CHAPTER 8

RESULT AND DISCUSSIONS
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8.1 Characterization of Drug and Excipients

8.1.1 Characterization of Drug
From the section 7.3.1, it was confirmed that Nevirapine anhydrous is complying the test like of assay, infrared spectroscopy, polymorphic identity, DSC and thermo-gravimetric analysis.

8.1.2 Assay
The assay of Nevirapine anhydrous was carried out by HPLC method which was found to be 99.56% w/w within the USP34 limit of 90-110% of label amount. The chromatogram of assay preparation by HPLC test is shown in figure 7.1.

8.1.3 Microscopy
From the microscopy study, it was concluded that drug sample appeared as rod shaped crystals with birefringence under cross-polarized light (Figure 7.2).

8.1.4 Infrared Spectrum
The IR spectrum of nevirapine anhydrous recorded maxima at wavelengths similar to those observed for working standard and complying for identification test. Both the test and standard spectra are given in figures 7.3 and 7.4 respectively.

8.1.5 Powder X-Ray Diffractometry
From the powder X-ray diffractometry (XRD), it was concluded that polymorphic form of API was similar to that of innovator drug product i.e. anhydrous form (Figure 7.5).

8.1.6 Differential Scanning Calorimetry
The DSC thermogram of drug test sample recorded single sharp melting endotherm at 245.36°C, similar to that reported in literature (Figure 7.6).
8.1.7 Thermo-Gravimetric Analysis (TGA)
From the TGA thermogram, it was concluded that drug sample was non-hygrosopic (Figure 7.7).

8.1.8 Water Vapor Sorption Analysis
The Nevirapine test sample exposed to varying humidity conditions isothermally (25°C) gained around 1.1% moisture at 90% RH (during 1st adsorption cycle) and desorbed completely at 0% RH (during 1st desorption cycle). No hysteresis was observed between 1st adsorption and desorption cycles, suggesting physical stability of sample in the presence of moisture. The adsorption profile in 2nd cycle was similar to that in 1st is shown as figure 7.8.

8.1.9 Stress Stability of API
The results of stress stability of Nevirapine are recorded in table 7.3. All the impurities at stress and super stress conditions were found to be within acceptable limit.

8.2 Characterization of Innovators (Reference) Drug Product

8.2.1 Physical Characterization of Innovators
From the physical characterization of innovator drug product (Viramune XR®), it was observed that tablets are packed in HDPE bottles are of 30s count and closed with a child resistant closure. Innovator tablets had ~ 1075 mg average weight with ~ 9.2 mm width. The dissolution profiles of these tablets were almost similar in all buffer i.e. pH 1.2, pH 4.5 and pH 6.8 buffers containing 2% SLS. The other excipients in innovator tablets are lactose monohydrate, hypromellose, iron oxide and magnesium stearate.
8.2.2 Decoding of Innovator Drug Product

Decoding (deformulation) of innovator drug product was carried out with the help of ATR-IR imaging to find out grade of polymer, its concentration in tablets and particles size of API. The results of ATR-IR imaging are given in figure 7.12 and are elaborated below.

Relative Abundance of Components

ATR-IR Images (500x500'm and 400x40'm) were analyzed via spectral correlation and via chemo-metric assessment. Five main components were identified as API, hypromellose, lactose monohydrate magnesium stearate, iron oxide yellow (shown in figure 7.12), of which magnesium stearate and iron oxide yellow appeared very finely distributed and nearly unidentifiable. From the figure 7.12; the three dominant components of the tablet are API, lactose, and HPMC, which are very homogeneously intermixed and possess nearly the same abundance, followed by abundant and large lactose particles.

Analysis of HPMC Content and Viscosity Grade in Nevirapine ER Tablets

The tablets were crushed into a powder and taken up in the size exclusion chromatography mobile phase. The dosage forms of the innovator product appear to contain HPMC as the polymer. The polymer levels are approximately 20% - 35%; grade is further confirmed by chemical imaging.

Particle Size of the API

ATR-IR images were measured with a lateral resolution of 1.6 µm and a spectral resolution of 8 cm⁻¹. ATR-IR images were analyzed via spectral correlation and via chemo-metric assessment. API particles were found abundant within the tablet, with the size ranging from 10 to 30 µm. From size analysis, on an average particle size (based on number) of 25 µm can be derived.

8.2.3 Stability Innovator Drug Product

The result of stress stability of innovator drug product is recorded in table 7.8. Viramune XR® 400 mg tablets were found to be physically as well as chemically stable at 40ºC/75% RH. All the impurities at stress were found to be within acceptable limit as per ICH guideline.
8.3. API-Excipient Compatibility

The compatibility of API alone and their combination with excipients similar to those present in innovator drug product was studied. The results for API-excipient compatibility study are recorded in table 7.13. In accordance with the stress data of API, a highest level of unknown impurity (0.05%) was observed at 40°C/75% RH at 4 weeks condition. In API and HPMC combination, highest level of impurity A (0.22%) was observed at 4 weeks at 50°C moist condition which was a very harsh condition. In API & lactose monohydrate combination, highest level of impurity A (0.02%) was observed at 4 weeks 40°C/75%RH condition. Also with magnesium stearate, highest level of impurity was observed at 4 week 50°C. With iron oxide, highest level of impurity C was observed at 4 weeks 50°C dry condition (0.04%). From the data of compatibility, it was concluded that all excipients are compatible with Nevirapine anhydrous.

8.4 Formulation Development

8.4.1 Initial Concept

Formulation approach was to have a composition qualitatively similar to that of the innovator. All the excipients were chosen accordingly based on compatibility study. Initial trial batch NVP /01 was taken with dry granulation process. But with dry granulation, various processing problems were observed, like poor flow of blend through hopper, tablets defects like appearance, capping and weight variation, dissolution profile was faster than innovator. Hence, it was decided not to develop product with dry granulation technique.

During evaluation of the wet granulation process, it was observed that with 20% concentration of HPMC in formulation; dissolution profile was faster compared to the innovator. Trials taken with 30-35% concentration of HPMC showed slow release of drug because of higher concentration of HPMC. Dissolution profile with high viscosity grade of HPMC did not match the innovator and also erosion of tablet was observed. Trial taken with 25% of HPMC was executed successfully and dissolution profile was matching with innovator. Based on the outcome, upscale batch using composition of Batch No. NVP/03 was planned and wet granulation in high shear mixer process was selected for further development.
8.4.2 Critical Material Attributes

8.4.2.1 API Particle Size

Thus, after preparation of different design batches, 25% drug to polymer ratio formulation was selected as an optimized formula. Formula optimization was started on this formulation with QbD approach. To see the impact of API particle size on the formulation; three batches were taken and results are recorded in table 7.24. In all three batches, compression was found to be satisfactory and in content uniformity result, difference in lower and upper range was observed. Dissolution profiles of all three batches are comparable as shown in table 7.24. There was no significant impact of API particle size observed on drug product’s CQAs like physical attributes, assay, content uniformity and dissolution profile.

8.4.2.2 Granulating Fluid Volume

To see the impact of granulating fluid volume on the formulation; different batches were taken and results are recorded in table 7.25. With the increase in binder volume by 10% w/w there was no impact on compression parameters whereas dissolution profile was similar to optimum binder volume of batch NVP/08. There was significant effect on release profile with increase of 20% w/w binder volume of batch NVP/12 as compared to batch NVP/08 because of heavier granule formation. Tablet surface was also found to be rough during compression of batch with 20% extra binder volume. Significant impact of granulating fluid volume on drug product’s CQAs like physical attributes and dissolution profile was observed.

8.4.2.3 HPMC Particle Size and Viscosity

The effect of HPMC particle size and viscosity on drug release profile is showed in table 7.26. To see the effect of viscosity of HPMC on drug release profile; two batches with higher (NVP/20) and lower particle (NVP/21) were formulated, dissolution profile of both batches was almost similar and matched with innovator. With respect to effect of HPMC viscosity on dissolution profile, batches NVP/19 with lower viscosity and higher viscosity batch NVP/18 showed similar dissolution profile with centre point batch NVP/17. The compression parameters of all batches matched with the centre point batch and was found to be a within a limit. No significant impact of CMA of HPMC i.e. viscosity and particle size was seen on drug product’s CQAs like physical attributes, content uniformity, assay and dissolution profile.
8.4.2.4 Lactose Monohydrate Particle Size

Lab scale batches were taken with different particle sizes of lactose monohydrate and results are recorded in table 7.27. All the formulation parameters of different particle size batches were found to be satisfactory. There was no significant impact of CMA of lactose monohydrate i.e. higher and lower particle size was seen on drug product CQAs like physical attributes, content uniformity and dissolution profile.

8.4.3 Critical Process Parameters

8.4.3.1 Optimization of Dry Mixing Time

Blend uniformity samples were withdrawn at 5 mins, 10 mins and 15 mins of dry mixing time and results are recorded in table 7.28 and represented graphically in figure 7.13. Based on data, 5 mins dry mixing could be considered as optimum as % RSD is minimum, individual values are within a narrow range and near to 100 %.

8.4.3.2 Optimization of Kneading Time

In the wet granulation process, the kneading time of the formulation was a very important parameter. Under granulation or over granulation was possible due to changes in kneading time during granulation. To evaluate impact on drug product’s CQAs like physical attributes, dissolution, manufacturing process and physical properties of granules; batches NVP/08 and NVP/04 were prepared with optimum and high kneading time. The observations for different batches are recorded in table 7.29. In the batch with the increase in kneading time from 3 mins. to 6 mins. % fines below #60 sieve was increased; indicating increase in finer fraction of blend due to over kneading and also harder granules were seen. Density of blend was found to increase with higher kneading time. Kneading time has significant impact on physical properties of granules. For the processing of higher kneading batch (NVP/08), sizing of granules will take long time as compared to optimum batches and previous design batches. Dissolution profile of high kneading batch was slow as compared to optimum batch because of harder granules formation. Significant impact was seen on drug product’s CQAs like physical attributes, dissolution of this critical process parameter (CPP). Based on this study and formula composition details, it is recommended to keep minimum kneading time for wet mass.
8.4.3.3 Optimization of Inlet Drying Temperature
Two batches having higher inlet temperature (NVP/31) and lower inlet (NVP/33) temperature during drying were formulated to see the effects on physical characteristics of granules and degradation product at stability. The process results are summarized in table 7.30 and stability results are recorded in table 7.31. In the batch with increase in the inlet temperature; there was no significant change in particle size distribution and LOD of granules. But based on the formula composition and excipients compatibility details it was advisable not to dry at higher inlet temperature. Target inlet temperature of 55°C ±10°C (45°C - 65°C) during drying should be kept. The impurity level after 3 months in 40°C/75% RH were within the limits and comparable to the innovator stability data. No significant impact was seen on physical characteristics of granules and degradation product of this critical process parameter (CPP).

8.4.3.4 Impact of LOD of Dried Granules on Compression Parameters
In batch NVP/35B with 0.90% LOD, capping was observed due to very low moisture but batch NVP/35A with 1.8% LOD compression parameters was found to be satisfactory. So Based on the formula composition and available LOD data of various batches, LOD range was kept between 1.5 - 2.0% for safer side.

8.4.3.5 Optimization of Milling Parameters
The see the effect of different milling screens on formulation; two different batches NVP/37 & NVP/38 with sieves 0.8 mm and 1.0 mm were used respectively during sizing of dried granules. The observations for different milling batches are shown in table 7.33. From the result, it was concluded that there was no more difference in particle size distribution (PSD) of lubricated granules when screen size was varied from 0.8 mm to 1.0 mm. Dissolution profile was found comparable with innovator product. There was no significant impact of milling on drug product’s CQAs.
8.4.3.6 Optimization of Lubrication Time
For the optimization of lubrication time blend uniformity data was generated on batch NVP/37 at 3 mins, 5 mins and 7 mins lubrication time to see impact on assay & blend uniformity of the formulation. The results are recorded in table 7.34 and represented graphically in figure 7.14. The result was satisfactory for all 3 time points. Based on this, it can be concluded that lubrication time would not have critical impact on product CQAs like assay and content uniformity. Based on the data, 3 mins could be considered as optimum blending time as % RSD is minimum as compared to 5 mins and 7 mins lubrication time.

8.4.3.7 Optimization of Compression Parameters
Scale up batch NVP/SCA/01 was taken at higher scale to see the process feasibility and different compression parameters like compression machine speed, compression run times and hardness range. The result of each parameter is recorded in tables 7.35 to 7.37. The observations drawn are given below.

- Based on the available data of compression; it is advisable to keep the compression machine speed range 30-70 rpm, but target speed for compression is 50 rpm. Compression parameters were found to be within acceptable limits at different speed ranges of machine. At all machine speed ranges; tablet passed the test for content uniformity.

- There was no significant effect at different stages of compression run i.e. start, middle and end of compression on the physical parameters and content uniformity.

- Dissolution profile was found to be satisfactory at different hardness range i.e. low, optimum and high hardness.

8.4.3.8 Stability Study
The results for stability study are given in table 7.38. No significant changes were observed in at initial and stability time points for assay and impurities. The dissolution profile after 3 months 40°C/75% RH is almost identical to the initial and innovator’s drug release profile.
8.4.4 Scale up of Optimized Formulation

The scale up batch NVP/SCA/02 of Nevirapine ER matrix tablets 400 mg was prepared at 1X to 5X scale and all final process parameters for validation batches are given in table 7.40. All the physical parameters were found to be satisfactory and the analytical result was within the acceptable limit and matched with innovator. *In vitro* (Table 7.42) study showed that dissolution profile of scale up batch was similar with innovator product and $f_2$ value was found to be 80.

8.4.5 Final Risk Assessment

Based on process characterization and scale up final risk matrix is given in table 7.43. The critical quality attributes were evaluated and optimized. The formulation was found stable in the stability study. Thus, PHA has helped to develop a design space to work under and the control strategy for the robust process development of Nevirapine ER matrix tablets 400 mg.