Co-delivery of Riboflavin Immediate-Release Granules and Topiramate Extended-Release Pellets: Toward Reducing the Frequency of Migraine Attack

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Abstract

The aim of this work was to develop oral capsules containing 200 mg of topiramate in a form of XR pellets and 100 mg of riboflavin in a form of IR blend. This innovative combination was developed as a super-generic of the reference drug product Qudexy® 200 mg capsules which contains topiramate in a form of XR pellets. Topiramate core pellets were prepared by extrusion-spheronization technique. The core pellets were then coated with a coating suspension made of EC and HPMC. QBD approach was applied for the development of topiramate XR pellets to ensure complete understanding of formulation and process variables that may impact the physical properties of core pellets and the dissolution rate of topiramate from the coated pellets. Topiramate core pellets contain MCC and HPMC in addition to the active substance. To reach the optimized core pellets three development studies were carried out. These studies focused on the optimization of HPMC level and viscosity grade, the optimization of water quantity in granulation stage, and the optimization

of spheronization process. In the development of coated pellets the level and the viscosity of the used polymers were optimized (HPMC and EC). In addition, the impact of plasticizer on the dissolution of coated pellets was studied. Two plasticizers were used in this study (DEP and TEC). The dissolution profile of optimized topiramate XR pellets was similar to Qudexy® XR pellets. Dissolution studies were carried out using the FDA recommended dissolution medium; Tris buffer pH 7.2. Both topiramate and Qudexy® XR pellets showed a prolonged-release pattern with a complete release after 8 hours. Riboflavin IR blend was prepared by direct mix approach. In addition to riboflavin supplement, the blend contains lactose fast flow grade, magnesium stearate, and colloidal silicon dioxide. Riboflavin showed immediate-release profile; where 98.2% of riboflavin amount was released after 30 minutes. The optimized topiramate XR pellets and riboflavin blend were weighed separately and filled into HPMC capsules. The capsules passed the storage conditions of 40°C/75 %RH after 3 months without significant decline in assay and dissolution rate of topiramate and riboflavin. Therefore, a novel super-generic of the reference product Qudexy® XR pellets was successfully developed.