



The Effect of Sampling Cannula on *In Vitro* Dissolution Testing with USP Paddle Method

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Abstract

In vitro dissolution tests are widely used as quality control tools for drug products in development and manufacturing. Dissolution acceptance criteria are one of the important factors assessed during the regulatory review process. Understanding potential sources of variability is critical and a key to assuring reliable results are obtained when using a standardized system for *in vitro* dissolution testing. Sampling cannulas are commonly used to withdraw sample aliquots from dissolution medium and are potentially one of the testing factors that can contribute to variabilities in dissolution testing. However, there are still no clear requirements on the size or setting (intermittent or stationary) of sampling cannulas for dissolution testing. Thus, the objective of this study is to evaluate whether various sizes and sampling cannula settings yield different dissolution results using the USP 2 apparatus. Sampling cannulas with outer diameter (OD) ranging from 1.6 mm to 9.0 mm were used in dissolution testing with either intermittent or stationary setting to collect sample aliquots at multiple time points. The dissolution results at each time point were statistically analyzed for effects of both OD and setting of sampling cannula on drug release from 10 mg prednisone disintegrating tablets. Dissolution results indicated both size and setting of the sampling cannula may cause significant systematic errors, even though the dissolution apparatus has been calibrated. The degree of interference in dissolution results was directly related to the OD of the sampling cannula. Size of sampling cannula and setting of sampling procedure should be documented in standard operating procedures (SOP) for dissolution testing during method development.

Keywords dissolution testing · medium hydrodynamics · sample cannula · sampling process · USP apparatus · variability

Introduction

In vitro dissolution tests are widely used as quality control tools for drug products in development and manufacturing. Dissolution acceptance criteria are one of the important factors assessed during the regulatory review process. A recent publication by scientists from the US Food and Drug Administration (FDA) demonstrated dissolution results as one of the major product quality attributes to calculate a process performance index to evaluate the variability in manufacturing of drug products. (1) As a standard method, the repeatability and reproducibility of dissolution testing have always been a concern after the methods

became official in the US Pharmacopeia (USP) in the early 1960s. Understanding potential sources of variability is critical for ensuring reliable results when using a standardized system for *in vitro* dissolution testing. FDA scientists have conducted extensive research since 1980 to gain insight into possible testing variables associated with compendial USP dissolution apparatuses. (2–17) These studies showed the importance of physical alignment of compendial dissolution apparatus (3, 4, 12, 16, 17), possible effects from dissolved air in dissolution medium (6, 10), and deviations that may be caused by random environmental vibrations (13–15). FDA scientists also conducted gage repeatability and reproducibility studies on the paddle dissolution method (USP apparatus 2) to examine contributions of variability from the apparatus assembly, operators, and tested samples. (11) Most testing variables show direct impacts on hydrodynamics of dissolution medium that can be responsible for the poor reproducibility and inconsistencies of the dissolution results. In the past twenty years, many investigations focused on determining the hydrodynamics of dissolution medium in standard USP vessels by experimental and computational methods such as particle image velocimetry (PIV) and computational fluid dynamics

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(CFD). (18–23) The results show that medium hydrodynamics is highly nonhomogeneous with directions and intensities of fluid velocities highly dependent on the location within the USP vessel, especially at the bottom of the vessel where the testing sample is usually located during the test. The advance of technology and knowledge of possible testing variables and their impacts on medium hydrodynamics became the foundation to support FDA Guidance for Industry and standardized methods (American Society for Testing and Materials – ASTM), which led to improved mechanical calibration procedure to assure the performance of USP basket and paddle methods. (24, 25)

Sampling cannulas are commonly used to withdraw sample aliquots from dissolution medium. An automated sampling procedure is useful in a QC environment, and when the method requires sample aliquots at multiple time points. Considering the sampling procedure for dissolution apparatus 1 and 2, USP general chapter <711> requires to withdraw a specimen (sample aliquot) from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. (26) However, a requirement for the size (outer diameter, OD) of sampling cannula does not appear in this USP general chapter. As a recommendation, USP general chapter <1092> states that sampling probes (cannulas) or fiber-optic probes can disturb the hydrodynamics of the vessel; therefore, adequate validation should be performed to ensure that the probes are not causing a significant change in the dissolution rate. (27) The USP chapter provides no guidance on the OD of a sampling probe/cannula and whether a sampling probe/cannula may or may not remain in the vessel throughout the entire run. Additionally, “significant change” mentioned in the USP chapter is subjective, lacks statistical meaning, and is hard to apply during the assessment of methods.

The sampling cannula is potentially one of the essential testing factors that can contribute to variability in dissolution testing, even for a calibrated dissolution system. The effect of sampling cannula on dissolution testing attracted the attention of FDA scientists in early 1980s. (2, 5) They used the USP paddle method to test different sizes of sampling cannulas and found that dissolution rates for some formulations were consistently higher with large OD (6–8 mm) cannula. The change in rates was less evident with small OD (1.5 mm) cannula, and no difference in dissolution results was observed between automated and manual sampling. Another study compared various sampling methods with 50 mg Sotaxin tablet (drug name is as stated in the reference) using USP apparatus 1 and 2. (28) In this study, the comparative tests with or without a sampling cannula in the dissolution medium during the test showed markedly different release profiles. One research group also studied the effects of sampling cannula on the hydrodynamics of dissolution medium in USP apparatus 2 vessel by velocity measurements using PIV. (29) The study used one commercially available sampling cannula to compare variations in flow field between the testing system with

and without permanently inserted sampling cannula. The results from the PIV measurements showed that the hydrodynamics in the dissolution vessel was slightly affected by the introduction of sampling cannula (3.14 mm OD); however, the dissolution results for non-disintegrating salicylic acid tablets did not show statistical difference in the presence or absence of studied sampling cannula.

Sampling cannulas in sizes from 1.6 to 3.6 mm (OD) are commercially available and commonly used, but some sampling systems require a filter at the end of each sampling cannula. The filters are commercially available in a common size of 9 mm OD by 100 mm in length and feature a large surface area to optimize sampling flow rate of dissolution medium containing particulates. The sampling cannula with filter at the end may be inserted into the sample zone of the dissolution medium when sampling (intermittent) or may remain in the sample zone permanently throughout the dissolution testing (stationary). With this large size of filter in the dissolution medium, no matter in either intermittent or stationary setting, the dissolution results may be varied by possible medium hydrodynamic disturbances.

Though early studies show possible impacts of large-sized sampling cannula on dissolution results, and USP recommends adequate validation to ensure that the cannulas are not causing a significant change in the dissolution rate, the current practice of selecting sampling cannula for dissolution testing lacks rigorous considerations. Some recommendations consider hydrodynamic disturbances when using “resident dwelling probes” (stationary setting) and suggest using a sampling manifold to lower the cannulas at sample times and to lift the cannulas between time points (intermittent setting).

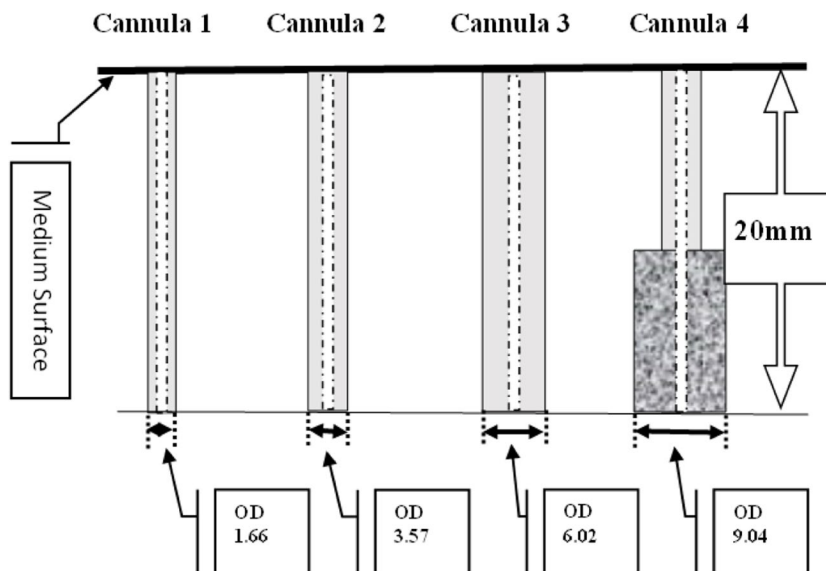
The objective of this study was to investigate whether various size and setting of sampling cannula yield different dissolution results using USP apparatus 2. A wide range of sampling cannulas (OD between 1.6–9.0 mm) was used in dissolution testing with either intermittent or stationary setting to collect sample aliquots at multiple time points. The dissolution results at each time point were statistically analyzed for effects of both OD and setting of sampling cannula on drug release from 10 mg prednisone disintegrating tablet. Dissolution results indicated both size and setting of the sampling cannula may cause significant systematic errors, even though the dissolution apparatus has been calibrated. Details on sampling cannula should be documented in standard operating procedure (SOP) for dissolution testing during method development.

Experimental

Sampling Cannulas

Four sampling cannulas with different ODs were used in this study as illustrated in Fig. 1. Cannula 1 was made of

Fig. 1 Illustration of sampling cannulas used in this study with labeled outside diameters (OD) and depth merged in the medium with unit in millimeter (mm). The inside diameters are the same for all four sampling cannulas



type 316 stainless steel. Cannula 2 was made of polyether ether ketone. Both cannula 1 and 2 were commercially available and purchased from Quality Lab Accessories LLC (Telford, PA). Cannula 3 was assembled in house by encasing cannula 2 in thick plastic tubing. Cannula 4 was cannula 2 with a filter connected to its end. The OD of each cannula and the depth of part of cannula submerged in the medium is shown in Fig. 1, and OD measurements by a digital caliper are listed in Table I.

Physical Properties of Testing Tablets

Prednisone 10 mg disintegrating tablets (NCDA#2) was selected for the study because of its sensitive to medium hydrodynamics. (9, 12) The hardness, dimensions, and weights of NCDA#2 tablets (*n* = 8) were measured by a Sotax SmartTest 50 tablet testing system (Westborough, MA, USA). Results are shown in Table II.

Table I The Dimension (OD at the Tip, mm) of 6 Individual Sampling Cannulas in Each Size Category

	Cannula 1	Cannula 2	Cannula 3	Cannula 4
1	1.66	3.65	6.02	9.04
2	1.67	3.60	5.99	9.07
3	1.67	3.56	6.13	8.94
4	1.65	3.55	5.92	8.99
5	1.67	3.47	6.05	9.09
6	1.66	3.60	6.00	9.12
Average	1.66	3.57	6.02	9.04
SD	0.01	0.06	0.07	0.07
RSD%	0.49	1.71	1.16	0.74

Dissolution Testing

The dissolution testing was performed in 500 mL degassed deionized (DI) water at 37 °C with 50 rpm paddle rotation speed using a USP paddle method (Hanson Vision 8 apparatus, Thousand Oaks, CA, USA). The dissolution apparatus was mechanically calibrated following the ASTM procedure. (24) The dissolution apparatus comes with AutoMag™ manifold, which is capable of programing sampling cannula setting as either intermittent or stationary configuration. Intermittent setting is defined as the sampling cannula is immersed in the dissolution medium only at predetermined sample times. Stationary setting is defined as the sampling cannula to be permanently immersed in the dissolution medium from the beginning of the test throughout the entire test. For each sample cannula setting, AutoMag™ vertically moves

Table II Physical Properties of NCDA#2 Tablets

	Hardness (N)	Diameter (mm)	Thickness (mm)	Weight (mg)
1	37	8.79	2.76	218.4
2	38	8.79	2.79	219.7
3	33	8.81	2.80	214.1
4	36	8.79	2.78	216.7
5	35	8.79	2.79	220.5
6	36	8.79	2.79	220.7
7	35	8.81	2.75	215.4
8	32	8.80	2.77	215.7
Average	35	8.80	2.78	217.7
SD	2	0.01	0.02	2.5

Table III Average Weights and Standard Deviations (SD) of NCDA#2 Tablets for Dissolution Testing

Weight, mg average (SD)	Intermittent setting				Stationary setting			
	Cannula 1	Cannula 2	Cannula 3	Cannula 4	Cannula 1	Cannula 2	Cannula 3	Cannula 4
For each cannula	217.4 (3.1)	218.1 (2.3)	217.2 (2.9)	217.7 (2.3)	217.4 (2.6)	218.2 (2.8)	217.2 (2.5)	217.9 (3.5)
For each setting	217.7 (2.9)				217.9 (2.8)			
For all tablets	217.8 (2.8)							

sampling cannulas to insert or lift from the medium. The different sampling cannula sizes used in this study have average ODs of 1.66 mm, 3.57 mm, 6.02 mm, and 9.04 mm as shown in Table I. Aliquots of 5 mL were collected at six time points as: 5, 15, 20, 30, 45, and 60 min without medium refill. All aliquots were drawn from the dissolution medium and passed through a 10- μ m filter (either in-line filter or tip filter, polyethylene filter purchased from Quality Lab Accessories, LLC.) into labeled sample collectors. Sample aliquots were analyzed with an UV-vis spectrophotometer (Agilent 8454 UV/Vis, Santa Clara, CA, USA) measuring the absorbance at 242 nm with a single 400 nm wavelength background correction. The medium remaining in the sampling cannula (and tubing) from the previous sampling was returned to the vessel after each sampling time, to avoid carry-over in the next sampling cycle. Under each testing condition (size and setting of sampling cannula), dissolution testing of 6 test tablets in each run was repeated 5 times.

With JMP software (version 15.0.0, Cary, NC, USA), a paired-samples t-test with 95% confidence was conducted to statistically analyze dissolution results at each time point from using sampling cannulas with different sizes in either intermittent or stationary setting.

Results and Discussions

Accuracy and repeatability of the automated sampling system were verified by taking a 5 mL sample aliquot 5 times from each vessel with the cannulas immersed in dissolution medium. The volumes of withdrawn sample aliquots were measured as results in average of 4.9901 mL with a standard deviation (SD) of 0.0029 mL. Before each dissolution testing, tested tablets were weighed to observe consistency

of tablet weight. A summary of tablet weight is listed in Table III. For each dissolution testing, an infinity test at 150 rpm was conducted for 30 min after the 60-min sampling time, and the dissolution results were collected. The summary of the infinity time point result for 10 mg prednisone tablet is listed in Table IV. The assay and physical properties are consistent for all tested prednisone tablets.

The dissolution profiles with four ODs of sampling cannulas at two different settings are shown in Fig. 2. The dissolution profiles indicate a trend of increasing drug release with the increased cannula OD. Regardless of the cannula settings, a larger cannula OD resulted in a greater dissolution rate. When dissolution results from the smallest sampling cannula 1 (1.7 mm OD) and the largest sampling cannula 4 (9.0 mm OD) are compared side by side, this trend is much more apparent with more than 25% difference at 30-min time point. This result shows a similar trend to early published reports on increased dissolution rate of prednisone tablet at the 30-min time point. One reported the dissolution result was about 17% increase comparing small (1.3 mm) and large (5.8 mm) OD of sampling cannula used. (2) Another report showed about 18% difference in dissolution results comparing small (1.5 mm) and large OD (8.0 mm) of sampling cannula. (5)

Early reports indicated that a smaller sampling cannula (1.3 or 1.5 mm OD) had no observed effect on the dissolution rate when compared without using a sampling cannula. (2, 5) The medium hydrodynamics in the dissolution vessel measured by PIV showed a small effect from the introduction of sampling cannula (3.1 mm OD). The dissolution results for non-disintegrating salicylic acid tablets did not show statistical difference in the presence or absence of 3.1 mm sampling cannula. (29) The studies imply that the smaller sampling cannula (≤ 3.1 mm OD) may cause noticeable difference in medium hydrodynamics, but the

Table IV Average %Dissolution Results at Infinity Time Point and Standard Deviations (SD) of NCDA#2 Tablets for Dissolution Testing

%Dissolution average (SD)	Intermittent setting				Stationary setting			
	Cannula 1	Cannula 2	Cannula 3	Cannula 4	Cannula 1	Cannula 2	Cannula 3	Cannula 4
For each cannula	94.8 (1.4)	94.6 (2.5)	94.1 (2.2)	93.9 (1.6)	94.5 (1.9)	94.3 (2.2)	94.2 (2.3)	94.7 (1.9)
For each setting	94.5 (2.0)				94.6 (2.1)			
For all tablets	94.5 (2.1)							

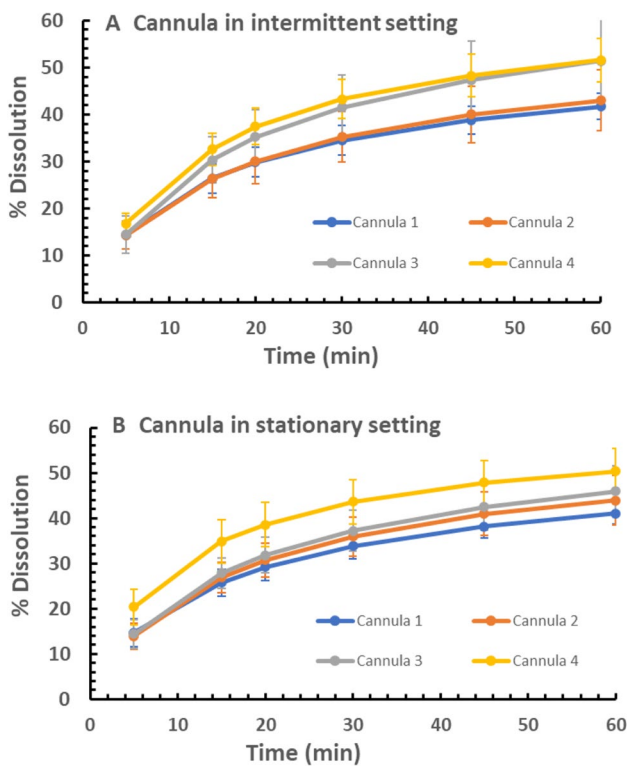


Fig. 2 The dissolution profiles with four ODs of sampling cannulas in the intermittent (A) and stationary setting (B). Vertical bars represent standard deviations

disturbance may not be enough to affect the dissolution rate of tested dosage forms.

Figure 3 shows box plots of percent dissolution results at 30 min with different ODs of sampling cannulas in intermittent (A) and stationary (B) settings. The horizontal line within the box (red) represents the median value.

The confidence diamond contains the mean and the upper and lower 95% of the mean (green lines). The blue horizontal line is standard deviation. With the intermittent setting (Fig. 3A), dissolution results from sampling cannulas 1 and 2 are around 34–35% of percent drug release, and statistical analysis shows no significant difference ($p=0.57$); and dissolution results from sampling cannulas 3 and 4 have faster drug release around 42–43%, but also no statistically difference ($p=0.17$). However, the results show significant difference between cannulas 2 and 3 ($p<0.001$). The trend line (red dash line) for average percent drug release shows an abrupt increase (18%) when OD of sampling cannula changes from 3.6 mm to 6.0 mm. This result supports previously reported observations that the disturbance may not be enough to affect the dissolution rate of tested dosage forms when the OD of sampling cannula is around 3 mm. But with a large size of sampling cannula (≥ 6 mm OD), intermittent immersion of the cannula into the dissolution medium at the sampling time severely disturbs medium hydrodynamics which greatly increases the dissolution rate.

Figure 3B shows percent dissolution results at 30 min in stationary setting using four different ODs of sampling cannulas. The effect of sampling cannula OD on dissolution results shows different patterns compared to that in intermittent setting (Fig. 3A). The percent dissolution increases gradually when the OD of sampling cannula changes from 1.7 mm to 6.0 mm, then markedly increases about 17% when the OD increases from 6.0 mm to 9.0 mm. Statistical analysis shows that dissolution results between sampling cannulas 1 and 2 and between cannulas 2 and 3 have no significant differences with p values above 0.05. However, dissolution results between sampling cannulas 1 and 3 show a significant difference ($p=0.002$) with a mean %dissolved at 30 min of 34% for sampling cannula 1 and 37% for sampling cannula 3. The dissolution results also

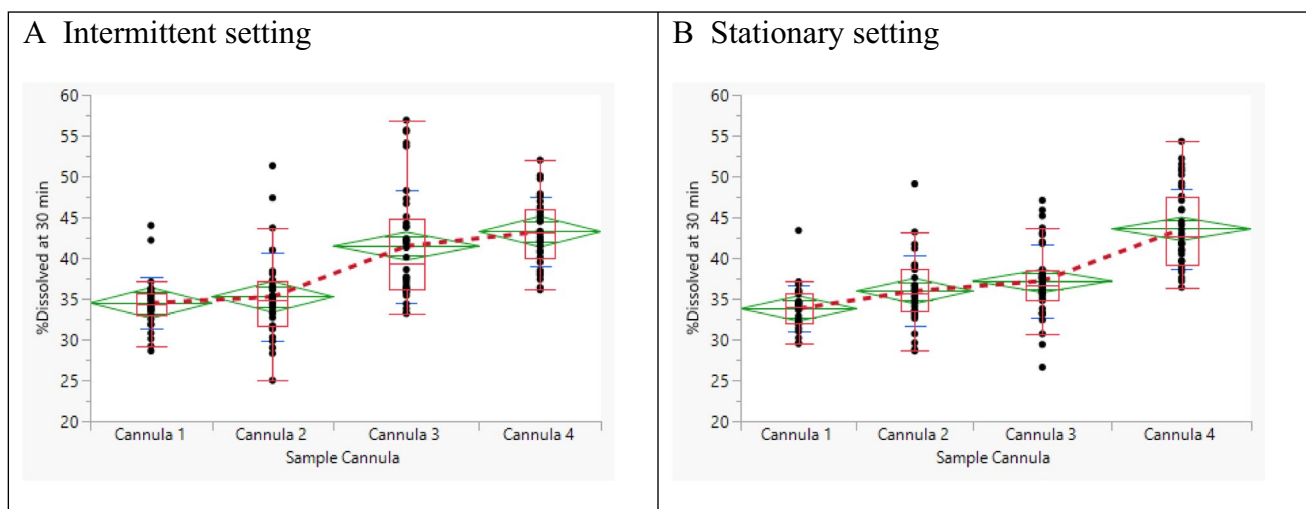


Fig. 3 The %dissolved at 30 min using four sizes of sampling cannulas in the intermittent (A) and stationary setting (B)

show pronounced difference between sampling cannulas 3 and 4 ($p < 0.0001$). As with stationary setting, the sampling cannula stays in the dissolution medium from the beginning throughout the entire test. According to early studies, the sampling cannula can act as a small baffle in a symmetrical system like dissolution vessel when it stays in the medium. The resulting loss of symmetry and the introduction of a baffling effect result in changes in medium flow velocity profile and shear rates, which can cause variability in dissolution results comparing to the condition without using a sampling cannula. (29) Under this baffle effect, our studies showed that even with a small OD increase from 1.7 mm to 3.6 mm for sampling cannula, a noticeable drug release increase (about 6%) has been observed though the change is not statistically significant ($p > 0.05$). For sampling cannula 3 with 6.0 mm OD, there is a significant 10% increase ($p = 0.002$) in dissolution results at 30 min compared to cannula 1. In Fig. 3, dissolution results show a dramatic difference between the intermittent and stationary settings for cannulas 2 and 3. This difference indicates that a sampling cannula with 6.0 mm OD may severely interrupt the hydrodynamics of the dissolution medium when it periodically enters and immerses in the dissolution medium under the intermittent setting. On the other hand, the same 6.0 mm cannula in the stationary setting may cause a baffle effect without disturbance on the medium hydrodynamics by moving sampling cannula in and out of the medium during each sample time. This may make sampling cannula ($OD > 6$ mm) act differently

in stationary setting compared to situation in intermittent setting. With an OD of sampling cannula at 9.0 mm, no matter under intermittent or stationary setting, the dissolution result at 30 min reaches to the level about 43–44%, which may indicate the large OD of cannula greatly disturbs the hydrodynamics of the dissolution medium.

Figure 4 focuses on the effect of intermittent and stationary settings on dissolution results with four different ODs of sampling cannulas. When comparing the same size of sampling cannula under intermittent and stationary settings, there is no observed difference in entire dissolution profiles (solid lines) for sampling cannulas 1 and 2. As also discussed above (Fig. 3) on percent dissolutions at 30 min from sampling cannulas 1 and 2, there was no significant differences ($p > 0.05$) in either intermittent or stationary setting. However, the standard deviations (dash lines) increased for sampling cannula in the intermittent setting and became more obvious when cannula OD increased to 3.6 mm as shown in dash lines in Fig. 4A and B. The increased standard deviations indicate that sampling cannula under intermittent setting which periodically enters the dissolution medium may have more adverse impacts on dissolution results compared to that in stationary setting.

Figure 4C (solid lines) shows dissolution profiles using sampling cannula 3 with 6 mm OD under intermittent and stationary setting. The dissolution results with the intermittent setting showed a greater drug release after the first sample time point at 5 min. Figure 5A shows the statistical comparisons between

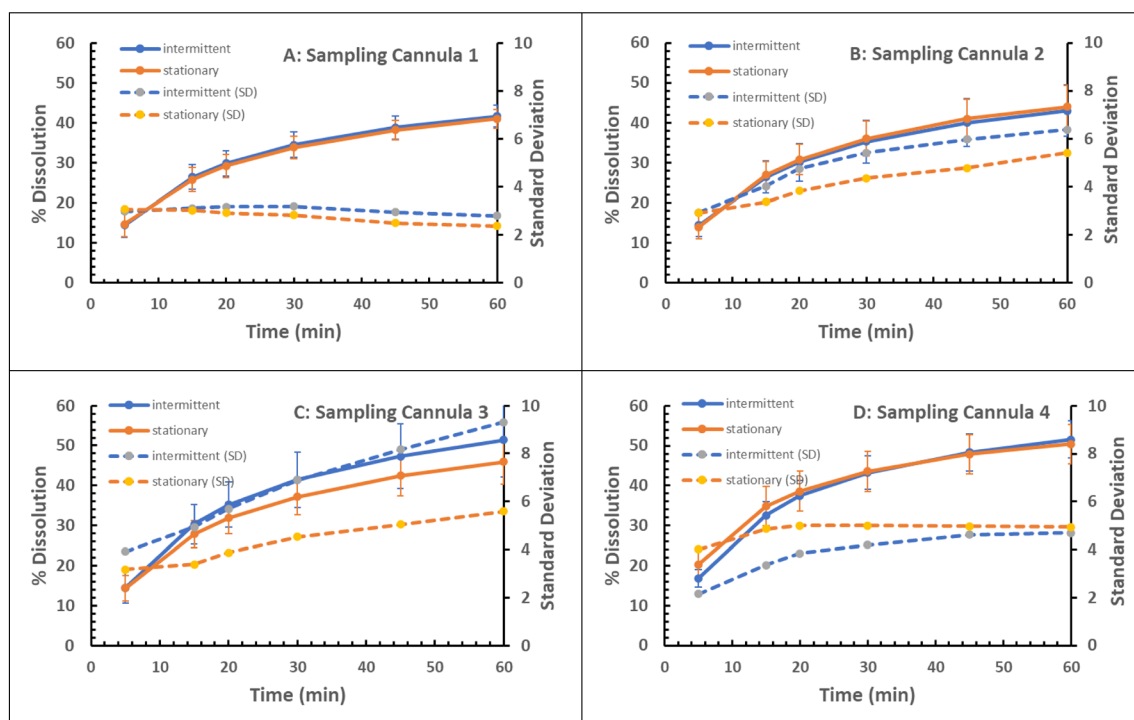


Fig. 4 Comparison of dissolution profiles (solid lines) and standard deviations at each time point (dash lines) under the intermittent and stationary settings with sampling cannulas 1 (A), 2 (B), 3 (C), and 4 (D). Vertical bars represent standard deviations

intermittent and stationary settings for sampling cannula 3 at the 30-min time point. %Dissolved results from intermittent setting are significantly higher ($p < 0.05$) than those in stationary setting. The standard deviations (dash lines in Fig. 4C) were also much higher for intermittent setting compared to those in stationary setting. The differences in percent dissolution and standard deviations clearly indicate that constant insertion of the sampling cannula with 6 mm OD in the dissolution medium under intermittent setting may cause more disturbance compared to the condition under stationary setting.

For sampling cannula 4 with 9 mm OD, results in Fig. 4D showed an increased drug release (solid lines) and standard deviation (dash lines) at the early sampling time before 20 min under the stationary setting and were getting similar dissolution profiles and standard deviation after 20-min time point. Figure 5B statistically compared dissolution results at 5-min time point. The %dissolved results with stationary setting are significantly higher ($p < 0.05$) than results with intermittent setting. This was caused by no hydrodynamic disturbance for intermittent setting before the first 5 min without insertion of sampling cannula. After 20 min of dissolution testing, the similarity of dissolution profiles and standard deviations with both intermittent and stationary settings implies a similar level of hydrodynamic disturbance is reached by this sampling cannula (9 mm OD) no matter either multiple inserted, or permanently left in the dissolution medium.

In summary, statistical comparisons of dissolution results obtained with various ODs of sampling cannula under intermittent and stationary settings indicate the size and setting of the sampling cannula may cause significant systematic errors in dissolution results in spite of required calibration and performance check of the dissolution apparatus. The degree of interference on dissolution results is directly related to the

size of the sampling cannula. The large sampling cannula (OD > 6 mm) may cause severe hydrodynamic disturbances as observed in significant changes in the dissolution results of tested prednisone tablets. The disturbances can be minimized by using sampling cannulas with the OD less than 3.6 mm and eliminated with smaller OD of sampling cannula (< 1.7 mm) despite cannula setting. The size of sampling cannula has a major impact on the dissolution results and specifying the use of small OD sampling cannula (less than 3.6 mm) during sampling procedure may be necessary. Because a filter tip dramatically increases OD of sampling cannula, a sampling procedure requiring a filter at the end of each sampling cannula should be avoided. The setting of sampling cannula (intermittent or stationary) may affect dissolution results when a larger OD cannula (> 3.6 mm) is used. Intermittent sampling setting by sampling manifold may cause hydrodynamic disturbances of similar or greater magnitude than those caused by “resident dwelling probes” (stationary setting). Using inappropriately sized OD of sampling cannula with intermittent setting can introduce large variability in the dissolution results than those observed with the stationary setting. It is recommended that sampling procedure should be evaluated as part of method development. This study may provide considerations to assess for *in vitro* dissolution testing when experimental design requires placing foreign bodies (cannula, thermometer, pH sensor, UV probe, etc.) in the test vessel.

Conclusions

Understanding potential sources of variability is critical to ensure reliable results with a standardized system for *in vitro* dissolution testing. Sampling cannulas are commonly used

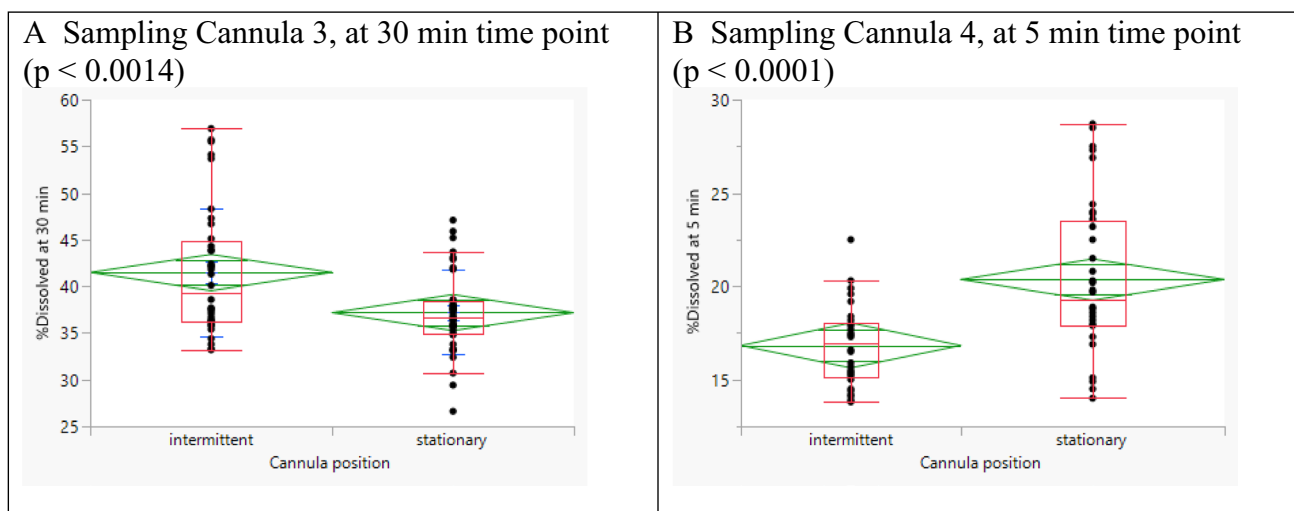


Fig. 5 Comparison of dissolution results in intermittent and stationary settings. **A** %Dissolved at 30 min using sampling cannula 3. **B** %Dissolved at 5 min using sampling cannula 4

to withdraw sample aliquots from dissolution medium. This study shows that sampling cannulas contribute to variability in dissolution testing. Both the size and setting of the sampling cannula may cause significant systematic errors in dissolution results despite required calibrations and performance checks of the dissolution apparatus. The degree of interference on dissolution results is directly related to the size of the sampling cannula. Large sampling cannulas (OD > 6 mm) are shown to cause significant changes ($p < 0.05$) due to severe hydrodynamic disturbances in the dissolution results of tested 10 mg prednisone tablets. Using smaller sampling cannulas (OD < 3.6 mm) may be required to minimize error in dissolution results, especially for drug products that are sensitive to medium hydrodynamics. Because a filter tip may dramatically increase the OD of sampling cannula, the sampling procedure requiring a filter at the end of each sampling cannula should be avoided. Sampling cannulas in the intermittent setting may introduce large variability in dissolution results compared to those in the stationary setting. Current practices that purposely apply intermittent sampling cannula setting to avoid hydrodynamic disturbances may need to be reconsidered. It is recommended that details on sampling cannula should be documented in the standard operating procedure (SOP) for dissolution testing during method development. The study results also provide a helpful point to consider for *in vitro* dissolution testing when experimental design requires placing foreign bodies (cannula, thermometer, pH sensor, UV probe, etc.) in the test vessel.

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Author Contribution Dr. Zongming Gao and Ms. Anjanette Smith were involved in conceptualization, methodology, data analyses, interpretation, writing, reviewing, and editing of the manuscript.

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Declarations

Conflict of Interest The authors declare no competing interests.

References

- Fisher AC, *et al.* Quality testing of difficult-to-make prescription pharmaceutical products marketed in the US. *JAMA Netw Open.* 2020;3(8):e2013920.
- Wells CE. Effect of sampling probe size on dissolution of tableted drug samples. *J Pharm Sci.* 1981;70(2):232–3.
- Cox DC, Furman WB. Systematic error associated with apparatus 2 of the USP dissolution test I: effects of physical alignment of the dissolution apparatus. *J Pharm Sci.* 1982;71(4):451–2.
- Cox DC, *et al.* Systematic error associated with apparatus 2 of the USP dissolution test II: effects of deviations in vessel curvature from that of a sphere. *J Pharm Sci.* 1982;71(4):395–9.
- Savage TS, Wells CE. Automated sampling of *in vitro* dissolution medium: effect of sampling probes on dissolution rate of prednisone tablets. *J Pharm Sci.* 1982;71(6):670–3.
- Cox DC, Furman WB, Page DP. Systematic error associated with apparatus 2 of the USP dissolution test IV: effect of air dissolved in the dissolution medium. *J Pharm Sci.* 1983;72(9):1061–4.
- Cox DC, *et al.* Systematic error associated with apparatus 2 of the USP dissolution test III: limitations of calibrators and the USP suitability test. *J Pharm Sci.* 1983;72(8):910–3.
- Cox DC, Furman WB. Systematic error associated with apparatus 2 of the USP dissolution test V: interaction of two tableted prednisone formulations with glass and plastic vessels. *J Pharm Sci.* 1984;73(8):1125–7.
- Cox DC, Furman WB. Collaborative study of the USP dissolution test for prednisone tablets with apparatus 2. *J Pharm Sci.* 1984;73(5):670–6.
- Gao Z, *et al.* Effects of deaeration methods on dissolution testing in aqueous media: a study using a total dissolved gas pressure meter. *J Pharm Sci.* 2006;95(7):1606–13.
- Gao Z, *et al.* Gauge repeatability and reproducibility for accessing variability during dissolution testing: a technical note. *AAPS PharmSciTech.* 2007;8(4):E82.
- Gao Z, *et al.* Studies of variability in dissolution testing with USP apparatus 2. *J Pharm Sci.* 2007;96(7):1794–801.
- Gao Z, Moore TW, Doub WH. Vibration effects on dissolution tests with USP apparatuses 1 and 2. *J Pharm Sci.* 2008;97(8):3335–43.
- Gao Z, *et al.* The random vibration effects on dissolution testing with USP apparatus 2. *J Pharm Sci.* 2009;98(1):297–306.
- Gao Z, Thies A, Doub W. Vibration effects of lab equipment on dissolution testing with USP paddle method. *J Pharm Sci.* 2010;99(1):403–12.
- Gao Z. Mathematical modeling of variables involved in dissolution testing. *J Pharm Sci.* 2011;100(11):4934–42.
- Gao Z, *et al.* Effects of vessel geometric irregularity on dissolution test results. *J Pharm Sci.* 2011;100(3):1093–101.
- Kukura J, *et al.* Engineering tools for understanding the hydrodynamics of dissolution tests. *Drug Dev Ind Pharm.* 2003;29(2):231–9.
- Kukura J, Baxter JL, Muzzio FJ. Shear distribution and variability in the USP apparatus 2 under turbulent conditions. *Int J Pharm.* 2004;279(1–2):9–17.
- Baxter JL, Kukura J, Muzzio FJ. Hydrodynamics-induced variability in the USP apparatus II dissolution test. *Int J Pharm.* 2005;292(1–2):17–28.
- Bai G, Armenante PM, Plank RV. Experimental and computational determination of blend time in USP dissolution testing apparatus II. *J Pharm Sci.* 2007;96(11):3072–86.
- Bai G, *et al.* Hydrodynamic investigation of USP dissolution test apparatus II. *J Pharm Sci.* 2007;96(9):2327–49.
- Bai G, Armenante PM. Hydrodynamic, mass transfer, and dissolution effects induced by tablet location during dissolution testing. *J Pharm Sci.* 2009;98(4):1511–31.
- Standard practice for qualification of basket and paddle dissolution apparatus. American Society for Testing and Materials, 2007. ASTM, E 2503 – 07.
- FDA Guidance for Industry - The use of mechanical calibration of dissolution apparatus 1 and 2 – current good manufacturing practice (CGMP) U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2010 (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>).

26. US Pharmacopeia General Chapter < 711 > Dissolution. DocId: 1_GUID-AC788D41-90A2-4F36-A6E7-769954A9ED09_1_en-US, 2021.
27. US Pharmacopeia < 1092 > The dissolution procedure: development and validation. DocId: 1_GUID-CE0902BA-77 AC-422D-8BF0-A221B5DE6012_5_en-US, 2021.
28. Schauble T. A Comparison of various sampling methods for tablet release tests using the stirrer methods (USP apparatus 1 and 2). *Dissolution Technologies*, 1996. May: p. 11–15.
29. Liu Q. Hydrodynamic effects of a cannula in a USP dissolution testing apparatus 2, in Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering. 2013, New Jersey Institute of Technology. p. 81.

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