World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:9, No:07, 2015

Quality by Design in the Optimization of a Fast HPLC Method for Quantification of Hydroxychloroquine Sulfate

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Abstract : Initially developed as an antimalarial agent, hydroxychloroquine (HCQ) sulfate is often used as a slow-acting antirheumatic drug in the treatment of disorders of connective tissue. The United States Pharmacopeia (USP) 37 provides a reversed-phase HPLC method for quantification of HCQ. However, this method was not reproducible, producing asymmetric peaks in a long analysis time. The asymmetry of the peak may cause an incorrect calculation of the concentration of the sample. Furthermore, the analysis time is unacceptable, especially regarding the routine of a pharmaceutical industry. The aiming of this study was to develop a fast, easy and efficient method for quantification of HCQ sulfate by High Performance Liquid Chromatography (HPLC) based on the Quality by Design (QbD) methodology. This method was optimized in terms of peak symmetry using the surface area graphic as the Design of Experiments (DoE) and the tailing factor (TF) as an indicator to the Design Space (DS). The reference method used was that described at USP 37 to the quantification of the drug. For the optimized method, was proposed a 33 factorial design, based on the QbD concepts. The DS was created with the TF (in a range between 0.98 and 1.2) in order to demonstrate the ideal analytical conditions. Changes were made in the composition of the USP mobile-phase (USP-MP): USP-MP: Methanol (90:10 v/v, 80:20 v/v and 70:30 v/v), in the flow (0.8, 1.0 and 1.2 mL) and in the oven temperature (30, 35, and 40ºC). The USP method allowed the quantification of drug in a long time (40-50 minutes). In addition, the method uses a high flow rate (1,5 mL.min-1) which increases the consumption of expensive solvents HPLC grade. The main problem observed was the TF value (1,8) that would be accepted if the drug was not a racemic mixture, since the co-elution of the isomers can become an unreliable peak integration. Therefore, the optimization was suggested in order to reduce the analysis time, aiming a better peak resolution and TF. For the optimization method, by the analysis of the surface-response plot it was possible to confirm the ideal setting analytical condition: 45 °C, 0,8 mL.min-1 and 80:20 USP-MP: Methanol. The optimized HPLC method enabled the quantification of HCQ sulfate, with a peak of high resolution, showing a TF value of 1,17. This promotes good co-elution of isomers of the HCQ, ensuring an accurate quantification of the raw material as racemic mixture. This method also proved to be 18 times faster, approximately, compared to the reference method, using a lower flow rate, reducing even more the consumption of the solvents and, consequently, the analysis cost. Thus, an analytical method for the quantification of HCQ sulfate was optimized using QbD methodology. This method proved to be faster and more efficient than the USP method, regarding the retention time and, especially, the peak resolution. The higher resolution in the chromatogram peaks supports the implementation of the method for quantification of the drug as racemic mixture, not requiring the separation of isomers.

Keywords : analytical method, hydroxychloroquine sulfate, quality by design, surface area graphic
Conference Title : ICPPT 2015 : International Conference on Pharmacology and Pharmaceutical Technology
Conference Location : Paris, France
Conference Dates : July 20-21, 2015