Evaluation of Dissolution Hydrodynamics in the USP, Peak™ and Flat-Bottom Vessels Using Different Solubility Drugs

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Summary

This article is intended to share the preliminary results of studies that were conducted to gain a basic understanding of the role of hydrodynamics in dissolution testing. The existence of the 'dead zone' at the bottom of the USP vessel was confirmed by performing perturbation (vessel tilt) studies using the USP Prednisone calibrator tablets, and two Novartis Development tablet formulations containing a low and a high solubility drug. All formulations formed a 'cone' of disintegrated mass at the bottom of the vessels. The hydrodynamic environment in the Peak™ and in flat-bottom vessels was also evaluated using the low and high solubility drug formulations. There was no significant difference between the dissolution rates obtained by using the USP and flat-bottom vessels. The Peak vessel provided the highest release rates that were significantly different from those obtained by using USP and flat-bottomed vessels. Finally, at higher paddle speeds of 60 and 75 rpm, the results obtained from USP vessels were comparable to results from the Peak vessel operated at 50 rpm.

In developing dissolution methods, one must determine if the formulation is sensitive to this hydrodynamic artifact. If so, the paddle speed should be increased incrementally until this effect is minimized. The need for discriminating ability must be balanced against the agitation rate because at higher agitation rates the method tends to become less discriminating.

1. Introduction

The Dissolution test has evolved over the past three decades to become one of the most important tools in pharmaceutical testing. It provides assurance that the dosage form disintegrates and that its contents deaggregate, liberating the drug to go into solution for absorption to occur in the systemic circulation. Therefore, from a patient's perspective, Dissolution is an extremely critical test.

The USP Paddle Apparatus 2 is the most widely used instrument in dissolution laboratories (1). However, there is documented evidence that the paddle apparatus is sensitive to several variables such as vibration, rotation speed fluctuations, vessel shape and vessel imperfections leading to variable and inaccurate dissolution (2). Therefore, the robustness and ruggedness of the test must be thoroughly evaluated during method development and validation.

The variability in dissolution rates is more pronounced in Apparatus 2 at the commonly used rotation speed of 50 rpm due to radial flow in the cylindrical USP vessel. At this rotation speed, a 'dead zone' forms at the bottom of the USP vessel where the agitation rate is minimum. The disintegrated mass of a dosage form settles in this zone forming a 'cone' of trapped drug particles leading to low dissolution rates (3).

During recent years there has been renewed interest in the hydrodynamic aspects of dissolution testing. A variety of techniques such as ultrasound pulse echo (4), particle image velocimetry (5) and computational fluid dynamics (5, 6) have been successfully utilized for the characterization of vessel hydrodynamics. These articles have recon-firmed the presence of a dead zone at the bottom of the USP vessel underneath the paddle. For practitioners of Dissolution, cone formation has been a source of serious concern. Several vessel design modifications have been proposed to overcome the problem. One such proposal is a modified vessel design with a convex bottom such as the one found in wine bottles (7). This vessel became commercially available about eight years ago under the brand name of Peak vessel. It is not an official pharmacopeial standard and perhaps for that reason has not gained more acceptance. It is primarily used as a research tool in development laboratories rather than in quality control laboratories where routine testing is performed for batch release.

In most cases the coning artifact effect can be easily minimized or eliminated by simply increasing the paddle rotation speed rather than utilizing modified dissolution apparatus. This study was designed to evaluate the effect of paddle rotation speed. Furthermore, flat-bottom vessels were investigated as a potential solution to the hydrodynamic artifacts. It must be understood that in either case, the discriminating ability of the method is compromised. Therefore, during method development, one must manipulate the hydrodynamic effects in such a way that the method is robust and has the desired discriminating ability.

2. Experimental

Perturbation studies were performed in order to determine the existence of the dead zone in the USP vessel. The dissolution vessels were tilted by inserting shims between the lip of each vessel and the base plate of the dissolution equipment resulting in a tilt of 3 mm and 4.5 mm, respec-

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* The trade name Peak is property of Varian Corporation.
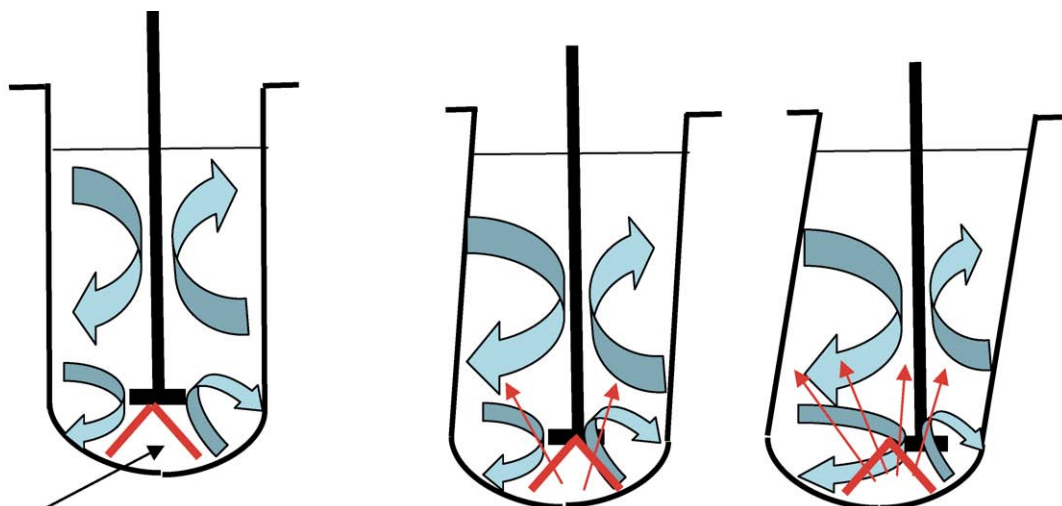
A 'cone' of disintegrated mass forms in the 'dead zone' trapping the drug particles

As the vessel is progressively tilted while keeping the paddle straight, the 'dead zone' experiences increasing agitation causing the 'cone' to disperse. The trapped drug is released and goes into solution.

Figure 1. Schematic of the perturbation study demonstrating the existence of a dead zone at the bottom of the USP vessel.

tively. Dissolution of the USP Prednisone Calibrator Tablets (Lot N) was performed using paddle apparatus (Apparatus 2) under each of the perturbed angles and under the normal set-up conditions. The premise was that the dissolution rate should increase as the hydrodynamics are altered causing more agitation within the dead zone of the tilted vessels. This would be a good indicator of the presence of the dead zone. A schematic of the altered vessel hydrodynamics caused by perturbation (vessel tilt) is shown in Figure 1. The dissolution was performed using paddles at 50 rpm with 500 mL of water as the medium. The Prednisone dissolution samples were analyzed using a UV-Visible spectrophotometer at a wavelength of 242 nm.

The study was repeated with a low solubility (LS) drug product that is currently under development at Novartis. The drug solubility in water is comparable to that of Prednisone. Just as with the USP Prednisone calibrator tablets, this formulation upon disintegration formed an insoluble mass at the bottom of the vessel. Dissolution of the tablets was performed in paddle apparatus under normal set-up (unperturbed condition) at 50 rpm, 60 rpm and 75 rpm. A perturbation study was performed by tilting the vessels by 4.5 mm. Finally, the dissolution test was performed in the Peak and flat-bottomed vessels at 50 rpm. The medium was 1000 mL of borate buffer, pH 8.0 containing 0.1% Tween® 80. The samples were pulled at 45 minutes, filtered and analyzed using a UV-Visible spectrophotometer at a wavelength of 277 nm.

The next experiments were performed to understand the effect of the hydrodynamics on a high solubility drug (HS). For this purpose a cone forming product that is currently under development at Novartis was chosen. Dissolution was

Table 1. Prednisone Tablets—Results of perturbation study (% prednisone released vs vessel tilt)

	Untilted	Tilted 3 mm	Tilted 4.5 mm
1	34.7	42.9	49.7
2	34.0	40.9	45.4
3	32.4	38.4	39.4
4	29.3	37.8	43.4
5	37.7	41.9	48.2
6	30.2	38.2	42.1
Average	**33.0**	**40.0**	**44.7**
Std Dev	**3.1**	**2.2**	**3.9**

performed in paddle apparatus under normal set-up (unperturbed conditions) at 50 rpm, 60 rpm and 75 rpm. A perturbation study was performed by tilting the vessels by 4.5 mm. Dissolution tests were also performed in the Peak and flat-bottomed vessels at 50 rpm. The medium was comprised of 900 mL of 0.1 N hydrochloric acid. The samples were pulled at 30 minutes, filtered and analyzed using a UV-Visible spectrophotometer at a wavelength of 240 nm. In all cases, the bath temperature was maintained at 37 ± 0.5 °C.

3. Results and Discussion
3.1. Hydrodynamic Evaluation Studies

Under the normal (unperturbed) apparatus set-up, only 30.0 ± 3.1% of the Prednisone was released. When the ves-

sels were tilted (perturbed) by 3.0 mm and 4.5 mm, the release rate increased to 40.0 ± 2.2% and 44.7 ± 3.9%, respectively. Unless specified otherwise, each experiment was run with 6 tablets (n=6). The gradual enhancement in the release rate implies that the flow at the bottom of the vessel increases when the vessels are tilted. This in turn disrupts the cone and exposes more drug to the dissolution medium, enabling the drug to go into solution. These results indicate that the flow is minimal at the bottom of the vessel. A linear regression analysis of tilt (mm) versus dissolution rate was performed. The correlation coefficient (r) was 0.997 indicating that within the ranges studied the dissolution rate increased linearly as the vessel tilt was increased.

The ANOVA test was performed to determine the *F*-ratio for the unperturbed and the two perturbed conditions. There is a statistically significant difference at the 95.0% confidence level between the means of the normal and the two perturbed conditions. The data are presented in Table 1. The bar graph and Box-and-Whisker plots are presented in Figure 2a and Figure 2b, respectively.

3.2. Hydrodynamic Impact on Different Solubility Drugs

The coning effect is mainly confined to dosage forms that are formulated with high amounts of insoluble excipients that form a disintegrated mass at the bottom of the vessel. It is also conceivable that the effect would be more pronounced with low solubility drugs. To test these hypotheses, two cone forming tablets were chosen, one containing a low solubility drug (LS) and the other containing a high solubility drug (HS). As described in the Experimental section, dissolution of the two formulations was performed first under normal set-up. Then the test was repeated under the perturbed condition by tilting the vessels. Finally, the dissolution was performed at higher rotation speeds of 60 rpm and 75 rpm. The data are presented in Table 2.
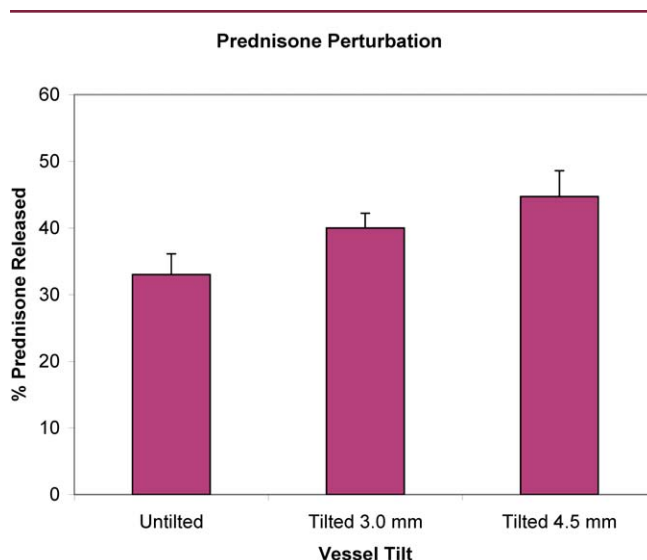

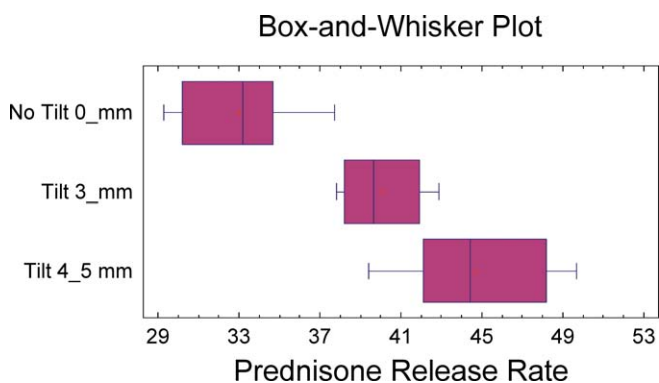Figure 2a. Plot of Prednisone tablets perturbation study (% prednisone released vs vessel tilt)

Figure 2b. Box and Whisker Plots of the Prednisone tablets perturbation study (% prednisone released vs vessel tilt)

Table 2. Release rates of LS (low solubility) and HS (high solubility) drugs with normal set-up at paddle speeds of 50, 60 and 75 rpm, and at the perturbed condition (vessel tilt of 4.5 mm)

	% LS Released in 45 Minutes				% HS Released in 30 Minutes			
	50 rpm		60 rpm	75 rpm	50 rpm		60 rpm	75 rpm
	Normal	Perturbed			Normal	Perturbed		
1	83.9	97.3	94.2	97.7	92.0	94.8	94.0	98.9
2	79.8	97.0	91.7	98.0	93.7	97.0	96.0	98.5
3	90.4	97.3	96.0	100.6	84.5	92.6	92.9	99.3
4	85.7	98.1	91.7	97.7	92.3	97.5	92.4	99.7
5	93.4	98.6	95.7	97.4	90.5	96.8	95.7	98.8
6	87.8	98.8	88.6	96.1	89.2	93.9	96.8	99.6
Average	86.8	97.8	93.0	97.9	90.4	95.4	94.6	99.1
Std Dev	4.8	0.7	2.9	1.5	3.3	2.0	1.8	0.5

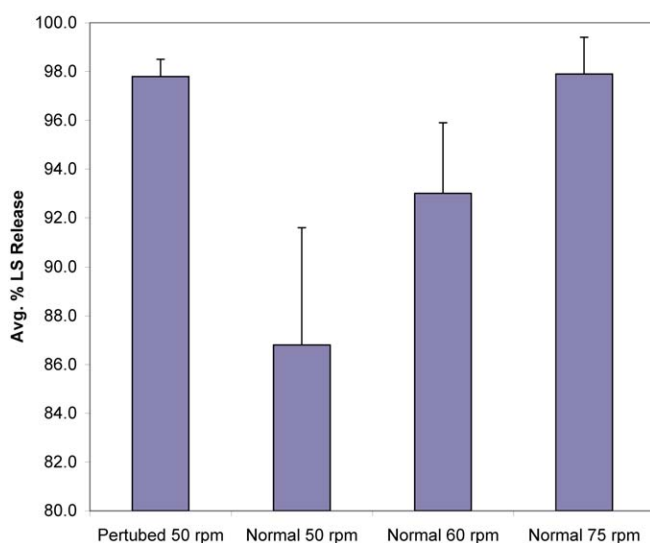**Avg. % LS Drug Release Under Different Experimental Conditions**

Figure 3a. Release rate of LS (low solubility drug) at different agitation rates in the USP vessel operated under normal set-up and perturbed conditions.

Avg. % HS Drug Release Under Different Experimental Conditions
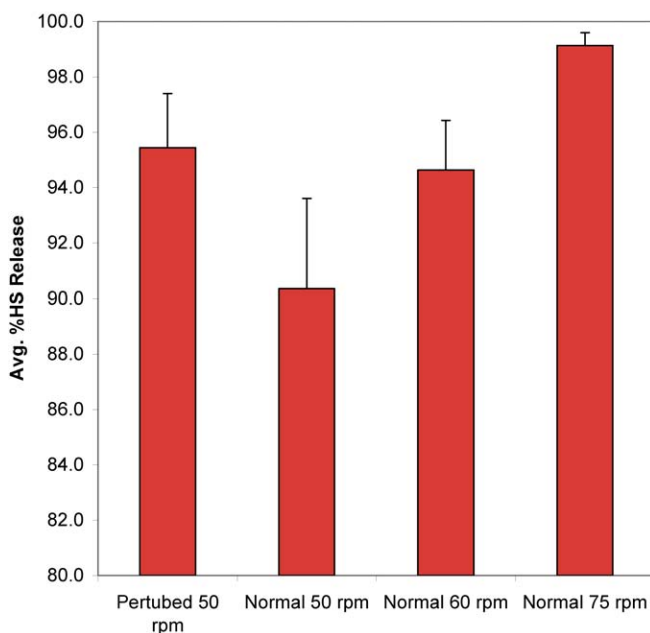
Figure 3b. Release rate of HS (high solubility drug) at different agitation rates in the USP vessel operated under normal set-up and perturbed conditions.

3.2.1. Results for LS (Low Solubility Drug)

Under normal set-up, the mean percentage LS released was 86.8% with a standard deviation of 4.8%. The LS release at 60 rpm and 75 rpm was 93.0% ± 2.9% and 97.9% ± 1.7%, respectively. For the perturbed condition with tilted vessels operated at 50 rpm, the LS release was

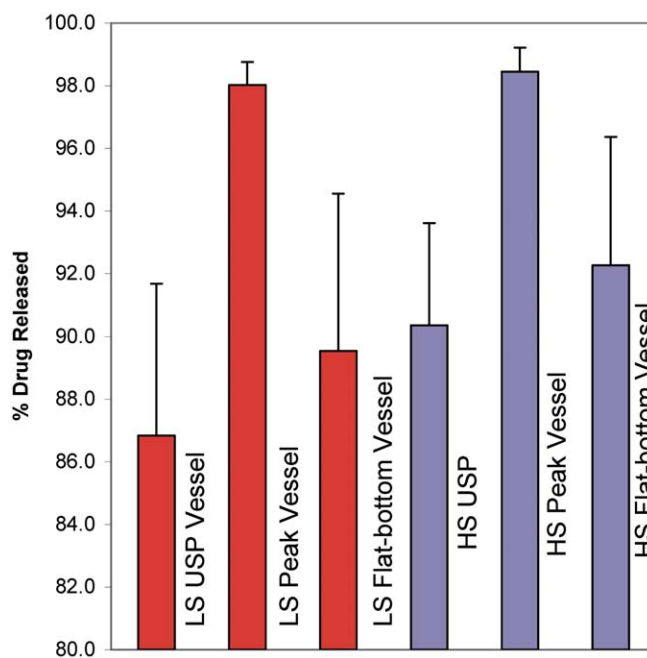**Average % LS and % HS Release in Regular, Peak and Flat-bottom Vessels**

Figure 4. Release rate of LS (low solubility drug) and HS (high solubility drug) from USP, Peak and Flat-bottom vessels

97.8% ± 0.7% which is very similar to that of normal set-up at 75 rpm. A plot of the data is presented in Figure 3a.

ANOVA test showed that the LS release obtained from the normal set up operated at 50 rpm was significantly different at 95% confidence level from that obtained at agitation rates of 60 rpm and 75 rpm. There was also a significant difference between the LS release obtained from the normal set up and the perturbed condition with tilted vessels. However, the results obtained from normal set-up operated at 75 rpm and the perturbed condition at 50 rpm were not significantly different.

3.2.2. Results for HS (High Solubility Drug)

Under normal set-up, the mean percentage HS released was 90.4% with a standard deviation of 3.3%. The HS release at 60 rpm and 75 rpm was 94.6% ± 1.8% and 99.1% ± 0.5%, respectively. For the perturbed condition with tilted vessels operated at 50 rpm, the HS release was 95.4% ± 2.0%. A plot of the data is presented in Figure 3b.

ANOVA test showed a statistically significant difference at the 95.0% confidence level between the mean HS release obtained from the normal set-up operated at 50 rpm and at the higher agitation rates of 60 rpm and 75 rpm. There was also a significant difference between the HS release obtained from the normal set-up and the perturbed condition with tilted vessels. Unlike LS, in this case there was a significant difference between the results obtained from normal set-up operated at 75 rpm and the perturbed condition at 50 rpm. This may be attributed to the fact that the
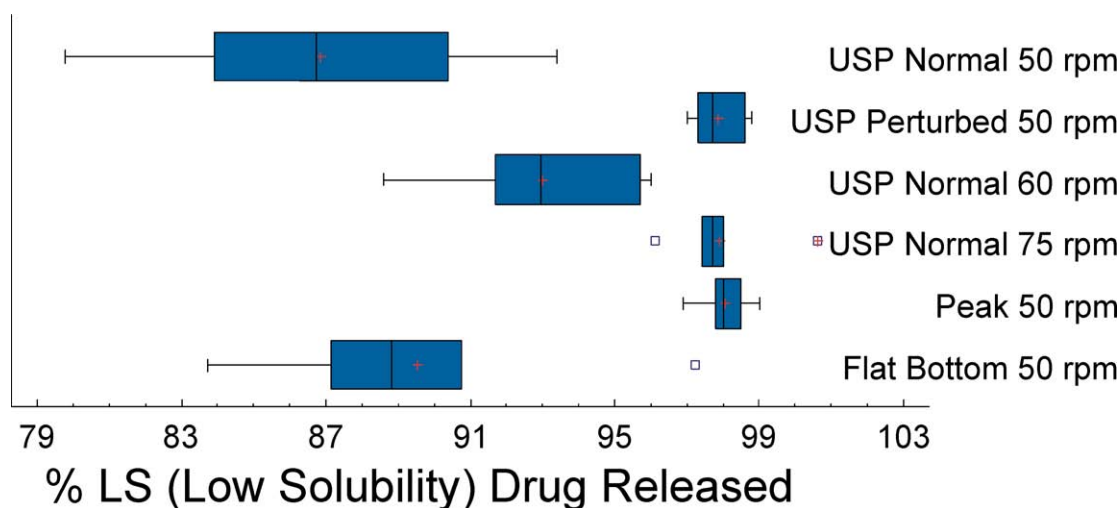
Figure 5a. Box-and Whisker Plots-Release rate of LS (low solubility drug) from USP, Peak and Flat-bottom Vessels and in USP Vessel Operated at Different Agitation Rates.
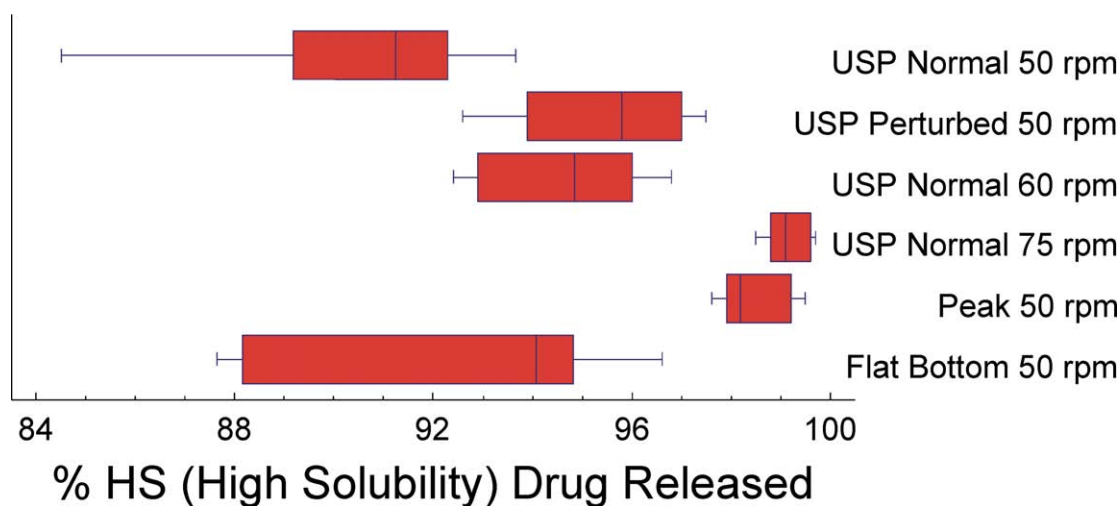

Figure 5b. Box-and Whisker Plots-Release rate of HS (high solubility drug) from USP, Peak and Flat-bottom Vessels and in USP Vessel Operated at Different Agitation Rates.

HS tablets formed a smaller cone packed with more dense and smaller particle size excipients as opposed to the cone formed by the LS tablets. An agitation rate of 50 rpm may not be sufficient to disrupt the denser cone formed by HS.

The difference between absolute average drug release for the LS under normal and perturbed setting was 11%. In the case of the HS it was only 5%. Similarly the difference between drug release for LS at 50 rpm and 75 rpm was 11.1% while for HS it was 8.6%. The results were less variable under perturbed condition and at higher rotation speeds when compared to the results from normal set-up. It can be concluded from these two examples of different solubility drugs that the hydrodynamics have a greater impact on the release rate of the low solubility drug. A more thorough analysis involving more drugs with varying solubility will have to be conducted in order to further

understand this hydrodynamic artifact. Every attempt will be made to study the drugs using the same volume of dissolution media. In the current study, for the HS and LS drugs the dissolution volumes were similar (900mL and 1000 mL). However, in the case of Prednisone, 500 mL of the dissolution media was utilized in order to comply with the official USP-validated method.

These studies suggest that the effect of hydrodynamics that lead to an artifact (cone formation) in the USP vessel can be minimized or even eliminated by simply increasing the agitation rate. The discriminating ability of the method may be maintained by selecting an optimum agitation rate which minimizes the effect of the hydrodynamic artifact but still provides the necessary discriminating ability. Further studies will be conducted to gain a better understanding of the aforementioned optimization.

Table 3. Release rates of LS (low solubility) and HS (high solubility) drugs from USP, flat-bottomed and Peak™ vessels

	%LS Release in 45 Minutes			%HS Release in 30 Minutes		
	USP	Peak Vessel	Flat Bottom	USP	Peak Vessel	Flat Bottom
1	83.9	96.9	90.8	92.0	97.9	94.1
2	79.8	97.9	97.2	93.7	99.5	96.6
3	90.4	98.5	88.8	84.5	97.6	94.8
4	85.7	98.1	87.2	92.3	98.5	87.6
5	93.4	97.8	83.7	90.5	97.9	88.2
6	87.8	99.0	***	89.2	99.2	***
Average	**86.8**	**98.0**	**89.5**	**90.4**	**98.4**	**92.3**
Std Dev	**4.8**	**0.7**	**5.0**	**3.3**	**0.8**	**4.1**
*** Tablets from the same lot not available						

3.3. Hydrodynamic Evaluation in Different Vessel Shapes

Dissolution of the LS and HS was performed in USP, Peak and flat-bottom vessels. The diameter and height of the all three vessels was within the USP <711> tolerances. The average release rate of LS in the USP, Peak and flat-bottom vessels operated at 50 rpm was 86.8% ± 4.8%, 98.0% ± 0.7% and 89.5% ± 5.0%, respectively. In case of HS, the release rate was 90.4% ± 3.3%, 98.4% ± 0.8% and 92.3% ± 4.1%, respectively. The data are presented in Table 3, Figures 4, 5a and 5b. There was no significant difference between the release rates obtained from the USP and flat-bottom vessels for either of the drugs. The Peak vessel generated the highest release rate for both drugs. In the USP and flat-bottomed vessels, the cone formed at the bottom of the vessel underneath the paddle. The cone was a bit flatter in the flat-bottom vessel when compared to the one in the USP vessel. No residue was observed at the corners of the flat-bottom vessel. The location of the cone in the flat-bottomed vessels varied slightly in relation to the paddle axis whereas in the USP vessel the cone was more or less right underneath the paddle. This may explain the slightly higher variability of results obtained from flat-bottomed vessels. The cone in the USP vessels shifted from the center location only if the dimensions of the hemispherical bottom of the USP vessels were different, with everything else being the same. The cone in the Peak vessel was located on top of the convex-shaped bottom. Unlike in the other two vessels, the cone was not stationary. It seemed to be rotating around the central axis. That would explain the higher release rates obtained using the Peak vessels.

4. Conclusions

Perturbation studies in which the USP vessels were slightly tilted resulted in higher dissolution rates for Prednisone calibrator tablets indicating the presence of minimal flow or dead zone at the bottom of the vessel underneath the paddle. Consequently the disintegrated mass cone that forms in this region traps the drug in it, resulting in artificially low results. The experiments were repeated with cone forming formulations of both a low and a high solubility drug. The results indicate that this artifact is more pronounced in low solubility drugs but can be easily resolved by increasing the shaft rotation speed.

The hydrodynamics in the USP, Peak and flat-bottom vessels were evaluated using the two formulations. There was no significant difference in the dissolution rates obtained using the USP and flat-bottom vessels for either the low and or the high solubility drug formulations. The dissolution rate for both formulations was significantly higher in the Peak vessels and was comparable to the results obtained at higher rotation speeds of 60 rpm and 75 rpm in the USP vessels.

More elaborate experiments are planned to further evaluate the effect of hydrodynamics on dissolution in different vessels. The findings will be shared in a separate paper.

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