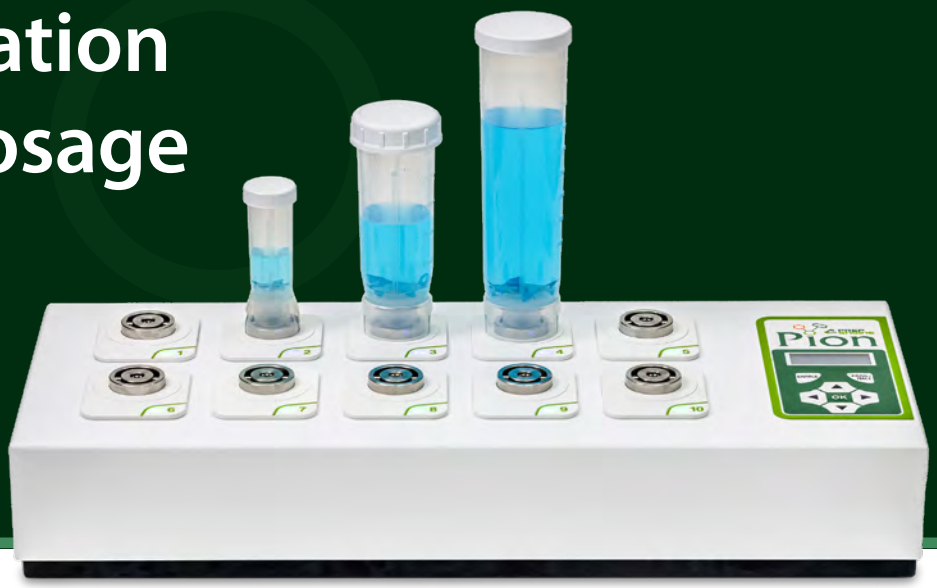
APPLICATION NOTE

Rapid and Reproducible Sample Preparation of Solid Oral Dosage Formulations



Pion's PrepEngine

Introduction

Sample preparation plays a critical role in pharmaceutical analytical testing and is commonly performed as part of assay, impurity, and content uniformity evaluations for solid oral dosage forms. Content uniformity testing, as described in USP <905>, is used to confirm that active pharmaceutical ingredients (APIs) are uniformly distributed throughout a dosage form and that each unit contains the intended amount of drug substance within an acceptable range. Assay testing is used to quantify the amount of API present in a formulation, while impurity and degradation product testing evaluate the presence of related compounds that may impact product quality or stability.

Traditional sample preparation methods for these analyses commonly utilize sonication baths, reciprocal shakers, heated water baths, and solvent extraction procedures to disperse tablets or capsules and extract compounds into solution prior to HPLC analysis. Depending on the formulation type and extraction procedure, these methods may involve multiple preparation steps including solvent additions, extended mixing periods, filtration, dilution, and cleanup procedures. These processes can also introduce variability depending on operator technique, mixing conditions, and sample characteristics.

Several conventional approaches evaluated during this study included reciprocal shaker extraction, heated water bath extraction, sonication-assisted extraction, and multi-step solvent extraction procedures. These workflows were compared against the PrepEngine sample preparation system across multiple solid oral dosage forms to evaluate sample preparation performance, extraction efficiency, potency recovery, reproducibility, and overall preparation workflow.

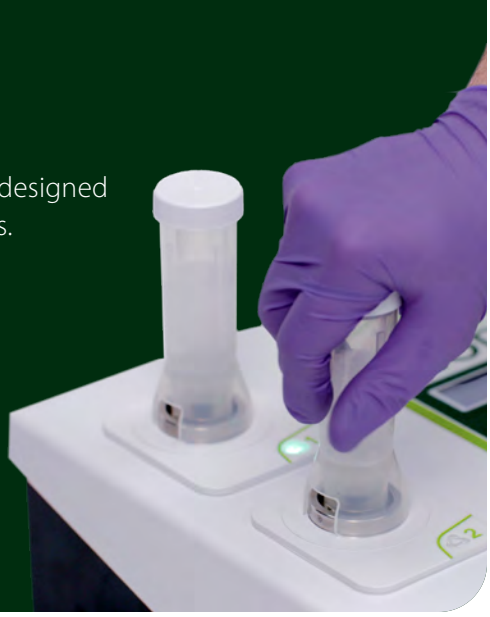
The Pion PrepEngine utilizes a rotating stainless steel blade within a sealed PrepTube to mechanically disperse and homogenize samples directly within the extraction solvent. The system supports programmable processing speeds and processing times and allows multiple samples to be processed simultaneously under controlled conditions.

PrepEngine System Overview

The PrepEngine is a high-throughput benchtop sample preparation system designed for tablet and capsule dispersion, homogenization, and extraction workflows.

Key system features include:

- Processing speeds from 500 RPM to 6000 RPM
- Programmable processing times ranging from 5 seconds to 4 hours
- 50 mL, 250 mL, and 500 mL PrepTube configurations
- Wet or dry grinding capability
- Up to 10 independently activated stirring stations
- Simultaneous preparation of multiple samples



Experimental Overview

The evaluation focused on comparing conventional pharmaceutical sample preparation procedures against PrepEngine-based preparation methods across several formulation types, including immediate release tablets, modified release tablets, softgel capsules, and swellable core technology formulations.

Formulations Evaluated

Formulation Type	Formulation Characteristics	Conventional Preparation Method
Compound A: Immediate Release (IR) Tablet	Standard compressed tablet	Reciprocal shaker extraction
Compound B: Extrudable Core System (ECS) Tablet	Modified release coated tablet	Sonication and extended shaking
Compound C: Softgel Capsule	Gelatin capsule containing viscous fill material	Heated water bath extraction
Compound D: Swellable Core Technology (SCT) Tablet	Bilayer coated tablet with swellable polymer matrix	Multi-step solvent extraction and overnight shaking
Compound E: Swellable Core Technology (SCT) Tablet	Coated swellable core tablet	Acetonitrile extraction and reciprocal shaking

Conventional Sample Preparation Procedures

The conventional methods evaluated during the study relied on several commonly used laboratory preparation techniques. Depending on the formulation, these included shaker extraction, sonication, heated extraction, and filtration. Several formulations required complex preparation procedures involving multiple solvent additions and extended extraction times to achieve complete dispersion and extraction.

For example, the swellable core technology tablet (Compound D) preparation procedure included:

1. Initial acetonitrile addition and shaking
2. Multiple sequential solvent additions
3. Overnight storage and continued shaking
4. Silica gel cleanup procedures
5. Final filtration prior to HPLC analysis

The complete conventional workflow for this formulation required approximately 24 hours to complete.

The modified release ECS tablet procedure similarly

required multiple shaking and solvent addition steps over approximately 5.5 hours, while softgel capsule preparation utilized heated shaking water bath extraction procedures at 45°C for periods ranging from approximately 2.5 to 6 hours.

PrepEngine Sample Preparation Procedure

PrepEngine preparation procedures generally consisted of:

1. Addition of solvent directly into the PrepTube
2. Addition of the tablet or capsule sample
3. Processing at a defined RPM and processing time
4. Optional dilution, centrifugation, or filtration depending on the formulation
5. Direct transfer for HPLC analysis

Most PrepEngine procedures evaluated during the study utilized processing conditions of 3000 RPM for approximately 6 minutes depending on formulation type.

Results and Performance

The evaluation compared conventional pharmaceutical sample preparation procedures with PrepEngine-based methods across multiple formulation types. Results showed that the PrepEngine achieved potency values and %RSD performance comparable to conventional preparation techniques while significantly reducing overall sample preparation and extraction times.

Summary of Results

Formulation	Manual Method	PrepEngine Conditions	Potency (% LC) N=10	PrepEngine Extraction Time vs Manual Method
Compound A: IR Tablet	30 mins (Reciprocal shaker)	2 min @ 3000 rpm	100.9 (0.59 % RSD)	15X Faster
Compound B: ECS Tablet	5.5 hrs (Sonication & shaking)	6 min @ 3000 rpm	98.6 (1.21 %RSD)	55X Faster
Compound C: Softgel capsules	2.5 – 6 hrs (Reciprocal shaker, w/ water bath @ 45°C)	6 min @ 3000 rpm	99.5 (0.7 % RSD)	25 – 60X Faster
Compound D: SCT Tablet	24 hrs (Reciprocal shaker)	6 min @ 3000 rpm	103.7 (1.38 % RSD)	240X Faster
Compound E: SCT Tablet	4 hrs (Cut tablet / reciprocal shaker)	6 min @ 3000 rpm	104.7 (3.41 %RSD)	40X Faster

Immediate Release Tablet Evaluation

Immediate release tablets were successfully dispersed and extracted using the PrepEngine at 3000 RPM for approximately 2 minutes. Conventional preparation for this formulation utilized reciprocal shaking for approximately 30 minutes followed by centrifugation and dilution.

The PrepEngine preparation produced potency values comparable to the manual preparation method with low variability between replicates.

Parameter	Conventional Method	PrepEngine
Preparation Method	Reciprocal shaker	Mechanical dispersion
Approximate Prep Time	30 minutes	2 minutes
Potency (% LC)	101.3	100.9
%RSD	1.3	0.59

ECS Modified Release Tablet Evaluation

The extrudable core system (ECS) modified release formulation represented a more challenging extraction due to the coated tablet structure and formulation composition.

The conventional procedure utilized multiple shaking steps and sonication over approximately 5.5 hours. Using the PrepEngine, the same formulation was processed using 85/15 perchloric acid/acetonitrile solvent at 3000 RPM for approximately 6 minutes.

The resulting potency values remained consistent with the conventional preparation procedure while substantially reducing total preparation time.

Parameter	Conventional Method	PrepEngine
Preparation Method	Sonication + reciprocal shaking	Mechanical dispersion
Approximate Prep Time	5.5 hours	6 minutes
Potency (% LC)	98.7	98.6
%RSD	1.28	1.21

Softgel Capsule Evaluation

Softgel capsule preparation conventionally relied on heated water bath extraction procedures operated at 45°C for periods ranging from approximately 2.5 to 6 hours.

PrepEngine processing resulted in rapid capsule rupture and extraction within approximately 6 minutes while maintaining potency values near expected label claim with low %RSD values.

Parameter	Conventional Method	PrepEngine
Preparation Method	Heated water bath extraction	Mechanical dispersion
Approximate Prep Time	2.5-6 hours	6 minutes
Potency (% LC)	99.0	99.5
%RSD	Not reported	0.70

Swellable Core Technology Tablet Evaluation

The swellable core technology (SCT) formulation represented the most complex sample preparation workflow evaluated during the study.

The conventional preparation procedure required multiple solvent additions, overnight shaking, and silica gel cleanup procedures to address viscosity challenges associated with the swellable polymer matrix.

The conventional workflow consisted of:

1. Initial acetonitrile addition
2. Two-hour reciprocal shaking
3. Sequential solvent additions
4. Additional four-hour shaking periods
5. Overnight storage and extraction
6. Silica gel cleanup and filtration prior to HPLC analysis

Using the PrepEngine, the same formulation was processed using a 50/50 methanol/ethanol diluent system at 3000 RPM for approximately 6 minutes. The evaluation demonstrated complete tablet dispersion, reduced viscosity concerns compared to conventional preparation methods, comparable potency recovery, low variability between replicates, and significant reductions in overall preparation time.

Swellable Core Technology Tablet Evaluation

This formulation demonstrated the largest overall reduction in preparation time observed during the evaluation, reducing sample preparation from 24 hours to approximately 6 minutes.

Parameter	Conventional Method	PrepEngine
Preparation Method	Sequential solvent extraction + overnight shaking	Mechanical dispersion
Approximate Prep Time	24 hours	6 minutes
Potency (% LC)	103.6	103.7
%RSD	1.7	1.38

Composite Sampling and Parallel Processing

A separate composite sampling evaluation was also performed to assess PrepEngine performance when processing multiple dosage units within a single PrepTube. In this portion of the study, composite samples consisting of five dosage units per PrepTube were prepared and evaluated across multiple formulation types including immediate release tablets, ECS modified release tablets, softgel capsules, and swellable core technology formulations.

Composite sample preparation was successfully demonstrated across all evaluated formulations while maintaining acceptable potency recovery and reproducibility. PrepEngine processing conditions generally remained consistent with the single-unit evaluations, with most formulations processed at approximately 3000 RPM for 2 to 6 minutes depending on formulation type.

Summary of Results

Formulation	Composite Sample Size	PrepEngine Conditions	Mean Potency (% LC)	%RSD
Compound A: IR Tablet	5 units	2 min @ 3000 rpm	100.7	0.44
Compound B: ECS Tablet	5 units	6 min @ 3000 rpm	96.1	0.80
Compound C: Softgel capsules	5 units	6 min @ 3000 rpm	98.6	Not reported
Compound D: SCT Tablet	5 units	6 min @ 3000 rpm	101.8	0.74
Compound E: SCT Tablet	5 units	6 min @ 3000 rpm	101.6	3.03

The evaluation also included composite sample preparation procedures involving multiple dosage units processed within a single PrepTube. Composite sample preparation was successfully performed across multiple formulation types while maintaining acceptable potency and reproducibility.

The system configuration additionally allowed multiple samples to be processed simultaneously under identical preparation conditions. This approach may be beneficial in laboratories performing high-throughput assay or content uniformity testing where multiple units are routinely prepared within the same analytical batch.

Cleaning Evaluation

PrepTube cleaning procedures were also evaluated following processing of multiple formulation types. Cleaning procedures generally consisted of water rinses followed by agitation with sample diluent depending on the formulation being processed. Subsequent HPLC analysis following cleaning procedures demonstrated no observable API carryover or residual particulate material.

These results indicated that the PrepTubes could be effectively cleaned between samples using relatively simple cleaning procedures with minimal potential for cross contamination.

Discussion and Conclusion

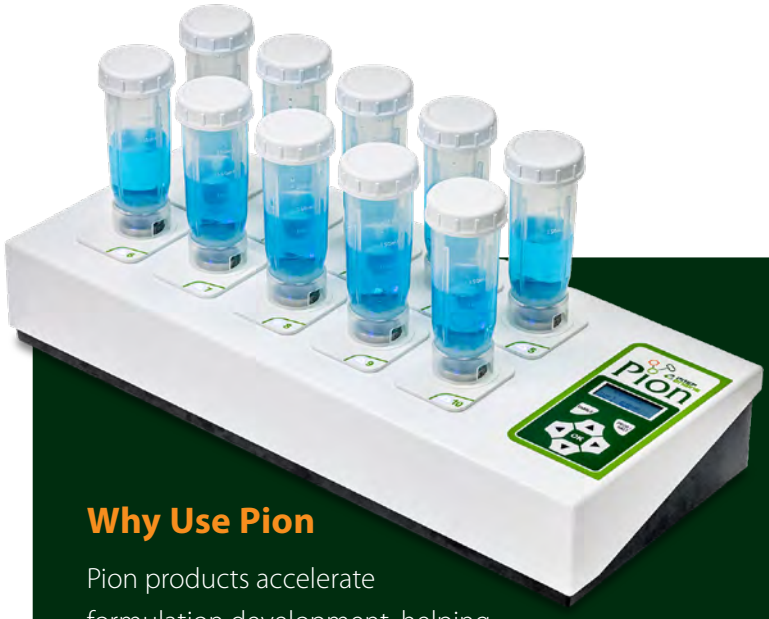
The evaluation demonstrated that mechanical dispersion using the PrepEngine produced potency and reproducibility results comparable to conventional pharmaceutical sample preparation procedures across multiple dosage form types while significantly reducing overall preparation time.

The largest performance differences were observed with more complex formulations including modified release tablets, softgel capsules, and swellable core systems that traditionally require extended extraction workflows and multiple preparation steps. In several cases, preparation procedures that conventionally relied on extended shaking, sonication, or overnight extraction were completed in minutes using the PrepEngine approach while maintaining comparable %RSD values.

The SCT formulation evaluation was particularly notable due to the complexity of the conventional preparation workflow. A preparation procedure requiring approximately 24 hours using conventional extraction techniques was replaced with a PrepEngine procedure requiring approximately 6 minutes while maintaining comparable potency and reproducibility results.

The evaluation also demonstrated successful preparation of composite samples and simultaneous processing of multiple samples under controlled conditions. PrepTube cleaning procedures additionally showed no observable API carryover following standard cleaning procedures.

The PrepEngine demonstrated significant reductions in sample preparation time across all formulation types evaluated, delivering equivalent potency results while accelerating extraction workflows by 15X to 240X compared to conventional methods.



Why Use Pion

Pion products accelerate formulation development, helping you save time, reduce costs, and improve outcomes. We developed the PrepEngine to streamline pharmaceutical content uniformity, assay, impurity, and analytical sample preparation workflows. We know that accurate determination is essential to select the right candidates in order to define the optimal path for drug development.

Pion empowers the pharmaceutical R&D community helping to make important decisions on candidate selection based on trusted data for drug optimization, which will impact people's lives. In other words, we help scientists to find the right answers faster to select the best strategy for a successful drug.