, and then a maximum RPN of 1000 and a minimum RPN of 1 are possible.

The RPN threshold was set at 80, and any formulation variable with an RPN 40 or above was regarded as a potential critical factor, that is, potential risks are evaluated by subsequent formulation variable studies since it possibly has a potential impact on CQAs and in consequence on product safety and efficacy, while factors with a lower RPN can be eliminated from further study (Vogt F G et al., 2011; Masoud H, 2011). The initial risk assessment of the overall manufacturing process presented in Table 5.34 identified the risk of the drug loading step to impact assay of the drug product as high. Subsequently, assay of the drug loaded pellets was identified as a CQA for the drug layering step. Process variables that could potentially impact assay of the drug loaded pellets were identified and their associated risk was evaluated. Initially, all process variables ranked as low to medium risk during the assessment were set constant based on feasibility studies and previous experience. The variables ranked as high risk were evaluated by conducting more trials to understand process.
Figure 5.3 Initial risk assessment of drug loading process

Assay of the drug loaded pellets will be controlled in the range of 90.0-110.0% (Target : 95.0 – 105.0%) of label claim. A suboptimal process may generate excessive fines or agglomerates which could adversely affect the drug loaded pellets assay. Figure 5.3 summarized the initial risk assessment of the identified drug loading process variables that may impact the drug loaded pellets assay.

Table 5.36 Drug loading process parameters

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>DLP1</th>
<th>DLP2</th>
<th>DLP3</th>
<th>DLP4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size</td>
<td>500gm</td>
<td>500gm</td>
<td>500gm</td>
<td>500gm</td>
</tr>
<tr>
<td>Air distribution plate</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Partition column height</td>
<td>12-18 mm</td>
<td>12-18 mm</td>
<td>12-18 mm</td>
<td>12-18 mm</td>
</tr>
<tr>
<td>Nozzle tip diameter</td>
<td>1.0 mm</td>
<td>1.0 mm</td>
<td>1.0 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Bonnet filter porosity</td>
<td>100 µ</td>
<td>100 µ</td>
<td>100 µ</td>
<td>100 µ</td>
</tr>
<tr>
<td>Product temperature</td>
<td>35-38°C</td>
<td>38-41°C</td>
<td>41-45°C</td>
<td>35-38°C</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.1 bar</td>
<td>0.9-1.1 bar</td>
<td>0.9-1.1 bar</td>
<td>1.1-1.4 bar</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-11 g/min</td>
<td>4-11 g/min</td>
<td>4-11 g/min</td>
<td>4-11 g/min</td>
</tr>
</tbody>
</table>
Formulation V4 used for optimization trial. Starting MCC spheres size was 150-300µ hence air distribution plat type B selected as per Wurster vendor’s guidance and 100µ bonnet filter selected to avoid loss of pellets during fluidization. Ranges of spray rate, and air volume studies during preliminary trials and finalized. Initially, partition column height kept 12 mm and as coating proceeded and weight build up increased, height increased at intervals up to 18 mm to keep pellets in optimum fluidization condition.

Product temperature and atomization air pressure were the main process variables impact the drug loaded pellets assay. Product temperature below 34°C, agglomerate formation start at spray rate more than 8 g/min. During spray test, it was observed that atomization air pressure below 0.8 bar, big droplets formed of coating suspension which may leads to agglomerates formation. Hence, product temperature study range start from 35°C and atomization air pressure from 0.9 bar.

5.8.2. Seal coating and cushion coating process development

![Initial Risk Assessment](image_url)

Figure 5.4 Initial risk assessment of drug loading process
Seal coating and cushion coating contains common ingredients like HPMC, talc and the both coating process has intend to protect the previous coat. Process parameters were same for both coating. As per Table 5.35, seal coating and cushion coating processes not impacted any drug product CQAs. Hence both processes were found less critical than other processes. During these processes, severe static charge generated which overcome by maintaining dew point up to 10°C.

Table 5.37 Seal coating process parameters

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>SCP1</th>
<th>SCP2</th>
<th>SCP3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size</td>
<td>600gm</td>
<td>600gm</td>
<td>600gm</td>
</tr>
<tr>
<td>Air distribution plate</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Partition column height</td>
<td>12-18 mm</td>
<td>12-18 mm</td>
<td>12-18 mm</td>
</tr>
<tr>
<td>Nozzle tip diameter</td>
<td>1.0 mm</td>
<td>1.0 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Bonnet filter porosity</td>
<td>100 µ</td>
<td>100 µ</td>
<td>100 µ</td>
</tr>
<tr>
<td>Product temperature</td>
<td>35-38°C</td>
<td>38-42°C</td>
<td>42-45°C</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.1 bar</td>
<td>0.9-1.1 bar</td>
<td>0.9-1.1 bar</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-10 g/min</td>
<td>4-10 g/min</td>
<td>4-10 g/min</td>
</tr>
<tr>
<td>Air volume</td>
<td>45-60 cfm</td>
<td>45-60 cfm</td>
<td>45-60 cfm</td>
</tr>
<tr>
<td>LOD</td>
<td>NMT 1.5 %</td>
<td>NMT 1.5 %</td>
<td>NMT 1.5 %</td>
</tr>
</tbody>
</table>

5.8.3. Enteric coating process development

Enteric coating was one of the critical process in manufacturing of PTZ MUPS tablets. Enteric coat efficiency is depend on enteric coating dispersion and coating process. Eudragit L30D-55 has higher Tg which reduced by using plasticizer. So it is challenging to run the enteric coating process without hampering the enteric coat integrity.

The initial risk assessment of the overall manufacturing process presented in Table 5.35 identified the risk of the EC coating step to impact drug release from the drug product as high. Subsequently, drug release from the EC pellets was identified as a CQA for the EC step. Process variables that could potentially impact drug release from the EC pellets were identified and their associated risk was evaluated. Conducting Design of experiments (DoE) to evaluate all the variables involved in a
Wurster coating process was not feasible. Therefore, variables ranked as low to medium risk during the assessment were set constant based on feasibility studies and previous experience. The variables ranked as high risk were evaluated by conducting DoE studies to gain process understanding. Table 5.38 summarized the initial risk assessment of the EC process.

Table 5.38 Initial and updated risk assessment of PTZ EC process

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk assessment</th>
<th>Justification for updated risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>Low</td>
<td>Pam GPCG 1.1 selected for all experimentation</td>
</tr>
<tr>
<td>Partition column diameter</td>
<td>Low</td>
<td>72 mm Wurster column diameter was fixed by equipment</td>
</tr>
<tr>
<td>Air distribution plate</td>
<td>Medium</td>
<td>ADP affected the distribution of pellets during coating however, plate 'B' selected throughout the process based on vendor's specification and practically suitable</td>
</tr>
<tr>
<td>Partition column height</td>
<td>Medium</td>
<td>Partition column height drived the pellets in coating zone. Gap more than optimal or less, could impacted the coating quality. So risk was medium.</td>
</tr>
<tr>
<td>Nozzle tip diameter</td>
<td>Medium</td>
<td>Nozzle tip size might impact atomization and droplet size of coating solution which ultimately affected on coating quality. The risk was medium. However, 1.0 mm nozzle was selected for all batches and hence risk was low.</td>
</tr>
<tr>
<td>Filter type</td>
<td>Medium</td>
<td>Higher the filter porosity, increased the material loss and lower the filter porosity, chances of filter blocking due to spray dried coating material. The risk was medium. A filter porosity of 150µm was selected based on previous experience and kept constant throughout the process. Hence risk was low.</td>
</tr>
<tr>
<td>Coating dispersion variables</td>
<td>Low</td>
<td>The solids content of the coating dispersion was kept 20% based on supplier recommendation and previous experience. Hence risk was low.</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Solids content</td>
<td>Low</td>
<td>The viscosity of coating dispersion was very low 60-110 cps which not affect the coating quality. Hence the risk was low.</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Low</td>
<td>Mixer speed impacted the coating dispersion. The risk of impact on drug release was medium. Proper mixer selection was based on previous experience.</td>
</tr>
<tr>
<td>Mixing</td>
<td>Medium</td>
<td>Higher the temperature, cause excessive static charge, leads to process difficulties. Hence, pre-warming inlet temperature 30-45°C selected.</td>
</tr>
<tr>
<td>Pre-heating variables</td>
<td>Medium</td>
<td>Air volume range of 80-120 cfm was selected based on the past experience and visual observation.</td>
</tr>
<tr>
<td>Inlet air dew point</td>
<td>Medium</td>
<td>Higher the temperature, cause excessive static charge, may leads to process difficulties. Hence, pre-warming product temperature 30-40°C selected because during spraying product temperature required NMT 35°C.</td>
</tr>
<tr>
<td>Inlet air temperature</td>
<td>Medium</td>
<td>Higher the temperature, cause excessive static charge, and affect the drying efficiency. Enteric coating was aqueous based, so no risk of static charge. A dew point of 10-15º C was selected based on previous experience.</td>
</tr>
<tr>
<td>Product temperature</td>
<td>Medium</td>
<td>Higher the temperature, cause excessive static charge, leads to process difficulties. Hence, pre-warming inlet temperature 30-45°C selected.</td>
</tr>
<tr>
<td>Air Volume</td>
<td>Medium</td>
<td>Higher the temperature, cause excessive static charge, may leads to process difficulties. Hence, pre-warming product temperature 30-40°C selected because during spraying product temperature required NMT 35°C.</td>
</tr>
<tr>
<td>Spray variables</td>
<td></td>
<td>Air volume more than optimal increased the attrition of seal coated pellets and lower than optimal cause poor pellets fluidization directly affect the coating quality. The risk was medium. The air volume range of 80-120 cfm was selected based on the past experience and visual observation.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Level</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Inlet air dew point</td>
<td>Medium</td>
<td>Dew point important minimize the static charge and affect the drying efficiency. Enteric coating was aqueous based, so no risk of static charge. A dew point of 10-15°C was selected based on previous experience.</td>
</tr>
<tr>
<td>Shaking interval/duration</td>
<td>Low</td>
<td>Shaking prevents beads from trapping the filter bonnet. The risk was low. Based on previous experience, 120 sec for 3 sec was selected.</td>
</tr>
<tr>
<td>Inlet air temperature</td>
<td>Medium</td>
<td>In this case of enteric coating, higher and lower temperature leads to sticking problem. Hence inlet temperature selected in the range of 30-45°C to achieve product temperature 28-32°C.</td>
</tr>
<tr>
<td>Product temperature</td>
<td>Medium</td>
<td>Enteric coating dispersion contained PlasACRYL HTP20 used as a plasticizer. Product temperature 28-32°C was the best range to form rigid enteric film on the pellets as per supplier specifications and no sticking issues anticipated.</td>
</tr>
<tr>
<td>Air volume</td>
<td>High</td>
<td>Air volume more than optimal might increased the attrition of seal coated pellets and lower than optimal cause poor pellets fluidization directly affect the coating quality. The risk was high. Investigated with DoE to optimize and reduce the risk.</td>
</tr>
<tr>
<td>Spray rate</td>
<td>High</td>
<td>If spray rate was higher than optimal, agglomeration may occur. If spray rate was lower than optimal, spraying time might be long and spray drying might occurred which directly affect the coating quality. Hence risk was high. Investigated with DoE to optimize and reduce the risk.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Level</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>High</td>
<td>If atomization air pressure was higher than optimal, attrition to the beads may occur. If atomization air pressure was lower than optimal, agglomeration may occur, which directly affect the coating quality. Hence risk was high. Investigated with DoE to optimize and reduce the risk.</td>
</tr>
<tr>
<td>Coating time</td>
<td>Low</td>
<td>The coating dispersion not contained ingredients has tendency to settle down. Even though continuous stirring at slow speed was given so no impact on homogeneity of the coating dispersion. The risk was low.</td>
</tr>
<tr>
<td>Drying variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inlet air dew point</td>
<td>Medium</td>
<td>Dew point not affected the functionality of enteric coating however higher dew point reduced the drying efficiency and less increased the static charge. A dew point of less than 10ºC was selected based on previous experience.</td>
</tr>
<tr>
<td>Inlet air temperature</td>
<td>Medium</td>
<td>Enough inlet air temperature was required to dry the pellets after coating. The range was selected 35-45ºC based on previous experience.</td>
</tr>
<tr>
<td>Air volume</td>
<td>Medium</td>
<td>Air volume more than optimal may increased the attrition of seal coated pellets and lower than optimal cause poor pellets fluidization directly affect the coating quality. The risk was medium. The air volume range of 80-120 cfm was selected based on the past experience and visual observation.</td>
</tr>
<tr>
<td>Drying time</td>
<td>Medium</td>
<td>Water content was controlled to prevent microbial growth. The LOD target was NMT 1.5% based on previous experience.</td>
</tr>
</tbody>
</table>
5.8.4. Enteric coating process feasibility study

Feasibility study was performed to test the initial process parameters selected based on scientific literature and previous experience and to set the scope of future studies. The optimized enteric coated pellets formulation V4 was used for this study. After preparation, the coating dispersion was mixed for at least one hour prior to the commencement of spraying. The solids content of the coating dispersion was 20%. Initially dew point was kept 5°C which was increased to 10 ± 2°C. The spray rate was initially 4 g/min and was incrementally ramped up during the course of the feasibility batch. At 10 g/min, agglomeration was observed hence spray rate not exceeded 10 g/min. All process parameters for the lab scale coating feasibility study are summarized in Table 5.39.

Table 5.39 Enteric coating process parameters

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>ECP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td>Batch Size</td>
<td>600gm</td>
</tr>
<tr>
<td>Air distribution plate</td>
<td>B</td>
</tr>
<tr>
<td>Partition column height</td>
<td>12-18 mm</td>
</tr>
<tr>
<td>Nozzle tip diameter</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Bonnet filter porosity</td>
<td>100 µ</td>
</tr>
<tr>
<td>Product temperature</td>
<td>26-28°C</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td>0.9-1.2 bar</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-10 g/min</td>
</tr>
<tr>
<td>Air volume</td>
<td>45-60 cfm</td>
</tr>
<tr>
<td>LOD</td>
<td>NMT 1.5 %</td>
</tr>
</tbody>
</table>

In order to optimize the EC process, DoE studies were performed.

Enteric coating process optimization

A $2^3$ full factorial design with two center points was performed to screen the effect of process parameters on the drug release profile of EC pellets, the amount of fines and agglomerates generated. Moisture content for EC pellets was controlled to not more than 1.5%. The EC pellets were sieved to remove the agglomerates (> 425 µm) and
fines (< 250 µm). Only the pellets fraction between 250 µm and 425 µm will be used for subsequent processing. Yield was also calculated. Table 5.40 summarized the study design and acceptance criteria.

Table 5.40 2³ Full Factorial Design - factors, levels and successful operating range (DoE 2)

<table>
<thead>
<tr>
<th>Independent variables (Process Variables)</th>
<th>Unit</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>X₁ : Air volume</td>
<td>cfm</td>
<td>46 58 70</td>
</tr>
<tr>
<td>X₂ : Spray rate</td>
<td>g/min</td>
<td>3 6 9</td>
</tr>
<tr>
<td>X₃ : Atomization Air Pressure</td>
<td>bar</td>
<td>0.8 1.1 1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dependent variables (CQAs)</th>
<th>Unit</th>
<th>Successful operating range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y₁ : Fines (&lt; 250 µm)</td>
<td>%</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Y₂ : Agglomerate (&gt; 425 µm)</td>
<td>%</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Y₃ : Assay</td>
<td>%</td>
<td>95.0 &lt; Y₃ &lt; 105.0</td>
</tr>
</tbody>
</table>

5.8.5. Blending and lubrication

The initial risk assessment of the overall manufacturing process presented in Table 5.34 identified blending and lubrication as high risk steps that could impact tablet CU and hence drug release from tablets. Subsequently, blend uniformity of the final blend was identified as a CQA for the blending and lubrication step. Process variables that could directly impact blend uniformity were assessed to identify which variables may cause poor blend uniformity.

For further scaling up from pilot scale, following scale up rules was applied.

a. Geometric similarity (constant fill ratio)

Blenders used at different scales shall be geometrically scalable. Percentage occupancy of blend in blender at larger scale shall be kept constant or ± 5% of the pilot scale batch. In lab scale batches, octagonal blender used.

b. Dynamic similarity (maintaining the constant forces)

This shall be done by using Froude’s number (Fr). The formula for Froude’s number is given below.

Fr = Ω² X r / g

Where
Fr = Froude constant  
\( r \) = Radius in meter  
\( \Omega \) = Revolutions/ second  
\( g \) = Gravitational force i.e. 9.81m/sec\(^2\)  

Radius of the Blender shall be calculated considering octagonal blender as sphere:  
Volume in \( M^3 = \frac{4}{3} \pi r^3 \) (Volume of Sphere)  
Where \( \pi = 3.14 \) & \( r \) = Radius in meter.  
\[ R = \left( \frac{3 \times \text{Volume}}{\pi \times 4} \right)^{1/3} \]

Keeping the Froude number constant, RPM shall be calculated for the equipment to be used for scale-up operation.  
e.g. Pilot scale batches dry mixing operation was carried out using 30L capacity octagonal blender and scale up batch planned in 100L capacity octagonal blender.  
For scaling up the dry mixing operation from pilot scale to scale-up, calculate the Froude constant as per below.  
\[ Fr = \frac{\Omega^2 \times r}{g} \]
\[ = (0.3)^2 \times 0.193 / 9.81 \]
\[ = 0.001771 \]
\( r \) = Radius in meter. (0.193m of 30L Capacity blender)  
\( \Omega \) = Revolutions/ second (Blender speed is 18RPM so 0.3 will be revolution per second)  
\( g \) = Gravitational force i.e. 9.81m/sec\(^2\).  
Keep Froude number constant on scale up process in 100L Octagonal blender (Radius- 0.288m).  
\[ Fr = \frac{\Omega^2 \times r}{g} \]
\[ 0.001771 = \frac{\Omega^2 \times 0.288}{9.81} \]
\[ = 0.001771 \times 9.81 / 0.288 \]

\( (\text{Revolutions/ second})^2 = 0.060324 \)
\( \text{Revolution/ second} = 0.245586 \)
\( \text{Revolution/ Minutes} = 0.245586 \times 60 \)

RPM = 14.73 i.e. 15 RPM  
So for 100L octagonal blender 15 RPM shall be maintained.  
c. Kinematic similarity (maintaining consistent number of revolution at all scales)
Based on the total number of revolutions (Dry mixing or Lubrication time X RPM) obtained at pilot scale batch, dry mixing/ lubrication time required at larger scale shall be calculated to achieve the same number of revolutions.

The results of the initial risk assessment of the blending and lubrication process variables are summarized in Table 5.41.

Table 5.41 Risk assessment of blending and lubrication process

<table>
<thead>
<tr>
<th>Output material CQA : Blend uniformity of final blend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Input material attributes</strong></td>
</tr>
<tr>
<td>CC pellets assay</td>
</tr>
<tr>
<td>CC pellets size distribution</td>
</tr>
<tr>
<td>MCC grade (Ceolus KG 1000) PSD</td>
</tr>
<tr>
<td>MCC grade (Avicel 200) PSD</td>
</tr>
<tr>
<td>Mannitol grade (Pearlitol 400 DC) PSD</td>
</tr>
<tr>
<td>Co-processed super-disintegrant Pearlitol Flash PSD</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Crospovidone PSD</td>
</tr>
<tr>
<td>Magnesium stearate specific surface area</td>
</tr>
</tbody>
</table>

**Blending variables**

<table>
<thead>
<tr>
<th>Blender type</th>
<th>Medium</th>
<th>Fixed: Octagonal blender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order of addition</td>
<td>Medium</td>
<td>The risk of the order of addition to impact blend uniformity was medium. The best possible co-sifting and sandwiching method was preferred.</td>
</tr>
<tr>
<td>Rotation speed</td>
<td>Medium</td>
<td>The risk of rotation speed to impact blend uniformity was medium. The rpm was fixed based on Froude number calculation.</td>
</tr>
<tr>
<td>Number of blender revolutions</td>
<td>High</td>
<td>Under- or over-blending may occur if the number of revolutions is not optimized. Investigated to reduce the risk.</td>
</tr>
<tr>
<td>Blender fill level</td>
<td>High</td>
<td>Under-blending may occur due to a suboptimal blender fill level. Blender fill volume always maintained 60% ± 10%.</td>
</tr>
<tr>
<td>Holding time</td>
<td>High</td>
<td>Segregation may occur during holding. The risk of impact on BU is high. Investigated to reduce the risk.</td>
</tr>
<tr>
<td>Blender discharge</td>
<td>High</td>
<td>Segregation may occur during discharge. The risk of impact on BU was high. Investigated to reduce the risk.</td>
</tr>
<tr>
<td>Container to</td>
<td>High</td>
<td>Segregation may occur during transfer. The risk of</td>
</tr>
</tbody>
</table>
hopper transfer impact on BU was high. Investigated to reduce the risk.

**Lubrication variables**

| Number of blender revolutions | Low | Investigated during formulation development. The risk of the number of blender revolutions during lubrication to impact BU was low. |

5.8.6. **Blending and lubrication process optimization**

Geometry of blender (i.e. Octagonal) kept constant from initial trial to prototype formulation. Blender occupancy maintained 60% ± 10% as per previous experience for better blend uniformity. Blender speed calculated based on Froude number calculation. Generally, 300 ± 10 revolution for blending and 50 ± 5 revolution for lubrication enough for better blend uniformity. Optimization performed for 250 and 300 revolution for blending and 40 and 50 revolution for lubrication. Bulk density of formulation V4 was 0.65 g/ml. Blend uniformity studied at blending and lubrication stage.

**Sifting and Co-sifting process:**

All extragranular excipients sifted through 40 mesh sieve. Placebo pellets co-sifted with Ceolus through 40 mesh sieve, labeled as co-sift I. Crospovidone, flavour and neotame co-sifted through 40 mesh sieve, labeled as co-sift II. Aerosil co-sifted with 1/4th quantity of Pearlitol DC 400 through 40 mesh sieve, labeled as co-sift III. Pre-sifted Avicel PH 200 added followed by co-sift I, co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol DC 400 in double cone blender for 250/300 revolutions and sifted magnesium stearate added and lubricate for 40/50 revolutions.

**Table 5.42 2° Blending and lubrication process parameters**

<table>
<thead>
<tr>
<th>Variables</th>
<th>BLP1</th>
<th>BLP2</th>
<th>BLP3</th>
<th>BLP4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blender type</td>
<td>Double cone</td>
<td>Double cone</td>
<td>Double cone</td>
<td>Double cone</td>
</tr>
<tr>
<td>Blender volume</td>
<td>3 Litre</td>
<td>3 Litre</td>
<td>3 Litre</td>
<td>3 Litre</td>
</tr>
<tr>
<td>Blender occupancy</td>
<td>60% ± 10%</td>
<td>60% ± 10%</td>
<td>60% ± 10%</td>
<td>60% ± 10%</td>
</tr>
<tr>
<td>Blender speed</td>
<td>25 rpm</td>
<td>25 rpm</td>
<td>25 rpm</td>
<td>25 rpm</td>
</tr>
<tr>
<td>Blending</td>
<td>250</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>
**5.8.7. Tablet compression process development**

Based on the initial risk assessment of the overall manufacturing process showed in Table 4.35, the risk of the compression step to impact assay, content uniformity, drug release and splitability was identified as high. Process variables that could directly impact these four CQAs were assessed to identify which variables may cause a CQA failure. The results of the initial risk assessment of the compression process variables are summarized in Table 5.43.

<table>
<thead>
<tr>
<th>Variables</th>
<th>DP CQAs</th>
<th>Risk assessment</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Input material attributes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blend assay</td>
<td>Assay</td>
<td>Low</td>
<td>The blending and lubrication process variables were optimized and the assay of the final blend was consistently within 95-105%.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
<td>Low</td>
<td>The risk of the blend assay to impact tablet assay, CU, and tablet drug release was low.</td>
</tr>
<tr>
<td></td>
<td>Content uniformity</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splitability</td>
<td>Low</td>
<td>Splitability was determined by the formulation, tooling design and compression force. Therefore the risk was low.</td>
</tr>
<tr>
<td>Blend uniformity</td>
<td>Assay</td>
<td>Low</td>
<td>The blending and lubrication process variables were optimized and RSD achieved less than 5% RSD. The risk of the blend assay to impact tablet assay, CU, and tablet drug release was low.</td>
</tr>
<tr>
<td></td>
<td>Dissolution in Stage I</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Content uniformity</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
### Splitability

**Low**

Splitability is determined by the formulation, tooling design and compression force. Therefore the risk was low.

### Blend flowability

**Assay**

**Low**

Blend flowability could impact powder flow from the hopper to the feeder frame and ultimately to the die cavity. However, adequate flow was demonstrated during formulation development. Thus, the risk of blend flowability to impact tablet assay, CU and drug release was low.

### Dissolution in Stage I

**Content uniformity**

**Low**

Adequate flow was demonstrated during formulation development. Thus, the risk of blend flowability to impact tablet assay, CU and drug release was low.

### Splitability

**Low**

Blend flow study performed and it easily passed through 15 mm orifice funnel without stirrer. Hence risk is low.

### Blend compressibility and compactability

**Assay**

**Low**

Tablet assay is mainly related to blend flowability, uniformity and tablet weight control. The risk is low.

### Dissolution in Stage I

**Low**

If the compressibility and compactability of the final blend suboptimal, then a greater compression force may be required to form a tablet which may ruptured the polymer coating on the EC pellets. However, the compressibility and compactability were optimized during prototype development. The risk of impact on drug release from whole tablets was low.

### Content uniformity

**Low**

Tablet CU is directly related to BU and flowability. The compressibility and compatibility of the blend, while important, have no direct impact on tablet CU. The risk was low.

### Splitability

**Low**

Compressibility and compactability were optimized during prototype tablet formulation development and tablet easily split. Hence
risk was low.

<table>
<thead>
<tr>
<th>Drug release from the pellets component of the blend</th>
<th>Assay</th>
<th>Not applicable</th>
<th>The drug release profile of the CC pellets was not applicable to tablet assay, CU and splitability.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug release from the pellets component of the blend</td>
<td>Content uniformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splitability</td>
<td>Dissolution in Stage I</td>
<td>Medium</td>
<td>If functional coating is adequate and results of CC pellets are on the border then it may failed after compression. Hence risk was medium.</td>
</tr>
</tbody>
</table>

### Compression variables

<table>
<thead>
<tr>
<th>Tooling Design</th>
<th>Assay</th>
<th>Low</th>
<th>Tooling design was selected to compress a tablet with a suitable size, shape, and score. The tooling was fixed and the risk of its design to impact all tablet CQAs was low.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooling Design</td>
<td>Dissolution in Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tooling Design</td>
<td>Content uniformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tooling Design</td>
<td>Splitability</td>
<td>Medium</td>
<td>The design of score on critical decide the uniform split up of tablet. Hence the risk was medium.</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>Assay</td>
<td>High</td>
<td>Due to higher feeder speed, might damaged the enteric coat and at lower speed, incomplete die would be fill which leads to variation in assay and hence CU and dissolution. The risk was high.</td>
</tr>
<tr>
<td>Feeder speed</td>
<td>Dissolution in Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeder speed</td>
<td>Content uniformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeder speed</td>
<td>Splitability</td>
<td>Low</td>
<td>Tablet splitability not related to feeder speed hence risk was low.</td>
</tr>
<tr>
<td>Pre-compression force and Main compression</td>
<td>Assay</td>
<td>Low</td>
<td>Tablet assay and CU were dominated by blend flowability and uniformity. The risk was low.</td>
</tr>
<tr>
<td>Pre-compression force and Main compression</td>
<td>Content uniformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-compression force and Main compression</td>
<td>Dissolution in Stage I</td>
<td>High</td>
<td>A greater than optimal pre-compression force might cause damaged of EC and at lower force, air trapped in tablet. Hence the risk was high.</td>
</tr>
<tr>
<td>Pre-compression force and Main compression</td>
<td>Splitability</td>
<td>Low</td>
<td>A greater than optimal pre-compression force would increased tablet hardness and might</td>
</tr>
</tbody>
</table>
subsequently impacted tablet splitability and low force leads to capping. Hence the risk was low.

<table>
<thead>
<tr>
<th>Compressional speed</th>
<th>Assay</th>
<th>Content uniformity</th>
<th>Dissolution in Stage I</th>
<th>Splitability</th>
<th>Assay</th>
<th>Content uniformity</th>
<th>Dissolution in Stage I</th>
<th>Splitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>compression machine speed</td>
<td>High</td>
<td>A faster than optimal press speed might cause inconsistent die filling and affect tablet assay, CU, hardness, and drug release. The risk of press speed to impact tablet assay, CU and drug release was high.</td>
<td>Medium</td>
<td>Any change in machine speed directly change in dwell time and which may change the tablet hardness and splitability. Hence risk was medium.</td>
<td>Low</td>
<td>Tablet splitability is mainly related to the formulation compactability and compression force. Hence risk was low.</td>
<td>Medium</td>
<td>Tablet splitability was mainly related to the formulation compactability and compression force. Hence risk was low.</td>
</tr>
<tr>
<td>Assay</td>
<td>Medium</td>
<td>The flow of the blend and the potential for segregation might impacted by the tablet press vibrations and the hopper angle design. The hopper design might impacted tablet assay, CU, and drug release. The risk was medium.</td>
<td>Low</td>
<td>Tablet splitability was mainly related to the formulation compactability and compression force. Hence risk was low.</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
</tr>
<tr>
<td>Hopper design and vibration</td>
<td>Hopper fill level</td>
<td>Hopper fill level</td>
<td>Drop height of finished tablet</td>
<td>Drop height of finished tablet</td>
<td>Assay</td>
<td>Content uniformity</td>
<td>Dissolution in Stage I</td>
<td>Splitability</td>
</tr>
<tr>
<td>Hopper fill level</td>
<td>Medium</td>
<td>If the hopper fill level is suboptimal, the mass effect on flow could be insufficient to supply a consistent amount of blend to the feeder frame, thus impacting tablet assay, CU, and drug release. Hence risk was medium.</td>
<td>Low</td>
<td>Tablet splitability was mainly related to the formulation compactability and compression force. Hence risk was low.</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
</tr>
<tr>
<td>Hopper design and vibration</td>
<td>Hopper fill level</td>
<td>Hopper fill level</td>
<td>Drop height of finished tablet</td>
<td>Drop height of finished tablet</td>
<td>Assay</td>
<td>Content uniformity</td>
<td>Dissolution in Stage I</td>
<td>Splitability</td>
</tr>
<tr>
<td>Hopper fill level</td>
<td>Medium</td>
<td>If the hopper fill level is suboptimal, the mass effect on flow could be insufficient to supply a consistent amount of blend to the feeder frame, thus impacting tablet assay, CU, and drug release. Hence risk was medium.</td>
<td>Low</td>
<td>Tablet splitability was mainly related to the formulation compactability and compression force. Hence risk was low.</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
<td>Medium</td>
<td>A higher than optimal finished tablet drop height might affected tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the</td>
</tr>
</tbody>
</table>
in Stage I drop height on finished tablet CQAs was medium.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Splitability</td>
<td>Medium</td>
</tr>
</tbody>
</table>

5.8.8. Tablet compression process optimization

The compression process parameters and ranges were selected based on the knowledge gained from the compression trials of feasibility study. A $2^3$ full factorial design with two center points was performed to screen the effect of process parameters on physical and chemical parameters. Table 5.44 summarized the study design and acceptance criteria.

Table 5.44 $2^3$ Full Factorial Design - factors, levels and successful operating range (DoE 3)

<table>
<thead>
<tr>
<th>Independent variables (Formulation Variables)</th>
<th>Unit</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$: Pre-compression force kN</td>
<td></td>
<td>-1 2</td>
</tr>
<tr>
<td>$X_2$: Main compression force kN</td>
<td></td>
<td>3 10</td>
</tr>
<tr>
<td>$X_3$: Turret speed rpm</td>
<td>rpm</td>
<td>4 14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dependent variables (CQAs)</th>
<th>Unit</th>
<th>Successful operating range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Y_1$: Hardness N</td>
<td></td>
<td>&gt; 30</td>
</tr>
<tr>
<td>$Y_2$: Disintegration time Sec</td>
<td></td>
<td>&lt; 30</td>
</tr>
<tr>
<td>$Y_3$: Friability %</td>
<td>%</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>$Y_4$: Weight variation %</td>
<td>%</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>$Y_5$: Content uniformity %</td>
<td>%</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>$Y_6$: Drug release in 0.1N HCl %</td>
<td>%</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>$Y_7$: Assay %</td>
<td>%</td>
<td>95 &lt; $Y_7$ &lt; 105</td>
</tr>
</tbody>
</table>

5.9. Scale up

In the manufacturing of PTZ MUPS tablets total three manufacturing processes were involved i.e. Pellets coating, blending and lubrication, and compression. Among these, scaling up of pelletization was critical due to number of process variables involved and quality of finished product majorly depend on pellets.
5.9.1. Scale up of coating process

Trials up to prototype formulation performed in Wurster GPCG 1.1. It was preferred to use same geometry, same manufacturer and less capacity commercial used Wurster for scale up activity. We had selected FBE 125 C for scaling up. Wurster column is the functional area where 100% pellets coating done and about 70% drying happened. Wurster column base area is the consider to calculate scaling up factor. When scaling up done from GPCP 1.1 to FBE 125C, scaling up factor calculated 9. These factor is applicable for all potential process variables like inlet air volume, spray rate and atomization air pressure.

Below is the enteric process parameters calculated for FBE 125C in Table 5.45.

Table 5.45 Scale up parameters EC process for FBE 125C

<table>
<thead>
<tr>
<th>Scale up Parameters</th>
<th>Units</th>
<th>GPCG 1.1</th>
<th>Scale up factor</th>
<th>FBE 125 C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipment Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wurster Diameter</td>
<td>m</td>
<td>0.072</td>
<td>-</td>
<td>0.219</td>
</tr>
<tr>
<td>Wurster Column height</td>
<td>m</td>
<td>0.20</td>
<td>-</td>
<td>0.36</td>
</tr>
<tr>
<td>Base plate Area</td>
<td>m²</td>
<td>0.0145</td>
<td>-</td>
<td>0.1918</td>
</tr>
<tr>
<td>Suitable Air Distribution Plate</td>
<td>-</td>
<td>B</td>
<td>-</td>
<td>B-I</td>
</tr>
<tr>
<td>Working volume</td>
<td>Litre</td>
<td>2.4</td>
<td>35</td>
<td>84</td>
</tr>
<tr>
<td>Batch Size (preferred)</td>
<td>Kg</td>
<td>0.6</td>
<td>35</td>
<td>21.0</td>
</tr>
<tr>
<td>Wurster Column base Area</td>
<td>m²</td>
<td>0.0041</td>
<td>9</td>
<td>0.0377</td>
</tr>
<tr>
<td><strong>Process Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inlet air temperature</td>
<td>°C</td>
<td>26-35</td>
<td>-</td>
<td>26-35</td>
</tr>
<tr>
<td>Product temperature</td>
<td>°C</td>
<td>26-28</td>
<td>-</td>
<td>26-28</td>
</tr>
<tr>
<td>Wurster Column height from base plate</td>
<td>mm</td>
<td>15-20</td>
<td>-</td>
<td>40-45</td>
</tr>
<tr>
<td>Inlet air volume</td>
<td>CFM</td>
<td>46</td>
<td>9</td>
<td>414</td>
</tr>
<tr>
<td>Spray rate</td>
<td>gm/min</td>
<td>10-20</td>
<td>9</td>
<td>90-180</td>
</tr>
<tr>
<td>Atomization air pressure</td>
<td></td>
<td>At 1.0 bar, the air flow is 1.2 CFM</td>
<td>The CFM is 1.2 x 9 i.e. 10.8 equivalent to 2.5 bar for Normal</td>
<td></td>
</tr>
</tbody>
</table>
The calculations for critical coating process parameters apart from EC process were calculated same as provided in Table 5.36. Comparative process parameters provided in Table 5.46. Coating suspension/dispersion preparation step same as lab scale batches.

**Table 5.46 Comparative coating process parameters of lab scale and scale up batch**

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Unit</th>
<th>Drug Loading</th>
<th>Seal coating</th>
<th>Enteric coating</th>
<th>Cushion coating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
<td>GPCG 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GBE 125C</td>
<td>GBE 125C</td>
<td>GBE 125C</td>
<td>GBE 125C</td>
</tr>
<tr>
<td>Batch Size (Starting load)</td>
<td>Kg</td>
<td>0.5*</td>
<td>18.0*</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31.5</td>
<td>31.5</td>
<td>31.5 x 2 lots</td>
<td>23.7 x 3 lots</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td></td>
<td>30</td>
<td>30</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Inlet temp °C</td>
<td></td>
<td>36-48</td>
<td>36-50</td>
<td>40-55</td>
<td>26-35</td>
</tr>
<tr>
<td>Product temp °C</td>
<td></td>
<td>35-38</td>
<td>35-38</td>
<td>38-42</td>
<td>26-28</td>
</tr>
<tr>
<td>Spray rate g/min</td>
<td></td>
<td>4-11</td>
<td>36-99</td>
<td>4-10</td>
<td>36-90</td>
</tr>
<tr>
<td>Atomization air pressure bar</td>
<td></td>
<td>0.9-1.1</td>
<td>2.4-2.6</td>
<td>0.9-1.1</td>
<td>2.4-2.6</td>
</tr>
<tr>
<td>Air volume cfm</td>
<td></td>
<td>45-60</td>
<td>405-540</td>
<td>45-60</td>
<td>405-540</td>
</tr>
</tbody>
</table>

*Considered bulk density = 0.7 g/ml

**5.9.2. Scale up of blending and lubrication process**

Blending and lubrication revolutions kept same as lab batches i.e. 300 and 50 revolutions only blender rpm changed accordingly time as per Froude no calculation.

The comparative blender and lubrication process parameters provided in Table 5.47.

**Table 5.47 Comparative blending and lubrication process parameters of lab scale and scale up batch**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unit</th>
<th>Lab scale batch</th>
<th>Scale up batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blender type</td>
<td>-</td>
<td>Octagonal</td>
<td>Octagonal</td>
</tr>
<tr>
<td>Blender capacity</td>
<td>L</td>
<td>3</td>
<td>1200</td>
</tr>
<tr>
<td>Blender occupancy</td>
<td>%</td>
<td>60 ± 10</td>
<td>60</td>
</tr>
</tbody>
</table>
5.9.3. **Scale up of tablet compression process**

Compression process parameters kept same as lab scale batches. The comparative compression process parameters provided in Table 5.48. The compression of lab scale trials and optimized compression process variables batch performed on Fette 102i compression machine. Fette 102i and Fette P2020 has same capacity of load cells and compression process parameters were scale independent which was suggested by machine vendor and proved in studies of earlier products. Hence, scale up batch ran on Fette P2020 based on optimized compression process parameters from Fette 102i to study the impact on tablet quality.

**Table 5.48 Comparative compression process parameters of lab scale and scale up batch**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unit</th>
<th>Lab scale batch</th>
<th>Scale up batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machine</td>
<td>-</td>
<td>Fette 102i</td>
<td>Fette P2020</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>kN</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Main compression force</td>
<td>kN</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Turret speed</td>
<td>rpm</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

The tablets were characterized for physical and chemical parameters.