

# Design of Experiments for Wet Granulation of Solithromycin 200 mg Capsules: Process Development for Manufacturing

**AAPS 2014**  
**Abstract 4310**

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**Purpose:** In order to optimize the manufacturing process of the Solithromycin 200 mg capsules in preparation for registration and validation batches, this study was performed to identify the critical process parameters (CPP) of the granulation process. A Design of Experiment (DOE) approach, in support of Quality by Design (QbD) was used to guide the study.

**Methods:** The manufacturing process of the Solithromycin 200 mg capsules involves wet granulation, fluid bed drying, milling, blending (lubrication) and encapsulation. For the wet granulation part of the process, a 3-factorial, 2-level, 1-center point approach was used in the DOE. The three factors that were evaluated at two levels are the amount of added water, the rate of water addition and the kneading time. A fourth categorical variable was also evaluated in the study. The DOE was generated and analyzed by the Minitab<sup>®</sup>16 Software.

**Results:** Physical properties (bulk and tapped densities), blend uniformity, uniformity of dosage unit (by weight variation), assay, and dissolution profile of the blends were evaluated. The tapped density was an important determinant of encapsulation performance and in turn was shown to be influenced by the categorical variable, the amount of water added, the kneading time, or a combination of all of the three. From the total water added, kneading time, and the categorical variable, a regression equation was generated and was used to predict the tapped density value. There was also a strong positive correlation between the dissolution results at 10 and 15 minute time points and the average particle size of the blend ( $d_{50} > 150\mu\text{m}$ ). The results indicated that a tapped density of 0.58 to 0.62 g/mL for the blend was optimal for encapsulation. This property could be achieved by adding water at its upper (+) limit level of the DOE and a total kneading time of 8-10 minutes.

**Conclusions:** Using a Design of Experiments approach, the range of operation for the critical process parameters, including the amount of added water, the rate of water addition, the kneading time and the categorical variable were identified for use in registration and validation batch manufacture for solithromycin 200 mg capsules.