Improving Efficiency and Throughput With Advances in Automated Dissolution Testing

Patricia A. Fowler, Michael E. Swartz, Ph.D.,Michael D. Jones

Waters Corporation

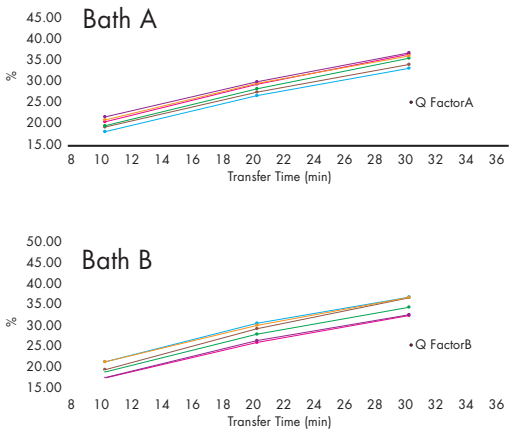
www.Waters.com

WA20698

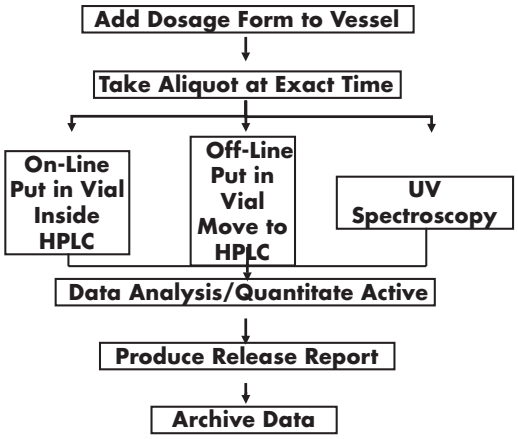
Abstract

Pharmaceutical researchers are required to reduce the analytical burden of test procedures, and increase productivity while satisfying regulatory compliance. Validated single source software control of the entire automated system for HPLC and on-line UV analysis of dissolution samples, as well as data acquisition and calculations, (i.e. SUPAC F1/F2 calculations), further streamline the work flow. Systems must be capable of handling complex formulations, such as multiple actives, widely varying dosages, and different media types. Studies showing improvement in efficiency and productivity for automated HPLC and on-line UV dissolution test results will be presented. Applications illustrating the use of problematic dissolution test media and complex multiple active formulations will be provided.

Prednisone Dual Bath Test Individual Bath Comparison



Overview of Dissolution Testing



Applications Using an Advanced Automated Dissolution System

- Immediate vs. Extended Release
- Rapid Sampling
- Sample Pooling
- Complex Media
  - Surfactants, cyclodextrin
  - High viscosity media
    - Slow speed syringe draw
    - Increased post sample wash
- HPLC vs. On-line UV Analysis

Advances in Automated Dissolution Technology

- Increased Productivity
  - Dual bath operation of multiple sample sets
  - Complex formulations
  - Multiple actives
  - Varying dosages
  - Different media types
  - Automatic Dissolution Calculations
  - F1/F2 Calculations for SUPAC
  - Customizable reporting
  - HPLC and On-Line UV Analysis
    - Common calculations and validation

Immediate Vs. Extended Release Dual Bath Test

In this example, both immediate release tablets and extended release capsules can be sampled and analyzed on a dual bath system. Both tests were run automatically from sample collection to the final report. The samples from the two different baths were collected and analyzed simultaneously. The bath conditions were different for each of the tests although the HPLC conditions were the same. The ability to run two different test conditions simultaneously gives greater flexibility as well as saving time in the laboratory.

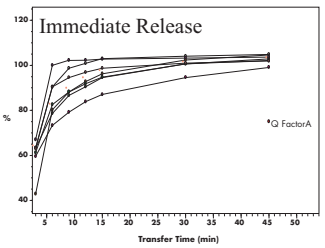
Improving Efficiency and Throughput With Advances in Automated Dissolution Testing

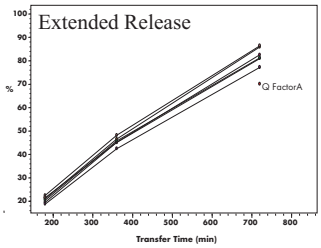
Patricia A. Fowler, Michael E. Swartz, Ph.D.,Michael D. Jones

Waters Corporation

www.Waters.com

Phenylpropanolamine-HCl Dual Bath Test



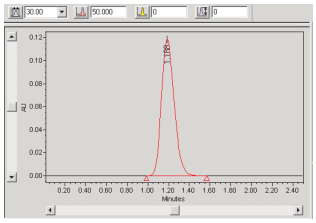


- Sample:
  Phenylpropanolamine HCl Tablet
- Dissolution Conditions (n=6):
  Apparatus 2 at 50 rpm
  Q factor is >75% release at 45 min.
- HPLC Conditions:
  Symmetry® C18 (3.9 x 50 mm)

- Sample:
  Phenylpropanolamine HCl Extended Release Capsule
- Dissolution Conditions (n=6):
  Apparatus 1 at 100 rpm
  Q factor is >70% release at 720 min.
- HPLC Conditions:
  Symmetry® C18 (3.9 x 50 mm)

Online UV Analysis

- How does it work?
  - Online UV testing by pumping samples through a flow cell on a spectrophotometer is equivalent to pumping samples through a flow cell in an absorbance detector.
  - The dissolution test is performed in the usual manner on the same system except that a reaction coil (from the Waters® Online UV Analysis Kit) is used in place of the HPLC column. The same software for calculations and reporting is used.

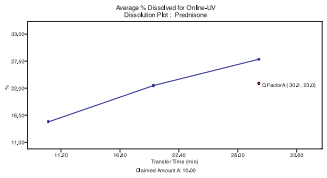


Rapid Sampling Protocol

- Rapid Dissolution Sampling Times
  - Sampling begins one minute, and every two minutes thereafter
- Used in Formulation Development to Determine Dissolution Kinetics
  - Changes in excipients
  - Developing generic formulations
- Provide Data to Support *in vivo* Bioavailablity Waivers

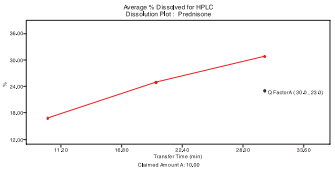
Online Vs. HPLC Comparison

These results show the similarities between the online UV dissolution test and the HPLC dissolution test. Each of the average profile results pass the acceptance Q factor range of 23%-42% as defined by the USP.



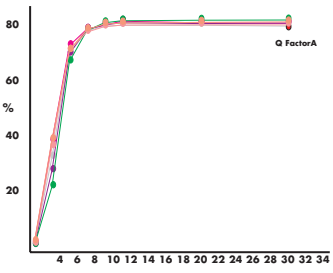
Online UV Dissolution Profile

versus...



HPLC Dissolution Profile

Rapid Sampling Dissolution Test

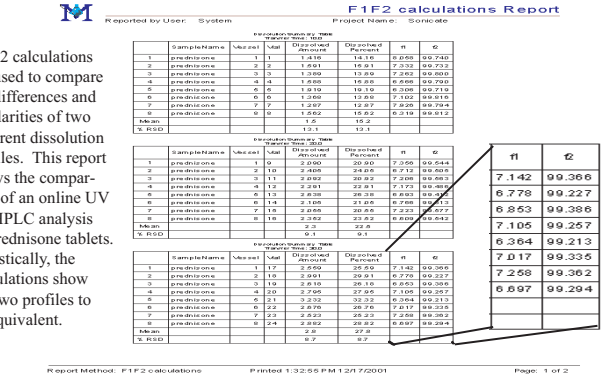


- Sample:
  Acetaminophen Tablet
- Dissolution Cond. (n=6):
  Rapid Sampling Protocol collecting at 1, 3, 5, 7, 9, 11, 20, and 30 min.
  Q factor is >80% release at 30 min.
- HPLC Conditions:
  Symmetry® C18 (3.9 x 50 mm)

Sampling began at 1 minute after the pill was dropped, and every 2 minutes thereafter. Each point represents the time of each sample transfer from the dissolution bath directly into vials for HPLC analysis.

Online Vs. HPLC Comparison: F1/F2 Calcs.

F1/F2 calculations are used to compare the differences and similarities of two different dissolution profiles. This report shows the comparison of an online UV vs. HPLC analysis of Prednisone tablets. Statistically, the calculations show the two profiles to be equivalent.


F1F2 calculations Report

Reported by User: System Project Name: Sonicate

Dissolution Summary Table (Vessel Type: 900)

	SampleName	Vessel	Vial	Dissolved Amount	Dissolved Percent	f1	f2
1	prednisone	1	1	1.435	14.16	8.668	99.740
2	prednisone	2	2	1.691	16.91	7.332	99.732
3	prednisone	3	3	1.389	13.96	7.262	99.800
4	prednisone	4	4	1.689	16.88	6.668	99.790
5	prednisone	5	5	1.919	19.19	6.308	99.719
6	prednisone	6	6	1.269	12.86	7.102	99.816
7	prednisone	7	7	1.297	12.97	7.928	99.794
8	prednisone	9	9	1.562	15.62	6.219	99.912
Mean				1.5	15.2		
% RSD				13.1	13.1		

Dissolution Summary Table (Vessel Type: 900)

	SampleName	Vessel	Vial	Dissolved Amount	Dissolved Percent	f1	f2
1	prednisone	1	9	2.090	20.90	7.359	99.644
2	prednisone	2	10	2.495	24.95	6.712	99.605
3	prednisone	3	11	2.892	28.92	7.208	99.683
4	prednisone	4	12	2.291	22.91	7.173	99.481
5	prednisone	5	13	2.838	28.38	6.883	99.647
6	prednisone	6	14	2.166	21.66	6.768	99.613
7	prednisone	7	15	2.855	28.55	7.223	99.677
8	prednisone	8	16	2.352	23.52	6.809	99.642
Mean				2.3	22.8		
% RSD				9.1	9.1		

Dissolution Summary Table (Vessel Type: 900)

	SampleName	Vessel	Vial	Dissolved Amount	Dissolved Percent	f1	f2
1	prednisone	1	17	2.859	28.59	7.142	99.366
2	prednisone	2	18	2.991	29.91	6.778	99.227
3	prednisone	3	19	2.816	28.16	6.853	99.386
4	prednisone	4	20	2.795	27.95	7.105	99.257
5	prednisone	5	21	3.232	32.32	6.364	99.213
6	prednisone	6	22	2.878	28.78	7.017	99.335
7	prednisone	7	23	2.823	28.23	7.258	99.362
8	prednisone	9	24	2.892	28.92	6.897	99.294
Mean				2.8	27.8		
% RSD				8.7	8.7		

f1	f2
7.142	99.366
6.778	99.227
6.853	99.386
7.105	99.257
6.364	99.213
7.017	99.335
7.258	99.362
6.897	99.294

Report Method: F1F2 calculations Printed 1:32:55 PM 12/17/2001 Page: 1 of 2

Improving Efficiency and Throughput With Advances in Automated Dissolution Testing

Patricia A. Fowler, Michael E. Swartz, Ph.D.,Michael D. Jones

Waters Corporation

www.Waters.com

Waters
RIGHT ON TIME.

Dissolution Sample Pooling

- Proposed by USP, PF vol. 21(1), pg. 177, 1995
  - "…If macro (batch, source) differences within the specification are insignificant to fitness for use, then unit to unit (micro) differences do not matter."
- PF, vol. 22(5), pg. 2777, 1996
  - 70 USP Monographs Forwarded to In-process Revision
- USP 23, Ninth Supplement (11/15/98), Pooling Is Incorporated Into Chapter 711 on Dissolution
- USP 24 NF 19 Chapter 711 specifies acceptance criteria for pooled samples.
  - 70 USP monographs include pooling

Sample Description	Avg. Retention Time over 25 injections	Avg. Retention Time SD
Sample 1- no SDS	2.00	.005
Sample 2- 0.1% SDS	1.98	.005
Sample 3- 0.5% SDS	1.98	.006
Sample 4- 1.0% SDS	1.97	.006
Sample 5- 5.0% SDS	1.96	.008
Repeat Sample 1	1.98	.011

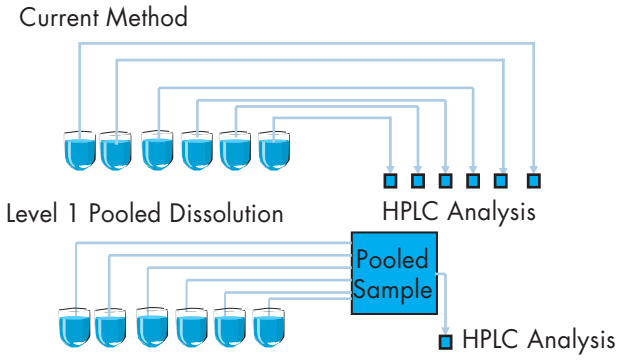
Sample: USP Prednisone Calibrator Tablets with varying concentrations of sodium dodecyl sulfate (w/v)

System: Waters Alliance® Dissolution System

Separation Conditions: 50:50 MeOH:water @ 1 mL/min.
20 µL injection run on a 2487 detector
3.9 x 50 mm Symmetry® C18 column at 30°C

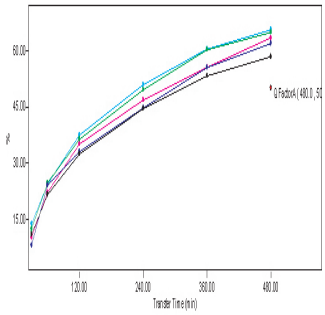
Equivalent results are obtained regardless of surfactant.

Pooled Dissolution Sampling



Currently each sample is analyzed separately and the results averaged. Pooling averages the samples, resulting in one analysis with significant time savings.

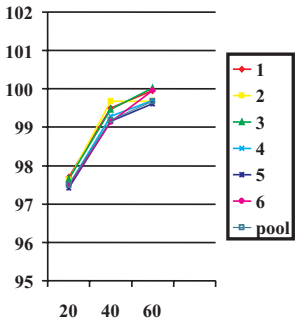
Do Cyclodextrins Affect Dissolution Sample Transfer and Analysis?



- Media type: 0.1%Hydroxypropyl beta Cyclodextrin
- Media volume: 900 mL
- Sample volume: 1.0 mL

Vitamin # 1 Pyridoxine HCl Pooling vs. Individual Analysis

- Use of Method 2040 USP23/NF18 to Compare Analysis of Individual Dosage Forms to Sample Pooling
- The pooled sample is compared to 6 individual samples with equivalent results



Flexible Reporting Structure

- Automatic dissolution profile generation
  - Multiple Q factors
  - Separate profile for each component
- Average profile report
- F1F2 calculations
  - SUPAC
- 21 CFR Part 11 Compliance Ready
  - Complete audit trail capability
- System Suitability
- Statistical Computation of Results
- Temperature and Apparatus Speed

Improving Efficiency and Throughput With Advances in Automated Dissolution Testing

Waters Alliance® Dissolution System

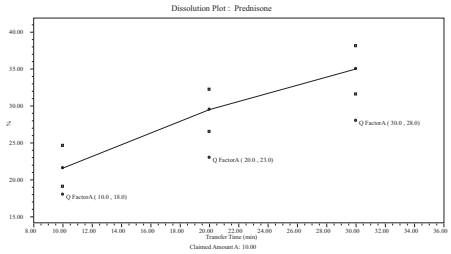
Patricia A. Fowler, Michael E. Swartz, Ph.D.,Michael D. Jones

Waters Corporation

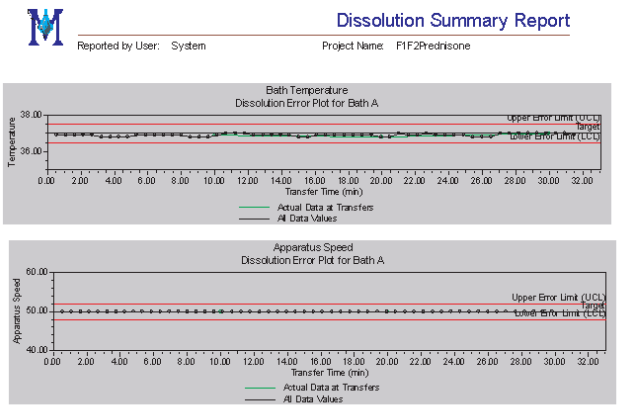
www.Waters.com

Q-Factor Documentation

- New Reporting Feature Documents Q-Factor Specification
  - Multiple Q-Factors
  - Average Results



Temperature and Bath Speed Documentation



Conclusion

- Improving Efficiency and Throughput in Automated Dissolution Technology
  - Operation of multiple dissolution sample sets
  - Specialized dissolution sample analysis
    - Complex formulations, multiple actives, varying dosages, different media types
  - Advanced automated sampling techniques
- Improved Productivity
  - Online UV vs. HPLC analysis
  - Dual bath operation
  - Pooling of samples
- Specialized Reporting
  - Customizable
  - 21 CFR 11 compliant, F1F2, averaging, multiple Q factor plotting, and statistical results