CHAPTER 9

SUMMARY & CONCLUSION
9.1 Summary

✓ In this study depending on market requirements formulation of Nevirapine ER matrix tablets was planned based on QbD application.

✓ For the solid state characterization of Nevirapine API, different tests were performed like FTIR, optical microscopy, powder X-ray diffractometry (XRD), differentials scanning calorimetric (DSC), dynamic vapor absorption (DVS). Stress stability data was also generated on Nevirapine API. API and excipient compatibility was conducted at different ratios using moist and dry conditions. Samples were kept at 50°C and 40°C/75% RH and evaluated for impurities.

✓ Deformulation of innovator product was also carried out with various methods like size exclusion chromatography & ATR-IR imagining. Also multimedia dissolution and stress stability data was generated on innovator product.

✓ Quality target product profile was prepared based on properties of drug substance, preliminary characterization of reference product and pack insert.

✓ Critical quality attributed data for Nevirapine ER tablets was generated as shown in table 7.10. Based on API characterization data, critical material attributes were identified as critical and non-critical. Risk levels were assigned to drug product CQAs as shown in table 7.12.

✓ Based on innovator formulation; HPMC, Lactose monohydrate, Iron oxide, Magnesium stearate, were chosen as excipients. Critical material attributes were also chosen for excipients based on their effect on final formulation. Risk levels were also determined for potential impact of excipients on drug product CQAs as shown in table 7.16.

✓ Matrix tablets were prepared with composition qualitatively similar to that of the innovator tablet.

✓ Nevirapine matrix tables were prepared using dry and wet granulation method. But dry granulation method showed processing issue, while wet granulation method was found to be satisfactory.

✓ Different design batches were prepared using different viscosity polymer such HPMC K4M and K15M in different polymer ratio i.e. 20-35%. All these formulations were subjected for various parameters such as weight variation, hardness, friability and in
*vitro* dissolution studies. Based on *in vitro* dissolution profile, formulation batch NVP /03 was selected as optimum formulation.

- QbD based approach was implemented for the development of Nevirapine ER matrix tablet and process optimization was performed on prototype formulation. Impact of CMAs like particle size, granulating fluid volume, HPMC particle size and viscosity, lactose monohydrate particle size were studied on prototype formulation. Process optimization for mixing time, kneading time, inlet drying temperature, milling parameters and lubrication time was performed.

- Scale up batch (NVP/SCA/02) was manufactured with final composition at higher scale (1X-5X) with all optimized process parameters. Further, this batch was subjected to stability study for 3 months at 40°C/75% RH.
9.2 Conclusion

✓ Identification of Nevirapine anhydrous was performed according to USP and in house method and it was found that drug showed FTIR as per as the reported literature. From the powder X-ray diffractometry (XRD) technique, it was found that polymorphic form of drug was similar to the innovator. The DSC thermogram of drug test sample recorded single sharp melting endotherm with onset temperature of 245.36°C, similar to that reported in literature. Dynamic vapor absorption technique of Nevirapine suggested it to be a non-hygroscopic material. From the optical microscopy, drug substance appeared as rod shaped crystals with birefringence under cross-polarized light.

✓ From the deformation of innovator drug product with the help of size exclusion chromatography, it was concluded that dosage forms of reference product appeared to contain HPMC as the polymer. The polymer levels are approximately 20%-35%. Grade was further confirmed by chemical imaging. With the help of ATR-IR imagining, it was found that, API particle size (based on number) was 25µm in innovator product.

✓ Excipients chosen were found compatible with API as seen in compatibility study.

✓ From the formulation development, wet granulation process seemed to be more robust and satisfactory physical attributes were obtained. Formulation NVP/03 was finalized as it was showing dissolution similar to innovator product.

✓ Based on QbD application, no significant impact of particle size of API, lactose monohydrate and HPMC was seen on drug product CQAs like physical attributes, content uniformity and dissolution granulation profile. Whereas, granulating fluid volume showed significant effect on CMA.

✓ Based on optimization study, following parameters were finalized.
  Dry mixing time 7 mins, Kneading time 3 mins, Inlet drying temperature 55°C ±10°C (45°C -65°C), LOD of granules 1.5-2.0% and compression speed 30-70 rpm.

✓ The scale up batch NVP/SCA/02 of Nevirapine ER matrix tablets 400 mg was prepared at 1X to 5X scale. All the physical parameters were found to be satisfactory and the analytical results were within the acceptable limit and matched with innovator. In vitro study showed that dissolution profile of scale up batch was similar to innovator product and f2 value was found to be 80. Stability studies carried out at accelerated condition showed that developed formulation is stable.
✓ This study showed that, stable extended release matrix tablets of Nevirapine were developed and scale up study was successfully done.