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.
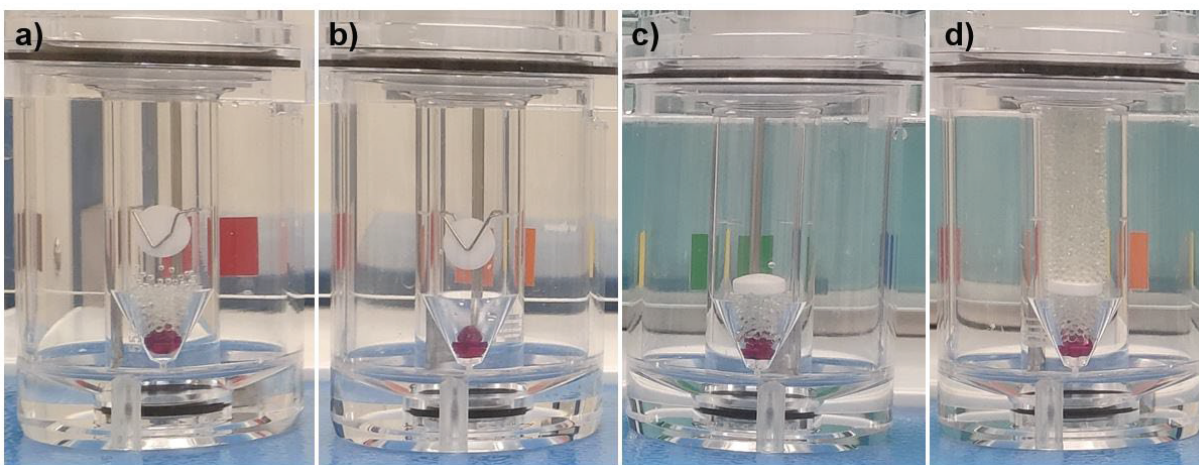

Figure 1. The tablet loading patterns: a) on tablet holder with glass beads (HWB); b) on tablet holder without glass beads (HWOB); c) on top of the glass bead bed (T); d) embedded (E).

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 $\pm t$ 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.
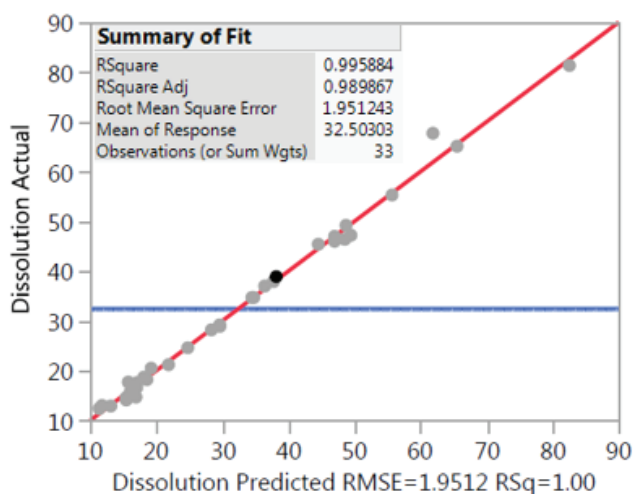

Figure 2. Mathematical model fitting results.

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.
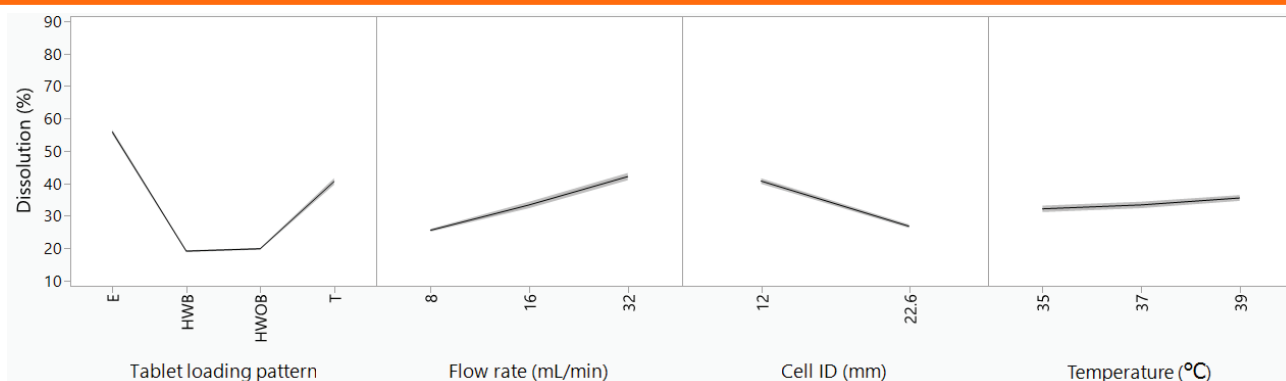

Figure 3. Influence of the four parameters on dissolution of salicylic acid tablets as predicted by the mathematical model. Tablet loading patterns are coded as HWB: on tablet holder with glass beads; HWOB: on tablet holder without glass beads; T: on top of the glass bead bed; E: embedded (see Fig. 1).

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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