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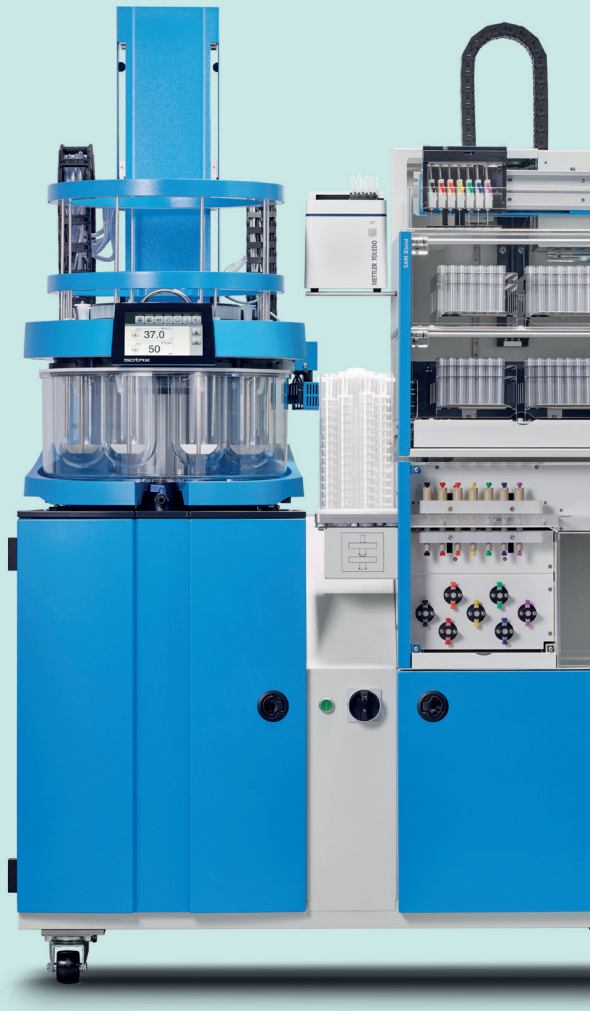

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Impact of Vessel Inner Diameter in USP Dissolution Apparatus 2

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ABSTRACT

Commercially available dissolution vessels used with United States Pharmacopeia (USP) apparatus 1 and 2 typically have nominal inner diameters of 100 or 104 mm. Little data are available in the literature to evaluate whether equivalent dissolution results are obtained when the same product is tested in both types of vessels. This study provides some additional data. Three immediate-release tablet products and a suspension product were tested in the two vessel types, across a range of paddle speeds. Superimposable dissolution profiles were obtained for all experiments. These data, although not exhaustive, suggest that these two vessel diameters may be considered equivalent from a hydrodynamic perspective, and thus, represent a low risk for method transfers between instruments that use vessels with 100-mm and 104-mm inner diameters.

KEYWORDS: Dissolution, vessel, inner diameter, *USP* <711>, rate, extent, paddle

INTRODUCTION

Dissolution is an analytical technique for assessing the likely pharmacokinetic performance of pharmaceutical formulations and is widely used for both quality control and research purposes. Transfers of dissolution test methods between laboratories, for example from a research and development site where the method is validated to a commercial manufacturing site, are critical to ensure consistent analytical results and proper control of product quality. However, method transfers are occasionally unsuccessful. Root cause analyses sometimes identify the use of different brands of equipment at different sites as a potential factor, but it may be less clear exactly which attributes of the instruments (if any) are causing different dissolution results. Minor differences in vessel geometry within United States Pharmacopeia (USP)-defined tolerances can exist and are sometimes postulated as a source of variability (*1*). The inner diameter of the vessel is one element of vessel geometry, but little data are available in the literature regarding the effect of this variable. Perivilli et al. conducted a computational study of the potential impact of this and other variables on fluid dynamics in the vessel, finding no significant impact from vessel inner diameter across the *USP* <711> specification range of 98–106 mm (vessel radius 49–53 mm) (*2*, *3*).

The present study aimed to investigate, across multiple products using different paddle speeds, whether changing the vessel inner diameter from 100 to 104 mm could give rise to variations in dissolution results. Vessels with inner diameters at the extremes of 98 and 106 mm were not available for this study. Although the same vessel is used for USP apparatus 1 (baskets), apparatus 2 (paddles) is more commonly used. Therefore, this study examined apparatus 2 only.

METHODS

USP Performance Verification Tests (PVT)

The USP performance verification tests (PVTs) were conducted with Prednisone Tablets RS (USP-proposed lot #: R072M0, Bulk Lot #: B160351, Item #: B559505) at Sotax (Westborough, MA) to establish a baseline with the specific vessels used in this study. Current USP guidelines for apparatus 2 testing were followed with manual sampling

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(*4*). All runs were performed by the same operator on the same equipment. A Sotax AT Xtend dissolution bath and SOTAX Specord 200 plus UV spectrophotometer were used. Vessels with 100-mm and 104-mm inner diameters were tested. The exact dissolution vessels were shipped to GSK for use in this study.

GSK Pharmaceutical Products

Tests of four GSK products (three immediate-release tablets and a suspension) were performed using the same Sotax MultiDose G3 fully automated dissolution system with a Sotax AT bath. Vessels with inner diameters of 100 mm and 104 mm were tested over a range of paddle rotation speeds (20–65 rpm). Additional method details are proprietary.

Sample solutions were analyzed using online UV spectroscopy (Agilent 8453), with the exception of one tablet product (Product #3), for which samples were analyzed by reverse phase high-performance liquid chromatography (HPLC) (Agilent 1100 series). Dissolution profiles were generated according to each product's test method at GSK (Upper Merion Township, PA).

RESULTS AND DISCUSSION

The comparison of vessels with 100-mm and 104-mm inner diameters did not result in a significant change in either the mean result or repeatability (coefficient of variance) with USP apparatus 2 dissolution testing. This was true for both the USP PVT tablets (Table 1) and all GSK products tested in this study (Fig. 1–3), representing a range of rotation speeds from 40–65 rpm. Even with a suspension dosage form at very low rotation speed (20 rpm), where maximum sensitivity to hydrodynamics might be expected, no significant difference was observed (Fig. 4).

Table 1. PVT Results for Vessels with 100-mm and 104-mm Inner Diameter

Run Number	Geometric Mean (% Dissolved)	%CV	Vessel inner diameter (mm)
1	36	3.1	104
2	34	4.9	104
3	35	2.8	104
4	35	2.7	104
5	36	3.6	100
6	35	3.7	100
7	35	7.5	100
8	34	3.3	100

CV: coefficient of variation.

These results suggest that there is no significant difference in hydrodynamics when the vessel inner diameter is 100 or 104 mm, which is consistent with the predictions of CFD modelling (*2*).

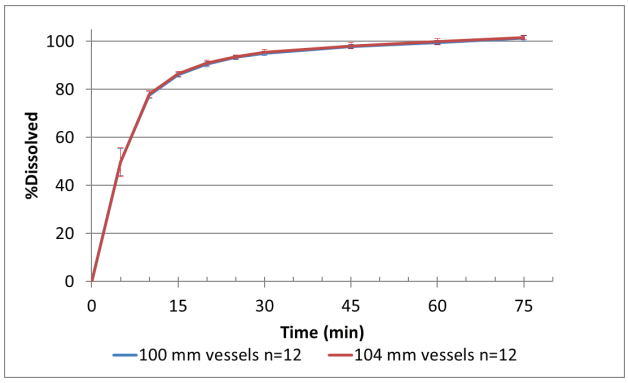

Figure 1. Dissolution profile of immediate-release tablets at 60 rpm in USP paddle apparatus (product #1). All error bars represent ± one standard deviation.

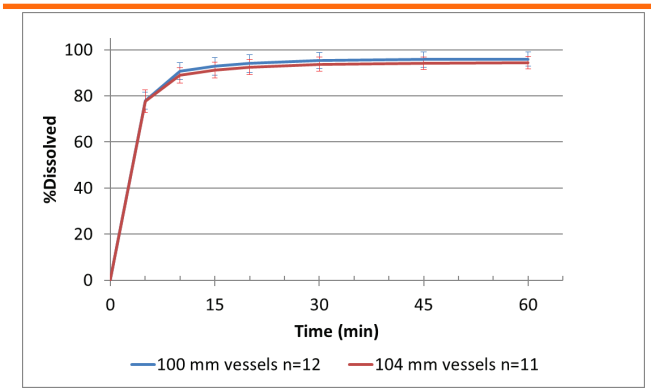

Figure 2. Dissolution profile of immediate-release tablets at 40 rpm in USP paddle apparatus (product #2). All error bars represent ± one standard deviation. Some experiments provided n = 11 replicates due to isolated instrument malfunction.

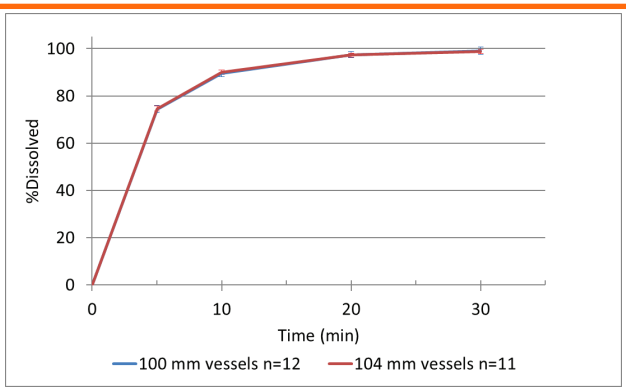

Figure 3. Dissolution profile of immediate-release tablets at 65 rpm in USP paddle apparatus (product #3). All error bars represent ± one standard deviation. Some experiments provided n = 11 replicates due to isolated instrument malfunction.

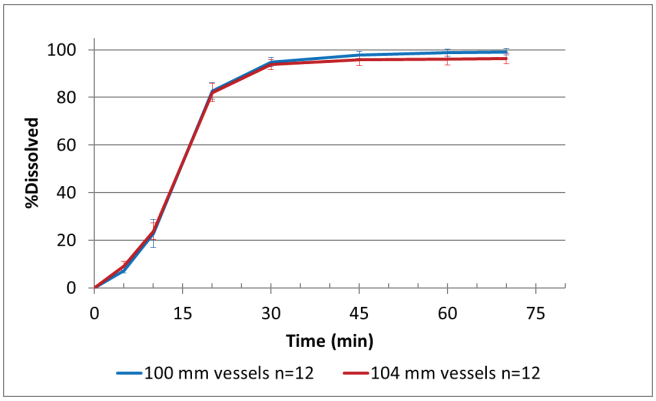

Figure 4. Dissolution profile of immediate-release suspension at 20 rpm in USP paddle apparatus (product #4). All error bars represent ± one standard deviation.

The authors cannot project whether extending the testing range to 98 and 106 mm, the minimum and maximum of the USP tolerance, would have an impact on results.

CONCLUSIONS

The data obtained in this study suggest that use of vessels with 100-mm and 104-mm inner diameters may be considered low risk for any cross-platform dissolution method transfer.

ACKNOWLEDGEMENTS

The authors would like to thank Sotax and the steering committee of the American Association of Pharmaceutical Scientists (AAPS) In Vitro Release and Dissolution Testing (IVRDT) community for their support of this study.

DISCLOSURES

David Curran and Xiaoling Zhang are paid employees of GSK. The other authors have no conflicts of interest.

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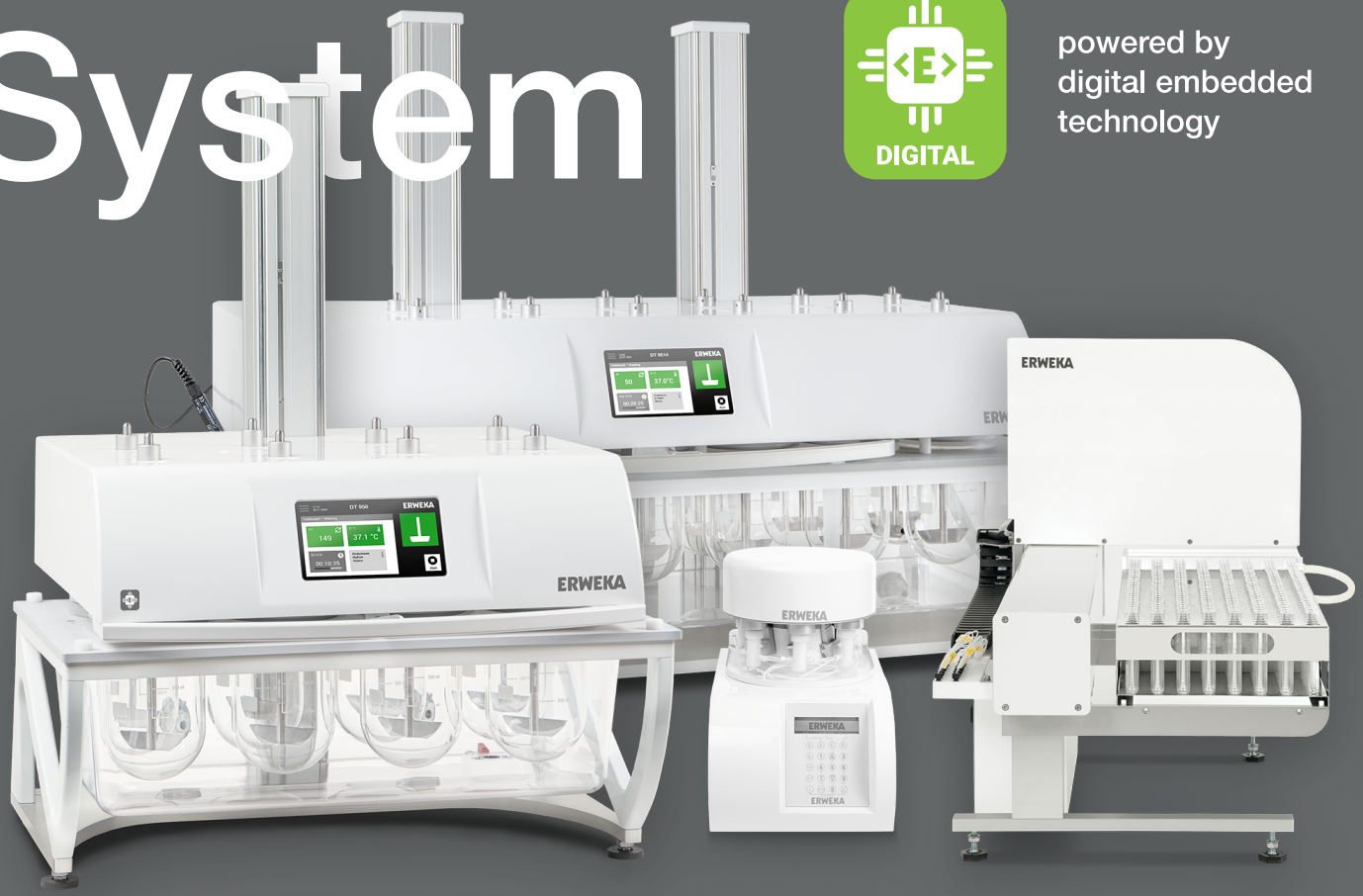

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Application of Salicylic Acid Tablets in the Performance Verification Test for the Flow-Through Cell Apparatus

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ABSTRACT

The flow-through cell is the preferred apparatus for dissolution testing of controlled-release dosage forms, poorly soluble drugs, and many special dosage forms, such as suspensions, soft capsules, implants, microspheres, and liposomes. Although the flow-through cell apparatus has been included in pharmacopoeias for years, there is no official performance verification test (PVT) method. In this study, salicylic acid tablets were used to develop a PVT for the flow-through cell apparatus. Using the same erosion and zero-order release mechanism as the basket and paddle apparatus, the salicylic acid tablet proved to be a good potential reference standard in PVT for the flow-through cell apparatus. In phase I, four parameters were systematically investigated for their influence on dissolution of salicylic acid using the design of experiment (DoE) method. The tablet loading pattern was the most important parameter influencing dissolution; flow rate and cell inner diameter (ID) also had a significant impact. Temperature had a negligible effect on dissolution. In phase II, dissolution tests were conducted by four different analysts on different flow-through cell apparatus (i.e., four collaborators) in two test facilities for repeatability and reproducibility assessments and to determine preliminary acceptance criteria for the PVT. The experimental condition for phase II was tablets placed on the tablet holder with glass beads, cell ID of 12 mm, flow rate of 16 mL/min, and temperature of 37 °C, and sample collected at 90 minutes. Reproducibility of the PVT was confirmed with data from a fifth collaborator.

KEYWORDS: dissolution, flow-through cell, performance verification test (PVT), salicylic acid, design of experiment (DoE), preliminary acceptance criteria

INTRODUCTION

The flow-through cell is a dissolution testing apparatus that uses the flow of dissolution medium through a cell containing a dosage form (*1*). The flow-through cell apparatus consists of media reservoirs, pump, water bath, flow-through cells, filtering system, and a fraction collector. Generally, the dissolution medium (buffer) is pumped into the cells where dosage forms are placed. The dosage form is isolated from the medium reservoir, which facilitates the adjustment of medium volume or pH during dissolution tests. The flow-through cell apparatus has two configurations, closed loop and open loop. In closed-loop configuration, the medium volume can be well changed according to the reservoir capacity. This configuration is especially suitable for dissolution tests of low dosage strength drugs, in which a small volume of medium is usually required to achieve adequate concentration. The open-loop configuration offers infinite sink conditions, which is often preferred for controlled-release dosage forms and poorly soluble drugs (*2*). In open-loop configuration, the flow-through cell apparatus enables a medium change during the drug dissolution process, simulating the in vivo environment with relevant pH changes. This is particularly suitable for the dissolution test of pH-sensitive drugs, such as targeted dosage forms and targeted drug release systems (*2–4*). Equipped with various types of cells, the flow-through cell apparatus also demonstrates great superiority in the dissolution tests of new and special dosage forms, including but not limited to liposome, nanoparticles, microsphere, powders, granules, suspensions, soft capsules, implants, suppositories, microspheres, oil-based agents, and gels (*5*).

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Historically, the flow-through cell apparatus was firstly applied in dissolution tests in the United States in the 1960s, then it was introduced to many countries and international organizations (*1, 6–10*). In China, a similar device to the flow-through cell apparatus was first included in *Chinese Pharmacopoeia* in 1985, but it was withdrawn in 1990; In 2020, the flow-through cell apparatus was officially included in the *Chinese Pharmacopoeia* (*9*). With the popularization of flow-through cell apparatus in China, a standard performance verification test (PVT) is needed to guarantee the quality of dissolution tests. In general, mechanical calibration and PVT are required to determine suitability of the dissolution apparatus. The PVT is a method for evaluating the overall procedure, which includes the apparatus, analytical procedure, and analyst. The development of a PVT involves considering several factors, such as the ease of performing tests in a short period of time and precision (i.e., repeatability, ruggedness, and reproducibility). Additionally, the reference standard should be a stable and preferably non-toxic product, with an analytical marker that can be easily quantified. Finally, the results of the PVT should be responsive to changes in critical operational parameters of the apparatus (*11, 12*). Early development of a PVT for the flow-through cell apparatus was reported by Eaton and colleagues with salicylic acid tablets as a candidate reference standard, in which flow rate, temperature, amount and size of glass beads, deaeration level, tablet orientation, tester manufacturer, and analyst were investigated (*13*). From a policy perspective, however, there have been no widely accepted guidelines for mechanical verification nor standards for PVT in the world.

The scope of the current study is to develop PVT for flow-through cell apparatus, in which major variables of dissolution will be evaluated and the preliminary acceptance criteria of PVT will be determined. Salicylic acid tablets are expected to be an ideal testing dosage form because they are non-disintegrating, non-toxic, and have good performance stability, and have been successfully used in PVT development by Eaton et al (*13*). More importantly, salicylic acid reference tablets are currently used in PVTs for the basket, paddle, and small cup apparatus in China, so tablet quality can be guaranteed, which could also facilitate good compliance for a future flow-through cell apparatus PVT.

The study includes two phases: In phase I, various parameters will be systematically investigated for their influences on dissolution of salicylic acid by the design of experiment (DoE) method, a powerful statistical tool to determine correlations between the factors and responses in the process (*14*). In phase II, referring to the analytical methodology for PVT of United States Pharmacopeia (USP) apparatus 1 and 2, repeatability and reproducibility assessment will be conducted by different analysts on various apparatus in two test facilities, and preliminary acceptance criteria for a PVT of the flow-through cell (apparatus 4) will be achieved and applied (*11, 12, 15–18*).

METHODS

Materials

The following materials and reagents were used: salicylic acid reference material (99.8%, lot 100106-202106, National Institutes for Food and Drug Control (NIFDC), China), salicylic acid reference tablets (See Table 1, lot 100103-202114, NIFDC, China), potassium phosphate monobasic (99.5%, lot 68887172, Meryer, China), sodium hydroxide flake (98%, lot 78687053, Meryer, China), ultrapure water (Resistivity 18.2 MΩ·cm at 25 °C), and glass microfiber filters GF/F (diameter 25 mm, lot 9817071, GE Healthcare Life Science Whatman, made in China). Physical and chemical properties of the tablets were assessed and are presented in Table 1.

Table 1. Physical and Chemical Characteristics of Salicylic Acid Tablets

Test	Result	SD	RSD%
Appearance	Round, white	NA	NA
Diameter (mm), mean	9.48	0.02	0.26
Thickness (mm), mean	4.18	0.01	0.29
Weight variation (mg), mean	297.0 (n = 214)	3.4	1.1
Hardness (kp), mean	10.5 (n = 10)	0.8	7.4
Friability (% of weight loss), mean	< 1.0%	NA	NA
Assay (% of label claim), mean	100.1% (n = 10)	1.1	1.1
Content uniformity (mg), mean	300.2 (n = 10)	3.4	1.1

SD: standard deviation; RSD, relative SD; NA: not applicable.

Dissolution Medium and Standard Solutions

The dissolution medium was prepared by dissolving 47.6 g of potassium dihydrogen phosphate and 11.06 g of sodium hydroxide into 7 L of ultrapure water. The pH of the medium was adjusted within the range of 7.4 ± 0.05. The medium was stirred and heated to 45 °C with a magnetic stirrer and degassed for 5 minutes with a vacuum pump (pressure lower than 100 mbar).

To prepare salicylic acid stock solution, 20 mg of salicylic acid reference material was weighed and transferred into a 250-mL volumetric flask. About 1 mL of ethanol was used to dissolve the powder and diluted to 250 mL with dissolution medium.

To prepare salicylic acid working solution, 10 mL of the stock solution was transferred into a 50-mL volumetric flask and filled to volume with dissolution medium.

Dissolution Tests Phase I: Investigation of Variables Influencing Dissolution

The objectives of phase I were to 1) investigate the potential influence of major variables on dissolution results, and 2) determine a proper experimental condition for the reproducibility and repeatability assessments in phase II. Through preliminary experiments (data not shown), four parameters were initially determined as the independent variables: cell inner diameter (ID), flow rate, temperature, and tablet loading pattern. Other variables including the medium components, volumes, degassing methods, configurations of the flow-through cell apparatus, glass bead dosage, and pump pulse, were not investigated in this study.

DoE methodology was used to systematically study the contribution of the four selected variables in dissolution testing. DoE and data analysis (residual maximum likelihood [REML] method) were conducted with JMP 13 software (SAS Institute Inc., USA). The DoE was set as a customized design with the dissolution value of salicylic acid as dependent variable. For the four independent variables, cell ID was set as categorical variable with two levels (12 and 22.6 mm); flow rate was set as discrete variable with three levels (8, 16, and 32 mL/min); temperature was set as continuous variable with three levels (35, 37, and 39 °C), and tablet loading pattern was set as categorical variable with four levels (on tablet holder with glass beads [HWB], on tablet holder without glass beads [HWOB], on top of the glass bead bed [T], and embedded [E]). Considering the difficulty of parameter adjustment, tablet loading pattern was set as easy, while the others were set as difficult. The primary effects of individual variables and the quadratic interaction effects of the variable combination were analyzed for their correlation with the dependent variable. The matrix of the DoE consisted of 33 trials distributed in 11 blocks (supplemental material, Table S1). For each trial, the apparatus parameters were set properly referring to this matrix.

The dissolution tests were conducted on Sotax CE 7smart systems (firmware 2.40) coupled with a CP7-35 piston pump and C 615 fraction collector (SOTAX AG, Switzerland). The pump flow rate was verified to the specified value (based on flow rates used in preliminary experiments) before testing. Maximum deviation of the flow rate in all seven channels should be less than 2% to meet the verification criteria.

The four tablet loading patterns are illustrated in Figure 1. For the HWB pattern, the detailed operation was as follows. Place a ruby and one spoonful glass beads (internal diameter 1 mm) into the cell sequentially, then place one tablet onto the tablet holder, then assemble the GF/F filter membrane on top of the cell. The HWOB pattern was the same as HWB, except without glass beads. The T pattern was also like HWB, except that the tablet was placed on top of the glass bead bed instead of on tablet holder. For the E pattern, the tablet was first placed on top of one spoonful of glass bead, then the remaining space in the cell was filled with glass beads. The other parameters of the dissolution tests were kept identical with each trial, which included seven channels with 900 mL of dissolution medium per channel, closed-loop configuration, pump pulse 120 r/min, and 2.5 mL fractions collected at 10, 30, 60, 90, and 120 minutes.

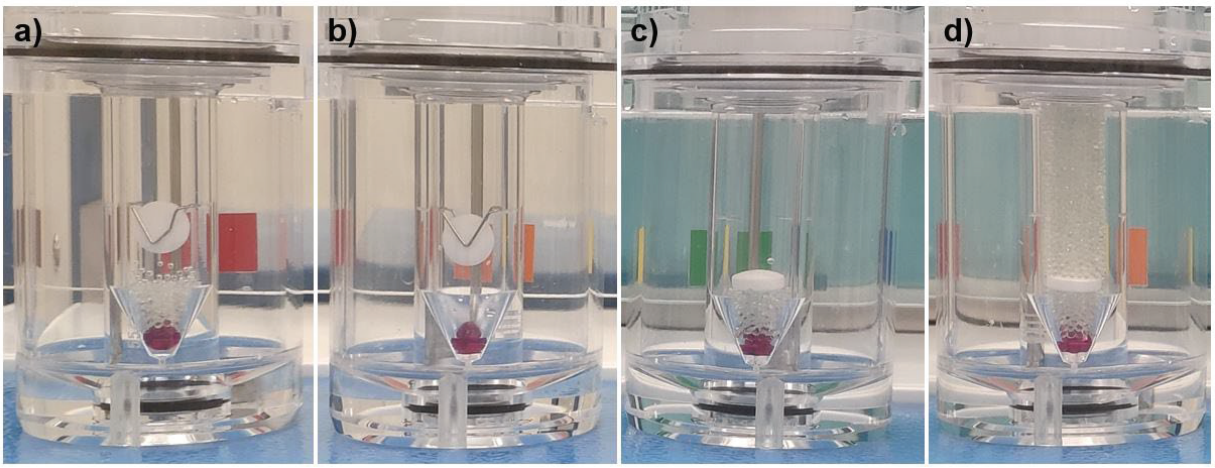

Figure 1. The tablet loading patterns: a) on tablet holder with glass beads (HWB); b) on tablet holder without glass beads (HWOB); c) on top of the glass bead bed (T); d) embedded (E).

Dissolution Tests Phase II: Repeatability and Reproducibility Assessment

The objectives of phase II were to 1) evaluate the feasibility of using salicylic acid tablets as reference standard in PVT for the flow-through cell apparatus; 2) investigate the repeatability and reproducibility of the dissolution tests; and 3) determine the preliminary acceptance criteria for the PVT. The dissolution tests were conducted in two test facilities. Four analysts and five assemblies (Sotax CE 7smart systems, manufacture years ranging from 2013–2021) were included in the phase II tests. The combination of one analyst and one assembly was called a collaborator. In this way, the data from one collaborator was achieved by the same analyst on the same assembly. There were five collaborators in total. The data from four collaborators were used to determine the preliminary acceptance criteria of PVT, and the fifth collaborator conducted a PVT with this acceptance criteria. All tests were conducted with identical conditions, as determined in phase I: 12 mm cell ID, 16 mL/min flow rate, 37 °C, HWB tablet loading pattern, 7-channels with 900 mL medium per channel, closed-loop configuration, pump pulse 120 r/min, and 2.5 mL fractions collected at 10, 30, 60, 90 and 120 minutes.

In this study, preliminary acceptance limits of single-stage and two-stage tests were established for the PVT of flow-through cell apparatus. The analytical methodology was similar with those for PVT of USP apparatus 1 and 2 (*11, 12, 15–17*). In detail, three variance components were estimated: inter-collaborator, inter-experiment, and residual (within experiment). The overall distribution pattern of percent dissolved values of salicylic acid tablets was plotted (supplemental material, Figure S1). Uneven tails for data distribution were observed, which were similar with the results of apparatus 1 and 2 (*11*). Thus, the natural log scale was employed to improve the symmetry of the distribution (converting normal distribution) of dissolved values (*12, 16*).

For the single-stage test, the preliminary acceptance limits were determined by the mean of percent dissolved values (log scale) with ± *t* SD, where *t* is the coefficient with 95% confidence and SD is the reproducibility standard deviation. For an assembly with seven channels (Sotax CE 7smart system), for example, two runs of seven tablets would be tested (14 tablets in total), and the preliminary acceptance limits would be:

$$exp\left(\bar{X} \pm t\sqrt{S_C^2 + \frac{S_E^2}{2} + \frac{S_R^2}{14}}\right) \qquad \text{Eq. 1}$$

In Eq. 1, exp represented for exponent, where the mean ($\bar{X}$) and variances (S^2) were estimated from repeatability and reproducibility assessment. The subscripts *C*, *E*, and *R* indicate inter-collaborator, inter-experiment, and residual variance components, respectively. In this study, *t* equaled 2.776 with 4 degrees of freedom in the SD of the mean. For the within-experiment variance in the log scale, the upper limit was found as $F \times S_R^2$, where *F* is the upper 5% limit of an *F*-distribution. In this study, *F* equals 1.933 with numerator degrees of freedom of 12 for a seven-channel assembly and denominator degrees of freedom of 55 within experiment. The coefficient of variation (%CV) in the original, percent-dissolved scale was achieved by transforming variances in the natural log scale with the lognormal formula:

$$\%CV = 100 \times \sqrt{exp(S^2) - 1} \qquad \text{Eq. 2}$$

To apply the single-stage test, two runs of experiments should be conducted, and the data of 14 tablets (7 tablets/run × 2 runs) would be evaluated against the preliminary acceptance limits of the single-stage test.

For the two-stage test, there were two preliminary acceptance limits, one for each stage. The estimation for stage 1 was similar to the single-stage test but used 80% confidence rather than 95% confidence, which would narrow the intervals (*17*). This stricter preliminary acceptance limit of stage 1 test would ensure the statistical power to evaluate the first run data in PVT. In the stage 2 of the two-stage test, the preliminary acceptance limit was determined to preserve the probabilities (95% confidence) of passing from the single-stage test. Thus, the data achieved from the stage 1 and 2 would be combined and be evaluated to get the preliminary acceptance limit of stage 2, of which the value should be the same as the one of the one-stage test.

Detection

UV-VIS spectrometry was used to determine the dissolved concentration of salicylic acid in the medium with two UV-VIS spectrometers: UV/VIS Excellence UV7 (Mettler-Toledo GmbH, Switzerland) with software version 3.0.1 and Cary 3500 UV-Vis Engine (Agilent Technologies, made in Malaysia) with Cary UV Workstation version 1.1.298. Each sample (2.5 mL) was diluted five times to 12.5 mL with blank dissolution medium, and their absorbances were measured at 296 nm in quartz cuvettes (10-mm light path).

RESULTS AND DISCUSSION

Feasibility Analysis of Using Salicylic Acid Tablets as Reference Standard

The dissolution mechanism of salicylic acid tablets is non-disintegration and erosion, which has been verified in dissolution tests with the basket and paddle apparatus (*19*). In this study, fractions at five time points (10, 30, 60, 90, and 120 mins) were collected, and their API concentrations were determined by spectrophotometry. These dissolution data were analyzed by linear regression with time as the independent variable. Excellent linearities were achieved for all 33 trials; 31 trials had correlation coefficients of 0.9911–0.9999 and the other two were 0.9742 and 0.9878. This indicated that dissolution of salicylic acid tablets represents the zero-order release mechanism in the flow-through cell apparatus, which is consistent with dissolution in the basket and paddle apparatus. Despite 33 trials with different conditions, this mechanism was not affected by the parameter adjustments from the flow-through cell apparatus. Therefore, salicylic acid tablets were sufficiently stable in physicochemical properties, and have the potential to be reference standard tablets in PVTs for the flow-through cell apparatus.

Fluctuations of dissolution data for the 33 trials were analyzed by calculating RSD. For the five time points, the RSD results were satisfactory, with median and third quartile RSD values of 2.7% and 4.9%, respectively. Only a few high RSD values were observed, which may result from unoptimized parameters in phase I for screening purposes and the small number of parallel experiments (n = 2). However, all RSD values at 90 min were less than 10% with no extreme values, which was relatively more stable. Considering the efficiency of the PVT method, 90 min was selected as key time point for subsequent analysis. These data are presented in supplemental material (Table S2–S4).

Parameters that Influenced Dissolution of Salicylic Acid

For DoE with the 33 trials, the dissolved values at 90 min were set as dependent variable, and the model was fit by the least squares REML method. The results of the fit analysis are shown in Figure 2, where the adjusted R^2 value is 0.99. This suggested that the model should be significant and have covered most of the main parameters that influenced the dissolution values.

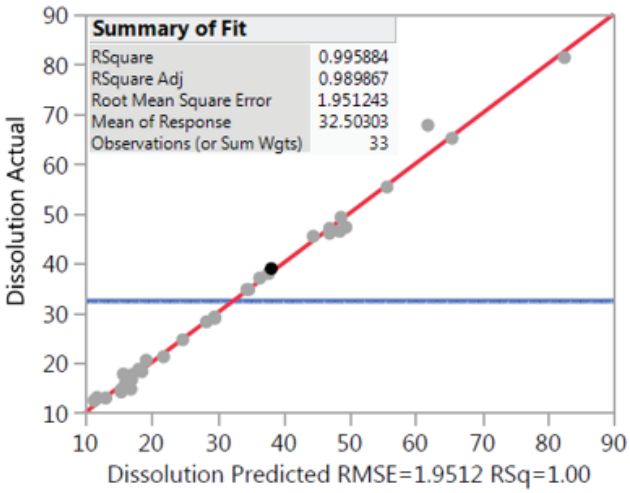

Figure 2. Mathematical model fitting results.

Table 2 shows the influences of the four individual parameters and their interactions. Three parameters and their paired interactions showed a significant difference ($p < 0.01$). Tablet loading pattern was the most important parameter influencing the dissolution. Flow rate and cell ID also had significant impact. Temperature, however, showed negligible effect on dissolution.

Table 2. Primary Effects of Individual Variables and Quadratic Interaction Effects

Source	LogWorth	p values
Tablet loading pattern	11.24	0.00000
Flow rate × tablet loading pattern	5.163	0.00001
Flow rate (range: 8–32 mL/min)	3.337	0.00046
Cell ID (range: 12–22.6 mm)	3.238	0.00058
Cell ID × tablet loading pattern	3.130	0.00074
Cell ID × flow rate	1.876	0.01331
Temperature (range: 35–39 °C)	0.997	0.10058
Flow rate × temperature	0.570	0.26909
Temperature × tablet loading pattern	0.178	0.66389
Cell ID × temperature	0.067	0.85684

ID: inner diameter.

Figure 3 illustrates the detailed trends of the four parameters. For tablet loading pattern, the E pattern had the highest dissolution value, T pattern had the middle value, and HWB and HWOB patterns had the lowest (similar) values. For flow rate, there was a proportional relationship with the dissolution value. For cell ID, 12 mm always had higher dissolution values than 22.6 mm. These three trends can be attributed to the zero-order release mechanism of salicylic acid in the flow-through cell apparatus, which was discussed above. Without disintegration, the erosion speed of the salicylic acid tablets was proportional to the volume flow rate. Under the same flow rate, the cell with the smaller ID and cross-sectional area produced higher linear velocity, which caused more turbulent erosion to the tablets. Similarly, the space filled with glass beads had even smaller cross-sectional area available for the flow to pass through, which led to much higher linear velocity. In E and T patterns, the spaces where the tablets were placed were totally and partly filled with glass beads, respectively. As for the HWB and HWOB patterns (with or without glass beads, respectively), the space where the tablets were placed was not filled with any glass beads. Therefore, the linear velocities decreased in the order of E, T, and HWB/HWOB, which produced the same trends in dissolution speed.

Preliminary Acceptance Criteria for PVT of Apparatus 4

In phase II, an experimental condition, which had proper percent dissolved values and small within-experiment variances, was selected for repeatability and reproducibility assessments to determine the preliminary acceptance criteria for the flow-through cell apparatus PVT. The within-experiment variances (data not shown) were smallest with the HWB pattern compared with other loading patterns. To keep the percent dissolved values of the flow-through cell apparatus comparable with those achieved with the basket and paddle apparatus, a combination of 12-mm ID cells and 16 mL/min flow rate were chosen. Therefore, the experimental condition was confirmed for phase II: tablets placed in HWB pattern, flow-through cells with 12 mm ID, flow rate of 16 mL/min, and temperature of 37 °C, and sample collected at 90 minutes. This experimental condition was not included in the 33 preliminary trials, its performance was calculated and predicted based on the above mathematical model established by JMP software. The estimated percent dissolved value under this condition was 22.2%, which is similar to the acceptance criteria for salicylic acid PVT tablets in the basket (21–26%) and paddle (20–26%) apparatus according to the *Chinese Pharmacopoeia* (*20*). This estimated value was compared with the experimental measurements to verify the fit of the mathematical model.

For the repeatability and reproducibility assessments, the geometric mean of dissolved values and variance components, corresponding to the parameters in Eq. 1, are listed in Table 3. The preliminary acceptance criteria for the flow-through cell apparatus PVT, calculated by Eq. 1 and listed in Table 4, included single-stage and two-stage testing. The predicted value of 22.2% by the mathematic model was within the preliminary acceptable criteria. The absolute error between the predicted value (22.2%) and experimental geometric mean (24.5%) was only 2.3%, which suggests that the mathematical model generated from DoE is a powerful tool for guidance and prediction of experiments.

Successful reproducibility was confirmed with data from the fifth collaborator. For the first run experiment (stage 1 of two stages), geometric mean dissolution values and %CV were 23.8% and 1.5%, respectively. These data satisfied the preliminary acceptance criteria (Table 4), so the second run experiment was not needed.

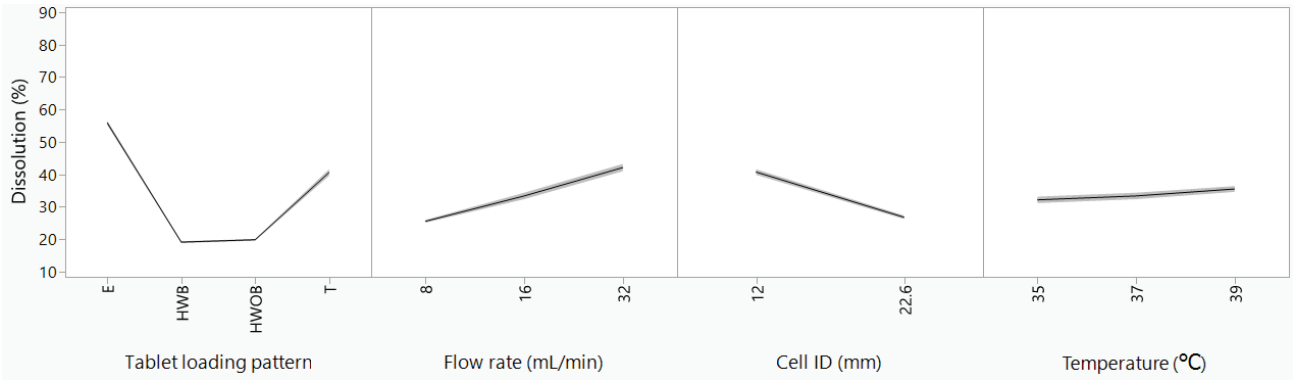

Figure 3. Influence of the four parameters on dissolution of salicylic acid tablets as predicted by the mathematical model. Tablet loading patterns are coded as HWB: on tablet holder with glass beads; HWOB: on tablet holder without glass beads; T: on top of the glass bead bed; E: embedded (see Fig. 1).

Table 3. Dissolved Values and Variance in Repeatability and Reproducibility Assessments

Dissolved value (geometric mean)		24.5
%CV	Inter-collaborator	2.6%
	Inter-experiment	0.9%
	Within experiment (residual)	2.0%

ID: inner diameter.

Table 4. Preliminary Acceptance Criteria in PVT for Flow-Through Cell Apparatus (7 Channels)

	SIngle Stage	1st stage of two stages	2nd stage of two stages
Lower limit of GM	22.7	23.5	22.7
Upper limit of GM	26.4	25.6	26.4
%CV Limit	2.8%	2.4%	2.8%

PVT: performance verification test; GM: geometric mean; CV: coefficient of variation.

Future collaborative studies should have larger coverage, involving laboratories from regulatory agencies, pharmaceutical companies, contract research organizations, and instrument manufacturers. The required number of laboratories participating in the collaborative study, taking variance into account, ISO Guide 21748 sets a minimum of 15 degrees of freedom for the laboratory (*15*, *21–23*).

CONCLUSION

In this two-phase study, salicylic acid tablets were used for development of the PVT for flow-through cell apparatus, which follows the same erosion and zero-order release mechanism as in the basket and paddle apparatus. Therefore, the salicylic acid tablet is a potential standard reference for the flow-through cell apparatus PVT. Phase I of this study identified that tablet loading pattern was the most important factor influencing dissolution, followed by flow rate and cell ID; however, temperature did not have a significant influence. Phase II determined preliminary acceptance criteria for the flow-through cell PVT with the following experimental conditions (based on phase 1 experiments): tablets placed on the tablet holder with glass beads, 12 mm cell ID, 16 mL/min flow rate, and 37 °C for 90 minutes. Repeatability and reproducibility assessment was confirmed by different analysts on various apparatus in two test facilities. This study established a preliminary acceptance limit for a dissolution PVT with the flow-through cell apparatus. More research is needed to investigate sensitivity of the salicylic acid tablet to operational parameters of the flow-through cell apparatus within a narrow range and with more collaborators.

SUPPLEMENTAL MATERIAL

Supplemental material available for this article may be requested by contacting the corresponding author.

DISCLOSURES

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Selection and Parameters Affecting Dissolution Media

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ABSTRACT

Dissolution of oral solid dosage forms refers to the process by which active pharmaceutical ingredient(s) are released from the dosage form into a liquid vehicle, called the dissolution medium. Dissolution is an essential test for the development and quality control of almost all dosage forms. The availability of the drug to release from the dosage form into the dissolution medium can be often linked to the availability of the drug for absorption and eventually for therapeutic action. Therefore, it is crucial to investigate the choice of dissolution media, especially in the case of poorly soluble drugs (BCS class 2 and 4). This article reviews the various parameters of dissolution media that influence drug release for research and development of pharmaceutical formulations, including temperature, pH, ionic strength, surfactant, enzymes, dissolved gas, hydrodynamics, viscosity, and the type of dissolution apparatus. Understanding the impact of these parameters will help in making a straightforward, realistic, and objective decision regarding the most effective dissolution medium.

KEYWORDS: biorelevant media, solubility, dissolution, Biopharmaceutical Classification System (BCS)

INTRODUCTION

Dissolution is the transformation process of a drug substance from a solid to a solution (i.e., mass transfer from the solid surface to the liquid phase) (*1*). The dissolution process demonstrates that the drug is being released from the product and is readily accessible in solution form for gastrointestinal (GI) absorption. The dissolution rate is determined by the amount of drug substance that goes into solution per unit of time under standard temperature, pH, and solvent composition conditions (*2*). The dissolution test is a pharmacopeial test to determine the extent and rate of drug release from solid oral dosage forms, such as immediate and sustained-release tablets and capsules (*3*, *4*).

In the early 19th century, dissolution studies were carried out to study the physicochemical properties of a substance. These studies set the basic laws for dissolution, which were later extended to different dosage forms. After it came into use for the development of dosage forms, several developments led to an understanding of various factors that affect bioavailability. Nowadays, much research is being done on dissolution because the drug release profile has great importance in the development of pharmaceutical products. Dissolution studies assist with selection of the drug, excipients, manufacturing process, and final dosage form to design a suitable formulation for in vivo studies. For example, a small change in the formulation may change the drug release profile of the developed formulation and thus, bioavailability. The drug release data obtained by use of different dissolution parameters may correlate with in vivo availability of the drug. In general, the parameters with the best correlation are used for developing the final drug release specifications. Dissolution tests are used to establish the in vitro-in vivo correlation (IVIVC) and develop clinically successful products in a short time with less cost. The results obtained from dissolution studies are analyzed with the help of certain mathematical formulas.

For immediate-release solid dosage forms, dissolution begins with disintegration of tablets or capsules into granules, which are further disintegrated into fine particles. This process continues in the dissolution medium, cumulatively leading to the drug in solution form (it may be in vitro or in vivo). In vivo, the drug in solution undergoes absorption and enters the blood, fluids, and tissues. Therefore, dissolution studies are important with respect to regulatory approval and commercial success of the dosage form. Dissolution studies are used to determine if the active ingredient is released as expected in the treatment location, if the drug meets established acceptance criteria, and if the formulation is stable over time.

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This review focuses on the impact of the parameters and selection of dissolution media for research and development of pharmaceutical formulations.

PARAMETERS OF DISSOLUTION MEDIA THAT AFFECT DRUG RELEASE

The selection criteria for dissolution media considers both physiological and physicochemical characteristics of the drug substance and formulation. The first stage in creating a discriminating dissolution method is pH solubility and stability profiling. To create a robust and repeatable dissolution procedure, the analyte must be stable in the dissolution medium to allow adequate time to complete the test. The choice of pH and buffered media is crucial in creating a sink environment for weakly soluble ionizable drugs that exhibit pH-dependent solubility. A surfactant may need to be added if the sink condition cannot be satisfied with the buffered medium alone (*5*). Hence, before the selection of dissolution media, one must be familiar with the parameters affecting it.

A sink condition is achieved when the concentration of drug in the dissolution medium is significantly lower than its solubility limit. When a sink condition is maintained, the concentration gradient between the undissolved drug in the tablet and the dissolved drug in the medium remains constant. Sink conditions in the dissolution medium more closely resemble the conditions in the gastrointestinal (GI) tract, where the drug is rapidly and effectively dissolved in a large volume of fluid, ensuring optimal bioavailability and absorption. Maintaining sink conditions is essential to ensure batch-to-batch consistency and predict how the drug will behave in the body for proper dosing and therapeutic efficacy. Sink conditions are affected by temperature, pH, ionic strength, surfactant, dissolved gases, hydrodynamics, viscosity, and dissolution apparatus. When choosing the composition of the dissolution media, the influence of these characteristics on the drug's solubility and stability must be considered (*6*).

Temperature

As the solubility of many drugs is temperature dependent, the drug release rate profile is significantly influenced by the temperature of the dissolution media. For oral dosage forms, 37 ± 0.5 °C is the permissible temperature for the dissolution media. Studies can be carried out by altering the media's temperature to evaluate the effect on drug release. Heng et al. examined the effects of environmental variables on the dissolution rate of amorphous and crystalline lurasidone hydrochloride (LH) (*7*). They observed that when the temperature of the dissolution medium increased, an increase in dissolution was observed for both the forms. This was attributed to the endothermic nature of LH dissolution. At corresponding temperatures, amorphous LH showed lower drug release than crystalline LH. The investigation revealed that amorphous LH converted to crystalline LH, resulting in a decrease in dissolution rate (*7*). Changes in temperature also affect the solubility and swelling index of many excipients like diluents, binders, and disintegrants, which influence the release of drug from the dosage form.

pH

The pH of the dissolution medium chosen is usually one that supports sink conditions. Knowledge of the acid dissociation constant (pKa), its impact on solubility, and ruggedness of the dissolution technique must all be considered (*8*). Kincl et al. estimated the impact of different factors on diclofenac sodium drug release, including the type of dissolution apparatus, rotation speed, pH, and ionic strength (*9*). The authors concluded that pH had a major impact on drug release, i.e., the release of active ingredients mostly depends on pH of the dissolution medium (*9*). If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the specified pH given in the individual monograph.

Ionic Strength

Ionic strength of the media is usually varied over a range of 0–0.4 M to simulate fed and fasted states and various physiological pH conditions in the GI tract. NaCl and KCl are some salts that are used in dissolution media to mimic biological fluids under fed and fasted conditions. Nashed et al. conducted experiments with various KCl concentrations and found that solubility was improved by alkaline ions like potassium, which led to an increase in the release rate (*10*). Also, increasing the ionic strength beyond a certain point eventually resulted in decreased dissolution efficiency by indicating the salting out of the polymer by the organic ions in the media, prolonging the drug release (*10*). Along with temperature, Heng et al. studied the dissolution profiles of crystalline and amorphous LH in 0.025, 0.05, and 0.1 M NaH_2PO_4 solutions (*7*). They found that increasing ionic strength slowed crystalline LH dissolution, as water molecules are attracted by salt ions, reducing interaction. Similar trends were seen with amorphous LH, but there was slower dissolution in buffer solutions with each concentration. Decreased dissolution in buffer solutions was attributed to the precipitation and gelation of amorphous LH (*7*).

Addition of Surfactants

The number of new drug candidates with poor solubility has been increasing. Surfactants can either be anionic, cationic, zwitterionic, or neutral, which can help enhance the solubility of the drug. It is preferable to use chemically well-defined surfactants, such as sodium dodecyl sulphate. Other utilized surfactants include polyoxyethylene 23 lauryl ether (Brij 35), polysorbates (Tween 20 or 80), and cetyltrimethylammonium bromide. The most commonly utilized chemicals are sodium dodecyl sulfate (SDS) and polysorbate 80 (Tween 80) (*11*, *12*). The reported concentration of SDS ranges from 0.01–3% (*13*).

The pH of the medium has less effect on dissolution for poorly water-soluble drugs (BCS class 2 and 4). For achieving higher solubility in the dissolution medium, a solubility enhancer (surfactant) can be added (*14*). The incorporation of different types of surfactants and levels can be of key importance for poorly soluble drugs (*15*). According to Dressman et al., poorly soluble drugs do not exhibit an IVIVC because they have limited solubility and need more surfactant to dissolve (*16*). To maintain the discriminatory power of the dissolution method, the concentration of the surfactant should be the lowest required to produce sink conditions and be supported by solubility data at 37 °C. Efentakis et al. studied the effect of surfactants (sodium lauryl sulfate, sodium taurocholate, cetylpyridinium chloride, cocamidopropyl betaine [CDB], and cetrimide) on drug release rates (*17*). They concluded that the drug release was rapid when the surfactant was more soluble due to the formation of pores or disruptions in the matrix (*17*).

Enzymes

Biorelevant media are fluids that are physiologically relevant and remarkably realistic approximations of the fluid found in the gut. These media are used to study the behavior of drugs and dosage forms in a laboratory to mimic the in vivo environment of the GI tract. Biorelevant media include fasted state simulated gastric fluid (FaSSGF), fed state simulated gastric fluid (FeSSGF), fasted state simulated intestinal fluid (FaSSIF), fed state simulated intestinal fluid (FeSSIF), fasted state simulated colonic fluid (FaSSCoF), and fed state simulated colonic fluid (FeSSCoF). (*18*). Surfactants, enzymes, and other substances found in the physiological environment are common components in biorelevant media. The most common enzymes in these media are pepsin, pancreatin, or papain. The concentration of enzymes, enzyme activity, and a pre-treatment procedure should be determined when the dissolution medium contains surfactant, or any other components suspected to inactivate the enzyme being used (*19*). Pennings et al. investigated the role of enzymes and found that dosage forms tested in media containing pancreatin or pepsin had improved dissolution performance of stressed hard gelatin capsules compared with deionized water or 0.1 N HCl (*20*).

Dissolved Gas

The dissolution profile can be affected by dissolved gases present in the medium. The dissolved gases can provide an abrasive force on the dosage form in the dissolution media. For example, air bubbles can cause the intact or disintegrated dosage form to float, spin, agglomerate, which can impact the drug release behavior (*21*). The air bubbles can act as a barrier to dissolution when present on the dosage unit or basket mesh. Heating the medium to 41 °C followed by filtration through a filter with porosity of 0.45 µm or less, room temperature filtration, sonication, and helium sparging are deaeration methods described in the *United States Pharmacopeia* (*USP*) (*22*). Transfer of deaerated dissolution medium to a jar and the rate of stirring with the paddle/ basket apparatus are the prime contributors of reaeration during dissolution. The importance of deaeration should be investigated by comparing the dissolution data with non-deaerated and deaerated mediums. However, because surfactant-containing dissolution media equilibrate quickly compared to aqueous media, the impact of dissolved gases is less of a problem. The reproducibility and quality of dissolution results increase after the dissolved gases reach equilibrium (*22*). A total dissolved gas pressure meter can be used for measuring dissolved gases.

Hydrodynamics

A good understanding of hydrodynamics is beneficial in the development of dissolution methods and formulations, as well as in complying with the pharmaceutical industry's quality requirements, such as batch-to-batch control. If the mass transfer mechanism is controlled by convection and/or diffusion, as is typically the case with poorly soluble compounds, hydrodynamics dominates the overall dissolution rate. The fundamentals of hydrodynamic laminar and turbulent flow are relevant to dissolution. Hydrodynamics is generally considered a variable for alteration in the creation of dissolution methods. Although a hydrodynamic environment can affect the rate of dissolution, hydrodynamic features of the dissolution conditions are normally not studied as part of dissolution testing, other than choosing an agitation rate and seeking to reduce fluctuation. Because dosage form placement and behavior (i.e., motion and disintegration) during a dissolution test might differ between apparatus, it

is challenging to evaluate the influence of hydrodynamics on dissolution between apparatus (*23*). Bai et al. used a computational-based model and experimental approach to investigate the effect of tablet position on dissolution rate and overall dissolution process (*24*). The enhanced hydrodynamics experienced by off-center tablets led to faster dissolution and disintegration of the tablet, resulting in a greater dissolved concentration of the drug during the early phase of the dissolution process (*24*).

Viscosity

The rate of transport of the reactants to and from the interface, which is determined by the transport process, is substantially slower than the interaction between the solid and the dissolution medium. Therefore, diffusion-controlled interactions are anticipated to decrease as viscosity increases. Elworthy and Lipscomb confirmed these findings by noting that at high surfactant concentrations, the viscosity of the dissolution medium increased significantly, thus slowing the dissolution rate of griseofulvin (*25*). When researching the effects of viscosity and solubilization on dissolution rate, Braun et al. discovered that the dissolution rate was inversely proportional to the viscosity (*26*). The viscosity of micellar solutions is raised by high polysorbate 80 concentrations to the extent that the dissolution rate is retarded even when overall solubility is markedly increased.

Dissolution Apparatus

The USP has seven different apparatus for dissolution testing; however, most tablets and capsules employ apparatus 1 or 2, popularly known as the basket and paddle, respectively. Wu et al. demonstrated the type of dissolution apparatus used to test tablet dissolution has an effect on the dissolution rate (*27*). The paddle method resulted in higher dissolution for class 1 drugs like theophylline, which has high dissolution and absorption, as well as class 2 drugs like naproxen, which has poor dissolution and high absorption. The paddle method provided faster dissolution rates than the basket method, and as rotational velocity increased, so did the drug release.

SELECTION OF DISSOLUTION MEDIA

Careful selection of a suitable dissolution medium is necessary in dissolution testing (*28*). The choice of dissolution medium is crucial for batch-to-batch quality testing, ensuring acceptable sink conditions are met. The task of finalizing the evaluation parameters comes after the dosage strength and intended release pattern for an oral solid dosage form are established. Thus, after understanding the parameters affecting the dissolution media, it is feasible to select the media. Most of the time, the active pharmaceutical ingredient (API) should dissolve in the fluid of the GI tract. Therefore, the location at which the drug is to be released for the drug product, chemical composition of the media in the GI tract, solubility in those media, as well as the overall time for a drug to be released from the product, should all be taken into consideration when choosing biorelevant dissolution media and conditions (*29*, *30*). The development of media over the years for determining solubility as well as dissolution and its applications in drug development was summed up by Bou-Chacra et al (*31*).

To evaluate the dissolution properties of oral formulations, media with a physiological pH range of 1.2–6.8 should be used (*32*). According to the percentage of drug release, the chosen dissolution media can be deemed satisfactory. Dissolution medium selection can be made according to the pharmacopeias, Biopharmaceutical Classification System (BCS), or U.S. Food and Drug Administration (FDA) database.

Pharmacopoeia

The dissolution media can be chosen using a number of pharmacopoeias, including the *Indian Pharmacopoeia*, *United States Pharmacopeia*, *British Pharmacopoeia*, and *European Pharmacopoeia*. These publications offer information on the unique monograph of each drug, depending on the dosage. They provide different dissolution media based on the drug's release profile. The choice of dissolution media for new drugs can be made using the pharmacopoeia's list of dissolution media for drugs in the same chemical class and dosage.

BCS Classification

A scientific framework for categorizing drug substances according to their aqueous solubility and intestinal permeability is known as the BCS. The BCS was created in 1995, and it has become the standard for regulating the bioequivalence of oral drug products. The BCS divides APIs into four classes based on solubility and permeability (*33*, *34*).

For drugs in classes 1 and 3, simple aqueous media such as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (with or without enzymes) are recommended. However, dissolution tests for classes 2 and 4 should be conducted in a biorelevant medium.

Most registered drugs are class 2 (high permeability, low solubility) or 4 (low permeability, low solubility) by the BCS (*34*, *35*). The oral absorption of BCS class 2 drugs is primarily limited by their solubility and/or dissolution

in the GI tract (*36, 37*). In such a scenario, it would be advantageous to have an in vitro dissolution test that could be utilized to predict in vivo behavior at different stages of formulation development. The rate-limiting step for the in vivo absorption of class 2 drugs is dissolution (*38*). Class 1 and 3 drugs display rapid or very rapid dissolution, and BCS provides for the waiver of in vivo bioavailability and bioequivalence testing for immediate-release solid dosage forms (*39*).

Fagerberg et al. tested 10 substances, including three bases and three acids with no net charge in the study pH range, for apparent solubility and dissolution rates of BCS class 2 drugs. In comparison to the corresponding blank buffers, most of the compounds demonstrated higher solubility and dissolution rates in FaSSIF and FeSSIF. Compounds with a neutral or positive charge were more soluble in FeSSIF compared to FaSSIF. Even though there were more solubilizing agents in FeSSIF than in FaSSIF, the acidic compounds still displayed a pH dependence (*40*).

Table 1 gives some examples of the development of dissolution profiles containing different media for dissolution of BCS class 2 drugs (*41–47*). The selection of dissolution media was primarily done based on solubility (*44*). The drug release profiles were then examined and the dissolution media were selected for the particular drug (*45–47*).

FDA Database

The selection of dissolution media can also be done by using data provided by the U.S. FDA. Information on a variety of media, including water or basic buffer solutions with varying pH levels and solutions with additional surfactants, organic solvents, and enzymes, is available in the FDA Dissolution Database. This database offers information that complies with suggestions made by the Division of Biopharmaceutics, Office of Pharmaceutical Quality for drug products without a dissolution test method in the *USP* (*48*). Along with the dissolution medium, the FDA database also provides the dosage form, USP apparatus, speed in rpm, and volume of the media for drugs (*13*). The database provides information specific to the drug and its dosage form, and it is independent of the variables such as excipients used, size, shape, etc. of the product.

CONCLUSIONS

The administration of medicine is necessary for the treatment of disease, and the dissolution of solid dosage forms is essential for evaluating the distribution of APIs. Thus, in dissolution testing, selection of an appropriate and effective dissolution medium is critical. The review is focused on the selection of a dissolution medium for correlating the in vitro and in vivo performance of the drug. Different dissolution media have different effects on the solubility of the dosage form. Temperature, pH, ionic strength, surfactant, enzymes, dissolved gas, hydrodynamics, viscosity, and the type of dissolution apparatus can affect the drug release profile. Pharmacopeias, BCS classification, and the FDA dissolution method database provide helpful information on drug dissolution specifications to aid in selecting a medium based on the drug's dosage form.

Table 1: Compilation of Case Studies on Dissolution for BCS Class 2 Drugs

No.	Summary of Case Studies
1	The dissolution profile of celecoxib tablets was studied by Babu et al. in seven different dissolution media: a) water, b) 0.1 N HCl (pH 1.2), c) phosphate buffer (pH 7.4), d) phosphate buffer (pH 8.0), e) methanol in water (5%, 10% v/v), f) Tween 80 in water (0.25%, 0.5%, 1% v/v), and g) SLS in water (0.25%, 0.5%, 1%, 1.5%, 2% w/v). The results suggested that 2% w/v SLS in water had the best correlation with in vivo studies (*41*).
2	Dissolution profile of aceclofenac was studied by Soni et al. using dissolution media: a) double distilled (DD) water, b) SLS in DD water (0.6%, 0.8%, 1%, 1.5%, 2% w/v), c) Tween 80 in DD water (0.2%, 0.5%, 1%, 2% v/v), d) 0.1 N HCl (pH 1.2), e) acetate buffer pH 4.5, f) phosphate buffer pH 6.8. The results suggested pH 6.8 phosphate buffer was satisfactory (*42*).
3	The dissolution profile of glipizide was studied by Mandal et al. using dissolution media: a) water, b) 0.1 N HCl (pH 1.2), c) acetate buffer (pH 4.5), d) methanol in water (5%, 10% v/v), e) phosphate buffer (pH 6.8, 7.2), f) SLS in water (0.5%, 0.75%, 1%, 2%, 3%, 4% w/v SLS in water, g) SLS in phosphate buffer (pH 6.8) (0.5%, 0.75%, 1%, 2%, 3%, 4% w/v), h) Tween 80 in water (0.5%, 0.75%, 1%, 2%, 3%, 4% v/v), i) Tween 80 in phosphate buffer (pH 6.8) 0.75% v/v. Satisfactory results were found with 0.75% w/v SLS in phosphate buffer pH 6.8 (*43*).
4	The dissolution profile of gliclazide was studied by Priya et al. using dissolution media: a) 0.1 N HCl pH 1.2, b) acetate buffer pH 4.5, c) distilled water pH 7.0, and d) phosphate buffer pH 7.4. The results suggested pH 7.4 phosphate buffer was satisfactory. Also, more discrimination in the dissolution profile was observed in 0.1 N HCl (*45*).
5	The dissolution profile of satranidazole was studied by Pawar et al. using different dissolution media: a) 0.1 N HCl (pH 1.2), b) 0.01 N HCl (pH 2.1), c) acetate buffer (pH 4.5), d) phosphate buffer (pH 6.8), e) phosphate buffer (pH 7.4), f) distilled water. The results suggested 0.1N HCl was satisfactory (*46*).
6	The dissolution profile of valdecoxib was studied by Subramanian et al with different dissolution profiles: a) water, b) 0.1N HCl, c) SLS (0.6%, 0.8%, 1.0%, 1.5%, 2.0% w/v), d) pH 7.4, e) Tween 80 in water (0.5%, 1% v/v), f) methanol in water (5%, 10% v/v). The results suggested 0.6% w/v SLS in water was satisfactory (*47*).

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Highlights from the 2023 AAPS 360 Annual Meeting – In Vitro Release and Dissolution

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INTRODUCTION

The American Association of Pharmaceutical Scientists (AAPS) successfully held its PharmSci 360 Annual Meeting and Exposition event on October 22–25, 2023, at the Orange County Convention Center in Orlando, FL. This year's meeting was held entirely in-person and did not include a hybrid element, allowing pharmaceutical scientists from around the world to convene in a physical setting. This was the first complete return to in-person annual meeting event post-pandemic among the pharmaceutical scientists of AAPS.

The fully in-person event facilitated a productive In-Vitro Release and Dissolution Testing (IVRDT) Community meeting, which was successfully led by Jie Shen, the community Chair, and Sanjaykumar Patel, the Chair-Elect. During the meeting, they highlighted the accomplishments of 2023 and outlined potential plans for 2024. The interactive nature of the session made it appealing to participants and aided in generating ideas and possible topics for community events in 2024.

In 2023, the IVRDT community within the AAPS achieved several notable accomplishments and collaborations. The community organized two AAPS-hosted webinars, namely "New USP Dissolution Performance Verification Standard: What, Where, and When" and "Titanium Dioxide Free Drug Products: Challenges During Drug Product Development." Both webinars attracted a substantial audience and featured highly interactive question and answer sessions, enhancing participant engagement.

The IVRDT community collaborated with the Society of Pharmaceutical Dissolution Sciences (SPDS) - US Chapter to organize two additional webinars. These webinars focused on the Dissolution of Complex Formulations and Dissolution for an Inhaled Product. These collaborative efforts fostered knowledge sharing and exchange within the dissolution sciences field, both within and outside of the AAPS organization.

In February 2023, the IVRDT community cooperated with the University of Philippines Manila to organize an outreach workshop on dissolution testing-related topics. The workshop received a positive response, indicating its value in disseminating knowledge and promoting engagement in the field.

During the AAPS 360 annual event, the IVRDT community proposed and presented the need for harmonization and the value of small-volume vessels. Ishai Nir led a rapid-fire presentation advocating for the use of small-volume vessels. This initiative aimed to address a pertinent issue in the field and stimulate discussions around the topic.

These accomplishments and collaborations signify the active involvement and contribution of the IVRDT community within the AAPS organization and the broader pharmaceutical science community.

One of the IVRDT community's most significant accomplishments was the nomination of Ms. Vivian A. Gray for the AAPS Distinguished Service Award. Her nomination was widely regarded as "ideal recipient," with unanimous agreement that she perfectly exemplified the award's description of an individual who has "contributed significantly and consistently over a long period to benefit AAPS in achieving its mission." Ms. Gray's notable contributions to AAPS and the field at large include her involvement in

Vivian A. Gray

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organizing programs, participating in expert panels at USP, and publishing and presenting extensively. Vivian helped organize and participate in many overseas workshops that included many speakers from the AAPS IVRDT Community. Her expertise and stature in the field were highlighted by her numerous invited talks, such as the recent invitation from the USP to provide an overview of the field to their Expert Panel. The IVRDT community took great pride in witnessing her well-deserved reception of the award.

Patrick J. Sinko (2023 AAPS President) and Doodipala Samba Reddy (2023 AAPS Awards Committee Chair) presented the Distinguished Service Award to Vivian A. Gray.

During the community meeting at the AAPS 360 annual event, the IVRDT community leadership team actively collected and compiled feedback to determine the focus areas for future events and proposals for the 2024 AAPS 360 annual meeting. The selected topics put forth for consideration included biorelevant/biopredictive dissolution, release and dissolution methods for nanomedicines, the current regulatory expectations of the quality control method, and the dissolution of complex formulations, including long-acting injectables. The meeting proved to be highly successful, fostering scientific engagement within AAPS and reinforcing the commitment to advancing dissolution science with the aim of achieving another fruitful year in 2024.

Below is a summary of the key presentations that were deemed vital during the community meeting at AAPS 360.

SYMPOSIUM: ACCELERATING THE DRUG DEVELOPMENT PROCESS THROUGH FORMULATION AND DELIVERY STRATEGIES

In the symposium, Dr. Shawn Zhang from DigiM delivered an informative presentation entitled “Novel Analytical Imaging and Dissolution Modeling.” This talk centered around novel methodologies that employing imaging, artificial intelligence (AI), and in silico modeling to accelerate the formulation development of complex formulations. The presentation pointed out the need and importance of understanding the internal microstructures to maintain the quality and performance of drug products. The presentation highlighted a wide range of significant microstructural attributes, from API size distribution to the spatial arrangement of excipients, which can be quantified and contribute to a quality-by-design approach. The use of imaging techniques was particularly emphasized, which can facilitate the vast array of formulation techniques and the library of parameters ideally suited for studies.

The presentation included the capability of DigiM, which consists of a suite of high-resolution imaging techniques, AI analysis, and in silico dissolution models to transform drug products and intermediates into a library of reusable digital twins. The quantified critical quality attributes (CQAs) and verified in silico models can be developed into mechanistic and predictive formulation via microstructure digital twins, which are integral to drug product understanding. This presentation showcased examples of AI-powered transformation applied in the formulation development of complex oral solid dosage forms, controlled release products, and nanocarriers. Additionally, Dr. Zhang discussed dissolution results on long-acting, diffusion-controlled dissolution results with polymer degradation modifications, and a new particle intrinsic dissolution model. The application of an image data management and microstructure engineering platform powered by generative AI was discussed in contexts of drug development and regulatory support.

Dr. Zhang's presentation provided valuable insights into the innovative application of analytical imaging and dissolution modeling, showcasing their potential to significantly enhance formulation development processes for complex drug products.

SUB-SCIENTIFIC TRACK: ADVANCED MODELLING AND PREDICTIVE APPROACHES IN DRUG DEVELOPMENT, MANUFACTURING, AND ANALYSIS

In this session, three in vitro release and dissolution-related presentations were provided by Mr. Ishai Nir, Dr. Hyunho Kang, and Dr. Devin Janai Swiner, respectively.

Firstly, Ishai Nir, representing the Instrumentation Subgroup of the In Vitro Release and Dissolution Testing Community, presented the Rapid Fire “Non-compendial

small volume dissolution for early-stage formulation model development."

This Rapid Fire talk began by outlining the unique challenges of optimizing more varied and complex new formulations in early-stage development. This work increasingly relies on modeling and other indirect techniques. The need for reference data to support these becomes a more pressing challenge. However, with limited material at these early stages, tests such as dissolution at standard compendial volumes are often impractical.

Nir introduced the array of commercially available non-compendial small-volume dissolution testing solutions. He pointed out that these, along with a desire to harmonize with the Chinese Pharmacopeia, which explicitly defines one such setup, has led the USP to launch a program to review some of these solutions for what they dubbed "Reduced Volume Dissolution" for possible inclusion in the General Chapters.

Nir then addressed one of the principal questions regarding this approach: the ability to correlate results derived from these non-compendial methods to future conventional dissolution studies. He presented data published by Prof. Piero Armenante's group at the New Jersey Institute of Technology, including CFD modeling and experimentally measured results. These demonstrated that scaling of only one setup parameter - agitation speed - generated data exhibiting a very high correlation of dissolution rate predictions between full scale and these small or reduced volume setups. The latter's advantage is the ability to run more studies with the same amount of material as conventional dissolution.

To conclude the talk, Nir proffered that the use of these small/reduced volume surrogate testing in early-stage development offers a solution to testing limitations due to the lack of availability of suitable amounts of test material and minimizes the cost and complexity for some of these studies that require "exotic" biorelevant media. Small/reduced volume dissolution testing can also continue to play a role in final dissolution methods in cases where the analytical method may have an issue with sensitivity due to a very low API dose or the desire to develop more discriminatory methods.

Finally, he summarized the talk with the critical observations that small/reduced volume dissolution is already an essential part of the modern performance testing portfolio because it is easily and reproducibly accomplished using existing baths and commercially available accessories while offering very similar dissolution profiles to complete scale testing with only a slight adjustment of agitation rate. Hopefully, these advantages will lead to the USP and other pharmacopeias, including harmonizing the *ChP* 250-mL option and other commercially available small/reduced volume dissolution setups.

Secondly, Dr. Hyunho Kang presented "Evaluation of Predicting Long-Term Release Rate of the Islatravir Implant." The talk began with information on long-acting implantable formulation with Islatravir, the product's general release dissolution behavior, and the strategy for collecting in-vitro release profiles using apparatus 7. It was emphasized during his presentation that due to the implant's targeted long-term release behavior, a significant amount of effort and duration is required to collect the real-time release profiles of the product. To overcome this limitation, an accelerated dissolution method can be critical to developing the formulation and predicting its release profile in the long term so that a proper evaluation can be performed on the materials before introducing the products to clinical trials and commercial areas.

He discussed that developing an accelerated in vitro release (Acc-IVR) method needs to consider many factors. The polymeric implant is sensitive to environmental conditions both in chemical and physical ways, which can quickly impact the dissolution, and a slight change in formulation composition can either accelerate or slow down the release. Furthermore, as the drug is released from the implant, a gradual depletion could cause a deviation from the previous release behavior of the implant. He highlighted that when the method is developed, it is critical to ensure that the correlation between the real-time in-vitro release (RT-IVR) and Acc-IVR can be acquired by accelerating the release but have very minimal or no effect on other characteristics of the materials being tested during in-vitro release.

The presentation introduced the Acc-IVR method for the product. Several case studies were also provided, where the RT-IVR data from multiple batches with varied potencies, which was acquired for more than a year, was compared to Acc-IVR data to evaluate the prediction capacity. Further, the driving force of this accelerated method and its relationship to the prediction modeling equation was investigated for better understanding, further development of the technique, and expanding its potential to apply to other implant drug products with varied formulations and other characteristics.

Finally, Dr. Devin Janai Swiner presented "Using Surface Dissolution Imaging to Understand the Mechanism of Weakly Basic Drug Solubility in Enabled Conventional Oral Formulations." The talk centered around the current challenges in formulation development of weak base pharmaceutical compounds, emphasizing additional risks for compounds with pH-dependent solubility. Drug performance of traditional strategies, such as amorphous solid dispersions (ASDs), were compared to an "enhanced conventional formulation," which incorporates small organic acid and polymer in the tablet blend, with the observation that high levels of acids can increase weak base solubility with the polymer sustaining supersaturation in two-stage biorelevant dissolution. Surface dissolution imaging technology was used to probe the solid-liquid interface and intrinsic dissolution rates of these formulations, showing how drug releases enhance conventional compacts and, in turn, increase the solubility.

Pictures of IVRDT community meeting.

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New USP Dissolution Performance Verification Standard: What, Where, and When

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INTRODUCTION

On April 6, 2023, the United States Pharmacopeia (USP) presented a webinar entitled "New USP Dissolution Performance Verification Standard: What, Where, and When." The webinar was sponsored by the American Association of Pharmaceutical Scientists (AAPS) and AAPS In Vitro Release and Dissolution Testing (IVRDT) Community and was led by Mark Liddell (USP). The webinar aimed to provide an overview of the introduction of the new USP Dissolution Performance Verification Standard – Prednisone RS (DPVS – Prednisone) for use in performance verification tests (PVT), highlight associated revisions of the *USP* General Chapter (GC) <711> Dissolution, and reviews some frequently asked questions (*1*). This article summarizes the webinar content, including responses to frequently asked questions and points for consideration.

WHY A NEW PVT REFERENCE STANDARD?

The design and introduction of new refence standard material was motivated by discussion and feedback received from various USP stakeholders collected over many years while the previous formulation of the 10 mg USP Prednisone Tablet RS was available to the market. The reformulation and redesign of the new tablet is part of the USP's commitment to continuous improvement of its products and services.

WHAT IS THE NEW USP DISSOLUTION PERFORMANCE VERIFICATION STANDARD (DPVS)?

A target product profile for the new DPVS – Prednisone tablet was developed based on challenges with the previous USP Prednisone Tablet RS formulation. The following four targets were used to improve on the existing formulation: 1) the formulation should be sensitive to changes in the setup and operational parameters of typical USP apparatus 1 and 2 dissolution tests (e.g., vessel centering, rotation speed, paddle/basket height, vessel geometry, basket quality, etc.); 2) the formulation should not be over-sensitive to dissolved gases in the media; 3) decrease intra-run variability for apparatus 1 and 2 dissolution experiments; and 4) the formulation should be physically and chemically stable over the shelf-life of the product.

The starting point for the redesign of the new formulation was rooted in basic understanding of the hydrodynamics in apparatus 1 and 2, which led to a redesign of the shape and size of the PVT tablet. It is commonly understood that directly beneath the paddle there exists a region of low fluid velocity sometimes referred to as a "dead zone." It was thought that increasing the mass and size and changing the shape of the existing tablet would promote more consistent placement of the dosage form in the paddle apparatus and may also benefit the performance of the basket apparatus. Feedback from users indicated that the previous tablet would sometimes float to the top of the rotating basket when the basket was lowered into the dissolution media. In apparatus 2 experiments, the positioning of the tablet at the bottom center of the vessel would vary based how the tablet was introduced to the vessel at the start of the dissolution experiment. The previous tablet was a typical round, bi-convex tablet having a mass of 222 mg (total weight with 10 mg of prednisone). The new tablet shape is a modified sphere with a total weight of 350 mg (with 10 mg of prednisone), as shown in Figure 1A. Changing the mass and shape of the tablet led to more consistent placement of the tablet in both the basket and paddle apparatus.

In addition to changes in the formulation, a new packaging configuration has been used to protect the individual blister cards containing DPVS – Prednisone tablets from moisture (Fig. 1B). An aluminum sachet is used to protect each individual blister card, which contains six tablets

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per card. Stability tests were conducted under accelerated (40 °C, 75% relative humidity [RH]) and long-term (25 °C, 60% RH) conditions, and the blister cards stored in aluminum sachets were stable throughout the period of testing. Throughout the stability studies, the tablets were sensitive to changes in setup and operational parameters that were evaluated as part of the product development.

A B

*Figure 1. Photograph of the new United States Pharmacopeia dissolution performance verification standard - Prednisone RS tablets (DPVS - Prednisone) (**A**) and push-through blister packaging configuration (**B**).*

At each step of re-designing the formulation, whether selecting the formulation components or compression and manufacturing parameters for the new formulation, a set of three types of dissolution experiments were conducted to evaluate the sensitivity of the potential product candidates to different dissolution conditions. The first set of experiments were referred to as baseline experiments. In these experiments, the dissolution apparatus was configured to minimize any deviation in the standard setup/operational parameters (vessel centering, basket/paddle height, rotation speed, degassed media, etc.). In the second set of experiments, non-degassed media was used with the same dissolution system as the baseline experiments. The third set of experiments was referred to as a 'perturbed' system – degassed media was used with specific setup and operational parameters adjusted to the edge of specification limits allowed according to GC <711> and the USP Dissolution Toolkit ("USP Guideline on Procedures for Mechanical Calibration and Performance Verification Test; Apparatus 1 and Apparatus 2") (1–3). These three dissolution experiments were run for each candidate formulation, and each time, the manufacturing parameters were altered. The selection criteria for moving a candidate forward were two-fold: 1) low intra-experimental variability and 2) a significant difference observed between the perturbed experiment and baseline and non-degassed experiments. Ultimately, a single formulation was selected that satisfied the above experimental conditions for both apparatus 1 and 2.

Characteristics of the final DPVS – Prednisone (lot F161Y0) formulation compared to the previous USP Prednisone Tablets RS are shown in Table 1. The decrease in intra-experimental variability was most significant for experiments with Apparatus 1 (basket). A modest decrease in the variability using Apparatus 2 (paddle) was also observed.

Table 1. Comparison of PVT Acceptance Criteria for Dissolution Systems with Six Positions Using Old and New Prednisone Reference Standard (RS) Tablets

USP Apparatus	Dissolution Test Stage	Prednisone RS (old formulation)		DPVS - Prednisone (lot F161Y0)	
		GM (% Dissolved)	%CV	GM (% Dissolved)	%CV
1 (basket)	Single stage	47–76	16	81–91	4.6
	Stage 1 of 2	51–70	12	83–89	3.4
2 (paddle)	Single stage	27–37	8.3	46–58	6.2
	Stage 1 of 2	28–35	6.2	48–56	4.6

PVT: performance verification test; GM: geometric mean; CV: coefficient of variation.

WHEN DID THE TRANSITION TO THE NEW DPVS – PREDNISONE OCCUR?

The transition to DPVS – Prednisone for use in the PVT requires revision of GC <711> and making the physical reference standard available in the USP product catalog. Stakeholders became aware of the new PVT reference standard when the Initial Notice of Intent to Revise (NITR) GC <711> was posted on Oct 29, 2021, which was updated on Jan 28, 2022. An Interim Revision Announcement (IRA) was posted on Sept 1, 2022, with a public comment period that ended on Jan 31, 2023. The revised GC <711> with DPVS – Prednisone became official on May 1, 2023 (*1*). From this point forward, DPVS – Prednisone is the only reference standard to be used in the PVT to demonstrate apparatus suitability for apparatus 1 and 2.

WHERE TO FIND MORE INFORMATION

The following resources are currently available for readers who would like more information about new USP DPVS – Prednisone tablets:

- General information regarding the PVT procedure: www.usp.org/small-molecules/pvt
- Information about the product: www.usp.org/dissolution

DPVS – Prednisone has been available in the USP catalogue since January 2023. Additional information and answers to frequently asked questions not covered in this report are available in the USP online store: store.usp.org/product/1222818.

QUESTIONS AND ANSWERS

As part of the webinar, commonly asked questions as well

as questions received from the live audience and their answers were presented. A summary of these questions and answers follows.

Note: the answers provided here have been abbreviated for publication and are the opinions and interpretations of the authors. These answers are not necessarily the official viewpoints of the USP.

Frequently Asked Question Related to the Transition to DPVS – Prednisone

Q. Will the old formulation of USP Prednisone Tablets RS be discontinued?

A. Yes, the USP Prednisone Tablets RS were discontinued along with the official revision of GC <711>, which indicates that the new DPVS – Prednisone tablet became official on May 1, 2023 (*1*). Therefore, the USP Prednisone Tablet RS is no longer valid for use in PVT as of this official date (May 1, 2023), even though the PVT tablets had a valid use date of July 31, 2023 on the label. The label is incorrect.

Q. Is a PVT performed before the revision to GC <711> still valid after the revision becomes official on May 1, 2023?

A. Yes, the chapter revision will not require laboratories to recalibrate an instrument qualified using USP Prednisone Tablets RS in the PVT before the official date. After May 1, 2023, the new DPVS – Prednisone tablet must be used to requalify apparatus 1 or 2 according to the updated GC <711> (*1*).

Q. Will there be significant changes to the mechanical and PVT processes with the introduction of DPVS – Prednisone?

A. No. Other than minor changes in the handling and storage conditions for the DPVS – Prednisone tablets, the mechanical calibration procedure prior to conducting the PVT, including standard preparation procedures, remains the same. For example, the new product has a push-through backing on the blister package, so there is no need to peel the backing off.

Q. Will the USP provide guidance documents and resources like the USP Dissolution Toolkit to assist with mechanical and PVT calibration with the new DPVS – Prednisone tablets?

A. Yes, the updated guideline was made available in March 2023 on the USP website (see www.usp.org/pvt), along with numerous video resources specific to DPVS – Prednisone tablets (*3*).

Attendee Questions During the AAPS/USP DVPS Workshop

Q. Has USP demonstrated a correlation between failing commercial batches and failing DPVS results?

A. Not currently; however, it is a research objective that USP intends to pursue. Some may argue that "the USP Prednisone Tablet is quite sensitive; however, my product is not as sensitive." It is important to note here that operational characteristics of a dissolution system that is not passing the PVT may be a result of perturbations within the dissolution apparatus that tend to increase the dissolution results. The reassurance here is that once the apparatus has passed stringent acceptance criteria for a sensitive product, then it should be sufficient to evaluate commercial batches, whether sensitive or not.

Q. What happens if a commercial lot passes dissolution acceptance criteria at initial release, then later fails with a dissolution apparatus that passes PVT acceptance criteria using DPVS – Prednisone?

A. From a USP perspective, if an apparatus passes with the new DPVS, it meets the compliance requirement according to GC <711>. Issues with conformance of the commercial product to acceptance criteria may be more of a compliance question for the U.S. Food and Drug Administration.

Q. Does the new DPVS use the same stage 1 and 2 paradigm? Is it still necessary to decide which approach to use before testing, as with the previous PVT (i.e., do you declare whether you'll use 12 or 6 units for testing)?

A. Yes, the same paradigm is used. This approach was adopted in 2010 when USP changed acceptance criteria to be based on geometric mean and coefficient of variation (CV) (2). Single-stage testing with 12 units (i.e., six units tested back-to-back) gets maximum use from the GM and CV acceptance criteria ranges. In contrast, two-stage testing (with 6 units in stage 1 and 6 more units in stage 2, if required) has tighter initial acceptance criteria in stage 1, and slightly tighter criteria in stage 2, compared with single-stage testing. USP resources are available to explain the statistical reasoning for stage testing by statistician, Walter Hauck, published in 2011 (*4*).

Q. Can we anticipate changes to DPVS formulation stability, such as a change in acceptance criteria, which had happened in previous formulations of the previous Prednisone PVT tablets?

A. Controlled stability studies were performed with accelerated and long-term conditions, demonstrating stability of the dissolution values and sensitivity to perturbations over time. As with all new USP standards, we conduct constant performance monitoring using products stored at the USP facility, and with this DPVS, the performance and test results have been consistent throughout the monitoring period. No changes are anticipated.

Q. Do we push the DPVS tablets through the foil on the blister package, because it was noticed there is no tab to pull back the aluminum on the blister pack?

A. Yes, the tablets are meant to be pushed through the backing of the blister package.

Q. What is the difference between the "USP Guideline on

Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and 2" and the older version of the USP Dissolution Toolkit (*2*, *3*)?

A. Mostly subtle changes were made to some of the methods used in the mechanical calibration procedures, and the PVT procedure was updated to include the DPVS – Prednisone product.

Q. Regarding reformulation of the product, because the new product is heavier, does this mean that there is more excipient present or does this simply mean that the tablet has higher density compared to the old formulation?

A. Both factors, more excipients and an increase in tablet hardness, likely contribute to the increased mass of the new formulation.

Q. Is degassing of the dissolution media as critical with the new formulation? If so, is there a recommended method for degassing the dissolution media?

A. The degassing method is still in the "USP Guideline on Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and 2" document, and videos describing the USP degassing method are available at the PVT website (www.usp.org/small-molecules/pvt) (*3*). As part of the transition process, collaborative studies were conducted with both the old and new formulations. The test procedure was the same for both products; hence, degassing was required for both. By extension, the new product requires media degassing as part of the experimental setup. Further studies will be conducted by USP to understand the impact of media degassing relative to the impact of other operational and setup parameters for the dissolution apparatus.

Q. Has there been studies of DPVS – Prednisone with either the 2-L vessels or small-volume vessels?

A. USP has conducted studies with reduced volumes, specifically with small-volume vessels that meet the requirements of the *Chinese Pharmacopeia*, but not with large-volume vessels. Further studies will be conducted by USP to investigate the impact of changes in volume on the dissolution of DPVS – Prednisone.

Q. Has any testing of the new DPVS – Prednisone formulation been done in apex vessels?

A. There is an active study to characterize apex vessels. After characterization of the apex vessels, studies will be conducted using the new DPVS – Prednisone formulation. In development of the new formulation, standard 1-L vessels were used for typical apparatus 1 and 2 dissolution testing.

Q. Because DPVS – Prednisone tablets are in the new sachet packaging configuration, what storage conditions are recommended?

A. Like all USP reference standards, the user should store the standard according to the instructions on the label. The old formulation of USP Prednisone Tablets RS required storage in dry conditions (not more than 40% RH at room temperature). The new DPVS – Prednisone formulation requires storage at controlled room temperature.

Q. Can autosampling be used with DPVS – Prednisone instead of manual sampling?

A. When the collaborative studies were conducted, manual sampling was required as part of the test protocol. The specification ranges shown on the product certificate are based on a manual sampling procedure. As with any modification to a procedure, it is incumbent on the end user to validate autosampling against the manual sampling method.

SUMMARY

The aim of this webinar was to provide information to dissolution practitioners regarding changes to *USP* GC <711> related to the introduction of a new reference standard to be used to demonstrate apparatus suitability for apparatus 1 and 2. The new USP DPVS - Prednisone tablets have been reformulated and redesigned to address concerns about variability, sensitivity, and stability. As of May 1, 2023, DPVS – Prednisone is the only reference standard to be used in the PVT for apparatus 1 and 2.

To provide feedback on DPVS - Prednisone, complete the survey at the following link: uspta.qualtrics.com/jfe/form/SV_b2S249T6JSVeemG?Source=DisTechArticleML.

DISCLOSURES

This USP webinar was sponsored by the American Association of Pharmaceutical Scientists and AAPS In Vitro Release and Dissolution Testing Community. Mark Liddell is a paid employee of the USP. The other authors have no conflicts of interest.

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Share your feedback!
Take a short survey about the new PVT standard, DPVS-Prednisone, by following the QR code or the link: https://go.usp.org/DPVS-Survey
Learn more at www.usp.org/dissolution
The standard of trust
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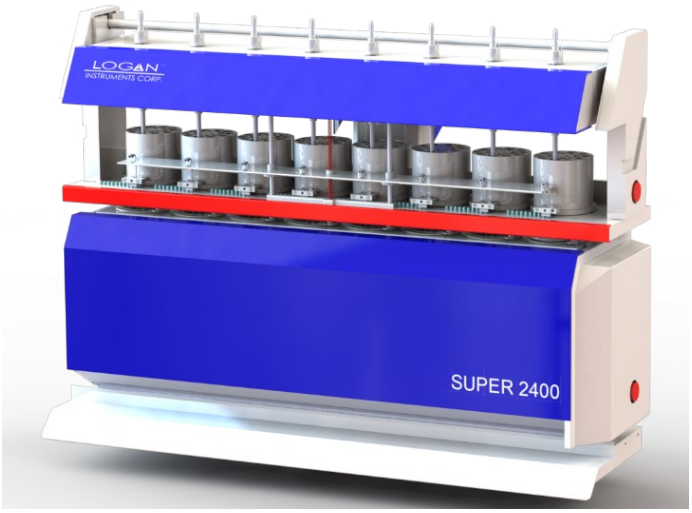

Logan System 2400 is a fully automated dissolution testing apparatus, which is designed and manufactured in the USA. Logan System 2400 can run 10 batches by USP apparatus 1 or 2 from media delivery to analysis unattended. A total of up to 80 tablets in one run. All stages of the dissolution process are computer-coordinated and carried out entirely without user intervention.

This system precisely delivers, preheats, and degasses media into 6 or 8 dry-heat vessels (no water bath required). Each vessel has bottom and side cameras, to record the entire dissolution process for further investigation. When each group of tablet tests is completed, the vessels automatically empty the media and are spray washed. The vessels are then blow-dried and system 2400 is ready for testing the next group of samples until the full test batch is completed.

Logan System 2400 has two types of filter changers. The filter tip changer is built-in if the endpoint is online UV analysis. An external membrane filter changer is available for offline HPLC analysis. Alternatively, this system can be installed with Fiber Optic probes for in situ detection.

Online UV analysis

Filter changer for collection of samples for offline HPLC

Fiber Optic UV-Vis Spectrometer

Logan Instruments has developed the "**EPVT-1200 system**" for USP Apparatus 1 & 2 Performance Validation Tests, aimed at revolutionizing the validation processes of dissolution testers. This innovative digital toolset not only performs but also records, dissolution validation performance electronically, thereby eliminating the uncertainties associated with manual recording methods.

For more information, please contact infoDT@loganinstruments.com.

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dx.doi.org/10.14227/DT310224P96

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 ***USP*** **General Chapter <701> Disintegration states that "the use of disks is permitted only where specified or allowed in the monograph." Can you elaborate on when disks can be applicable, or for which type of formulation disks shall be used?**

A The use of disks needs to be defined experimentally using the samples under evaluation. Their use is defined in a case-by-case approach. Generally, disks are used for dosage forms that tend to float in the disintegration media. The disks help to ensure that the dosage form is fully submerged. Also, some disintegration test equipment utilizes a sensor mechanism to determine the end point of the test. In some cases, the function of the endpoint detection depends on the presence of the disk.

Q **We are qualifying dissolution equipment with eight positions. Considering the complexity of this equipment, we have classified it as Group C according to** ***USP*** **General Chapter <1058> Analytical Instrument Qualification, and we are going to qualify the installation, operation, and performance. We think design qualification is not needed because we have already acquired the equipment. Is this rationale appropriate? For an equipment with eight positions, which acceptance criteria should be used, 6 or 8 positions?**

A It is up to your lab to decide how to classify the equipment. The instrument should be well described, and the user should have thorough knowledge of the equipment capabilities and specifications to ensure that the instrument purchased satisfies the requirements for the intended use. Typically, the detailed design specifications are maintained by the equipment manufacturer, which may satisfy the design qualification for off-the-shelf instruments. The major aspects of operating the dissolution equipment, such as how the samples are introduced into the dissolution media; whether it is possible to stagger both sample introduction and shafts operation; if sampling is going to be manual, semi-automated, or automated; and whether there is a source of vibration near the proposed location for the equipment are the responsibility of the purchaser. The question of which qualification approach should be used is answered by considering the intended use of the equipment. If all eight positions are going to be used for sample evaluation, then all eight positions should be qualified. If only six positions are used for sample evaluation and the remaining two are used as a reservoir for pre-warmed dissolution medium, then the six positions used to evaluate samples must be qualified.

Q **In** ***USP*** **General Chapter <711> Dissolution and in the certificate of the USP Dissolution Performance Verification Standard – Prednisone RS, it is stated that the performance verification should be carried out. Is this verification the same as the performance qualification stated in <1058> Analytical Instrument Qualification? For the periodical verification, should the same procedure be used or can a finished product be used?**

A Yes, the use of the USP Dissolution Performance Verification Standard – Prednisone RS (DPVS – Prednisone) satisfies the performance qualification phase of the instrument qualification, and it should be followed for dissolution apparatus 1 and 2 equipment verifications. The DPVS – Prednisone tablet is specifically designed to be sensitive to the setup and operational variables of the dissolution equipment. In contrast, most finished products are designed to meet the specific critical quality attributes required for the performance of the product in the patient, be it animal or human. More information on how to qualify the dissolution equipment can be found at www.usp.org/small-molecules/pvt.

Q What is the appropriate technique to validate the precision for a dissolution method?

A Precision has three components: repeatability, intermediate precision, and reproducibility. Repeatability is where the standard deviation of multiple sets of samples is calculated for dissolution experiments conducted by the same analyst on the same equipment. Intermediate precision is where at least two analysts perform the dissolution experiments using samples from the same batch or lot of finished product on two different days and the results compared at each time point in the dissolution profile using an appropriate statistical tool. Reproducibility can be evaluated when the dissolution method is transferred to another lab. See more information in *USP* General Chapter <1092> The Dissolution Procedure – Development and Validation.

Q When a dissolution method has different timepoints, how should a verification study be carried out? In the dissolution test in the USP monograph for Tamsulosin Hydrochloride Capsules, the sampling times are 2, 3, and 8 hours. Which time point should be used to verify the method?

A First, the dissolution test for Tamsulosin Hydrochloride Capsules is formulation dependent. In the example above, where the monograph method is established and three time points are required, the method verification should be carried out at each time point. For this example, each formulation is going to have its own specific and discriminative dissolution test. Normally, the validation of any dissolution method is done considering the entire dissolution profile, not only the final acceptance criteria. When developing a new method, the dissolution method needs to be validated as soon as it is finalized and prior to the establishment of acceptance criteria.

Q If the assay specification for a particular product is 95–105% and one of the six dissolution results is 135% and the average value is 103%, what should be done? Is there an upper limit for dissolution results?

A There is no upper limit for dissolution tests. Assay and dissolution results cannot be compared, as they measure different characteristics from the same product, and the sample is prepared in a completely different manner for each of these tests. In this scenario, the parameter that is likely to be most useful is to evaluate uniformity of dosage units for the batch in question. If dissolution results above 100% are found, an investigation should be done to identify the possible reasons for high drug content in an individual tablet. If it is determined that the uniformity of dosage units meets the specifications, an investigation to determine the source of high dissolution results could in include the following. The material, construction, and pore size of the filter used to prepare the dissolution samples should be evaluated; sampling should be considered, i.e., whether it was done at the appropriate time and at the appropriate location within the vessel; and potential analytical interference from the other formulation components or possible contamination of the reagents or solutions used in the dissolution test.

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:
Attn: Q&A
9 Yorkridge Trail, Hockessin, DE 19707
Email: vagray@rcn.com
Submit via our website:
www.dissolutiontech.com

Calendar of Events

May 17, 2024

Ensuring Drug Efficacy: Solid Dose Testing Essentials
Location: Online
Registration: https://microbiozindia.com/ensuring-drug-efficacy-solid-dose-testing-essentials/

May 23, 2024

Dissolution Discussion Group Quarterly Online Meeting—Key considerations for dissolution software and compliance
Location: DDG Online Meeting at 10:30 am ET
Registration: https://www.agilent.com/chem/dissolution-webinars

June 6–7, 2024

MIDD+ San Francisco 2024
Location: San Mateo, CA, USA
Registration: https://www.simulations-plus.com/events/midd-san-francisco-2024/

June 10, 2024

In Silico PBPK/PBBM Modeling and Simulation for Industry and Academia Workshop at the 2024 CSPS Annual Symposium
Location: Edmonton, AB, Canada
Registration: https://www.simulations-plus.com/events/in-silico-pbpk-pbbm-modeling-and-simulation-for-industry-and-academia-workshop/

June 11–12, 2024

Disso America 2024 Dissolution Science: Complex Drug Products
Location: Rutgers, NJ, USA
For information, visit http://www.spds.us

June 25, 2024

PAGE Pre-conference Workshop: Introduction to GPX™
Location: Rome, Italy
Registration: https://www.simulations-plus.com/events/page-pre-conference-workshop-introduction-to-gpx/

July 5, 2024

Dissolution Research Presentation International (DRPI-US) Competition (abstract deadline)
Location: Online
For information, visit https://drpi.spds.world/us

July 8–12, 2024

Controlled Release Society 2024 Annual Meeting
Location: Bologna, Italy
For information, visit https://www.controlledreleasesociety.org/events/2024-annual-meeting-and-expo

July 25, 2024

Dissolution Discussion Group Quarterly Online Meeting—Applications for predictive dissolution testing
Location: DDG Online Meeting at 10:30 am
Registration: https://www.agilent.com/chem/dissolution-webinars

October 20–23, 2024

PharmSci 360 AAPS Meeting
Location: Salt Palace Convention Center, Salt Lake City, UT, USA
For information, visit https://www.aaps.org/pharmsci/annual-meeting

November 18–20, 2024

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

November 21, 2024

Dissolution Discussion Group Quarterly Online Meeting—Dissolution method development guidance using QbD
Location: DDG Online Meeting at 10:30 am ET
Registration: https://www.agilent.com/chem/dissolution-webinars

On Demand Events

- ***Simplifying Dissolution Automation with In-Situ FIber Optic UV On Demand***
  https://www.distekinc.com/watch/webinar-simplifying-dissolution-automation-with-in-situ-fiber-optic-uv/
- ***Clarifying 21 CFR Part 11 & Data Integrity Requirements for Dissolution Testing On Demand***
  www.distekinc.com/watch/clarifying-21-cfr-part-11-and-data-integrity-for-dissolution-testing/
- ***Ocular Administration (OCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-ocular-administration-ocat-virtual/
- ***Oral Cavity Administration (OCCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-oral-cavity-administration-occat-virtual/
- ***Pulmonary Administration (PCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-pulmonary-administration-pcat-virtual/
- ***GastroPlus® ADR – 4 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™)***
  https://www.simulations-plus.com/events/gastroplus-adr-4-course-bundle-tcat-ocat-occat-pcat/
- ***GastroPlus® ADR – 5 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™ / Injectables)***
  https://www.simulations-plus.com/events/gastroplus-adr-5-course-bundle-tcat-ocat-occat-pcat-injectables/
- ***Transdermal Administration (TCAT™) in GastroPlus®***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-transdermal-administration-tcat-virtual/
- ***Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-injectables-incl-lai-biologics-virtual/

Industry News

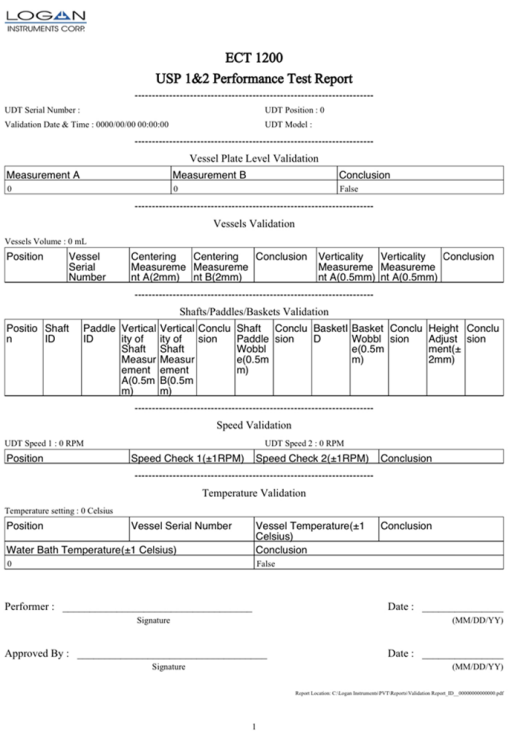
Logan Instruments Introduces the Electronic Performance Validation Testing Toolset "EPVT-1200 system"

Logan Instruments has developed the "EPVT-1200 system" for USP apparatus 1 and 2 Performance Validation Tests, aimed at revolutionizing the validation process of dissolution testers. This innovative digital toolset performs and records dissolution validation performance electronically, thereby eliminating the uncertainties associated with manual recording methods.

This cutting-edge validation toolset seamlessly conducts a comprehensive array of validations, including temperature, speed, shaft/paddle/basket wobbles, shaft/vessel centering, shaft/vessel verticality, and height adjustment.

The report is conveniently displayed on the PC screen, enabling immediate analysis. The options to record data directly onto the hard drive and print reports are also available. The results can be transferred to the Logan dissolution testers for spot-checking. With the implementation of this advanced toolset, the need for manual transfer of data is eliminated, ensuring compliance with FDA CFR 21 part 11 regulations.

For more information, please contact infoDT@loganinstruments.com.



LOGAN INSTRUMENTS CORP.

ECT 1200

USP 1&2 Performance Test Report

UDT Serial Number :
UDT Position : 0
Validation Date & Time : 0000/00/00 00:00:00
UDT Model :

Vessel Plate Level Validation

Measurement A	Measurement B	Conclusion
0	0	False

Vessels Validation

Vessels Volume : 0 mL

Position	Vessel Serial Number	Centering Measurement A(2mm)	Centering Measurement B(2mm)	Conclusion	Verticality Measurement A(0.5mm)	Verticality Measurement A(0.5mm)	Conclusion

Shafts/Paddles/Baskets Validation

Position	Shaft ID	Paddle ID	Verticality of Shaft Measurement A(0.5mm)	Verticality of Shaft Measurement B(0.5mm)	Conclusion	Shaft Paddle Wobble(0.5mm)	Conclusion	Basket ID	Basket Wobble(0.5mm)	Conclusion	Height Adjustment(±2mm)	Conclusion

Speed Validation

UDT Speed 1 : 0 RPM
UDT Speed 2 : 0 RPM

Position	Speed Check 1(±1RPM)	Speed Check 2(±1RPM)	Conclusion

Temperature Validation

Temperature setting : 0 Celsius

Position	Vessel Serial Number	Vessel Temperature(±1 Celsius)	Conclusion
Water Bath Temperature(±1 Celsius)		Conclusion	
0		False	

Performer : _____ Date : _____
Signature (MM/DD/YY)

Approved By : _____ Date : _____
Signature (MM/DD/YY)

Report Location: C:\Logan Instruments\PVT\Reports\Validation Report_ID_ 000000000000.pdf

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LOGAN INSTRUMENTS CORP.

Simulations Plus Extends Collaboration with Major Toxicology Research Agency

Research project with NIEHS includes focus on qualification of in silico methods for prioritization, assessment of risk, and identification of safety margins for chemical use

Lancaster, CA – Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of modeling and simulation solutions for the pharmaceutical, biotechnology, chemicals, and consumer goods industries, today announced an extension to the formal agreement with the Translational Toxicology Division at the National Institute of Environmental Health Sciences (NIEHS) to support the rapid safety assessment of chemicals in animals and humans.

"At NIEHS, we seek to expand scientific knowledge and approach methods linking the environment and human health. The Division of Translational Toxicology (DTT) at NIEHS provides health effects research to federal, state and local health agencies to identify emerging public health issues and support the conduct of formal risk assessments and decision-making," said Stephen Ferguson, Ph.D., scientific lead for the NIEHS project. "The agreement with Simulations Plus provides computational tools that support investigations of environmental chemicals and their potential health effects."

Computational model predictions from ADMET Predictor® and GastroPlus enable in vitro to in vivo extrapolation (IVIVE) that relates biologically active exposure levels to environmental exposure scenarios. This enables more accurate estimates of chemical safety margins (Sipes, et al. *Environ. Sci. Technol.* **2017**, *51* (18), 10786-10796. DOI: 10.1021/acs.est.7b00650) and a framework for integration of various types of toxicology data (e.g., mechanistic data, in vivo, and in vitro toxicology studies) for decision-making (e.g., risk assessments, safer product formulation).

"Importantly, these tools are being investigated for their potential to address a critical gap in toxicology research for understanding and modeling human bioactivation of environmental chemicals through xenobiotic metabolism," Ferguson added.

"It's critical to understand how chemicals may react in the body, and that can vary depending on whether they are inhaled or absorbed through the skin, whether the person was an adult or child, and if there are other health conditions present," said Michael Lawless, Sr. Principal Scientist in the Cheminformatics Solutions team at Simulations Plus. "As in vivo testing becomes more and more limited, the application of our software to support new approach methodologies (NAMs) to predict those outcomes becomes more crucial, and we are proud to be working with DTT/NIEHS to support their environmental health and safety research activities."

GastroPlus is a mechanistically based modeling and simulation software that simulates intravenous, oral, intraoral (oral cavity), pulmonary (respiratory), ocular, dermal (topical and subcutaneous), intramuscular, and intraarticular routes of administration, as well as biopharmaceutics, pharmacokinetics, and drug-drug interactions in humans and animals. It is the leading physiologically based pharmacokinetic/ physiologically based biopharmaceutics modeling (PBPK/PBBM) platform, built and refined over 25 years on the most up-to-date scientific research.

ADMET Predictor is a machine learning (ML) platform that predicts the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of new molecules. It incorporates more premium and extensively curated data from pharmaceutical and agrochemical partners than any other cheminformatics platform, which provides enhanced predictive accuracy and wider applicability of its models.

Learn more about GastroPlus and ADMET Predictor.

Simulations Plus and the University of Bath Awarded New FDA Grant

Partnership will produce an enhanced, validated dermal PBBM/PBPK model to inform product development and bioequivalence decisions

Lancaster, CA – Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation solutions for the pharmaceutical, biotechnology, chemicals, and consumer goods industries, today announced that, through a joint proposal with the University of Bath's Department of Life Sciences and other university partners, it has been awarded a new funded grant from the U.S. Food and Drug Administration (FDA). The grant will be used to expand and validate a multi-functional, multi-purpose physiologically based biopharmaceutics/pharmacokinetics (PBBM/PBPK) modeling solution for topical products within the GastroPlus® platform that can inform regulatory decisions for both innovator and generic products.

For this award, the Skin Biosciences group at the University of Bath led by M. Begoña Delgado-Charro, Professor in Biopharmaceutics, and Professor Richard Guy, and partners at the Colorado School of Mines (Professor Annette Bunge) and the University of Reading (Professor Adrian Williams) will generate in vitro data from a series of studies to capture the processes that occur when patients use topical formulations which transform when applied and rubbed into the skin. The scientific team at Simulations Plus will utilize these novel data sets, along with additional pathophysiology information for skin disease populations, to enhance and validate the Transdermal Compartmental Absorption and Transit (TCAT™) model within GastroPlus and determine the impact of changes to relevant quality attributes which impact the predictions of dermal absorption. The resulting outcome will provide the foundation of a viable alternative to in vivo studies for the establishment of bioequivalence (BE) for topical products.

"Collaborating with the University of Bath and other partners on this groundbreaking FDA grant is a remarkable opportunity. Our joint efforts are set to deliver an advanced, rigorously validated, and mechanistic dermal PBBM/PBPK model that leverages novel in vitro experimental designs," said Dr. Maxime Le Merdy, Associate Director, Research & Collaborations of PBPK Solutions, and lead investigator for this grant for Simulations Plus. "This innovation promises to revolutionize the prediction accuracy of topical drug product performance. By doing so, we aim to significantly expedite the regulatory decision-making process, ultimately benefiting patients and the pharmaceutical industry."

FDA scientific and program staff will actively collaborate with the University of Bath, Colorado School of Mines, University of Reading, and Simulations Plus. Dr. Le Merdy, with assistance from Dr. Jessica Spires and Dr. Jasmina Novakovic at Simulations Plus, will coordinate modeling and simulation activities of the contract.

"By combining our expertise with Simulations Plus' cutting-edge research, we are charting a course towards more efficient drug development and safer healthcare solutions. The project will be a great way for both industry and academia to make that leap from research into real life applications, with potential benefits of tangible patient outcomes," added Dr. Delgado-Charro. "Our primary objective is to enable the creation of innovative models that bridge the divide between in vitro and in vivo data. The comprehensive framework and best practices established through this contract will hold significant value for both the FDA and the companies involved in developing topical formulations."

Funding for this collaboration is made possible by the Food and Drug Administration through grant award 1U01FD007957-01. Views expressed in this press release do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

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- Supports App 1, 2, 5, 6, small volume and more

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Low dose? No problem. The 400-DS is suitable for any low-API dosage forms with dissolution tests taking days or more.

Low effort. High throughput. The 400-DS combines dissolution and sampling without the user having to intervene. Plus, up to 13 samples can be simultaneously tested.

Fully compliant. The 400-DS meets USP Apparatus 7 (Reciprocating Disk) requirements, and uses software that facilitates compliance with 21 CFR Part 11.

For more information about the 400-DS, visit:
www.agilent.com/chem/400-ds

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