**URE**

Sample preparation is perhaps the most important step in tablet assay analysis as it requires complete extraction of the analyte and must yield a final solution concentration suitable for quantification. According to a recent survey conducted by Majors (1), mechanical assisted extraction has shown a marked increase in use for automated sample preparation over the past ten years. This paper discusses one instrument for mechanically assisted extraction, the Tablet Processing Workstation (TPW), which fully automates sample preparation for methods development. The other instrument discussed, the PrepEngine, uses rotating disc blades with wet grinding for sample disintegration and mixing to facilitate sample extraction for rapid GC analysis. In this work, the use of homogenization combined with wet milling for sample disintegration and extraction of Spray Dried Dispersion (SDD) tablets is discussed as a replacement to the lengthy manual method using sonication and mixing with stir bars in volumetric flasks. Utilization of the TPW for method development and the PrepEngine as a tool for rapid GC sample preparation is evaluated for SDD tablet assay and content uniformity.

**Background**

- Manual tablet sample preparation using volumetric flasks and the inability to accurately control stirring speed of a stir bar using a stir plate is time consuming and inefficient and has resulted in numerous investigations into low assay for tablet sample preparations (2).
- Mechanical Assisted Extraction weight/weight tablet procedure allows systematic and calibrated controls over tablet disintegration and extraction. The use of automated instrumentation yields reliable, efficient and robust methods for measurement of Content Uniformity (CU) and assay determination.

- Two types of Mechanical Extraction instrument were evaluated:
  1. Tablet Process Workstation (TPW): A fully automated gravimetric guided serial sample preparation robot capable of execution of Design of Experiment (DOE) studies, a tool to select the appropriate and optimal conditions for tablet extraction.
  2. PrepEngine: A mechanically assisted extraction device allowing 10 simultaneous sample extractions. Like the TPW system, tablet extraction occurs using programmed RPM and time intervals to ensure consistent performance.

- Gilead has successfully implemented both instrument platforms to support method development and routine sample analysis. The fully automated capabilities of the TPW system allowed for efficient assay method development while the PrepEngine was used for routine analysis.

**RESULTS**

The following parameters were evaluated in one automated sequence:
- Evaluated grinding/blending speed
- Extraction Time to achieve 100% recovery of analyte from tablets.
- Establish filter compatibility for multiple filter types.
- Evaluated robustness of secondary dilution with regard to aqueous/oric dry/diluent composition.
- Solvent composition of the secondary dilution step
- Based on the method parameter design space evaluated using the TPW, optimal conditions were adapted to the PrepEngine platform.

### Advantages of PrepEngine as a Tool for Routine Analysis

- Extraction parameters controlled using calibrated blade speed and blending time.
- Simultaneous preparation of 10 samples yield high throughput.
- Scalable to from 50 mL to 500 mL volumes for extraction.
- Vessels can be washed and reused or considered single-use consumables.
- Automating only the primary extraction step is more suited to routine analyses at CMO testing sites as less specialized equipment are required.

**CONCLUSION**

Sample preparation using mechanical homogenization resulted in up to 6 times faster extraction times compared to the manual method, which can take more than 3 hours. The use of the fully automated TPW system for method development ensured that key method parameters impacting solubility and analyte recovery were evaluated. Adaptation of the method to the PrepEngine platform provided a robust and efficient method for routine use in the QC environment.

**REFERENCES**