Detection and Quantitation of Solithromycin Form II in Solithromycin Capsules, 200 mg by X-ray Powder Diffraction

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Background/Purpose: Solithromycin is a fluoroketolide in Phase 3 trials for the treatment of community acquired bacterial pneumonia. Two polymorphic forms (Forms I and II) and an amorphous form of solithromycin have been identified. Form I was selected for development. The purpose of these studies was to develop an X-Ray Powder Diffraction (XRPD) method for the identification and quantitation of solithromycin Form II in solithromycin capsules.

Methods: The analytical method uses XRPD to execute experiments (using Commander Software, v. 2.6) in a two-stepped approach – a primary qualitative scan over the 2 - 40° 2Θ range and a visual evaluation of the diffractogram to determine presence of Form II peaks followed by a secondary quantitation of crystalline Form II in the sample. If Form II peaks are not observed in the initial visual evaluation, the level of Form II in the product samples is determined as below the limit of detection and no quantitation is performed. If peaks associated with Form II are observed in the visual evaluation, then the second step involves integration of the peaks unique to Form II using the Bruker EVA data analysis, v.18.0.0.0 software for quantitation. 1%, 3%, 5% and 10% Form II was spiked into the solithromycin capsule blend in separate vials, vortexed and shaken to prepare homogeneous mixtures. Solithromycin drug substance and formulation samples were lightly ground in a mortar and pestle to generate representative powders prior to data acquisition. X-ray powder diffraction analyses were conducted on a Bruker AXS D8 Advance system with a Bragg-Brentano configuration using the CuKα radiation and scintillation detector. Bruker EVA data analysis software was utilized to evaluate powder patterns and determine peak area values.

Results: The analytical method was developed in the following sequence: Peak selection: The initial study spiked a solithromycin capsule formulation with approximately 10% Form II. Peaks near 5.5°, 7.7°, 9.2°, 11.5° and 12.8° 2Θ were unique to Form II and these were unobscured from peaks corresponding to Form I or excipients. Pre-validation linearity evaluation: A linearity study spiking approximately 1%, 3%, 5% and 10% Form II into the solithromycin capsule formulation was conducted to determine the limit of detection (LOD) and limit of quantitation (LOQ). Samples were prepared in triplicate and data sets analyzed to determine the net peak area values for the five unique Form II peaks stated earlier. Validation: Validation of the method was executed using the approach to collect net area values from three of the unique Form II peaks (5.5°, 7.7° and 11.5° 2Θ peaks) using a 4-point (1%, 3%, 5% and 10% concentrations) calibration series for the peak selection to yield the most sensitive LOD and LOQ values with the greatest R2 value. Validation also included accuracy, specificity, linearity, intra- and inter-sample reproducibility.

Conclusion: An XRPD method for the identification and quantitation of solithromycin Form II in solithromycin capsules was developed. The method was successfully validated and is suitable for supporting identification and quantitation of solithromycin Form II in the capsule drug product that consists principally of solithromycin Form I and pharmaceutically acceptable excipients.

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