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122 **Development of a Discriminating Dissolution Method Using Apex Vessels for Enzastaurin Tablets**
Min Xia, Xiao-Xiong Lu, Elizabeth Lin, Gerry Burke, Paul Sirois, David Jan, and Proma Phengsy

132 **Assessment of Small Volume (250-mL) Vessels for Use in Biorelevant Dissolution**
Angela Hu, Wei Chen, and Xujin Lu

140 **Evaluation of In Vitro Dissolution Behavior of Ibuprofen Suspensions Based on the Flow-Through Cell Method**
Li Xie, Yao Xiao, Rongqin Zhang, Xiangjin Lian, Mei Yang, Xin Li, Junhan Cao, and Li Su

149 **Question & Answer Section**
Margareth Marques and Mark Liddell


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Table of Contents

In This Issue

Development of a Discriminating Dissolution Method Using Apex Vessels for Enzastaurin Tablets...122

Assessment of Small Volume (250-mL) Vessels for Use in Biorelevant Dissolution.....132

Evaluation of In Vitro Dissolution Behavior of Ibuprofen Suspensions Based on the Flow-Through Cell Method.....140

Question and Answer Section.....149

Calendar of Events.....153

Industry News.....155

Advertisers

Sotax..... Inside front cover
Copley..... 121
Notice to Subscribers..... 129
Hanson/Teledyne..... 130
QLA..... 131
Pharma Test..... 137
Pion..... 138
***Handbook of Dissolution Testing*, 4th Edition..... 139**
EAS..... 148
USP..... 151
Erweka..... 152
Simulations Plus..... 154
Distek..... Back inside cover
Agilent Technologies.....Back outside cover

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Topics for the Next Issue

The November 2025 issue will include research articles on USP apparatus 3 (*Stimuli* article), ibuprofen orodispersible tablets, toremifene citrate tablets, and Franz cell; a book review; and the Q and A feature.

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Vivian Gray
vagray@rcn.com

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Development of a Discriminating Dissolution Method Using Apex Vessels for Enzastaurin Tablets

Min Xia[1*], Xiao-Xiong Lu[2], Elizabeth Lin[2], Gerry Burke[2], Paul Sirois[2], David Jan[1], and Proma Phengsy[1]
[1]*Alan Laboratories, Inc., San Diego, CA, USA.*
[2]*Denovo Biopharma LLC, San Diego, CA, USA.*

email: mxia_ca@yahoo.com

ABSTRACT

Introduction: This study aims to develop a discriminating dissolution method for 125-mg enzastaurin tablets using a United States Pharmacopeia (USP) apparatus 2 (paddle) with apex vessels. **Methods:** The release rate of enzastaurin tablets was studied using conventional USP vessels and apex vessels. Various dissolution operational parameters were evaluated including rotation speed, media composition, and medium volume. The dissolution method using apex vessels was developed and its discriminating power was evaluated by making deliberate changes in the drug product formulation and manufacturing process. **Results:** Dissolution of the enzastaurin tablets using USP vessels lacked discrimination power at the standard 75 rpm paddle rotation speed; further studies with different rotation speeds and medium volumes also lacked discrimination power. When the rotation speed was below 75 rpm, the drug release rate was slow and incomplete due to a coning effect. When apex vessels were used, the dissolution method was able to discriminate between formulation and manufacturing process changes. **Conclusion:** A discriminating dissolution method for enzastaurin tablets was developed using USP dissolution apparatus 2 with apex vessels at 35 rpm and 500 mL medium volume. The use of apex vessels reduced the coning effect, and this method was able to detect drug product formulation and process changes, while the method using conventional USP dissolution vessels was found to be non-discriminating.

KEYWORDS: apex vessel, dissolution release rate, discriminating, coning effect, PEAK vessel

INTRODUCTION

Dissolution is a critical quality attribute for product development and batch release that can be used to predict in vivo drug release behavior for certain products as well as for biowaiver applications (*1–8*). Regulatory agencies require pharmaceutical companies to have a discriminating dissolution method to ensure product quality and performance, because a discriminating method can indicate possible changes in the quality of the product before in vivo performance is affected (*6*, *9*, *10*). The two most used dissolution apparatus for oral dosage forms are United States Pharmacopeia (USP) apparatus 1 (basket) and apparatus 2 (paddle). Conventional USP vessels are cylindrical, hemispherical and made of glass or other inert, transparent material (*11*).

The current study aimed to develop a dissolution method with discriminatory power for 125-mg enzastaurin tablets (immediate-release formulation) using the paddle apparatus and 25 mM phosphate buffer (pH 2.0) as the medium. Due to the presence of the coning effect and a lack of discriminating power, the use of apex vessels was compared with conventional USP vessels to develop a discriminating dissolution method for enzastaurin tablets.

METHODS

Materials

Enzastaurin hydrochloride (HCl) drug substance was manufactured by Evonik Corp (USA), enzastaurin tablets were manufactured by Lonza (USA), and enzastaurin tablets for the DoE study were manufactured by Alan Laboratories, Inc. (USA). Potassium phosphate monobasic was purchased from Sigma-Aldrich (USA), phosphoric acid was from Supelco (USA), purified water was produced in-house by a Millipore (USA) water purification system, sodium phosphate monobasic monohydrate was from

*Corresponding author

VWR (USA), and methanol (HPLC grade) was purchased from Fisher Scientific (USA).

Solubility Study

The equilibrium solubility for enzastaurin HCl in aqueous media was studied to select the dissolution medium.

Dissolution Methods

The dissolution medium was 25 mM phosphate buffer, pH 2.0. To prepare the dissolution medium, 85 g of potassium phosphate monobasic was dissolved into 25 L of purified water, then 80 mL of phosphoric acid was added and mixed well. The pH was adjusted to 2.0 ± 0.05 (if required) by adding either phosphoric acid or 5 N sodium hydroxide. The dissolution medium was degassed by sonication under vacuum prior to use. For a larger volume of dissolution medium, materials volumes and quantities were scaled up as appropriate.

The initial dissolution method for enzastaurin tablets was developed with a USP paddle apparatus (Distek Dissolution System 2100C, Distek Inc., USA) with a rotation speed of 75 rpm in 1000 mL of the dissolution medium at 37.0 ± 0.5 °C. Various paddle rotation speeds and medium volumes were trialed as part of dissolution method development.

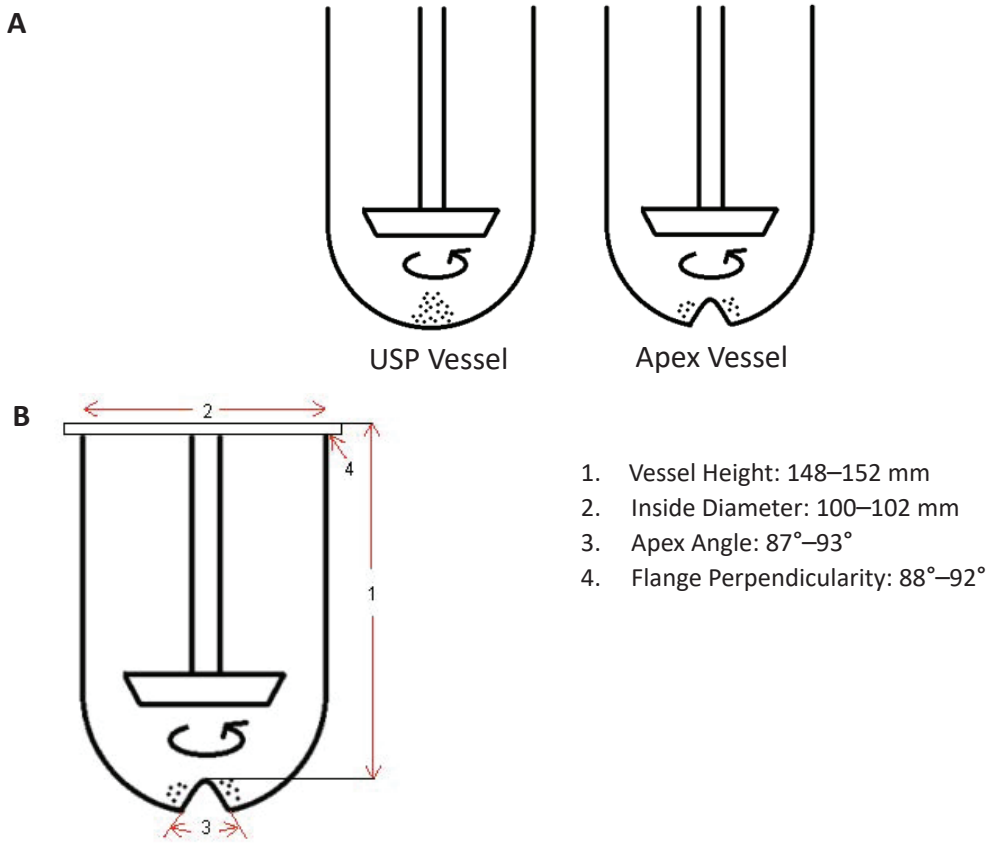
The modified dissolution method was developed using the same USP paddle apparatus, but using apex vessels (Quality Lab Accessories, LLC) instead of conventional USP vessels (round bottom), with a rotation speed of 35 rpm in 500 mL of dissolution medium at 37.0 ± 0.5 °C.

The differences between USP and apex vessels are illustrated in Figure 1.

Dissolution samples of 3.0 ± 0.1 mL (n = 6) were automatically withdrawn via online filters from each vessel at predefined time points of 5, 10, 15, 20, 30, 45, and 60 min. The online filters used for dissolution auto-sampling were 10-µ porous (full flow) filters (Quality Lab Accessories, LLC, PN: FIL010-01, USA). The final paddle speed was increased to 200 or 250 rpm for 15 min immediately after the 45-min sampling timepoint as infinity time, to ensure the full release of enzastaurin tablets.

High Performance Liquid Chromatography

The buffer for the mobile phase preparation was 17.5 mM sodium phosphate buffer (pH 2.5). This was prepared by dissolving sodium phosphate monobasic monohydrate in 1 L of water, mixing well, and adjusting pH to 2.5 ± 0.05 with phosphoric acid. The mobile phase for HPLC analysis



1. Vessel Height: 148–152 mm
2. Inside Diameter: 100–102 mm
3. Apex Angle: 87°–93°
4. Flange Perpendicularity: 88°–92°

*Figure 1. (**A**) Comparison of bottom geometry between USP and apex vessels. (**B**) Apex vessel dimensions.*

was prepared by mixing 50:50 (v/v) of methanol and 17.5 mM sodium phosphate buffer (pH 2.5).

The dissolution samples were analyzed by a reversed-phase HPLC method using an Agilent (USA) series 1100 or 1200 automatic system and Zorbax SB-C18 column (4.6 × 75 mm, 3.5 µm) at 35 ± 3 °C, with an ambient sample tray. Enzastaurin was detected by ultraviolet (UV) absorbance detection at a wavelength of 220 nm. The mobile phase flow rate was maintained at 1.5 mL/min. The injection volume was 10 µL.

Enzastaurin Tablet Formulation Variations

To study discrimination power of the initial USP vessel method and the modified apex vessel method, enzastaurin tablets were manufactured with deliberate and meaningful variations to the target formulation. All tablets were manufactured by blending on a VH 2 (2 L) blender (Vevor, USA), weighing individual blends equivalent to one tablet, followed by manual compression on a Manesty Betapress tablet press (Syntegon Technology Services, LLC, USA). The target tablet weight was maintained at 550 mg for all formulation variations.

Design of Experiment (DoE) Study

To further evaluate and confirm the discriminating power of the apex vessel method, an extensive DoE study was performed with 11 different tablet batches. All DoE batches except Batch 1 were compressed at two thicknesses: a target core tablet thickness per Lonza batch USTP-5035, and a minimum thickness tablet, representing higher hardness. Batch 1 was only compressed at one target thickness and no minimum thickness tablets were made.

RESULTS AND DISCUSSION

Solubility

The solubility data (supplemental material) showed that enzastaurin HCl is insoluble in aqueous media in general, and the highest solubility of enzastaurin HCl in aqueous media is in phosphate buffer, pH 2.0. Therefore, this was selected as the dissolution medium for enzastaurin tablets.

Dissolution

Initial USP Vessel Method

The dissolution data for enzastaurin tablets (Lonza, lot 190110.3) using the initial method with conventional USP vessels (75 rpm, 1000 mL of medium) are presented in Figure 2A. The dissolution rates were too fast: 85% at 5 min, 95% at 10 min, 98% at 20 min, 99% at 30 and 45 min. Because the initial dissolution method was not discriminating, the effects of paddle speed and medium volume on dissolution rate were investigated further. The dissolution medium was not varied because pH 2.0 was found to be the optimal aqueous medium for enzastaurin dissolution due to its high solubility.

The paddle speed was reduced from 75 to 65 rpm to evaluate the dissolution rate and discriminating power while keeping the other operational parameters unchanged. In separate trials, the volume was reduced from 1000 mL to 900 mL and 500 mL, at 65 rpm.

When the paddle speed was 65 rpm with 1000 mL of medium, the drug product appeared to slow down at 5 min; however, release was greater than 90% at 10 min. When the medium volume was reduced to 900 mL at 65 rpm, the dissolution rate slowed down a little (86% at 10 min); however, the drug release was incomplete (93% at 45 min), which indicated a coning effect. Coning was also observed at 60 rpm with 1000 mL of medium, and the maximum release was 85% at 45 min. Reduction of the medium volume to 500 mL also resulted in incomplete release. Therefore, none of these modifications to the initial dissolution method yielded a desired outcome.

The coning effect has been reported to affect the dissolution rate (*12–14*). Coning occurs when undissolved material forms a mound in the stagnant zone directly below the paddle, where there is less hydrodynamic flow present, thereby inhibiting drug release (*15*). This phenomenon can be overcome by either changing the stirring speed or using apex vessels, although research has shown that a minimum rotation speed is necessary to prevent coning phenomena in a compendium paddle dissolution apparatus (*16*). Because lowering the stirring speed in our case resulted in an incomplete drug release, and increasing stirring speed would have further reduced the discrimination power of the method, it was determined that the use of conventional hemispherical USP vessels could not address the coning issue in our case. For this reason, an alternative method using apex vessels was developed and studied.

Modified Apex Vessel Method

To address the issue of the coning observed at 60 rpm with USP vessels, the use of apex vessels was investigated, along with paddle speed and medium volume changes, to determine the effect on dissolution rate.

The generic apex vessel has the same design and shape as the patented PEAK vessel (Agilent). Research shows that apex vessels can address the impact of the coning effect on the dissolution rate, and it has been utilized in the dissolution method for some marketed

pharmaceutical products (*12*, *17–22*). However, users need to pay attention to the quality and dimensions of the apex vessels to ensure their performance consistency, as variations in dissolution results due to different apex heights have been observed (*23*).

As shown in Figure 2B, the dissolution profile for enzastaurin tablets using apex vessels with 500 mL and 1000 mL of medium at 35 rpm showed a substantially slower release of drug at all timepoints compared with the initial USP vessel method. Complete dissolution was achieved at 45 minutes for the 35 rpm and 500 mL operating condition.

The observed dissolution profiles are summarized below:

- Too fast: USP vessel, 65 rpm/1000 mL
- Too fast: Apex vessel, 50 rpm/1000 mL
- Optimum: Apex vessel, 35 rpm/500 mL
- Incomplete: Apex vessel, 35 rpm/1000 mL, 25 rpm/500 mL
- Incomplete: USP vessel, 65 rpm/500 mL, 60 rpm/1000 mL

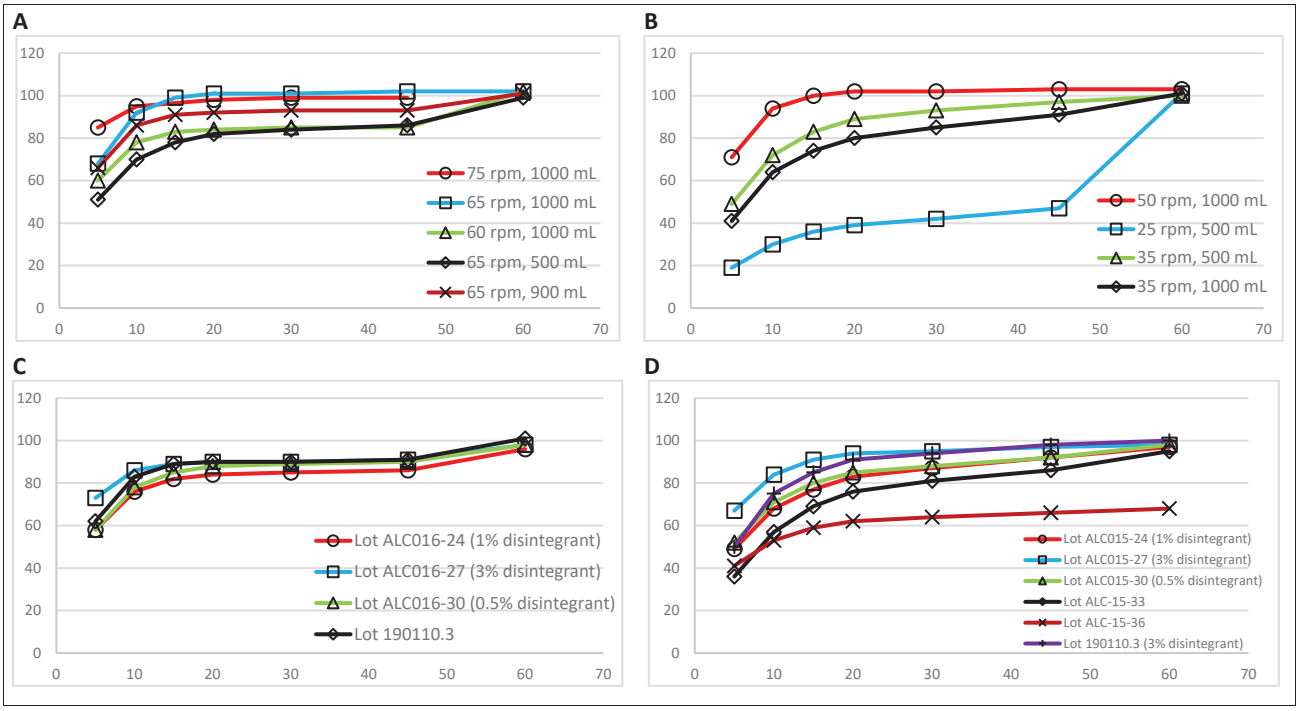


*Figure 2. Cumulative drug release (%) over time (min). Dissolution profiles for Lonza lot 190110.3 in USP Vessel (**A**) and apex vessel (**B**) with various paddle speeds and medium volumes. Dissolution profiles for variant tablets and Lonza lot 190110.3 in USP Vessel (900 mL media, 65 rpm) (**C**) and apex vessel (500 mL, 35 rpm) (**D**) (n = 12).*

Table 1. Composition of Drug Product (Enzastaurin Tablets 125 mg), Core Tablet, and Variant Enzastaurin Tablets Used for Testing Modified Dissolution Method

Lot	Enzastaurin HCl	Filler A	Filler B	Disintegrant	Surfactant	Glidant	Lubricant
Drug Product Current Formula (550 mg)	24.34 (133.85 mg)[a]	37.66 (207.14 mg)	32.00 (176.00 mg)	3.00 (16.50 mg)	1.00 (5.50 mg)	0.25 (1.38 mg)	1.75 (9.63 mg)
ALC-015-27	24.34	37.66	32.00	3.00	1.00	0.25	1.75
ALC-015-24	24.34	37.66	34.00	1.00	1.00	0.25	1.75
ALC-015-30	24.34	37.66	34.50	0.50	1.00	0.25	1.75
ALC-015-33	24.34	41.66	32.00	0.00	0.00	0.25	1.75
ALC-015-36	17.04 (HCl) + 6.82 (free base)	38.14	32.00	3.00	1.00	0.25	1.75

All values are percentages unless otherwise noted.
[a]Equivalent to 125 mg of enzastaurin
ALC-015-27: target formulation, 3% disintegrant, target hardness; ALC-015-24: 1% disintegrant, high hardness; ALC-015-30: 0.5% disintegrant, high hardness; ALC-015-33: 0% disintegrant, 0% surfactant, high hardness; ALC-015-36: target formulation except enzastaurin content was modified to contain 30% free base, high hardness.
HCl: hydrochloric acid

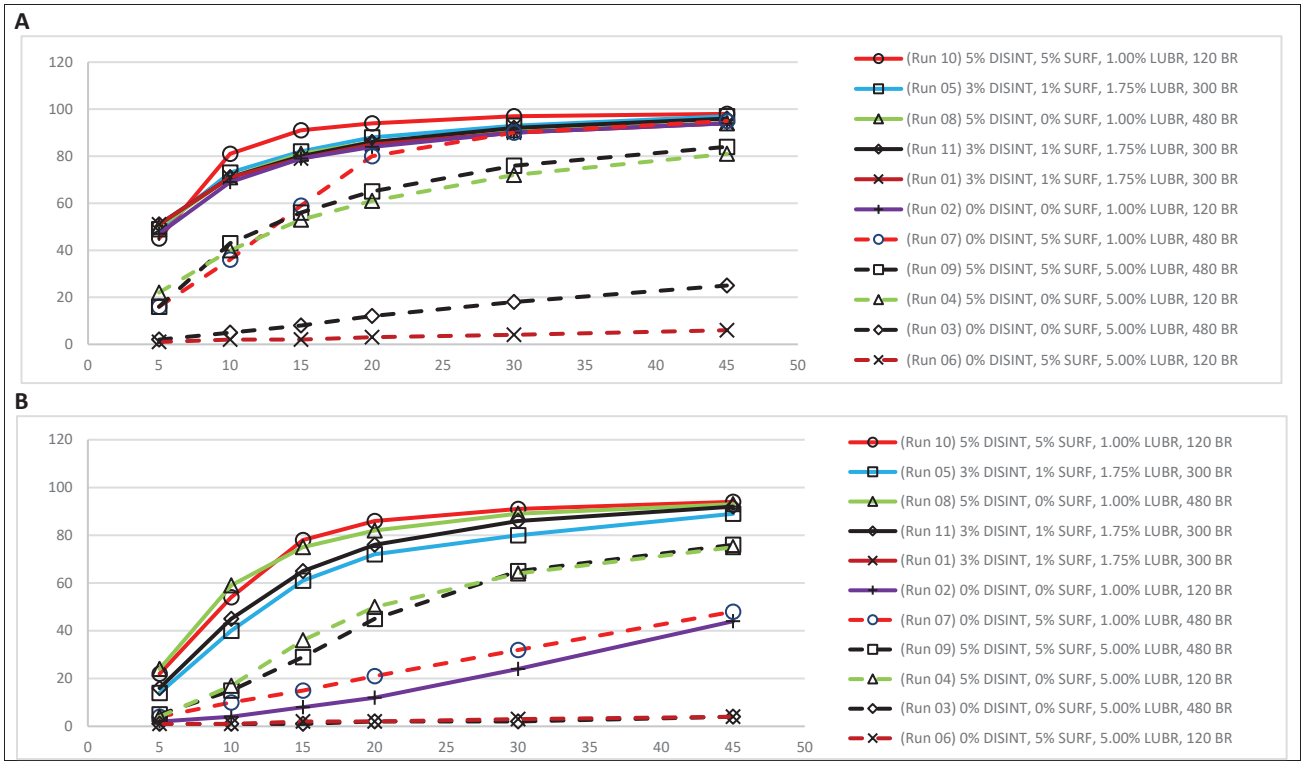


*Figure 3. Cumulative drug release (%) over time (min). Dissolution profiles for Design of Experiment batches 1–11: target thickness (**A**) and minimum thickness (**B**) (n = 3). DISINT: disintegrant; SURF: surfactant; LUBR: lubricant. BR: blender revolutions.*

Discrimination Power

To demonstrate the discrimination potential of the modified method using apex vessels, enzastaurin tablets were manufactured with deliberate variations to the current formulation and manufacturing process (Table 1).

To compare the dissolution profiles obtained with the USP vessel versus the apex vessel, 65 rpm and 900 mL of medium was used instead of the initial method (75 rpm and 1000 mL in the USP vessel). This is because the dissolution profile obtained by using 65 rpm and 900 mL with the USP vessel was found to be more discriminatory than the initial method; however, the 65 rpm/900 mL method was found to be an unsatisfactory method due to incomplete release.

The dissolution data for the USP vessel and apex vessel are presented in Figures 2C and 2D, respectively. The dissolution data further confirmed that the modified apex vessel method was more discriminating than the initial USP vessel method.

DoE Study and Additional Experiments

The composition and properties of the 11 DoE batches are shown in Table 2. The dissolution data for the DoE batches according to tablet thickness are presented in Figure 3.

Several additional formulation variation experiments were carried out (i.e., changes in lubricant, hardness, coating, free base, and disintegrant), which further demonstrated the discriminating power of the modified dissolution method (Fig. 4).

CONCLUSION

The DoE study and additional formulation variation experiments demonstrated the discriminating power of the modified dissolution method with apex vessels for enzastaurin tablets. The dissolution method with apex vessels was sensitive to changes in the formulation and manufacturing process and provided consistent results. Therefore, the apex vessel method is suitable as a quality control tool for enzastaurin tablets. Additionally, this data support the use of apex vessels as an effective alternative method to provide discriminating power when there is a prominent coning effect in the dissolution test. The 35 rpm/500 mL dissolution method using apex vessels was accepted by the FDA and is the current dissolution method for enzastaurin tablets.

SUPPLEMENTAL MATERIAL

Supplemental material is available from the corresponding author upon request.

Table 2. Composition and Properties of Tablet Batches 1–11 (Design of Experiment)

Batch	Enzastaurin HCl		Filler A		Filler B		Disintegrant		Surfactant		Glidant		Lubricant		BR[a]	Thickness[a] (mm)		Weight Range[a] (mg)	Disintegration Time Range (minute:second)
	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%	mg	%					
1	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.85–5.86	549–553	2:38–2:53
2	133.85	24.34	233.27	42.41	176.00	32.00	0.00	0.00	0.00	0.00	1.38	0.25	5.50	1.00	120	Target	5.87–5.88	550–551	1:34–1:34
																Min	5.44–5.45	550–551	N/A
3	133.85	24.34	211.27	38.41	176.00	32.00	0.00	0.00	0.00	0.00	1.38	0.25	27.50	5.00	480	Target	5.89–5.90	549–551	23:02–54:50
																Min	5.43–5.45	549–551	> 270:00 (30% remaining)
4	133.85	24.34	183.77	33.41	176.00	32.00	27.50	5.00	0.00	0.00	1.38	0.25	27.50	5.00	120	Target	5.88–5.88	551–551	3:25–3:25
																Min	5.49–5.50	549–552	13:10–13:50
5	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.86–5.87	550–550	2:15–2:30
																Min	5.48–5.49	550–551	10:15–10:20
6	133.85	24.34	183.77	33.41	176.00	32.00	0.00	0.00	27.50	5.00	1.38	0.25	27.50	5.00	120	Target	5.85–5.87	550–551	> 180:00 (60% remaining)
																Min	5.50–5.50	550–551	> 180:00 (90% remaining)
7	133.85	24.34	205.77	37.41	176.00	32.00	0.00	0.00	27.50	5.00	1.38	0.25	5.50	1.00	480	Target	5.86–5.87	550–551	8:25–8:40
																Min	5.43–5.45	550–551	52:10–52:30
8	133.85	24.34	205.77	37.41	176.00	32.00	27.50	5.00	0.00	0.00	1.38	0.25	5.50	1.00	480	Target	5.86–5.88	550–550	1:20–1:20
																Min	5.48–5.49	549–550	7:10–7:15
9	133.85	24.34	156.27	28.41	176.00	32.00	27.50	5.00	27.50	5.00	1.38	0.25	27.50	5.00	480	Target	5.87–5.88	549–551	6:45–7:20
																Min	5.56–5.58	550–551	16:40–17:10
10	133.85	24.34	178.27	32.41	176.00	32.00	27.50	5.00	27.50	5.00	1.38	0.25	5.50	1.00	120	Target	5.86–5.88	551–551	3:20–3:30
																Min	5.51–5.53	550–551	8:40–8:50
11	133.85	24.34	207.14	37.66	176.00	32.00	16.50	3.00	5.50	1.00	1.38	0.25	9.63	1.75	300	Target	5.87–5.88	550–551	2:35–2:40
																Min	5.47–5.50	549–552	10:30–10:45

[a]*Thickness and weight range data were as recorded at the time of manufacture.*
HCl: hydrochloric acid; BR: blender revolutions; Min: minimum

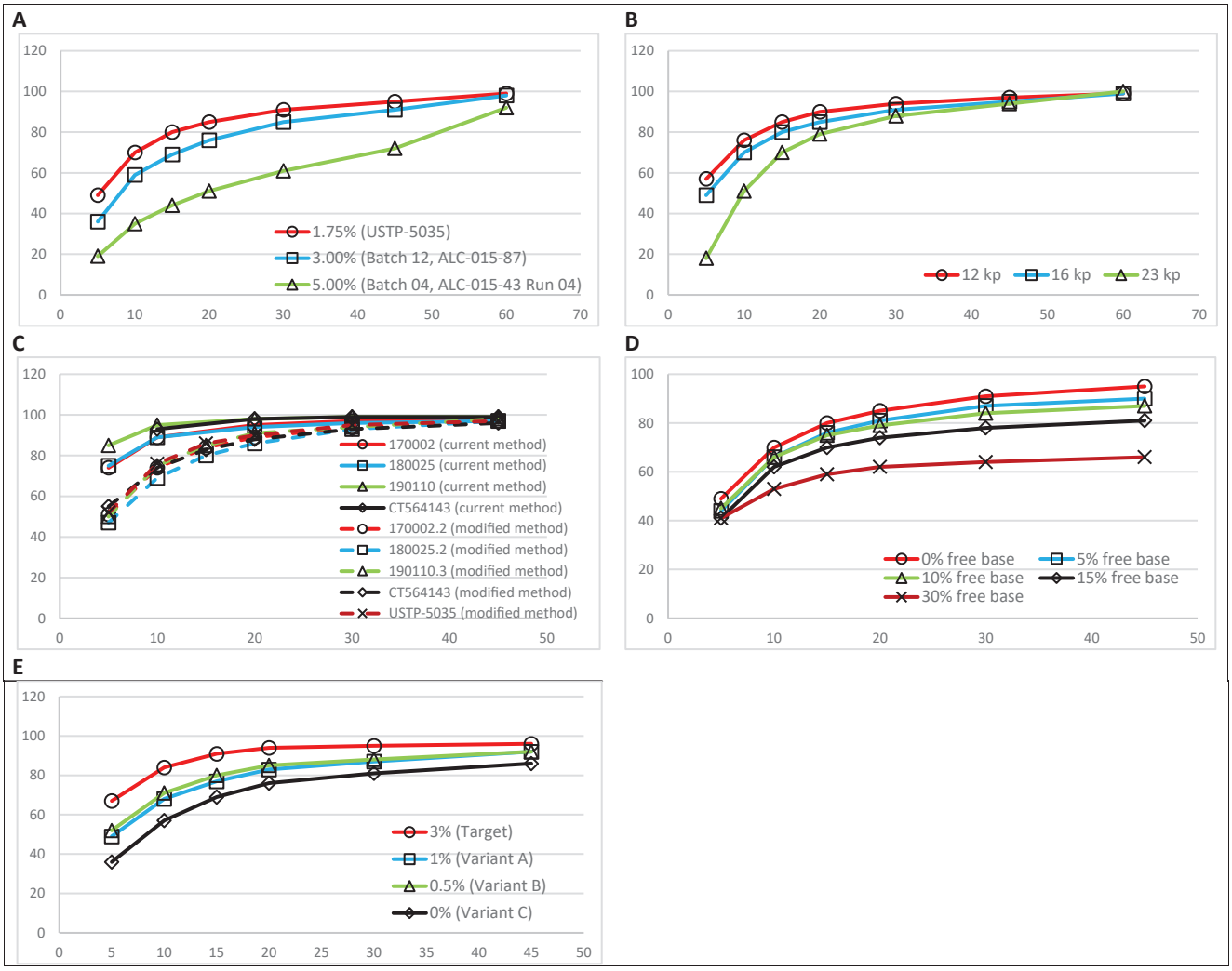


*Figure 4. Cumulative drug release (%) over time (min). Dissolution profiles for lubricant variation tablets (**A**), tablets with varying hardness, Lonza lot USTP-5035 (**B**), historical coated tablets (**C**), % free base variation tablets (**D**), and disintegrant variation tablets (**E**) (n = 12).*

DISCLOSURES

The study was conducted at Alan Laboratories, Inc. and was funded by Denovo Biopharma LLC. The authors have no conflicting interests.

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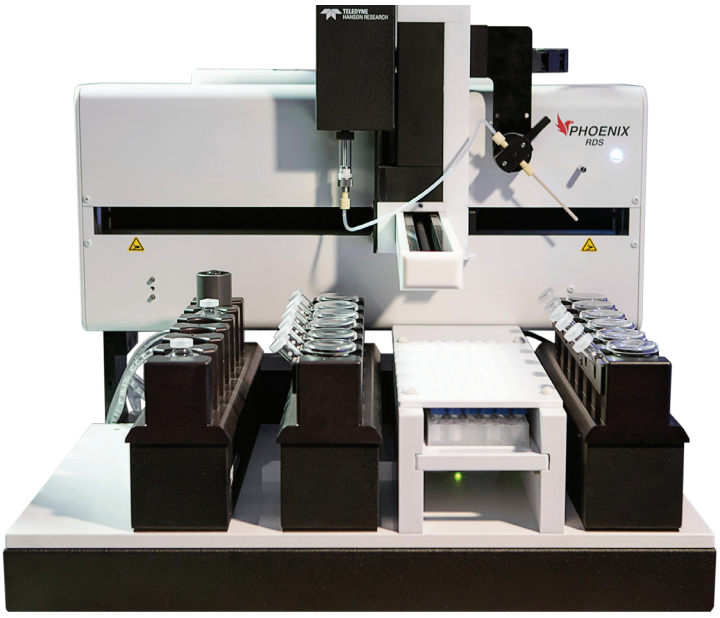

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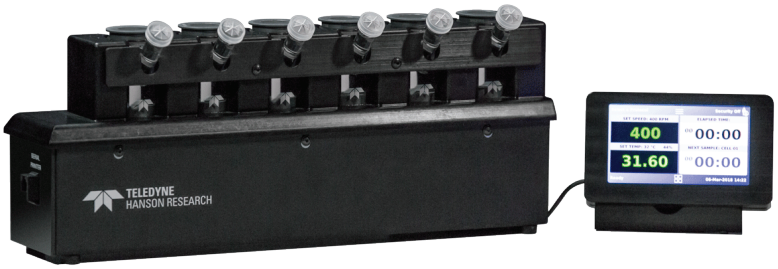

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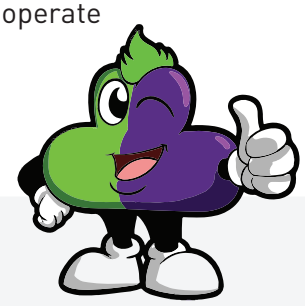

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Assessment of Small Volume (250-mL) Vessels for Use in Biorelevant Dissolution

Angela Hu, Wei Chen, and Xujin Lu*
[1]*Drug Product Development, Bristol-Myers Squibb, New Brunswick, NJ, USA.*

e-mail: xujinlu9@gmail.com

ABSTRACT

Introduction: In vitro biorelevant dissolution is an important tool for pharmaceutical development and formulation evaluation. Standard United States Pharmacopeia (USP) 1-L vessels and the paddle apparatus have been commonly used for biorelevant dissolution tests, including tests in a small volume (250 mL) of medium. When Chinese small volume (CSV) vessels (250-mL) became available and were described in the *Chinese Pharmacopeia* <931>, it was uncertain if biorelevant dissolution profiles obtained with the CSV vessel are comparable to those obtained with the standard USP vessel. **Methods:** To evaluate the two types of the vessels for biorelevant dissolution testing, a particle dissolution model was developed using computational fluid dynamics (CFD), the Noyes-Whitney equation, and experimental parameters, and a scaling factor (Sherwood number) was calculated using the model. A paddle speed for the CSV vessel setup that correlate with the USP vessel configuration was determined by the model using similar Sherwood numbers. The dissolution model was verified using USP Prednisone Tablets RS in 250 mL of water, then further verified using two proprietary drugs in 250 mL of biorelevant medium (fasted state simulated intestinal fluid). **Results:** The model predicted that the dissolution profile generated at 84 rpm in the CSV vessel would match that obtained at 50 rpm in the USP vessel. Indeed, similar dissolution profiles were obtained with both types of vessels under these conditions. **Conclusion:** This study demonstrated that by using a suitable scaling factor for agitation, CSV vessels for biorelevant dissolution in FaSSIF can generate similar results with standard 1-L USP vessels.

KEYWORDS: USP apparatus 2, paddle dissolution apparatus, small volume vessel, hydrodynamics, biorelevant dissolution

INTRODUCTION

In vitro biorelevant dissolution is an important tool used in drug development to assess in vivo performance of drug products. As part of an overall biopharmaceutics development assessment, in vitro biorelevant dissolution testing speeds up prototype formulation screening, identifies potential in-vivo/in-vitro relationships, and saves animal resources (*1–3*). Conventionally, biorelevant dissolution testing is performed using 250 mL of media to simulate the average volume of gastrointestinal fluids in the body. Commonly used media include fasted state simulated intestinal fluid (FaSSIF), fed state simulated intestinal fluid (FeSSIF), and fasted state simulated gastric fluid (FaSSGF). The medium is filled in either 500-mL or 1-L standard United States Pharmacopeia (USP) vessels on a paddle dissolution apparatus.

Several challenges have been encountered when using the 1-L USP vessel for biorelevant dissolution tests using 250 mL of medium. The design of the USP vessel and settings are optimized for testing with 500, 900, or 1000 mL of dissolution medium (*4*). When testing with only 250 mL, the level of medium in the vessel is decreased to the point that it barely covers the paddle. With this, manual sampling becomes difficult, using an autosampler is not possible, and in-situ ultraviolet fiber optics (UVFO) is challenging. Conventional dip-in UVFO probes cannot be used because the probes cannot be placed above the paddle. As a result, J-shaped probes that can be placed under the paddle are used. However, the placement of these J-shaped probes is inconvenient and increases measurement variability.

The compendial USP vessel is the most used for dissolution testing. Non-compendial small volume vessels (100 and 200 mL) are available and considered widely

*Corresponding author

acceptable for low-dose strength drugs (*5*). The 250-mL Chinese small volume (CSV) vessel and settings have been established in the *Chinese Pharmacopeia* (*ChP*) for dissolution testing of low-dose strength drug products in the Chinese market (*6*). The CSV vessel is commercially available and used by many pharmaceutical companies for Good Manufacturing Practice (GMP) testing purposes. Considering its size, the CSV vessel is an ideal option for the biorelevant dissolution test performed in 250 mL of medium. The *ChP* has established standards for the dimensions of the CSV vessel and its associated paddle. The settings allow for easy manual or auto-sampling. Straight UVFO dip-in probes can easily be placed above the paddle, and better experimental repeatability has been observed (*7*).

When a biorelevant dissolution test is performed using different sizes of vessels and settings, such as the compendial USP vessel and paddle and the CSV vessel and small paddle, a practical concern arises regarding the comparability of the biorelevant dissolution profiles. In many cases, biorelevant dissolution tests are performed at different laboratories where the same dissolution equipment and accessories are not available. Given the differences in hydrodynamics of the two vessels and settings, it is necessary to establish a set of operational parameters that can produce similar hydrodynamics in the USP vessel and the CSV vessel for correlation of biorelevant dissolution test results. Such efforts may benefit from utilizing computational fluid dynamics (CFD) modeling.

Various research groups have studied hydrodynamics of the USP paddle apparatus and vessels using CFD. Baxter et al. found through CFD simulation that the position of the tablet affected dissolution results in the USP vessel (*8*). Bai et al. used laser doppler velocimetry and CFD to study velocity profiles in USP vessels (*9*). Kukura et al. studied shear, flow, and homogeneity in USP vessels (*10*). These studies were conducted using a USP paddle dissolution apparatus with standard testing parameters.

Wang and colleagues studied the hydrodynamic effects of a 100-mL vessel using CFD and particle image velocimetry (*11*). In their follow up work, the authors studied the hydrodynamic characteristics of 100-mL vessels and the USP paddle dissolution testing system using standard 1-L vessels (*12*). They predicted the velocity distribution and strain rate around a model tablet and established the dynamic operating conditions under which dissolution in the 100 mL vessels could generate drug release profiles similar to those in the 1-L USP vessel.

A particle dissolution modeling framework has been proposed by Cao et al (*13*). This model combines CFD simulation and the Noyes–Whitney equation to predict the bulk particle dissolution profile by leveraging the initial particle and media properties, such as density, solubility, size distribution, and diffusivity. The particle dissolution profile can be directly linked with the energy dissipation rate (ε), which is a measure of energy that is being dissipated in the fluid and is crucial for mass transfer from particle to fluid. Using CFD simulation, ε is defined as the power per mass in the system and is correlated with particle mass transfer rate by the Sherwood number, which is a scaling factor that is used in the Noyes–Whitney equation. By varying dissolution conditions such as agitation speed, the results from experiments with both non-porous, single-ingredient particles and porous, multi-ingredient particles show that the model can predict bulk particles dissolving in a flow regime, where particles are well suspended in the mixing system (*13*).

This study presents a model that can predict and correlate the dissolution behavior in both 1-L USP vessels and 250-mL CSV vessels for in vitro biorelevant dissolution testing, with 250 mL of FaSSIF as the medium. The dissolution model incorporates CFD and the Noyes-Whitney equation to characterize the hydrodynamic performance of the different vessels and paddles, and determines a scaling factor (*14*). Using the scaling factor-predicted agitation speed, this study aims to use CSV vessels to generate similar results as standard 1-L USP vessels for the biorelevant dissolution of a model drug and two proprietary drugs in FaSSIF.

METHODS

Materials

USP Prednisone Tablet RS (10 mg, Lot #R080J1) was used as a model drug and was purchased from USP (USA) and used for model development and verification. Bristol-Myers Squibb (BMS, USA) formulations ("D1" and "D2") were used to further verify the modeling results. Powder for preparing simulated intestinal fluid (SIF) and buffer concentrates for FaSSIF were purchased from Biorelevant.com Ltd (UK). The FaSSIF medium was prepared according to the procedure from Biorelevant.com (*15*) and used within the recommended use time of 48 hours.

Dissolution Testing

Initial dissolution testing of USP Prednisone Tablets RS (n = 3) was conducted in 250 mL of water in a CSV vessel at 50, 100, and 140 rpm and in a USP vessel at 50 rpm. The cumulative release (%) of Prednisone over time was recorded using UVFO in situ measurements (described in

detail below). The purpose of this was to generate data for preparation of CFD modeling. Following verification of equivalency with Prednisone, the predicted conditions were applied to biorelevant dissolution of two drug products in 250 mL of FaSSIF.

For all dissolution tests, an Agilent 708-DS water bath was used and fitted with both TruAlign 1-L USP vessels and CSV vessels (250 mL) with the CSV conversion kit (Agilent, USA). The dissolution tests were performed using UVFO for in situ measurement, with no sample withdraw, filtration, or medium replacement. The vessels were fitted with rod-shaped and J-shaped UVFO probes with the UVFO-based Rainbow Dynamic Dissolution system (PION Inc., USA). The rod-shaped probes were used in the CSV vessels and the J-shaped probes were used in the 1-L vessels. The bath temperature was controlled at 37 °C. All vessels were filled with 250 mL of dissolution medium. The UVFO probes were fitted with a pathlength of 2 or 5 mm. In situ sample readings were taken for each dissolution run at the following intervals: 60 spectra at 10-sec intervals, 60 spectra at 30-sec intervals, 30 spectra at 1-min intervals, followed by 22 spectra at 5-min intervals. Sample time totaled 180 minutes and 172 timepoints.

Absorption was detected at a range of 200–720 nm. Data were plotted as percentage of release according to the target concentration as labeled on the drug product. Dissolution profiles for the Prednisone tablets were obtained with 5-mm probe tips, and data were analyzed using a wavelength of 288 nm with no baseline correction.

Dissolution profiles for formulation D1 were obtained with 2-mm probe tips and analyzed using second derivative spectra in a wavelength range of 342–352 nm with no baseline correction. For formulation D2, dissolution profiles were obtained with 5-mm probe tips and analyzed using spectra in a wavelength range of 315–325 nm with point baseline correction at 400 nm.

Dissolution Modeling

In both vessels, the Prednisone tablets used in the dissolution test disintegrated into small granules in a very short period. So, the model was developed based on the particle dissolution framework (*13*). Dissolution profiles are governed by Noyes-Whitney (Eq. 1) for different vessels and different agitation speeds, and the rate constant $K(t)$ was determined by the Sherwood number, $Sh(t)$, using Equation 2, in which energy dissipation rate (ε) was obtained through CFD simulation. In this study, CFD software (ANSYS Fluent 14.5, ANSYS Fluids) and a k-ε turbulent flow model were used to estimate ε.

Noyes-Whitney Equation:

$$\frac{dM}{dt} = -K(t)A(t)\left(C_p - C(t)\right), \text{ where } K(t) = \frac{Sh(t)D}{d_p(t)} \qquad \text{Eq. (1)}$$

where dM is the remaining mass of particles at time t, $A(t)$ is the exposing surface area of particle to solvent at time t, C_p is the solubility of the drug substance, $C(t)$ is solution concentration at time t, D is diffusivity, and d_p is the particle diameter.

Sherwood Number Equation:

$$Sh(t) = 2 + 0.47\left(\frac{\rho_f \varepsilon^{1/3} d_p^{4/3}}{\mu_f}\right)^{0.62}\left(\frac{\mu_f}{\rho_f D}\right)^{0.36}\left(\frac{d_{imp}}{d_{tank}}\right)^{0.17} \qquad \text{Eq. (2)}$$

where ρ_f is the medium density, μ_f is the medium viscosity, d_{imp} is the diameter of the paddle, and d_{tank} is the diameter of the stirring vessel.

The dimensions of the 1-L USP vessel and CSV vessel and their corresponding paddles are shown in Table 1. The dimensions of both vessels, paddle size, shape, and medium volume were used to create a computational domain mesh and the model input for the CFD simulation. The energy dissipation rate (ε) in both vessels was characterized by the CFD simulations, then the Sherwood numbers were calculated. The Sherwood number was used as a scaling factor to select the stirring speed for the dissolution test in the CSV vessel to produce a comparable dissolution profile with the 1-L USP vessels at a certain agitation speed. The results of the dissolution modeling were verified using USP Prednisone Tablets RS in 250 mL of water in both vessels.

Table 1. Dimensions of USP Dissolution Apparatus 2 and CSV Vessels and Paddles

	USP Vessel (1 L)	CSV Vessel (250 mL)
Vessel inner diameter (mm)	98–106	62 ± 3
Vessel height (mm)	160–210	15
Paddle height (mm)	25 ± 2	15
Paddle diameter at widest point (mm)	74.0–75.0	45
Shaft diameter (mm)	9.4–10.1	6

Based on information from References (4) and (6).
USP: United States Pharmacopeia; CSV: Chinese small volume.

RESULTS AND DISCUSSION

During the development and preparation for CFD modeling, Prednisone was selected and tested as a model drug because it has been globally accepted as a means to qualify dissolution equipment and has a high degree of sensitivity to distinguish changes with the testing

apparatus. As shown in Figure 1, there was a substantial difference in the initial Prednisone dissolution profiles generated with the same paddle speed of 50 rpm for agitation in the two vessels. The different hydrodynamics generated from the difference in vessel size, shape, and paddle dimensions could have affected the drug dissolution rate. All dissolution profiles obtained with the CSV vessel (250 mL) at different agitation speeds showed less variations in comparison with those obtained with the USP vessel (1 L) at 50 rpm. The dissolution profile from the USP vessel fell between those generated with the CSV vessel at 50 and 100 rpm.

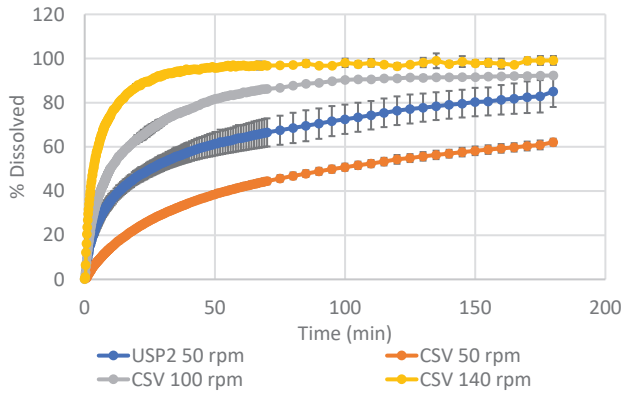

Figure 1. Initial dissolution test results with USP Prednisone Tablets RS (10 mg) in 250 mL water in 1-L USP standard vessels at 50 rpm paddle speed versus in CSV vessels with paddle speeds of 50, 100, and 140 rpm. USP: United States Pharmacopeia; USP2: USP apparatus 2; CSV: Chinese small volume.

To determine an agitation speed for the dissolution test in the CSV vessel so that it correlates to a similar dissolution profile in the USP vessel under standard agitation, a combined modeling and simulation approach was applied based on the Noyes-Witney equation and CFD to determine a scaling factor (Sherwood number). The dissolution behavior of Prednisone tablets at 37 °C and the hydrodynamic effects from different paddle sizes and agitation speeds were directly linked to the energy dissipation rate (ε) of the dissolution system in the two types of the vessels. A Sherwood number of 15.8 was calculated using ε (power draw by CFD divided by liquid weight) from the CFD simulation, dimensions of the USP vessel (1 L) and paddle, a stirring speed of 50 rpm, and a 250-mL volume of dissolution medium. The ε value used the bulk level value; however, the contours of turbulent distribution can be seen in Figure 2.

The developed dissolution model was leveraged to predict a stirring speed of 84 rpm in the CSV vessel for dissolution of USP Prednisone Tablets RS with an equivalent Sherwood number of 15.6, which represents similar hydrodynamics as the USP vessel. The predicted result showed that the dissolution profile generated at 84 rpm in the CSV vessel matched that obtained at 50 rpm in the USP vessel. The stirring speeds and related Sherwood numbers are listed in Table 2. These results prove the viability of the dissolution model predictions for both vessels.

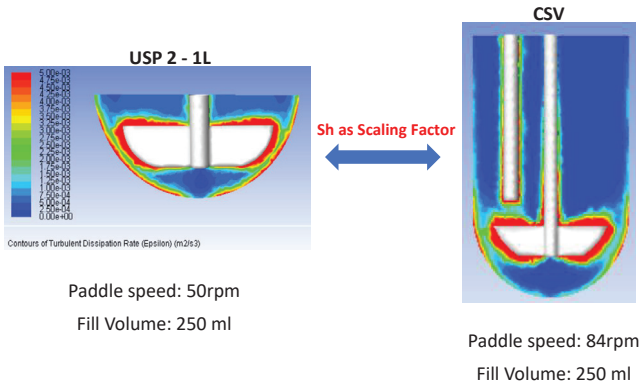

Figure 2. Contours of turbulent dissipation in the 1-L USP standard vessel and the 250-mL CSV vessel with 250 mL of water and scaled paddle speeds using the related Sherwood (Sh) number. USP: United States Pharmacopeia; CSV: Chinese small volume.

Table 2. Mixing Speed and Sherwood Number (Sh) for Dissolution Scale-Down Models

Scale Down Model (Size)	Dissolution Medium	Fill Volume (mL)	Mixing Speed (rpm)	Sh
CSV vessel (250 mL)	FaSSIF	250	84	15.6
USP vessel (1 L)	FaSSIF	250	50	15.8

USP: United States Pharmacopeia; CSV: Chinese small volume; FaSSIF: fasted state simulated intestinal fluid.

To verify the predicted paddle speed for CSV vessels, a dissolution test was conducted with USP Prednisone Tablets RS in 250 mL water in the CSV vessel at 84 rpm and in the USP vessel at 50 rpm. As shown in Figure 3, the two dissolution profiles were similar.

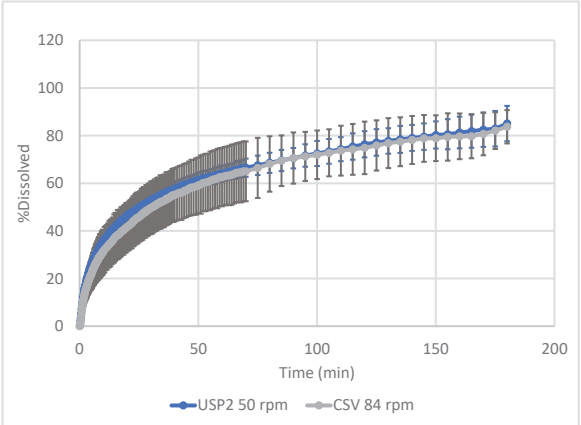

Figure 3. Dissolution profiles of USP Prednisone Tablets RS (10 mg) in 250 mL water in 1-L USP vessels at 50 rpm and CSV vessels at 84 rpm (predicted from the Sherwood number). USP: United States Pharmacopeia; USP2: USP apparatus 2; CSV: Chinese small volume.

Using the model-predicted conditions for dissolution, two BMS formulations (D1 and D2) were tested in 250 mL of FaSSIF with the USP vessel at 50 rpm and CSV vessel at 84 rpm for comparison. To minimize variability, each of the two BMS formulations was from a single batch and stored under the same storage conditions. For both formulations, the dissolution profiles obtained with USP and CSV vessels were similar.

Figure 4A displays the dissolution profiles of formulation D1. Initially, both vessels showed a fast drug release, but quickly slowed down and plateaued with very low drug release, approximately 6.5% at 180 minutes. Figure 4B displays the dissolution profiles for D2. The initial dissolution rate was slower than D1, but the total amount released in 180 minutes (≈ 35%) was much higher.

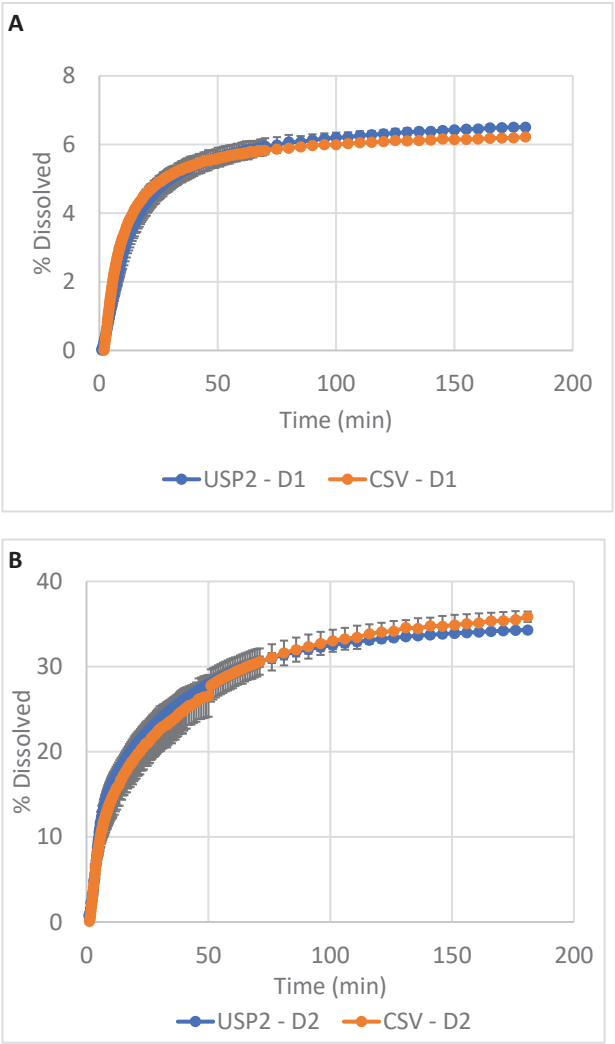

Figure 4. Dissolution of BMS drug formulations (D1 and D2) in 250 mL FaSSIF in 1-L USP vessels at 50 rpm versus CSV vessels at 84 rpm. (A) Comparison of USP versus CSV vessels for D1. (B) Comparison of USP versus CSV vessels D2. BMS: Bristol-Myers Squibb; USP: United States Pharmacopeia; FaSSIF: fasted state simulated intestinal fluid; USP2: USP apparatus 2; CSV: Chinese small volume.

This study was executed with multiple controls in place that may impact the modeling and prediction. Some of these influencers include the physical properties of the media used for dissolution of Prednisone and the D1 and D2 formulations. The pH and viscosity of water used for the Prednisone and FaSSIF media for the D1 and D2 formulations in this study are not significantly different. This may have helped with the prediction and comparability.

For future studies, considerations will include evaluations with FeSSIF and the other biorelevant media that have different pH and physical properties. In addition, model optimization will be considered to include more physical parameters of the dissolution media and characterization of dead zones in the vessels to better understand the impact of local energy dissipation distribution and obtain a more robust prediction and enable broader application of the CSV vessel.

CONCLUSION

This study developed and verified a biorelevant dissolution model with a scaling factor (Sherwood number) that can be leveraged to generate comparable dissolution profiles in a standard USP (1 L) or CSV (250 mL) configuration with a paddle apparatus. This model can be used for evaluating the impact of particle size and solubility, media properties, as well as vessel and paddle size and shape on dissolution behavior. The current work focused on the use of FaSSIF, and future testing is needed to determine if the scaling factor is applicable to other biorelevant media.

DISCLOSURES

The authors received no financial support for this work and have no conflicting interests.

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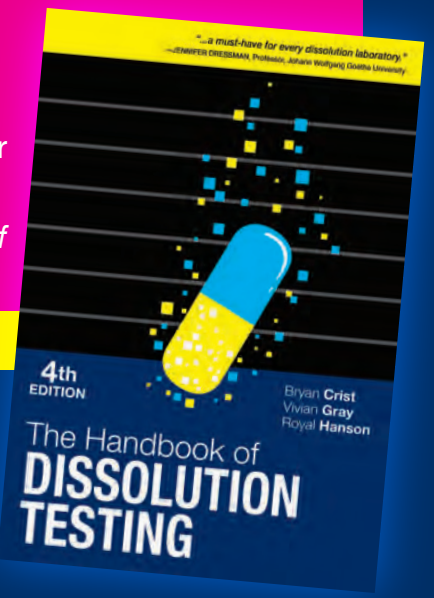

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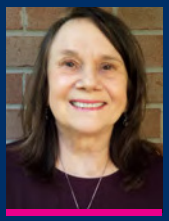
Bryan **Crist**
President of DissoAssist Consulting based in Wilmington, NC



Vivian **Gray**
President of V.A. Gray Consulting based in Hockessin, DE

Royal **Hanson**
Former Chairman, President, and CEO of Hanson Research Corp.

Dissolution Technologies, Incorporated
9 Yorkridge Trail • Hockessin, DE 19707 USA

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Evaluation of In Vitro Dissolution Behavior of Ibuprofen Suspensions Based on the Flow-Through Cell Method

Li Xie, Yao Xiao, Rongqin Zhang, Xiangjin Lian, Mei Yang, Xin Li, Junhan Cao, and Li Su*
Chengdu Institute for Drug Control, SCMPA Key Laboratory for Quality Research and Control of Chemical Medicine, Chengdu, Sichuan, China.

e-mail: 283125279@qq.com

ABSTRACT

Introduction: Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), is recommended for pediatric fever and pain management. Due to its low water solubility, pH-dependent solubility, and the nature of suspension formulations, understanding the in vitro release behavior of ibuprofen suspensions is critical. The paddle method for dissolution testing has limitations, while the flow-through cell method, which simulates in vivo pH changes, offers advantages for evaluating drugs with pH-dependent solubility. **Methods:** An in vitro release testing method for ibuprofen suspension was established using the flow-through cell method. Key parameters such as membrane filters, glass bead dosage, flow rates, and dissolution media, were optimized. The dissolution profiles of generic and reference ibuprofen oral suspensions were determined using both the paddle and flow-through cell method and evaluated according to the similarity factor (f_2). Particle size and crystal shape were analyzed via microscopy and laser diffraction. **Results:** The optimized flow-through cell method demonstrated strong discriminatory power, with dissolution profile similarity results aligning with consistency evaluation outcomes for quality and efficacy of generic drugs in China. The method could effectively distinguish between generic formulations that passed and those that failed the consistency evaluation. However, the paddle method may risk misjudgment, as having similar dissolution profiles may not guarantee consistency. **Conclusion:** This research established a dissolution profile determination method for ibuprofen suspensions based on the flow-through cell method, overcoming the limitations of the paddle method. It provides a precise tool for quality control and consistency evaluation of generic ibuprofen suspensions.

KEYWORDS: Ibuprofen suspension, flow-through cell method, dissolution profile, similarity factor (f_2), consistency evaluation, apparatus 4

INTRODUCTION

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is a first-line medication for pediatric fever and pain management as recommended by both the World Health Organization (WHO) and the United States Food and Drug Administration (FDA) (*1–6*). As of October 2023, information from the data query website of the National Medical Products Administration in China shows that many manufacturers in China have obtained approval for ibuprofen suspensions, and the quality has drawn much attention due to Ibuprofen's low solubility in water, high demand in pediatric use, and the nature of the suspension formulation.

The dissolution profile is a critical quality attribute (CQA) for ibuprofen suspension. The commonly used paddle method for dissolution testing has limitations like unfixed sampling position and inappropriate dissolution medium selection (*7, 8*). Because ibuprofen's solubility varies with pH, a pH 7.2 dissolution medium may not effectively evaluate product quality differences. In contrast, the flow-through cell method has advantages such as a fixed sampling position, and it can simulate in vivo pH changes (*9–13*). Thus, the flow-through cell method is suitable for evaluating liquid formulations and drugs with pH-dependent solubility, and it is valuable for generic drug quality consistency evaluation (*14–19*).

This study aims to optimize and establish an in vitro release testing method for ibuprofen suspension using the flow-through cell apparatus. The method will be used to assess the similarity of dissolution profiles between reference and generic products, compare the results of the paddle and flow-through cell methods, and investigate the

*Corresponding author

influence of factors like particle size, crystal shape, and formulation on in vitro release behavior. This will support in vitro release research and quality control of ibuprofen suspension and contribute to generic drug quality consistency evaluation.

METHODS

Materials

Ibuprofen reference substance (Batch No.100179-202308, content: 100.0%) was obtained from the National Institute for Food and Drug Control, Beijing, China. Fifteen batches of ibuprofen suspensions (2%) (coded "B1"–"B15") from eight manufacturers (coded "C1"–"C8") were purchased from pharmacies in Sichuan, China. The product of manufacturer C1 (Shanghai Johnson & Johnson Pharmaceutical Enterprise), a locally produced originator drug, served as the reference preparation, and the others (C2–C8) were generic drugs. All products were used at least 12 months prior to expiration. The chemicals and reagents used to perform the experiments included sodium hydroxide pellets (NaOH) (Kermel, China), potassium dihydrogen phosphate (KH2PO4) (Guanghua, China), sodium acetate (CH3COONa) (Kelong, China), glacial acetic acid (CH3COOH) (Guanghua), and hydrochloric acid (HCl) (Chuandong, China).

Aqueous buffer solutions (pH 1.4 HCl, pH 4.5 acetate, pH 6.0 acetate, pH 6.5 phosphate, and pH 7.2 phosphate) were used as dissolution media and were prepared in compliance with the *Chinese Pharmacopoeia* (ChP) (*20*).

The filter membranes used to perform the experiments included polyethersulfone (PES) (0.45 µm; PALL, USA), mixed cellulose ester (MCE) membrane (0.8 µm; JINTENG, China), glass fiber (2.7 µm and 0.7 µm; WHATMAN, UK), and polycarbonate track-etched (PCTE) membranes with various pore sizes (5, 8, and 10 µm; WHATMAN), and defatted cotton (Winner, China).

Equipment

The instruments used in this study included a pH meter (Mettler Toledo, S210), a liquid chromatograph (Agilent 1260 Infinity), an electronic balance (Sartorius CPA225D), two dissolution testers (SOTAX, CE 7smart and AT 7X), a laser particle size analyzer (Malvern Mastersizer 3000), and a microscope (Olympus BX43). All instruments were calibrated or verified annually following laboratory guidelines. The two dissolution testers, installed by the vendor, underwent 3Q (design qualification, installation qualification, and operational qualification). Subsequently, they were mechanically calibrated and performance-verified annually by an accredited laboratory. A Performance verification test of the Sotax AT 7X dissolution tester was carried out using salicylic acid tablets (national pharmaceutical reference substance of China) in accordance with their instruction manuals.

Dissolution Profile Determination Based on the Flow-Through Cell Method

For the flow-through cell method, the dissolution tests were conducted on Sotax CE 7smart system coupled with a CP7-35 piston pump and C 615 fraction collector. The closed-loop configuration was used, with a pump pulse of 120 r/min. The suspension was thoroughly mixed, and approximately 2.5 mL was transferred into a needle-free syringe. The syringe was weighed before and after the transfer to determine the exact sample volume based on weight and density. The sample was then introduced into a standard flow-through cell with an inner diameter of 22.6 mm. The cell was prepared by filling the conical section with 7 g of 1-mm glass beads and placing a ruby bead at the bottom. A filter membrane combination, consisting of defatted cotton (2.5 cm diameter, 0.1 g) and a glass fiber membrane (2.7 µm), was assembled on top of the cell. The experiment was conducted at a temperature of 37 ± 0.5 °C with a flow rate of 8 mL/min. HCl solution (pH 1.4) was used as the medium during the first 5 minutes of the test, then phosphate buffer (pH 6.5) was used. Samples were taken at a volume of 40 mL every 5 minutes from 0–30 minutes and 60 mL every 15 minutes from 30–120 minutes.

Optimization of the Flow-Through Cell Method

Filter membranes were selected based on the graded filtration principle to prevent tubing blockage while retaining undissolved ibuprofen particles. Flow rate, glass bead dosage, and sample volume were optimized by comparing the dissolution behavior of the reference drug (coded "C1B2") and a generic drug (coded "C6B11") that passed the consistency evaluation through calculating the similarity factor (f_2). Under the finally selected conditions, the f_2 factor of C1B2 and C6B11 should be relatively high. According to data from the Japanese National Institute of Health Sciences, the solubility of ibuprofen at 37 °C varies significantly with pH (pH 1.2: 0.053 mg/mL; pH 5.5: 0.433 mg/mL; pH 6.8: 2.010 mg/mL; water: 0.077 mg/mL), indicating that its dissolution behavior is heavily influenced by pH (21). To simulate the gastrointestinal pH environment of the human body, this study employed a multi-phase dissolution medium, with an acidic phase followed by a neutral phase. The pH values were based on the HCl condition (pH 1.4) in simulated gastric juice and the pH range (pH 5.0–6.5) of biorelevant dissolution media, including fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) (*22–24*). Different pH-variable dissolution protocols were

investigated, and the one with the highest f_2 was chosen. Two types of dissolution media were used as follows. For dissolution medium 1: HCl solution (pH 1.4) was used for the first 5 minutes; then acetate-acetic acid buffer (pH 4.5) was used from 5–10 minutes; then phosphate buffer (pH 6.5) was used from 10–120 minutes. For dissolution medium 2: HCl solution (pH 1.4) was used from 0–5 minutes, then phosphate buffer (pH 6.5) was used from 5–120 minutes.

Validation of the Flow-Through Cell Method

The dissolution method was validated for specificity, linearity, limit of quantitation, accuracy and solution stability according to International Council for Harmonization (ICH) guidelines (*25*). All validation parameters were within acceptable limits.

For filtration membrane and glass bead adsorption, an appropriate amount of ibuprofen suspension (Batch B2) was accurately weighed, dissolved, and diluted in phosphate buffer (pH 6.5) to prepare solutions with approximately 0.2 mg/mL and 1.0 mg/mL of ibuprofen, simulating sink and non-sink dissolution conditions, respectively. These solutions were treated by two methods: centrifugation and filtration through degreased cotton combined with a 2.7-µm glass fiber membrane, followed by chromatographic analysis. The membrane adsorption rate (%) was calculated as follows:

$$\frac{\text{Peak area of centrifuged sample} - \text{Peak area of filtered sample}}{\text{Peak area of centrifuged sample}} \times 100\%.$$

Under both concentration conditions, the membrane adsorption rate should not exceed 2%.

Moreover, the prepared solutions were vortexed or shaken with glass beads, then filtered through the degreased cotton-glass fiber membrane combination. The results were compared with samples without glass beads, processed identically. The glass bead adsorption rate (%) was calculated as follows:

$$\frac{\text{Peak area of sample without glass beads} - \text{Peak area of sample with glass beads}}{\text{Peak area of sample without glass beads}} \times 100\%.$$

The glass bead adsorption rate should also be no more than 2%.

Dissolution Profile Determination Method Based on the Paddle Method

According to the United States Pharmacopeia (USP), the dissolution of ibuprofen suspensions is determined using the paddle method. Dissolution curves in different media were measured by USP apparatus 2 (paddle). A 2.5-mL sample was used, and 900 mL of dissolution medium was employed with a stirring speed of 50 rpm. Samples were collected at 5, 10, 15, 20, 30, 45, and 60 minutes. The dissolution media included HCl solution (pH 1.4), water, acetate-acetic acid solutions (pH 4.5 and pH 6.0), and phosphate solutions (pH 6.5 and pH 7.2).

High-Performance Liquid Chromatography (HPLC) Analysis

Ibuprofen was analyzed and quantified by high-performance liquid chromatography (HPLC) using an Agilent 1260 Infinity system. Separation was achieved on a C18 column (Agilent, 250 × 4.6 mm, 5 µm) with a mobile phase consisting of methanol, acetonitrile, water, and phosphoric acid (65:10:25:0.03, v/v/v/v) at a flow rate of 1 mL/min. Detection was carried out at 220 nm, and the injection volume was 10 µL.

Evaluation of Dissolution Profile Similarity

The similarity of dissolution profiles between reference and generic formulations was evaluated using the similarity factor (f_2), the f_2 values must be between 50 and 100 (*26*, *27*). Alternatively, similarity can be established without f_2 comparison if both formulations achieve ≥ 85% drug release within 15 minutes.

Particle Size Analysis

The particle size distribution of ibuprofen suspensions, a critical factor influencing drug safety, efficacy, and stability (*28–30*), was characterized using microscopy (Olympus BX43) and laser diffraction (Malvern Mastersizer 3000 with Hydro MV wet dispersion unit) (*31–33*). Microscopy revealed both particle size and the crystal shape, while laser diffraction quantified the size distribution. For laser diffraction analysis, a saturated ibuprofen solution (0.5% Triton X-100) was prepared as the dispersion medium. Suspension samples (2 mL) were processed through two cycles of centrifugation (3000 rpm, 10 min) and redispersion in 6 mL medium. The final dispersion (2 mL) was analyzed under following conditions: 1500 rpm for 5 min; refractive indices of 1.550 (sample) and 1.33 (medium); sample absorbance of 0.01; non-spherical mode; obscuration range 3-12%. Triplicate measurements (10 s sample, 10 s background) were performed for each sample.

RESULTS

Flow-Through Cell Method

Optimization Results

During the assessment of multiple membrane combinations, such as PES (0.45 µm), MCE (0.8 µm), glass fiber (2.7 and 0.7 µm), and combinations of PCTE (5, 8, and 10 µm) with glass fiber (2.7 and 0.7 µm), various degrees

of blockage were detected. Particle size analysis revealed that particles larger than 2.7 µm accounted for over 99.6% of all samples (with the reference sample showing 100.0%). Although the 2.7-µm glass fiber membrane could theoretically retain undissolved ibuprofen effectively, samples from some manufacturers still caused pipeline blockages, likely due to viscous excipients like a large dosage of sucrose, glycerin, and cellulose. To overcome this, defatted cotton was added before the membrane. It effectively intercepted undissolved substances, solving the blockage problem. The final membrane combination was defatted cotton (2.5-cm diameter, 0.1 g) and the 2.7-µm glass fiber (2.7 µm) membrane.

The similarity factor f_2 between the reference formulation (batch B2) and the consistency-evaluated generic (batch B11) varied with different flow rates and glass bead quantities (Table 1). The optimal conditions were determined as a flow rate of 8 mL/min and 7 g of glass beads, which resulted in a higher f_2. Regarding sample volume, 10-mL loading caused significant tubing blockages, 5-mL loading led to some blockages, and 2.5-mL loading had no blockages. Thus, 2.5 mL was chosen as the final loading volume. In different pH-altering dissolution media, the f_2 values differed. Dissolution medium 2 (f_2 = 70) demonstrated better similarity between reference (B2) and generic (B11) batches compared to medium 1 (f_2 =52), so medium 2 was selected as the optimal medium (HCl solution pH 1.4 for first 5 minutes, then phosphate buffer pH 6.5 from 5–120 minutes).

Table 1. Optimization of Flow Rate and Glass Bead Dosage Based on The Flow-Through Cell Method

Flow Rate (mL/min)	Glass Bead Dosage (g)	Similarity Factor (f_2)
8	2	57
8	7	71
4	2	38
4	7	58

Formulation C1B2 was the reference; acceptable range for f_2 is 50–100.

Validation Results

The method demonstrated excellent specificity, with complete separation of ibuprofen from adjacent peaks and no interference from dissolution medium or excipients. Linearity was established over 0.0021–0.6270 mg/mL (y = 23249x + 52.85, r = 0.9999), with a limit of quantitation (LOQ) of 0.209 µg/mL. Method accuracy was confirmed by recovery rates of 100.0–102.1% across four concentration levels. No adsorption on membranes and glass beads was detected under both sink and non-sink conditions. Solution stability was studied, with an RSD of 0.7% for sample solutions over 24 hours and 0.3% for reference solutions over 7 days. These results validated the accuracy, reliability, and applicability of the established method.

Dissolution Profile Similarity Based on the Flow-Through Cell Method

The dissolution profiles and f_2 values obtained using the flow-through cell method are detailed in Figure 1 and Table 2.

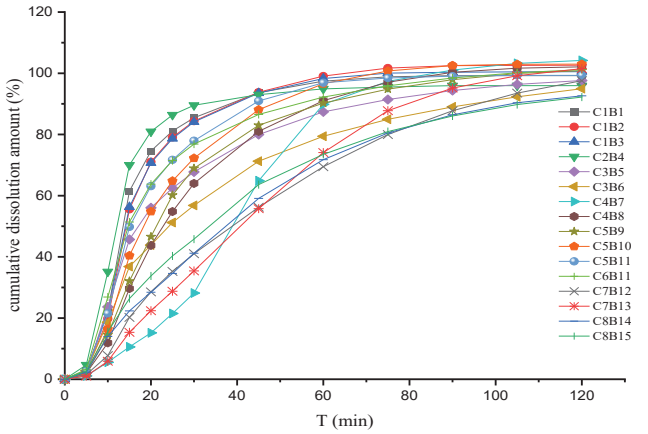

Figure 1. Dissolution profiles based on the flow-through cell method.

Three batches of the locally produced originator product (B1, B2, and B3) from manufacturer C1 served as the reference. To ensure no more than one point with cumulative release exceeding 85% was included, dissolution amounts from the first six time points were selected for calculating the similarity factor (f_2) between each generic formulation and the reference. Among the reference batches, B1 exhibited slightly faster dissolution compared to B2 and B3. Particle size analysis revealed that B1 had a smaller particle size (D_{90}: 47.7µm) compared to B2 and B3 (D_{90}: 66.1 and 65.9 µm, respectively),

Table 2. Similarity Factor (f_2) Based on the Flow-Through Cell Method

	Reference Products			Generic Products											
	C1B1	C1B2	C1B3	C2B4	C3B5	C3B6	C4B7	C4B8	C5B9	C5B10	C6B11	C7B12	C7B13	C8B14	C8B15
C1B1	N/A	74	76	58	41	31	16	31	34	40	62	21	19	21	24
C1B2	74	N/A	92	51	44	33	17	33	37	44	70	23	20	22	26
C1B3	77	92	N/A	52	45	33	17	34	37	44	72	23	20	22	26

Acceptable range for f_2 is 50–100. C1B1-C1B3: reference products (three batches [B1-B3] from one manufacturer [C1]); C2B4-C8B15: generic products (12 batches[B4-B15] from 7 manufacturers [C2-C8]).

suggesting that dissolution rate differences may be related to particle size.

Products from manufacturer C2 (B4) and C6 (B11) had f_2 values greater than 50 when compared to the reference (B2), indicating good dissolution profile similarity. B4 showed a slightly higher dissolution rate than the reference, while B11 was slightly lower. Other batches had f_2 values below 50, with slower dissolution rates compared to the reference. As of December 2023, the C6 ibuprofen suspension completed bioequivalence trials and passed consistency evaluation, whereas the C3 product failed. Other companies are either in the process of evaluation or have not yet submitted applications. Using the flow-through cell method, the C6 product (B11) showed f_2 values greater than 50 compared to the reference, and the C3 products (B5 and B6) had f_2 values below 50. These results indicated the method's discriminative power and correlation with consistency evaluation outcomes.

Dissolution Profile Similarity Based on the Paddle Method

Dissolution profiles obtained using the paddle method under varying pH conditions are illustrated in Figure 2. In HCl solution (pH 1.4) and water, cumulative dissolution at 60 minutes was low. Acetate-acetic acid buffer (pH 4.5) improved dissolution, but some batches remained below 80%. In contrast, acetate-acetic acid buffer (pH 6.0), phosphate buffer (pH 6.5), and phosphate buffer (pH 7.2) resulted in cumulative dissolution rates exceeding 90% for all batches.

Using C1B2 as the reference, f_2 values for each generic were calculated (Table 3). Lower pH levels resulted in lower dissolution amounts due to inadequate sink conditions, whereas higher pH levels reduced discriminative power. In phosphate buffers (pH 6.5 and 7.2), all samples showed cumulative dissolution greater than 85% at 15 minutes, indicating similarity to the reference. The paddle method identified four generic products (from C2, C3, C6, and C8) with dissolution profiles similar to the reference across various pH conditions. Notably, the C3 product, which failed consistency evaluation, showed similar dissolution profiles using the paddle method, potentially leading to misjudgment.

Particle Size Analysis

Microscopy and laser diffraction results revealed diverse crystal shapes (plate-like, polyhedral, granular, needle-like, and short rod-like) among manufacturers, likely due to differences in API sources and formulation processes (available as supplemental data). The C6 product, which passed consistency evaluation, exhibited plate-like crystals and a particle size distribution (D_{90}) similar to the reference. The C2 product had short rod-like crystals with a slightly larger D_{90} than the reference. The C5 and C7 products showed thicker plate-like and polyhedral crystals with significantly larger D_{90} values compared with the reference. The C3 and C8 products had granular crystals with low D_{90} values, and the C4 product featured aggregated needle-like crystals with a much larger D_{90} than the reference.

Differences in crystal shape and particle size distribution may impact dissolution behavior and bioequivalence. CQAs of ibuprofen suspensions, including particle size distribution, crystal shape, and solubilizer content, are summarized alongside dissolution profile results in Table 4.

DISCUSSION

In the paddle method, smaller particle sizes correlated with faster dissolution. The reference formulation, with smaller particles, showed rapid dissolution across all media. Generics with smaller particles were more likely to achieve similar dissolution profiles. However, the C3 product, despite having similar dissolution profiles, failed consistency evaluation, highlighting the method's limitations. The paddle method's vigorous stirring may not fully reflect the impact of formulation differences beyond particle size. Relying solely on this method for consistency evaluation risks misjudgment, as similar dissolution profiles may not guarantee consistency.

In the flow-through cell method, the C2 and C6 products showed dissolution profiles similar to the reference, with fast dissolution rates. The C6 product had crystal shapes and particle sizes consistent with the reference, facilitating similar dissolution profiles. The C2 product, despite having different crystal shapes and a slightly larger particle sizes, achieved similar dissolution due to a higher concentration of solubilizer (polysorbate 80, 0.3% vs. 0.05% in the reference). The flow-through cell method comprehensively reflected the effects of crystal shape, particle size, and formulation on dissolution behavior. It demonstrated excellent discriminatory capacity, with dissolution profile similarity results aligning with consistency evaluation outcomes. This method addresses the paddle method's limitations, such as sample positioning issues and inadequate reflection of pH-sensitive dissolution behavior.

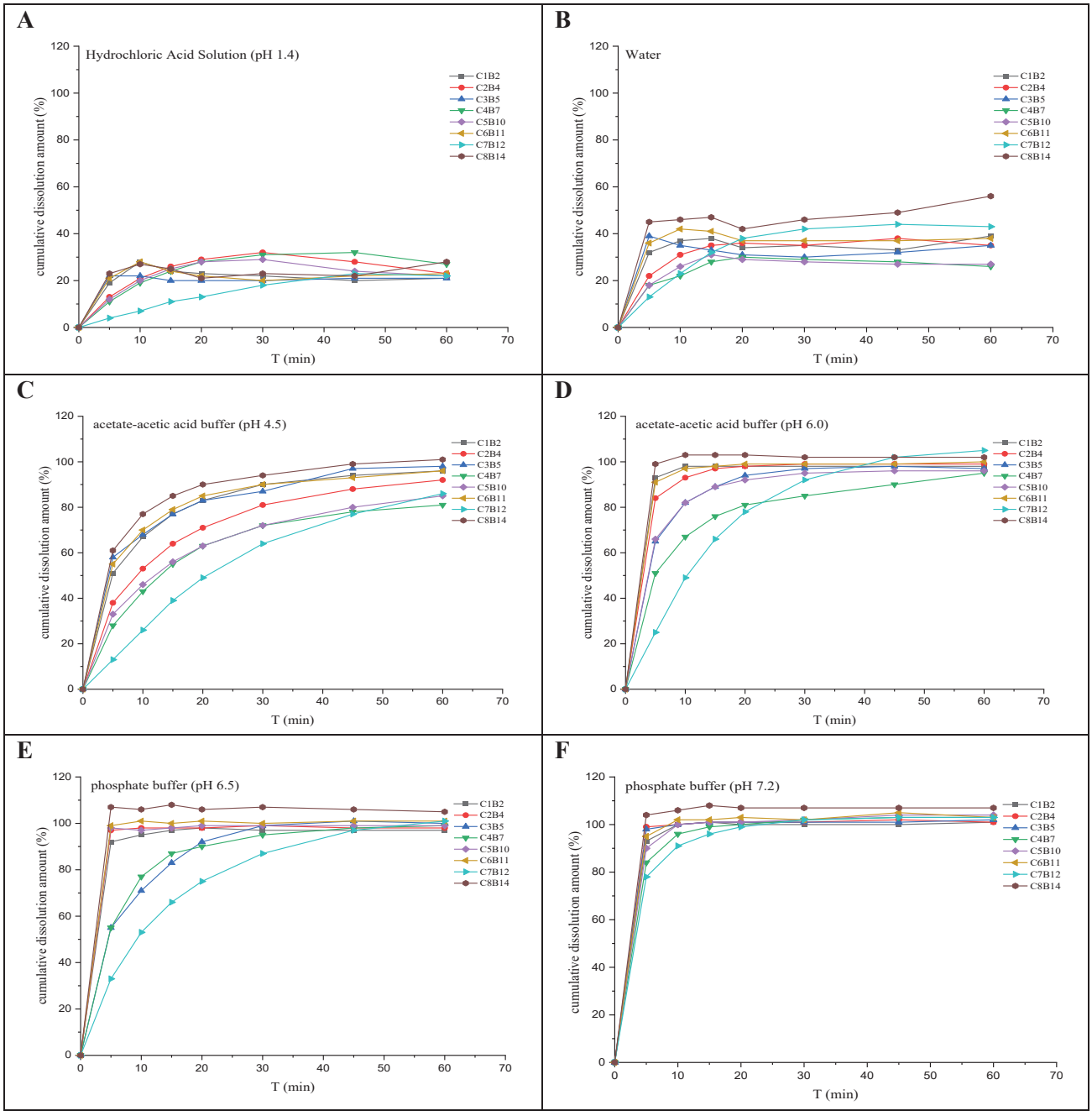

Figure 2. Dissolution profiles in different media based on the paddle method: (A) pH 1.4; (B) water; (C) pH 4.5; (D) pH 6.0; (E) pH 6.5; (F) pH 7.2.

Table 3. Similarity Factors (f_2) Under Various Dissolution Conditions Based on the Paddle Method

Parameter	Medium	C2B4	C3B5	C4B7	C5B9	C6B11	C7B12	C8B14
f_2	pH 1.4	58	73	54	61	91	45	84
	Water	63	69	50	53	71	47	50
	pH 4.5	53	72	36	36	80	24	56
Cumulative Dissolution > 85% at 15 min	pH 6.0	Yes	Yes	No	Yes	Yes	No	Yes
	pH 6.5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	pH 7.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes

C1B2 was used as the reference; acceptable range for f_2 is 50–100. C2B4-C8B14 represent the generic products (7 batches [B]] from 7 manufacturers [C]).

Table 4. Summary of Critical Quality Attributes and Dissolution Profiles Similarity

	Reference Product Manufacturers			Generic Product Manufacturers				
Attribute	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**
Crystal shape	Plate-like	Short rod-like	Granular	Needle-like	Plate-like and polyhedral	Plate-like	Plate-like and polyhedral	Granular
Particle size (D_{90})	66.1 µm	146.0 µm	51.5 µm	268.2 µm	217.9 µm	97.8 µm	145.8 µm	69.3 µm
Polysorbate 80 content (w/w)	0.05%	0.3%	0.1%	0.1%	0.3%	NA	0.4%	0.05%
Similarity (Paddle)	Reference	Yes	Yes	No	No	Yes	No	Yes
Similarity (Flow-Through Cell)	Reference	Yes	No	No	No	Yes	No	No

NA: Polysorbate 80 content unavailable for C6; D90: particle size at undersize values of 90%; Yes: dissolution profiles similar to reference; No: dissolution profiles dissimilar.

CONCLUSIONS

This study provides a technical foundation for quality control and consistency evaluation of ibuprofen suspensions. The flow-through cell method offers a precise assessment of product quality differences, particularly in vitro release, supporting quality enhancement and consistency evaluation of generics.

SUPPLEMENTAL MATERIAL

Supplemental data are available for this article and may be requested by contacting the corresponding author.

DISCLOSURES

The authors received no financial support for this work and have no conflicts of interest.

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Q+A Question & Answer Section

*The following questions have been submitted by readers of Dissolution Technologies. Margareth R. Marques, Ph.D., and Mark Liddell, Ph.D., United States Pharmacopeia (USP), authored responses to each of the questions. *Note: These are opinions and interpretations of the authors and are not necessarily the official viewpoints of the USP. E-mail for correspondence: mrm@usp.org.*

Q We are developing a new dissolution method, and we would like to know if we can use PEAK vessel to avoid cone formation?

A PEAK vessel (Agilent) is a trademark name. The generic name for this type of vessel is apex vessel. Apex vessels are not compendial equipment and their use must be justified. If you are using the basket, increasing the rotation speed may be required. If this change does not solve the coning phenomena, you may need to move to the paddle apparatus and select the appropriate rotation speed as part of the method validation. Typically, after exhausting the above compendial methods, then the use of apex vessels may be justified. As these vessels are not standardized, using vessels from the same supplier will help to ensure consistency in test results.

Q We are developing an oral suspension product that will be filled in multi-dose containers as well as unit dose cups. For dissolution testing, we are planning to pool the content of ten unit-dose cups into a larger container, to perform the testing. Six sample aliquots will be added to the six separate dissolution vessels for testing. Is this procedure appropriate?

A For any type of suspension, the dissolution test should be done with the samples reconstituted according to the instructions to the patient. The amount of sample to be transferred to the dissolution vessel must be equivalent to the highest dose that can be administered as a single dose. According to the description above this method would only satisfy the compendial requirements for suspension testing if the amount of drug in the aliquot transferred to the dissolution vessel is equal to the amount contained in highest administered dose and if the suspension is reconstituted according to the patient instructions.

Q I have trouble dissolving my standard in the dissolution medium and I've looked online for the information from https://www.usp.org/frequently-asked-questions/dissolution-procedure-development-and-validation. The answer is: "Under Validation, <1092> mentions the use of solutions made with not more than 5% organic solvent when evaluating accuracy/recovery and linearity and range. The use of the organic solvent is to promote the solubility of the pure drug substance but not interfere with the analysis. The solvent should not interfere with the analysis at the concentration used." If 5% organic solvent is not enough to solubilize the drug substance in my standard solution, is it acceptable to add more organic solvent (up to 10%) and perform method validation to prove that the solvent does not interfere with the analysis at the concentration used?

A This would be acceptable under the condition that the composition of the standard solution and sample solution are similar. The only acceptable difference should be the amount of the analyte in the two solutions. If higher amounts of organic solvent are used to dissolve the standard, it needs to be demonstrated that this difference between the composition of the standard solution and sample solution does not interfere with the quantitation of the drug substance in both solutions. We would also recommend checking the solubility of the drug substance in the literature and evaluating whether other organic solvents can be used.

Q Can 100% organic solvent be used to dissolve poorly soluble drugs for dissolution standard solution preparation?

A The composition of the standard solution and sample solution should be almost identical, the difference should be the amount of the analyte in the solutions. One common method to prepare standard solutions is to first prepare a stock solution using an organic solvent. Then, an aliquot of the stock solution can be transferred to a volumetric flask and filled to volume with dissolution medium. The amount of organic solvent in the aliquot should be no more than 5% of the total volume of the

final dilution with dissolution medium. Another option is to transfer an appropriate amount of standard to a volumetric flask, add a volume of the appropriate organic solvent not more than 5% of the total final volume, and then complete the dilution to the final volume with dissolution medium.

Q We have a dissolution method in our lab that uses 10 mesh basket. The performance verification test (PVT) of USP apparatus 1 was designed for 40 mesh baskets. Can we use this procedure with 10 mesh baskets?

A No. Because a collaborative study was used to establish the acceptance criteria for the PVT test reference standard (USP DPVS – Prednisone Tablet RS) and the use of 40 mesh baskets was specified in the collaborative study protocol, the acceptant criteria for USP apparatus 1 can only be applied to a dissolution apparatus that uses 40 mesh baskets. As an alternative, you can qualify the dissolution system using the standard 40 mesh baskets and then perform a mechanical calibration of the system after installing the 10 mesh baskets to ensure that the 10 mesh basket height, wobble, and centering are all within acceptable tolerances. Also, each time the dissolution equipment is used, the 10 mesh baskets should be inspected to ensure that the baskets are still in good condition.

Q Dissolution test 2 in the USP monograph for Pseudoephedrine Hydrochloride Extended-Release Tablets calls for the use of a nylon netting. What are the specifications for this material?

A Keep in mind that the dissolution test 2 in the USP monograph for Pseudoephedrine Hydrochloride Extended-Release Tablets is specific for an osmotic pump tablet and may be formulation dependent. The nylon netting mentioned in the text is used to hold the tablet in place and it does not play any other role in the dissolution test. This nylon netting is also known as tulle fabric, and it is used for bridal veils or for mosquito nets.

Q The USP procedure for the determination of the enzymatic activity of the pepsin to be used in the dissolution test states to use 2.5 mg of pepsin to prepare the sample solution. Is this amount applicable to any kind of pepsin or should this amount be modified considering the protein content of the pepsin being evaluated?

A It is important to note that only purified pepsin is recommended for use as an enzyme in dissolution media with a pH ≤ 4.0. The amount of 2.5 mg is appropriate for a sample of purified pepsin. The procedure determines the proteolytic activity of the purified pepsin to be used in dissolution media and not the amount of protein contained in the sample.

Q For how long can the temperature of the dissolution medium be out of the range 37.0 ± 0.5 °C during a dissolution run?

A The temperature of the dissolution medium must be within the range 37.0 ± 0.5 °C during the entire dissolution test. There are no allowances for excursions. If the dissolution bath cannot maintain the temperature of the dissolution media throughout the dissolution test, preventative maintenance or repair of the dissolution equipment may be required. See USP general chapter <711> Dissolution.

Q Regarding the use of enzymes in the dissolution media for dosage forms containing gelatin, if the dissolution medium is water, which theoretically has a pH of 7, but can actually range between pH 5 and 8. Should we use the theoretical pH of 7 and use pancreatin for a dissolution test using water as the media or should we measure the pH for each dissolution and adjust the enzyme accordingly depending on the pH of water?

A Determine the pH of the water that is going to be used as the dissolution medium and select the appropriate enzyme for the measured pH. Keep in mind that the pH of water may change upon storage.

Q+A

Every issue of *Dissolution Technologies* features a Question and Answer section. This section is designed to address general dissolution questions submitted by our readers.

Please send your questions to:
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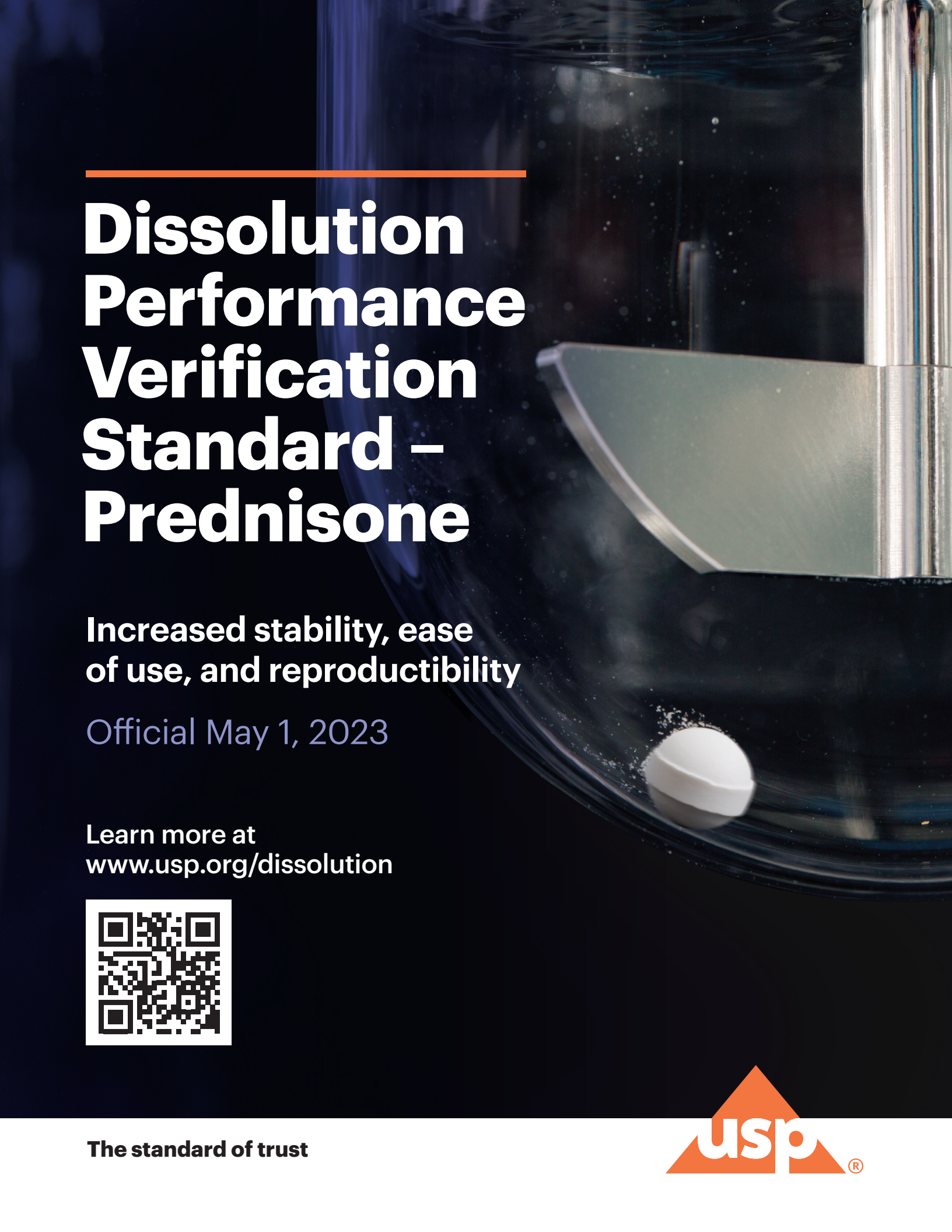

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Calendar of Events

September 18, 2025

Navigating Small-Volume and Other Specialty Accessories
Location: DDG Online Meeting at 10:30 am ET
Registration: https://www.agilent.com/chem/dissolution-webinars

September 23–24, 2025

Mastering Particle Size Analysis: A Step-by-Step Illustration of Techniques and Best Practices
Location: The Universities at Shady Grove, Rockville, MD, USA
Registration: https://www.complexgenerics.org/education-training/mastering-particle-size-analysis-a-step-by-step-illustration-of-techniques-and-best-practices

November 9–12, 2025

PharmSci 360 AAPS Meeting
Location: Henry B. Gonzalez Convention Center, San Antonio, TX, USA
For information, visit https://www.aaps.org/pharmsci/annual-meeting

November 16–18, 2025

Eastern Analytical Symposium and Exhibition
Location: Crowne Plaza Princeton-Conference Center, Plainsboro, NJ, USA
For information, visit eas.org

On Demand Events

- ***Powder Flow Testing***
  https://www.copleyscientific.com/events/webinar-foundations-of-powder-flow-testing/
- ***dissoLab Software: Predictive Dissolution Simulated from Microscopic Images***
  https://vimeo.com/1054617734?share=copy
- ***Fiber Optic UV: Better Dissolution Testing On Demand***
  https://www.distekinc.com/watch/fiber-optic-uv-better-dissolution-testing/
- ***Advances in In Vitro Bioequivalence Assessment for Topical Products Part 2***
  https://youtu.be/iqphypToHZ0?si=mn9FJLDhm-VBoWMm
- ***Ocular Administration (OCAT™) in GastroPlus® On Demand***
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- ***GastroPlus® ADR – 4 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™)***
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- ***Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs***
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- ***GastroPlus® X Tutorial Series***
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Industry News

Merel Instruments Partners with QLA to Elevate US Distribution of Advanced Analytical Solutions

Merel Instruments, a global leader in laboratory and analytical automation, is proud to announce a new distribution partnership with QLA in the United States. **QLA** will now serve as Merel's authorized distributor, ensuring local sales support, product demonstrations, and customer service across North America.

Cutting Edge Product Portfolio

Merel Instruments offers a comprehensive range of innovative instruments designed to streamline laboratory workflows, optimize precision, and enhance regulatory compliance.

dissoBOT® and **dissoDG®** - The dissoBOT is a fully automated dissolution solution powered by collaborative robotics and clip-on/off integration. It seamlessly connects to standard dissolution systems automating key tasks like sampling, vessel cleaning, and media dispensing. Complementing this is the dissoDG, a highly efficient degassing unit that removes dissolved gases from dissolution media in line with USP protocols—achieving gas levels under 6.72 ppm in just 20 minutes.

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dissoGUARD® and **dissoGUARD PRO®** - Data traceability and process integrity are strengthened by the dissoGUARD and dissoGUARD PRO, Merel's proprietary monitoring systems. These record visual data of dissolution processes and log critical motion or RPM anomalies, supporting GLP/GMP compliance.

Beyond dissolution, Merel also supports automation in power and petrochemical industries. The **GE 567 Transformer Oil Gas Analyzer** offers a fully automated system for dissolved gas analysis (DGA) in transformer oil. Additionally, the **AOS 125 Oxidation Stability Apparatus** delivers multi-position oxidation testing for insulating liquids.

Merel also offers a **Collaborative Laboratory System** — a modular, robot-integrated lab workstation, designed for smart automation of repetitive lab routines.

Why Choose Merel and QLA?

Merel Instruments is committed to delivering high-performance, regulation-ready equipment that meets the evolving needs of pharmaceutical, chemical, energy, and academic laboratories. Each product is developed with user experience in mind: intuitive interfaces, modular hardware, and seamless integration are standard across the entire portfolio.

With QLA now representing Merel in the U.S., customers benefit not only from innovative instrumentation but also from reliable, responsive local support. QLA's experience and presence in the market ensures faster implementation, hands-on guidance, and lasting service partnerships, allowing clients to focus on quality, efficiency, and compliance without compromise.

Together, Merel and QLA are bringing cutting-edge automation to laboratories across the United States—delivering innovation where it matters most.

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Logan Instruments Unveils New Logo

SOMERSET, NJ – July 1, 2025 – Logan Instruments has unveiled a new company logo. The new logo prominently spotlights the name Logan while dropping "Instruments Corp." from the design.

"Logan's previous logo served our company well for the past 35 years. As we embark on the next 35, and in line with the culture of the company, we felt it was the right time to refresh the logo into a sleeker, simpler version, while remaining true to our core business and core values, which is symbolized by retaining the same dissolution paddle from the previous logo", said Mr. Keith Hamman, President and CEO. Mr. Hamman joined Logan in October 2024.

"Dr. Luke Lee started Logan in his garage in New Jersey back in 1990 with very little funding. He grew the company into a global powerhouse with a solid portfolio of products that can be found in over 80 countries today. Dr. Lee is living the American dream", said Mr. Hamman.

Although Dr. Lee has stepped away from day-to-day executive management, he is still fully engaged in the business running the R&D department which is split between teams in the US and Shanghai, China. Logan's large, diverse R&D team gives the company the ability to accelerate new product designs aligning with the needs of the market.

"Building on Dr. Lee's success, this new logo represents our refreshed vision and our commitment to produce simple, easy to use products that address complex applications," said Mr. Hamman.

The new logo is expected to roll out systematically across the company over a 24-month period.

About Logan Instruments

Logan Instruments is a leading provider of sophisticated USP apparatus 1-7 testers, semisolid diffusion cell equipment, bioavailability testers, and other pharmaceutical formulation development and QC testing technologies. Logan's global headquarters is in Somerset, NJ USA with manufacturing plants in Somerset and Shanghai, China. For more information, visit Logan's website at www.loganinstruments.com.

Simulations Plus Supports New FDA Roadmap for Reducing Animal Testing in Preclinical Safety Studies

Modeling and simulation will be a key component for shift to non-animal methodologies:
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Lancaster, CA - Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of cheminformatics, biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, has announced its support of the U.S. Food and Drug Administration's (FDA) recently announced roadmap for reducing animal testing using new approach methodologies (NAMs). Simulations Plus has long provided the industry-leading software and consulting service expertise to successfully implement the FDA roadmap.

"We are excited to see that the FDA is elevating its continued commitment to reduce animal testing through innovative science, as outlined in the new "Roadmap to Reducing Animal Testing in Preclinical Safety Studies ," said Shawn O'Connor, Chief Executive Officer of Simulations Plus. "The science has evolved—today, modeling and simulation can offer human-relevant insights that not only complement but can begin to replace traditional animal studies in many cases. This allows our clients to get new treatments to patients faster and improve lives around the world. At Simulations Plus, we've supported this vision for nearly 30 years, and we're proud that our software and services are helping to make it a reality. Having collaborated with the FDA on more than 15 projects over the past decade, we understand the agency's focus on integrating new methodologies like computational modeling that will help reduce and eventually eliminate animal testing. This roadmap is an important step toward a future where safer, faster, and more sustainable drug development is possible, and we look forward to continuing our close collaboration with the FDA and industry to support this important transformation."

Over the past four decades, modeling and simulation for drug development has gained traction within the pharmaceutical industry and achieved broad acceptance by global regulators. Approaches such as population pharmacokinetics (popPK), exposure-response analysis, and physiologically based pharmacokinetic (PBPK) modeling are now widely used to support regulatory submissions and interactions. The new FDA roadmap outlines a path to incorporate methodologies such as organ-on-a-chip, advanced in vitro assays, and computational modeling in preclinical safety studies, with an initial focus on monoclonal antibody (mAb) testing.

Simulations Plus software platforms are utilized by mAb-focused researchers for key decision-making::

- **GastroPlus®** accelerates the assessment of dosing and delivery strategies needed to achieve desired clinical endpoints, enabling researchers to reduce—and in some cases, eliminate—animal testing during non-clinical development.
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In addition, Simulations Plus software and consulting services are relied upon by researchers to predict efficacy and safety of compounds and prioritize top drug candidates for further development—contributing to a reduction in animal testing and more focused clinical trials. These platforms include:

- **ADMET Predictor®** the flagship machine learning (ML) platform for Absorption, Distribution, Metabolism, Excretion, and Toxicity modeling, with extended capabilities for data analysis, metabolism prediction, and artificial intelligence (AI)-driven drug design.

- **DILIsym®** the leading quantitative systems toxicology (QST) platform for predicting and explaining drug-induced liver injury (DILI).
- **OBESITYsym™** the only quantitative systems pharmacology (QSP) platform for predicting drug efficacy for weight loss and nausea side effects.

Pharmaceutical companies also leverage the expertise of Simulations Plus consultants during development in the areas of PBPK, QSP/QST, clinical pharmacology, and pharmacometrics. The Simulations Plus PBPK services team delivers high-value scientific expertise to help clients replace or reduce animal testing by developing and validating predictive PBPK models that integrate standard in vitro and in silico data to simulate human and animal pharmacometrics. GastroPlus currently includes eight animal species and human models, including non-human primates, minipigs, and dogs. By tailoring these models to specific program needs—including interspecies extrapolation, first-in-human dose selection, and safety margin assessments—the team supports regulatory submissions that align with NAMs, helping clients accelerate development timelines while promoting ethical research practices.

"We applaud the FDA's forward-thinking approach to advancing non-animal methodologies, particularly for monoclonal antibody development," said John DiBella, President of PBPK Solutions of Simulations Plus. "At Simulations Plus, we've been pioneering the integration of artificial intelligence and machine learning (AI/ML) with mechanistic modeling for years—delivering predictive, human-relevant insights and toxicology forecasting for our clients. Our software has already been at the center of dozens of peer-reviewed publications validating our approach in the mAb research space. We are dedicated to advancing the industry through innovative, proven tools that accelerate this crucial regulatory evolution."

"QST modeling will be essential in reducing reliance on animal testing by predicting toxicologic risk for patients as well as providing mechanistic insights into drug safety that are grounded in human biochemistry and physiology," said Steven Chang, President of QSP Solutions of Simulations Plus. "Our safety-focused modeling approaches have long been used to inform regulatory as well as pharma company decision-making to identify safe and effective dosing paradigms. Our QST model, BIOLOGXsym, is well-positioned to bridge the need for reduced animal testing by incorporating 'liver-on-a-chip' data as inputs to help drug developers assess and improve liver safety in large molecules, including mAbs. We're proud to offer some of the most trusted and widely used toxicology modeling software platforms in the industry, empowering our partners to confidently align with the FDA's vision for the future."

Many organizations will need more than new modeling tools and in vitro systems. To follow the FDA roadmap, companies not currently incorporating NAMs into their development processes and timelines may also require consulting services, regulatory guidance and training on new tools.

"The FDA roadmap sends a clear signal that the future of preclinical safety assessment lies in innovative, non-animal methodologies—and modeling and simulation will be central to that shift," said Sandra Suarez-Sharp, President of the Regulatory Strategies Center of Excellence of Simulations Plus. "Software and models are already available to support several modeling activities, but where many biopharmas may encounter challenges is in developing regulatory strategies that effectively incorporate the key points outlined in the FDA roadmap. At Simulations Plus, we are positioned to help companies interpret and apply emerging expectations, offering expert guidance to integrate modeling and simulation and risk assessment into regulatory strategies with confidence and credibility."

Simulations Plus is pleased to introduce NAMVantage , its flagship package offering PBPK and QSP software, professional services and regulatory strategy combined with built-in coaching and training. This comprehensive solution offers clients full support for the FDA's NAM roadmap. In addition, companies seeking immediate training for their scientists will find quick access through the Learning Services program, which offers workshops and on-demand courses, and the popular MIDD+ events that offer free in-person training. For more in-depth training on actual projects, the Consult + Coach program allows researchers to learn alongside expert modelers during a consulting study.

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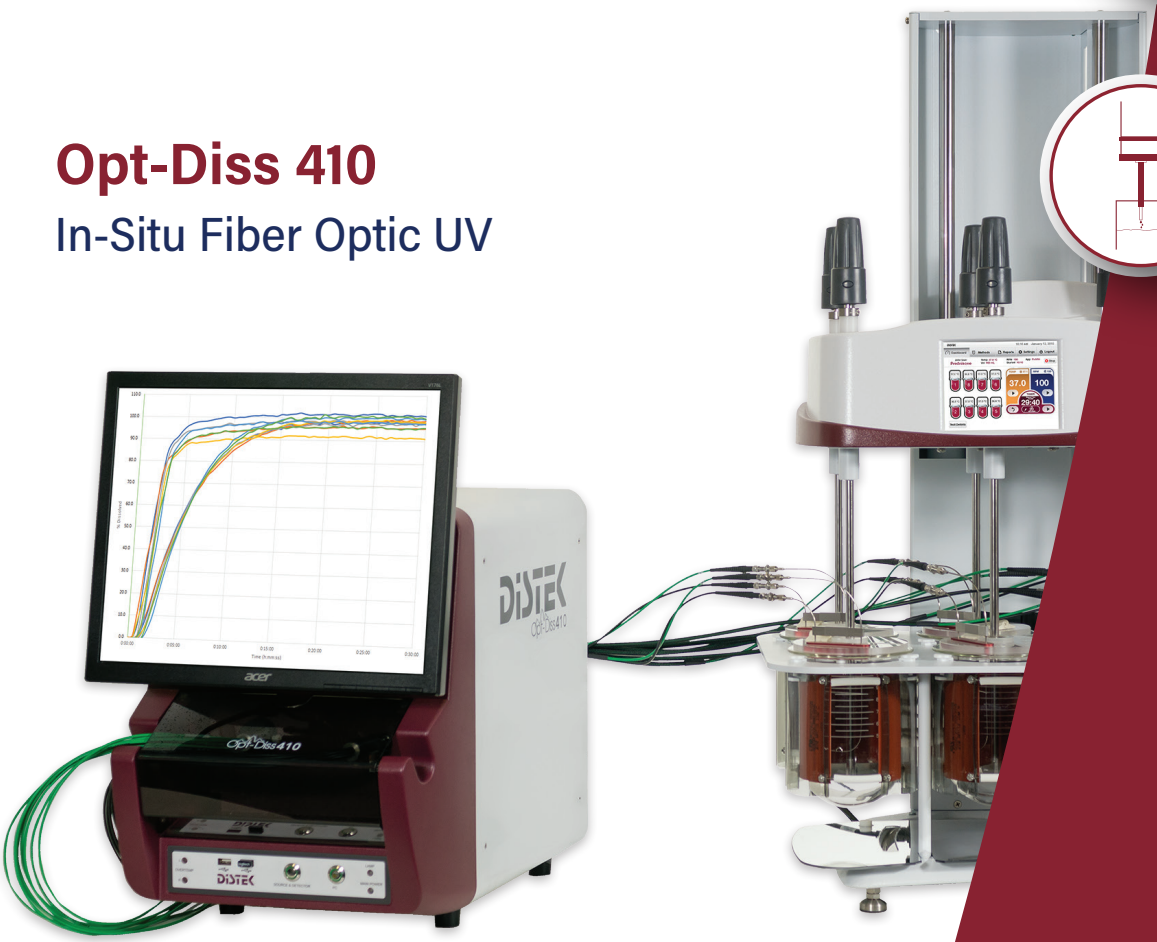
In-Situ Fiber Optic UV



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Demonstration Today!

"There is real time data, no volume correction, no line purging and no air bubble issues!"
- Director of Formulation, CA

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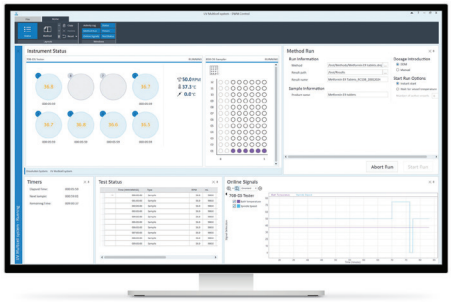

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