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A Fast Sample Preparation Procedure for Spray Dried Dispersion (SDD) Tablets Using Mechanical Assisted Extraction

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PURPOSE

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 combined with wet grinding for sample disintegration and mixing to facilitate sample extraction for rapid QC 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 QC 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 programed 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.

METHOD

SPRAY DRIED DISPERSION (SDD) TABLET ASSAY

Step 1	Step 2	Step 3	Step 4
Primary Extraction 200 mg Active in 50 mL 4 mg/mL Solution	Filtration	Secondary Dilution 5 mL in 200 mL 0.1 mg/mL Solution	Chromatographic Analysis

Historical Manual Preparation

Manual Extraction

- Disintegration by stir bar with uncontrolled stir rate
- Inefficient extraction
- 3 hour + extraction time
- Not robust
- Multiple investigations due to incomplete extraction

Mechanical Extraction Method Development

Tablet Process Workstation : TPW

- Disintegration by high shear homogenizer up to 10,000 RPM
- Established design space for primary extraction
- Filtration
- Secondary dilution
- Fully automated
- 30 minute extraction time

Mechanical Extraction Routine QC Analysis

PrepEngine

- Adapted method based on design space established using TPW.
- Disintegration by wet milling at 4,000 RPM.
- Simple platform for routine use
- Small footprint
- Efficient and Robust
- 30 minute extraction time

Advantages of Method Development Using the Automated TPW System

- *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/organic 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..

RESULTS

Assay

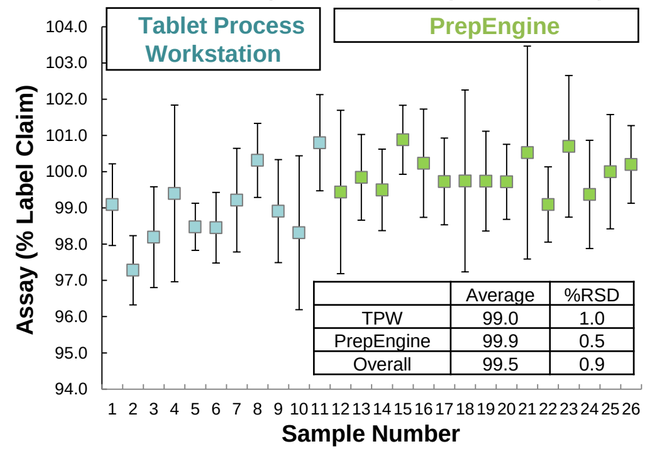
The table below displays a comparison of the composite assay testing of the PrepEngine, Manual and TPW sample preparation procedures for the SDD tablets, 200 mg label claim. The results demonstrate equivalency in extraction efficiency between the highly automated TPW and PrepEngine procedures and the very lengthy 3 hour Manual method for extraction.

Technique /Lot ID	Manual (10 Tablet Composite) Extraction Time=3hr	TPW (5 Tablet Composite) Extraction Time=30min	PrepEngine (5 Tablet Composite) Extraction Time=30min
Lot 1	**100.2 %**	**100.2%**	**99.0 %**
Lot 2	**101.1%**	**99.6%**	**100.4%**
Lot 3	**101.5%**	**99.8%**	**100.7%**

Content Uniformity

The graph below shows a comparison of the PrepEngine and TPW mechanical extraction precision based on %Strength determination for Content Uniformity (CU) of the SDD tablets. The results demonstrated precision of %RSD ≤ 3.0 (n=26 lots).

Comparison of TPW and PrepEngine Results for Content Uniformity Measurement (N=10 Tablets)



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

1. R.E. Majors. Trends in Sample Preparation. *LCGC North America*, 31(2013) pp190-202.
2. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, *Guidance for Industry* (2006).