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

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ABSTRACT

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

METHODS

Materials

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

Dissolution Testing

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

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

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

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

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

Dissolution Modeling

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

Noyes-Whitney Equation:

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

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

Sherwood Number Equation:

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

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

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

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

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

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

RESULTS AND DISCUSSION

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

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

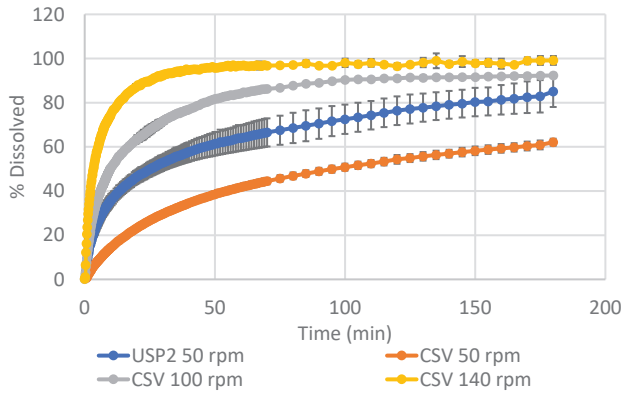

Figure 1. Initial dissolution test results with USP Prednisone Tablets RS (10 mg) in 250 mL water in 1-L USP standard vessels at 50 rpm paddle speed versus in CSV vessels with paddle speeds of 50, 100, and 140 rpm. USP: United States Pharmacopeia; USP2: USP apparatus 2; CSV: Chinese small volume.

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

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

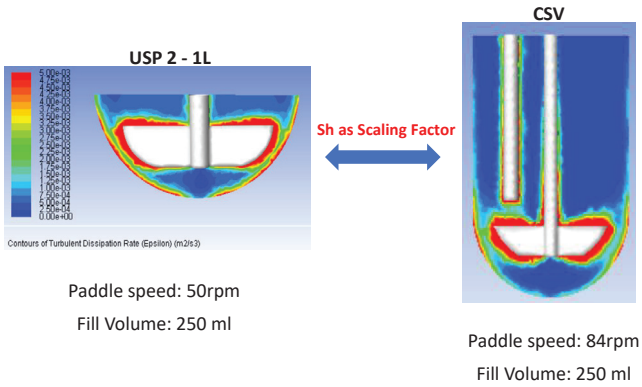

Figure 2. Contours of turbulent dissipation in the 1-L USP standard vessel and the 250-mL CSV vessel with 250 mL of water and scaled paddle speeds using the related Sherwood (Sh) number. USP: United States Pharmacopeia; CSV: Chinese small volume.

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

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

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

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

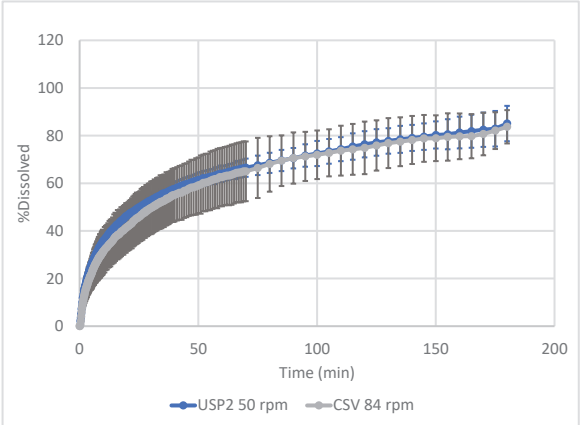

Figure 3. Dissolution profiles of USP Prednisone Tablets RS (10 mg) in 250 mL water in 1-L USP vessels at 50 rpm and CSV vessels at 84 rpm (predicted from the Sherwood number). USP: United States Pharmacopeia; USP2: USP apparatus 2; CSV: Chinese small volume.

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

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

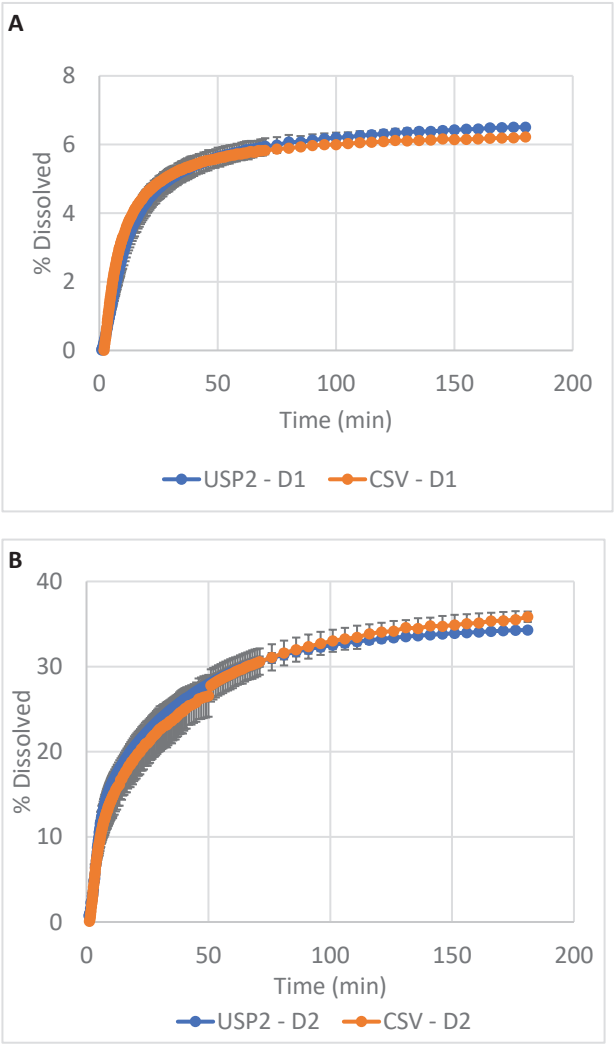

Figure 4. Dissolution of BMS drug formulations (D1 and D2) in 250 mL FaSSIF in 1-L USP vessels at 50 rpm versus CSV vessels at 84 rpm. (A) Comparison of USP versus CSV vessels for D1. (B) Comparison of USP versus CSV vessels D2. BMS: Bristol-Myers Squibb; USP: United States Pharmacopeia; FaSSIF: fasted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

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

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

CONCLUSION

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

DISCLOSURES

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