Chapter 5: Summary and Conclusion
5.0 SUMMARY AND CONCLUSION

In the present investigation, an attempt was made to formulate extended release capsules of topiramate as an anti-epileptic drug by using wurster coating technology. The final capsule formulation was compared with the commercially available reference product for in-vitro compliance in terms of similarity factor (f2 value) as well as in-vivo pharmacokinetic study in rabbit to check the bio-equivalence with respect to reference product (Trokendi XR 200mg).

Most challenging part of the project work was to develop robust and reproducible drug layering process to produce drug layered pellets. Initial trials were performed using API with particle size $D_{100}=50$ microns. However, particle size was critical to drug layering and hence, further trials were taken with API particle size $D_{100}=10$ microns. Another challenging part was to match extended release dissolution profile of topiramate extended release capsules with respect to reference product in multimedia and in pH 7.5 phosphate buffer as dissolution media. This was achieved by selection of right combination of extended release (ER) polymers as excipients and its weight gain. The most critical part of the development was optimization of wurster coater process parameters at development scale and at scale up scale.

Various criticality were observed at each stages of development and finally all the criticality were resolved by taking scientific approaches at each stages of development. Each stages of development with its criticality and resolved the same are mentioned as follows;

1. Literature review

   - Literature review was done on this project to evaluate the related research done on this direction and to understand the criticality of the project.
   - Based on the literature search and prior information available, need of the current research work was found.
Planing of the current research work was done based on the available literature information and finding the gap of the existing research work in this direction.

2. Design of out-of-scope strategy

This project was planned based on the initial information available on ongoing clinical trials of the reference product and its patent evaluation to evaluate the importance of the current research requirement and to understand the criticality of the project.

Based on the reference product’s patent, importance of the current project was evaluated but to launch the test product as one of the successful generic product, various approaches were evaluated to find out the commercially feasible, economic priced, pharmaceutical and therapeutic equivalent product as compared to reference product in step by step approaches as mentioned below section.

Based on the literature and patent informations, list of raw material and packing material shortlisted to initiate the development activities. Finally based on the development batch’s data final strategy was finalized.

3. Preformulation studies

Topiramate API was US-DMF grade, it was sourced from Hetero drugs. API supplier was provided open part of US-DMF for the API which had helped to develop the analytical method for the formulation.

API was authenticated using analytical techniques such as Differential scanning calorimetric (DSC) studies and Infra Red (IR) spectrum.

From API characterization it was clear that topiramate exhibits nearly pH-independent solubility, non-hygroscopic in nature and possess poor flow properties due to its micronized nature.

Formulation development was carried out using physically and chemically compatible excipients based on Drug-Excipients compatibility studies.

Based on reference product characterization, various physicochemical parameters were decided to develop extended release capsules of topiramate.
4. Formulation development trials

- Initial attempts were made to select suitable solvent system for drug layering process and it was found that aqueous solvent system was the best suited for drug layering to produce drug layered pellets.
- Trial with Colloid milling of API having particle size $D_{100}=50$ microns suggested that API particle size plays an important role in drug layering process. Hence, further development was carried out using API particle size $D_{100}=10$ microns.
- Combination of binders and their optimum concentrations using aqueous solvent system were selected for optimum drug layering process based on process efficiency and physicochemical parameters evaluated such as % LOD, % agglomerates and fines, % practical yield and assay.
- To improve the drug loading on the sugar spheres, seal coating strategy was chosen.
- Seal coating composition was kept similar as that of drug loading composition, except drug and sodium benzoate in the seal coating composition.
- Seal coating composition mainly contains, hypromellose as binder, mannitol and talc as anti-tacking agent with 28.3% solid content in aqueous dispersion media.
- Based on the drug layered pellets yield, the ratio of seal coated pellets to topiramate API was decided to 1:1.
- Based on reference product medication guide, patent analysis and dissolution study it was decided to use 80 to 95% dose as ER (160 mg to 190 mg) and 5 to 20% dose as IR (10 mg to 40 mg) in the proto-type batches to find out optimized composition.
- Dissolution study was carried out by coating drug layered pellets with various ER polymer and weight gain followed by optionally DR coating followed by immediate release drug layering on ER/DR coated pellets, finally moisture barrier coating.
- Extended release pellets of topiramate were prepared by coating with various ER coating polymers such as Ethyl cellulose 7 cps, Eudragit RS 30D, Cellulose acetate & novel ER-4 polymer. Eudragit RS 30D possessed excellent process efficiency...
and physicochemical parameter, however, was failed to achieve desired release profile.

- Ethyl cellulose coat was evaluated to check curing effect on storage associated with the use of aqueous polymeric dispersions, it failed in the curing study.

- Cellulose acetate coat was selected to avoid curing study associated with the use of non-aqueous polymeric dispersions along with hydrophilic pore former.

- Novel ER polymer ER-4 in combination with cellulose acetate and pore former (PF-3), test product was showing jump in the dissolution profile in pH 7.5 Phosphate buffer media as compared to multimedia as like reference product. Hence this ER coating strategy was finalize to further fine tuning of the formulation composition based on the design of experiment trials.

- Various release profiles were generated by design expert software predicted formulation design at different ER Polymer : Pore former ratios, ER coating weight gain, different ER/ IR layer drug distribution ratio in multimedia and OGD dissolution media.

- Cellulose acetate: ER-4 : pore former (PF-3) in the ratio of 70: 20 : 10% with 16% ER coating weight gain and Drug distribution in ER : IR layer in the ratio of 85% : 15% produced release profiles similar pattern as that of reference product in multimedia and OGD dissolution media.

- Further fine tuning of cellulose acetate: ER-4 : pore former (PF-3) ratio with ER coating weight gain and Drug distribution in ER : IR layer was done by using response surface method optimization techniques with the help of design expert software.

- Next part of the project was to overcoat immediate release drug layer in order to protect it from moisture. Moisture barrier system with efficient process during coating and acceptable physicochemical attributes without any impact on dissolution of immediate release drug layer was selected.

- Although Opadry AMB and Opadry 200 are considered as highly effective moisture barrier, it needs very vigorous process parameters which delaminates drug from pellets surface. Hence, Opadry II white with optimum process
parameters without any impact on dissolution of immediate release drug layer was selected.

- One of the proto-type development batch with qualitatively similar composition was charged for stability studies as per ICH storage conditions for the period of 6 month in different packing configuration and no significant changes were observed in any of the physicochemical parameters studies in all packing configuration. Hence the finished product is stable in all packing condition throughout 6 month at accelerated stability condition.

5. Optimization trials

- Optimization trials were performed based on the response surface method (RSM) statistical design generated by Design expert software.

- Four critical factors and their range were chosen based on the literature and reference product information such as immediate release portion’s drug distribution in the range of 5 to 20%, concentration of pore former in the range of 0 to 20%, Novel ER polymer concentration in the range of 5 to 40% and ER coating polymer weight gain in the range of 7 to 20%.

- Based on the software generated RSM design, total 25 nos. of batches were taken and evaluated dissolution in multimedia and pH 7.5 phosphate buffer as per OGD dissolution condition.

- Dissolution data of all 25 nos. of experiments were feed into software and analyzed the data by software. Then target required dissolution profile values range were incorporated at the optimization section of the software and we got the design space from software with 90% confidence interval from design space two formulation compositions were selected to go ahead with reproducible batch preparation.

- Two optimized formulation compositions were as follows; Strategy-I: ER coating polymer ratio of Cellulose acetate: ER-4 : pore former (PF-3) in the ratio of 74.17: 20 : 5.83% with 15.6% ER coating weight gain and Drug distribution in ER : IR layer in the ratio of 80.96% : 19.04%. Strategy- II: ER coating polymer ratio of Cellulose acetate: ER-4 : pore former (PF-3) in the ratio of 72.46: 20 : 7.54% with
15.6% ER coating weight gain and Drug distribution in ER : IR layer in the ratio of 93.9% : 6.1%.

6. Reproducibility/ Confirmatory batches

- Physical testing parameters of pellets at each stage of development such as % yield, % fines, % agglomerates, % LOD and bulk density were recorded for both the confirmatory batches (B#105 & B#106). All physical characterization data are similar in both the batches.

- Assay of both the confirmatory batches at drug layering-1 stage and at finished product were found satisfactory.

- Reproducibility of two optimized batch were checked with respect to dissolution profile in multimedia and OGD media dissolution conditions, then compared the actual value and predicted value by software of dissolution profile at each time points. Then checked the regression coefficient value of actual vs predicted value plot. One optimized batch having batch #105, was showing reproducibility result as actual and predicted value are matching with F2 76.04 in multimedia and 49.85 in OGD dissolution condition. Whereas other batch having batch #106, was not showing reproducibility result as actual and predicted value are not matching with F2 48.15 in multimedia and 27.58 in OGD dissolution condition.

- From drug release kinetic model, it was observed that both test formulations and reference formulation are following Higuchi release kinetic, hence drug release from the dosage form is mainly due to diffusion.

- Out of two reproducibility batch, one batch (batch #105) showed robustness of formulation. Its highest similarity factor (f2) value indicated that product has the capacity to pass in-vivo bioequivalence test. Hence this formula composition was taken forward for scale up/ Process evaluation batch.
7. Scale up & Process evaluation batch

- Scale up/ Process evaluation batch was executed with similar coating process parameters as that of development batches for inlet temp. Exhaust temp. Product temp. and related humidity. Spray rate was increased proportionally based on the scale-up factor (8.5 times) from development batch size to scale up batch size. Fluidization air volume was adjusted based on the manufacturing process observations. Atomization air pressure for coating solution spray was adjusted based on the spray nozzle size at scale-up scale and correlated with corresponding development batch atomization air pressure and spray nozzle size.
- Assay of drug coated and finished product of scale-up batch was found satisfactory.
- Dissolution profile in multimedia and in pH 7.5 phosphate buffer media were found satisfactory and comparable to one of the reproducible batch (batch #105) at development scale.
- As the dissolution profile in both the dissolution condition was satisfactory, this batch was taken for in-vivo pharmacokinetic study to find out bio-equivalence with respect to reference product (Trokendi XR 200 mg).

8. In-vivo Pharmacokinetic study

- In-vivo pharmacokinetic study was done with scale-up batch (batch #ACS00114) in rabbits in triplicate for test and reference product (trokendi XR 200mg), results for Cmax, AUC0-T and AUC0-inf for test product were slightly lesser than reference product.
- 90% confidence interval for in-vivo pharmacokinetic parameters such as Cmax, AUC0-T and AUC0-inf are 88.28-111.71%, 83.36-116.63% & 83.17-116.82% respectively which are between 80-125% as per the requirement of the bio-equivalence. Hence, it can conclude that test and reference products are bioequivalent.
Conclusion:
In this study, a stable, commercially feasible, extended release pellets of topiramate were formulated successfully using wurster technology and optimization design which were filled into capsules which is bioequivalent to reference product Trokendi XR 200 mg.

Future studies:
- There is a scope of Pilot bio-equivalence study in human volumeters with existing scale-up batch which was manufactured in c-GMP approved manufacturing facility.
- Based on the pilot bio-equivalent data in human, further fine tuning of the formulation composition shall be done if required.
- Manufacturing of scale-up batch for next pilot bio-equivalent study.
- Dose weight formulation composition finalization for getting bio-waiver of all the lower strengths based on the satisfactory in-vitro dissolution profile in multimedia and OGD dissolution condition.
- Three Exhibit batch manufacturing, stability study for submission to USA FDA regulatory body for getting approval for commercial supplies.
- Another reference product in the USA market of topiramate extended release capsules 25mg, 50mg, 100mg, 150mg & 200mg, brand name Qudexy XR, has approved on 11th Mar 2014. Test product which is equivalent to new reference product can also be targeted as in the current optimization trial various dissolution profiles are possible.