Design of Experiments: Critical Process Parameters Confirmation for the Scale-up Manufacturing of Solithromycin 200 mg Capsules

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Purpose: In the course of development, solithromycin 200 mg capsules were manufactured for use in clinical studies. To continue product development, a Design of Experiments (DOE) was used to establish the range of operation for critical process parameters (CPP) of the manufacturing process and the design space. It was of interest to confirm the operation ranges for the CPP by manufacturing a confirmation batch at the same scale as the planned registration batches.

Methods: The manufacturing process of the solithromycin 200 mg capsules involves wet granulation, fluid bed drying, milling, blending (lubrication) and encapsulation. From the analysis of the DOE results, the optimal target and operational ranges for producing capsules that met the critical quality attributes (CQA) were established. Since the DOE batches were manufactured at the 5 kg-scale, the quantitative formula was scaled-up to the registration batch scale of 52 kg. The equipment and equipment parameters were scaled-up appropriately. The confirmation and registration batches were manufactured with intervals of sample testing and bulk samples were collected for release testing. Samples were analyzed for assay, blend uniformity, uniformity of dosage units and dissolution profile.

Results: Physical properties (bulk and tapped densities, particle size distribution), blend uniformity, uniformity of dosage units (by weight variation), assay, and dissolution profile were evaluated. The obtained tapped densities were comparable to those of the DOE batch used to generate the scale-up parameters and to the predicted values from the regression equation obtained from the DOE. For the confirmation batch, at least 99.73% of the in-process fill weight of the capsules were within the control limits, blend uniformity testing had a %CV of NMT 5% and the uniformity of dosage units across all the intervals had an Acceptance Value of NMT 15. The dissolution profiles were consistent with those of the clinical batches. All other in-process and finished drug product analytical results were also within the specifications.

Conclusions: The confirmation and registration batches confirm that the CPP and operational ranges identified from the DOE batches were scalable. The DOE batches identified operating ranges for CPP that are necessary to consistently produce capsules with predefined CQA.

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