ABSTRACT

The main objective of the research activity was to design stable, effective pharmaceutically equivalent formulation of Topiramate modified release capsules 25mg, 50mg, 100mg & 200mg as compared to reference product, brand name “Trokendi XR”, manufacturer is Supernus Pharmaceuticals Inc.

Trokendi XR has launched with 4 strengths, 25mg, 50mg, 100mg & 200mg and Reference listed drug (RLD) is Trokendi XR 200mg. As per the U. S. Food and Drug Authority’s recommendation generic product of Topiramate modified release capsules 200mg should have comparable in-vitro dissolution profile and in-vivo plasma profile with that of marketed product Trokendi XR’s 200mg Extended release capsules as 200mg strength is RLD and other lower strengths should be dose-weight proportional composition with comparable in-vitro dissolution studies between respective lower strengths based on F_2 value (similarity factor) calculation.

Reference product’s strategy is - A sustained release formulation of topiramate for oral administration to a mammalian subject comprising an immediate release pellets portion (IR), a first extended release pellets portion (XR1), and a second extended release pellets portion (XR2) as per Patent no. US8298576 which will be expiring on Mar 18, 2029. Hence, to overcome this innovator’s patent - A single pellets portion containing multiple coating layers was proposed for formulation development. The step by step formulation development approaches was as follows:

1. Reference product’s patent evaluation
2. Choice of excipients
3. Topiramate API source identification and API characterization
4. Analytical method development mainly for assay, related substances and dissolution
5. Reference product evaluation
6. Prototype formula development
   i. Core pellets type and size size selection
   ii. Seal coat on core pellets optimization
iii. Drug layering optimization  
iv. Modified release coating optimization  
v. Moisture barrier coating optimization  

7. Formulation design and Manufacturing process finalization  
8. Formulation composition optimization  
9. Reproducibility batch/ confirmatory batch evaluation  
10. Scale-up process parameter optimization  
11. In-vivo pharmacokinetic evaluation  

A detail characterization of topiramate API and Reference product of all strengths were carried out to understand the impact and behavior of API and other excipients present in the reference product which had help us to design the test formulation with desired characteristics. Various dissolution studies were carried out to develop understanding on the product.  

The aim of this development was to examine and establish critical product composition and process parameters. Dissolution study in different dissolution conditions were conducted to understand the effect of various rate controlling polymers and their ratio on drug release from finished product. A significant correlation was obtained with selection of different grade of hydrophobic extended release polymers along with pore-former and its ratio. This would help to optimize their impact on the performance of the product on scale-up to commercial batches. Some of the critical formulation compositions studied partially was based on the trials performed during the formulation development at bench scale level. The critical formulation components can influence batch reproducibility, product performance and drug product quality.  

Primarily the development was focused on two main objectives, improving the drug loading efficiency and matching the dissolution profile pattern in two different dissolution conditions one in multimedia and other in either pH 6.8 or pH 7.5 Phosphate buffer media. After achieving the desired drug loading and dissolution profile pattern, formulation optimization was performed based on statistical optimization techniques.
(D-Optimal design of response surface method). Two optimized formulation compositions were obtained from software, same two strategies were manufactured and dissolution in two different media were performed to validate the optimized formula composition based on the regression analysis of actual value vs predicted value. One best formulation composition was selected based on the validation of optimized batches. Same selected optimized batch was taken forward for scale-up and in-vivo pharmacokinetic study.

Stability of one of the prototype development batch which contains qualitatively similar excipients were evaluated in four different packs in accelerated stability condition for 6 month and the test product was found stable in all packs in accelerated stability condition upto 6 month.