Vibration Measurements on Dissolution Systems and Effects on Dissolution of Prednisone Tablets RS

e-mail: svangani@amgen.com

Saroj Vangani[1], Tawnya Flick, Germinia Tamayo, Rick Chiu, and Nina Cauchon

Small Molecule Pharmaceutics, Amgen Inc., One Amgen Center Drive, M/S 8-1-C, Thousand Oaks, CA 91320

Abstract

Efforts are being made by various groups (*1, 2*) to focus more on mechanical calibration as a potential replacement for Prednisone tablets RS (calibrator tablets). Although some mechanical calibration is currently performed (e.g., wobble, centering), the PhRMA committee's original proposal was to replace the Prednisone tablets RS through use of enhanced mechanical calibration.

A collaborative study (*3*) executed by PhRMA members to determine the feasibility of this idea demonstrated that the results obtained from the Prednisone tablets are operationally sensitive to several critical bath parameters. In addition, it was found that insufficient information exists to establish a meaningful tolerance for vibration (*4*).

The present study was performed to collect vibration information using two commercially available vibration meters, VanKel QAII station and Balmac 200. Vibration measurements were taken under normal conditions and in the presence of perturbations (slight and forced) generated artificially using a vortexer and a Vorti-Siv mixer. The main objective of the study was to determine if the apparatus could meet the proposed 0.1-mil displacement tolerance limit at the centerline of the vessel plate, and to observe what level of vibration is associated with 0.2-mil displacement.

In addition, the effect of vibration on the release of Prednisone from Prednisone tablets RS was also evaluated on three representative bath models: Varian VK-7000, Varian VK-7025, and Distek 2100B.

Introduction

There is only a brief mention in the USP of vibration requirements, consisting of the statement, "No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element." Vibration is a complicated concept that can result in the addition of energy to a system. The addition of energy from an external source can alter the results of a dissolution evaluation. Such an alteration is an unacceptable source of error that must be minimized. It can be minimized by eliminating all external sources so that only the tester machinery is left as a potential vibration source that is external to the drug delivery system under evaluation.

Vibration is defined as "a periodic motion of particles of an elastic body or medium in alternately opposite directions from the position of equilibrium when that equilibrium has been disturbed." The energy (vibration) causing this movement is an interrelated function involving acceleration, velocity, displacement, and frequency (which can occur in three dimensions and can be designated z, x, and y). For the purpose of discussion, a frame of reference must be established. Using the vessel plate as a starting point, the x-axis will begin at the front left edge and go toward the back of the plate. This leaves the left-to-right vector as the y-axis and the up-and-down vector as the z-axis (Figure 1).

As a measure of vibration, displacement is often reported, since it is this relative motion that can be sensed by placing a hand on the tester. This is a measure of the up-and-down (in the z axis) motion of the item of interest, in this instance, a dissolution tester. How often this up-and-down motion occurs is of equal importance, and this is the frequency. To measure one without the other does not provide sufficient information concerning the overall vibration. Vibrations of the same displacement but with differing frequency would not input the same amount of energy into a system over a given period of time. Frequency can be estimated based on eq 1.

$$[1] \qquad F = \frac{V}{D}$$

where F is frequency, V is velocity, and D is displacement.

Common vibration meters display displacement in mils (which is an English unit that corresponds to 0.001 inch), velocity in inches/sec, and acceleration in units of gravity (g), which allows easier conversion between metric and common (English unit) values of velocity and displacement.
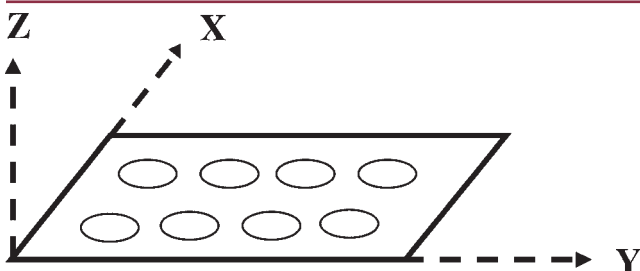

Z   X

Y

Figure 1. Frame of reference on dissolution baths for vibration measurements (5).

[1]Corresponding author.

Table 1. Vibration measurements in air using VanKel QAII station (n=3).

Condi-tions	Bath Mfg	Model	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
			x	y	z	x	y	z	x	y	z	x	y	z
Normal	VANKEL-1	VK-7000	0.001	0.000	0.001	33.66	6.51	53.26	0.001	0.001	0.002	0.008	0.017	0.009
Slight Vibra-tion			0.001	0.000	0.001	76.47	67.34	61.96	0.001	0.001	0.002	0.008	0.017	0.009
Forced Vibra-tion			0.040	0.038	0.041	51.28	61.21	62.80	0.040	0.039	0.045	0.2	0.202	0.240
Normal	VANKEL-2	VK-7025	0.000	0.000	0.000	0.000	6.01	0.000	0.000	0.0012	0.000	0.000	0.022	0.000
Slight Vibra-tion			0.012	0.016	0.010	54.88	46.75	21.98	0.0141	0.0223	0.0298	0.082	0.155	0.431
Forced Vibra-tion			0.034	0.016	0.029	41.80	40.12	40.62	0.0505	0.0259	0.0437	0.385	0.205	0.342
Normal	DISTEK-1	2100B	0.009	0.000	0.000	86.68	0.000	0.000	0.0065	0.000	0.000	0.024	0.000	0.000
Slight Vibra-tion			0.012	0.011	0.007	58.80	54.85	39.68	0.0127	0.0126	0.0112	0.068	0.073	0.090
Forced Vibra-tion			0.021	0.011	0.011	41.20	45.79	32.64	0.0326	0.0149	0.0218	0.253	0.103	0.214

This study was designed to evaluate the level of existing vibration on dissolution systems and to study and understand the effects of vibration on dissolution results.

Four studies were conducted using two commercially available vibration meters (Balmac 200 and a VanKel Technology Group QAII station). USP Apparatus 2 (paddle) was used as the stirring element in all the studies. All four studies were done on the baths available in our laboratory.

In the first study, vibrations were recorded on the vessel plate of dissolution testers under normal operation and with paddles rotating at 100 rpm in air. Normal operation consists of paddles (at 100 rpm) with six vessels each containing 900 mL of water, with the heater circulator operating at a set water bath temperature of 37.5 °C.

A second vibration study was conducted with a source of vibration placed on the bench close to the dissolution tester, measuring below the PhRMA proposal of 0.2-mil displacement.

A third vibration study was conducted with a source of vibration placed on the bench close to the dissolution tester, measuring close to or greater than the PhRMA proposal of 0.2-mil displacement. Measurements were taken using the two vibration meters, and visual observations of any detectable ripple patterns in the media were made.

The fourth study targeted the impact of vibrations on the performance of Prednisone tablets RS using three representative bath models.

Materials and Methods

Materials
Prednisone tablets RS (10 mg, lot # 00C056) and standard were obtained from USP.

Methods
Vibration measurements
Vibration information was collected using two different vibration meters (Balmac 200 and QAII station). The vibration measurements were made in x, y, and z directions at the center of the vessel plate on three different baths, VK7000

Table 2. Vibration measurements in water using VanKel QAII station (n=3).

Conditions	Bath Mfg	Model	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
			x	y	z	x	y	z	x	y	z	x	y	z
Normal	VANKEL-1	VK-7000	0.000	0.000	0.001	0.000	0.000	49.39	0.000	0.000	0.0014	0.000	0.000	0.009
Slight Vibration	VANKEL-1	VK-7000	0.009	0.004	0.001	94.20	103.66	54.95	0.0064	0.0025	0.0021	0.023	0.007	0.013
Forced Vibration	VANKEL-1	VK-7000	0.016	0.013	0.073	74.95	72.80	59.45	0.0142	0.0117	0.0756	0.063	0.051	0.404
Normal	VANKEL-2	VK-7025	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Slight Vibration	VANKEL-2	VK-7025	0.013	0.012	0.014	77.92	53.53	99.05	0.0112	0.0302	0.0092	0.045	0.044	0.031
Forced Vibration	VANKEL-2	VK-7025	0.008	0.017	0.014	23.18	27.84	23.25	0.0238	0.0394	0.0381	0.326	0.454	0.521
Normal	DISTEK-1	2100B	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Slight Vibration	DISTEK-1	2100B	0.003	0.004	0.009	38.53	36.54	41.80	0.0053	0.0078	0.0139	0.043	0.068	0.105
Forced Vibration	DISTEK-1	2100B	0.016	0.008	0.027	39.23	38.74	34.49	0.0267	0.0132	0.0488	0.217	0.108	0.450

(VanKel-1), VK7025 (VanKel-2), and Distek 2100B (Distek-1). Measurements were taken in triplicate for the following three conditions, and the mean was reported:

Figure 2. Displacement values for Distek 2100 B in x, y, and z directions using Balmac 200 and VanKel QAII station in air and water.

(a) Normal (No Vibration)
(b) Slight Vibration (~0.1-mil displacement)
(c) Forced Vibration (≥0.2-mil displacement)

Perturbations for slight vibration studies were accomplished by placing the VX2500 multiple vortexer (Speed 5) next to the dissolution bath, facing and touching the dissolution bath. Perturbations for forced vibration studies were accomplished by placing the Vorti-Siv next to the dissolution bath (this equipment did not have speed settings, hence the default settings were used).

Vibration Measurements in Air
Paddles were raised to the highest position above the dissolution plate and were set to rotate at 100 rpm. No dissolution medium was placed in the vessels. Measurements were taken in x, y, and z directions.
Note: *Balmac 200 does not display frequency. Hence, the reported values for frequency are the calculated values (based on eq 1) determined from measured displacement and velocity (Tables 3 and 4).*
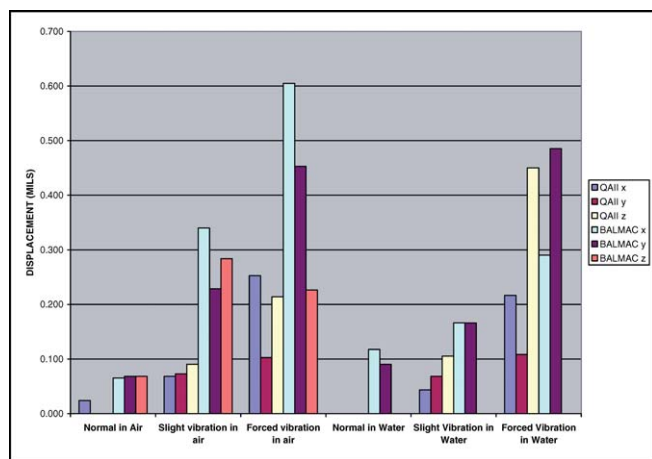
Table 3. Vibration measurements in air using Balmac 200 (n=3).

Condi-tions	Bath Mfg	Model	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
			x	y	z	x	y	z	x	y	z	x	y	z
Normal	VANKEL-1	VK-7000	0.004	0.005	0.006	69.616	61.728	58.789	0.004	0.005	0.006	0.035	0.044	0.058
Slight Vibra-tion			0.012	0.018	0.099	45.010	50.637	59.140	0.016	0.022	0.103	0.138	0.125	0.534
Forced Vibra-tion			0.125	0.152	0.420	77.160	97.522	63.181	0.100	0.096	0.411	0.771	0.621	1.995
Normal	VANKEL-2	VK-7025	0.005	0.004	0.004	61.728	37.037	53.319	0.005	0.007	0.005	0.076	0.094	0.074
Slight Vibra-tion			0.028	0.009	0.018	34.339	29.181	34.014	0.050	0.018	0.033	0.711	0.288	0.405
Forced Vibra-tion			0.037	0.031	0.065	42.295	29.745	39.337	0.054	0.064	0.102	0.440	0.531	0.727
Normal	DISTEK-1	2100B	0.005	0.004	0.004	61.728	66.872	4.066	0.005	0.004	0.056	0.065	0.068	0.068
Slight Vibra-tion			0.028	0.019	0.022	41.642	41.394	39.017	0.042	0.028	0.035	0.340	0.229	0.284
Forced Vibra-tion			0.041	0.044	0.014	35.768	41.675	38.468	0.071	0.066	0.023	0.605	0.453	0.226

Vibration Measurements in Water

Paddles were lowered into the dissolution vessels containing 900 mL of water and then maintained at 37 °C. The paddles were set to rotate at 100 rpm.

Notes: *It was not feasible to take vibration measurements in y and z directions in water on VanKel 7025 (VanKel-2) using Balmac 200 vibration meter due to the design constraints.*
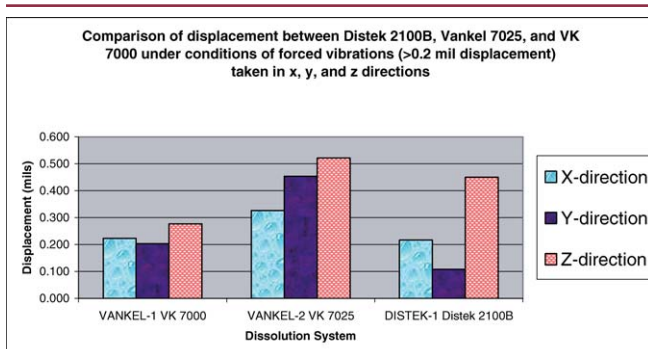

Figure 3. Comparison of displacement values between three bath models (Distek 2100B, VK 7000, and VK 7025) measured during conditions of forced vibrations using QAII station with the stirring units in water.

Hence, no results were reported for the same (Table 4).

Vibration measurements with the stirring elements in water involved lowering the drive unit. For some measurements, the vibration meters had to be placed between the drive unit and the vessel plate. Because of this, the paddles were slightly above the 2.5-cm USP specified limit from the bottom of the vessel for VK 7025 (VanKel-2) while taking the measurements.

Evaluation of the Impact of Forced Vibrations on Dissolution

The effect of vibration on the dissolution of Prednisone tablets was evaluated on three representative bath models, VK7000, VK7025, and Distek 2100B. Dissolution of Prednisone tablets was performed according to the USP procedure (50 rpm, USP Apparatus 2, 30 minutes, 900 mL of deaerated water at 37 °C).

Two sets of dissolution experiments were conducted using the Prednisone tablets RS (n=6), one under existing conditions (normal) and one under forced vibration conditions. Vibration measurements were taken in triplicate during the dissolution run, and the mean was reported.

Table 4. Vibration measurements in water using Balmac 200 (n=3).

Conditions	Bath Mfg	Model	Acceleration (g)			Frequency (Hz)-Calculated			Velocity (in/s)			Displacement (mil)		
			x	y	z	x	y	z	x	y	z	x	y	z
Normal			0.008	0.008	0.008	67.240	50.526	39.879	0.007	0.009	0.012	0.069	0.097	0.059
Slight Vibration	Vankel-1	VK7000	0.052	0.023	0.056	73.050	112.140	63.641	0.044	0.013	0.054	0.228	0.124	0.300
Forced Vibration			0.040	0.075	0.231	73.269	85.892	69.124	0.034	0.054	0.206	0.209	0.370	1.067
Normal			0.004	n/a	n/a	39.193	n/a	n/a	0.006	n/a	n/a	0.111	n/a	n/a
Slight Vibration	Vankel-2	VK7025	0.017	n/a	n/a	24.187	n/a	n/a	0.043	n/a	n/a	0.785	n/a	n/a
Forced Vibration			0.018	n/a	n/a	50.586	n/a	n/a	0.022	n/a	n/a	0.201	n/a	n/a
Normal			0.006	0.006	n/a	76.132	44.582	n/a	0.005	0.008	n/a	0.118	0.090	n/a
Slight Vibration	Distek-1	2100B	0.018	0.008	n/a	53.792	49.944	n/a	0.021	0.010	n/a	0.166	0.166	n/a
Forced Vibration			0.025	0.021	n/a	45.415	26.514	n/a	0.034	0.050	n/a	0.290	0.485	n/a

Note: It was not feasible to take vibration measurements in y and z directions in water on VanKel 7025 (VanKel-2) and Distek 2100B (Distek-1) using Balmac 200 vibration meter due to the design constraints. Hence, no results have been reported for the same in Table 4.

Results and discussion

Vibration Measurements Using VanKel QAII Station

Table 1 displays the vibration measurements taken in air, and Table 2 displays the measurements in water on various dissolution baths using the VanKel QAII station vibration meter.

It is clear from Tables 1 and 2 that the displacement, velocity, acceleration, and frequency values for all the baths were much lower in the presence of water than in air, particularly for measurements under normal conditions.

For measurements with stirring elements in water (Table 2), all baths showed comparable values (close to zero) in all directions and under all vibration conditions: normal, slight, and forced.

The effect of slight and forced vibrations was quite significant on the frequency measurements as compared to the displacement, velocity, or acceleration measurements.

As is clear from the displacement values (x, y, and z direction) taken with stirring elements in water (Table 2), the VK 7000 bath was least impacted by forced vibrations. The high frequency values (see section "Relationship Between
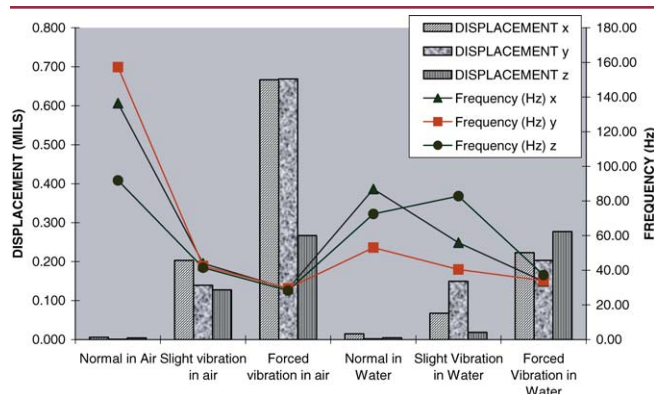

Figure 4. Frequency versus displacement relationship on VK 7000 using QAII station.

Table 5a. Percent release of Prednisone under normal conditions and under forced vibration conditions on VK7000.

Vessel	% Dissolved (with Vibration)	% Dissolved (Normal)	Pass with Vibration
1	80	37	NO
2	76	37	NO
3	62	31	NO
4	67	33	NO
5	88	33	NO
6	83	31	NO
Mean	76	34	
SD (±)	9.9	2.7	

Figure 5. Dissolution data of Prednisone tablets at normal conditions and under forced vibration.

Displacement and Frequency") for this bath under this condition confirmed the results.

Vibration Measurements Using Balmac 200

Table 3 displays the vibration measurements taken in air, and Table 4 displays the measurements in water on various dissolution baths using the Balmac 200 vibration meter.

It is clear from Tables 3 and 4 that the displacement, frequency, acceleration, and velocity measurement values in air and water were not significantly different for all the baths.

All measurements values (displacement, velocity, acceleration, and frequency) for forced vibration measurements on the VK 7000 bath (Table 3) indicate that this bath model was most impacted by the forced vibrations in air. No such conclusion could be made for other baths due to insufficient measurements in water.

Comparison of Balmac 200 and VanKel QAII Station in Terms of Displacement

It is clear from Tables 1–4 that all vibration measurements made using the Balmac 200 were much higher than those measured with the QAII station, particularly under normal conditions. For the forced vibration conditions, the
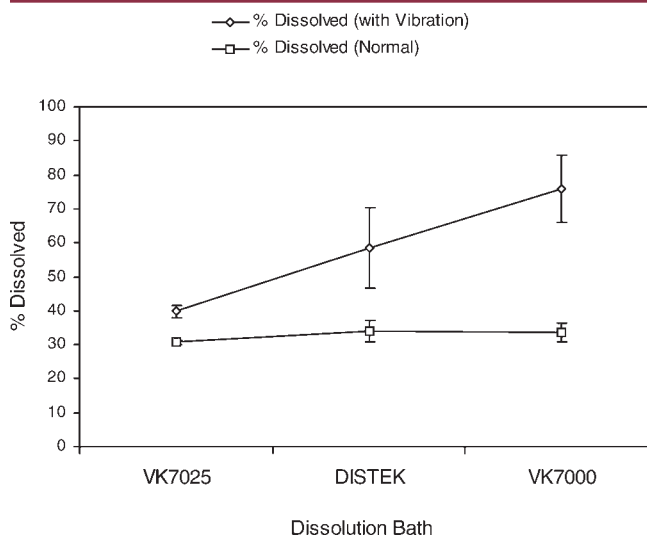
frequency values for the two vibration meters were not significantly different. The reason for the high vibration measurements for the Balmac 200 could be because of the high background noise associated with this vibration meter which led to large fluctuations and higher readings than for the VanKel QAII station. The handling of the Balmac 200 meter was more critical than for the QAII station.

Figure 2 is the graphical comparison of displacement values obtained in air and water using the two vibration meters on one of the baths, Distek 2100B (Distek-1). It is clear from the data that for both meters, there was an increase in the displacement values with an increase in vibration intensity (from external sources) in all directions (x, y, and z). This was true for both air and water.

It is also evident from the graph that QAII station was more sensitive (better correlation between forced vibration and changes in displacement measurements) in the z direction, whereas Balmac 200 was more sensitive in the x direction for displacement-value measurements.

Figure 3 is a graphical display of the comparison of displacement values in three bath models, Distek 2100B, VK 7000, and VK 7025 measured using VanKel QAII Station in water during the forced vibration study.

Table 5b. Mean of triplicate vibration measurements that were taken during the experiment.

Vibration Meter	Perturbation (Y/N)	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
		x	y	z	x	y	z	x	y	z	x	y	z
QAII	Y	0.007	0.017	0.013	28.58	35.11	28.86	0.017	0.032	0.029	0.189	0.291	0.318
Balmac 200	Y	0.019	0.028	0.041	41.89	42.16	37.22	0.028	0.041	0.068	0.336	0.469	0.691

Table 6a. Percent release of Prednisone under normal conditions and under forced vibration conditions on VK7025.

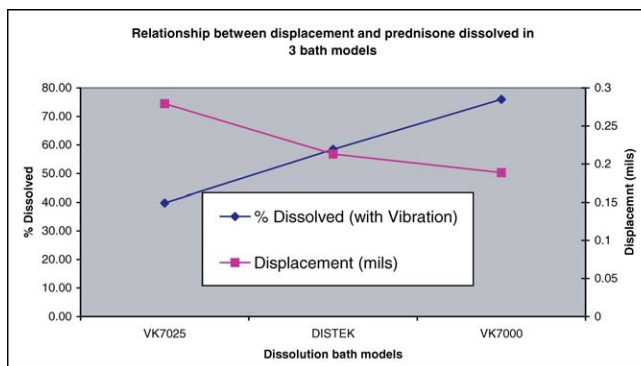| Vessel	% Dissolved (with Vibration)	% Dissolved (Normal)	Pass with Vibration
1	38	30	YES
2	39	30	YES
3	44	30	YES
4	39	30	YES
5	40	32	YES
6	39	31	YES
Mean	40	31	
SD (±)	2.1	0.8	

Figure 6. Relationship between displacement (x direction) values and percent release of Prednisone in three bath models in presence of forced vibrations.

It is evident from the graph that under conditions of forced vibrations, VK 7025 was most impacted in all directions as compared with the other bath models. Distek 2100 B showed minimum displacement values in the y direction. X-direction values were comparable for VK 7000 (VanKel-2) and Distek 2100B bath models under the same conditions.

Relationship between Displacement and Frequency

Measurements on VK 7000 using VanKel QAII station show the existence of an inverse relationship between the displacement and frequency. It is evident from the graph in Figure 4 that forced vibrations, both in air and water, showed maximum displacement values but minimum frequency values. Similarly, for measurements under normal conditions, the displacement values were minimal in air and water, but the frequency values were at the maximum, confirming the existence of this inverse relationship.

Frequency is a measure of how often the displacement occurs. Vibrations of the same displacement, but with differing frequency, will input different amounts of energy into the system during a given period. Measurement of displacement without frequency does not provide sufficient information about the overall vibration.

Dissolution Data on VanKel Dissolution Bath Model VK 7000

Table 5a contains the dissolution data obtained on Prednisone tablets under normal conditions and in presence of forced vibrations on the VanKel VK 7000 dissolution bath. Table 5b shows the mean of the triplicate vibration measurements taken using the two vibration meters during the actual run.

It is clear from Table 5a that in presence of forced vibrations (≥ 0.2 mil of displacement), all of the tablets failed to meet the USP limits (27–48% of Prednisone dissolved in 30 min). All tablets showed a significant increase in the percentage of Prednisone dissolved as compared with the USP limit.

Dissolution Data on VanKel Dissolution Bath Model VK 7025

Table 6a shows the Prednisone tablets RS dissolution data under normal conditions and in the presence of forced vibrations on VK 7025. The mean of the triplicate vibration measurements taken using the two vibration meters during the actual run is found in Table 6b.

It is clear from Table 6a that in presence of forced vibrations (≥ 0.2 mil of displacement), all tablets were within the USP limits (27–48% of Prednisone dissolved in 30 minutes).

Table 6b. Mean of triplicate vibration measurements that were taken during the experiment.

Vibration Meter	Perturbation (Y/N)	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
		x	y	z	x	y	z	x	y	z	x	y	z
QAII	Y	0.017	0.014	0.027	34.68	41.97	36.00	0.030	0.021	0.047	0.279	0.162	0.419
Balmac 200	Y	0.041	0.050	0.080	37.34	42.68	36.55	0.068	0.072	0.136	0.583	0.614	1.412

Table 7a. Percent release of Prednisone under normal conditions and under forced vibration conditions on Distek 2100B.

Vessel	% Dissolved (with Vibration)	% Dissolved (Normal)	Pass with Vibration
1	55	32	NO
2	65	32	NO
3	71	35	NO
4	43	35	YES
5	47	30	YES
6	70	39	NO
Mean	58	34	
SD (±)	12.0	3.2	

Dissolution Data on Distek Dissolution Bath Model 2100B

Table 7a contains the dissolution data on Prednisone tablets under normal conditions and in the presence of forced vibrations on Distek 2100B. The mean of the triplicate vibration measurements taken using the two vibration meters during the actual run is found in Table 7b.

It is clear from Table 7a that in presence of forced vibrations (≥ 0.2 mil of displacement), only two tablets were within the USP limits (27–48% of Prednisone dissolved in 30 min).

Relationship between Percentage Release of Prednisone and Displacement under Conditions of Forced Vibration

Figure 5 is a graphical comparison of the performance of Prednisone tablets under normal conditions and in the presence of forced vibrations in three representative bath models. It is clear from the graph that the forced vibrations had the least effect on the VK7025 dissolution bath. This could also be the reason that all the Prednisone tablets RS passed on this dissolution system even in the presence of forced vibrations.

Figure 6 shows the relationship between the percentage of Prednisone dissolved and displacement (measured in x direction using QAII) in 3 bath models under conditions of forced vibration. It is clear from the graph that the percentage of Prednisone did not change significantly even in presence of forced vibrations on VK 7025 bath model.

It is evident from Tables 5a, 6a, and 7a that forced vibrations caused both the percent release of Prednisone and the variability to shift towards higher values. For VK 7000, a 42% increase in the mean (from 34% to 76%) was observed with more than tripling of the SD (2.7 to 9.9). For VK7025, a 9% shift in the mean (31% to 40%) and an almost tripling of the SD (0.8 to 2.1) were observed. For Distek 2100B, a 24% shift in the mean (34% to 58%) and more than tripling of SD (3.2 to 12) were observed. It is important to note that many of the perturbed-condition experimental data produced out-of-range results. Interestingly, the statistics also point to a similar change and, in this case, more consistently.

Conclusion

The two vibration meters, Vankel QAII and the Balmac 200, gave different responses. It is evident from the data on vibration measurements that Balmac 200 is more sensitive (larger fluctuations) than the Vankel QAII vibration meter. This may be because the meter has higher background noise, which leads to large signal fluctuations in the measurements. A proposed 0.1-mil displacement tolerance limit seems to be achievable with the VanKel QAII meter but not with the Balmac 200 meter. The design of the sensors could be one of the causes of the directional sensitivity to vibration.

From the vibration information collected, there does not seem to be trend between the displacement values and the direction of measurement (x, y, and z orientation of the vibration meters). However, in most cases for both vibration meters, the displacement values in the z direction were higher than those in the x and y directions. In addition, in most cases, vibration measurements in water were lower than in air.

Table 7b. Mean of triplicate vibration measurements that were taken during the experiment.

| Vibration Meter	Perturbation (Y/N)	Acceleration (g)			Frequency (Hz)			Velocity (in/s)			Displacement (mil)		
		x	y	z	x	y	z	x	y	z	x	y	z
QAII	Y	0.019	0.004	0.005	42.76	40.99	37.92	0.028	0.008	0.009	0.213	0.063	0.073
Balmac 200	Y	0.014	0.018	0.099	46.28	55.82	38.41	0.019	0.020	0.161	0.163	0.177	1.208

Based on the data, displacement should be measured in a consistent direction with a specified vibration meter that has been proven to meet the specific tolerance under normal conditions. The best way to mimic the vibration during a true dissolution run would be to measure the vibration while the vessels are filled with water.

Two vibration sources causing the same displacement but at different frequencies will input different amounts of energy to the system. This can have variable effect on the dissolution rate. Hence, simultaneous measurement of both frequency and displacement will better allow us to understand the overall vibration effects.

In the Prednisone study, forced vibrations (≥ 0.2-mil displacement) resulted in a higher percentage of Prednisone dissolved in 30 min. However, all tablets met the USP limits on Prednisone tablets RS on the VK 7025 bath model. This could be related to the design of this dissolution bath or be simply a function of this particular bath and its placement within the laboratory.

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Edited by
JENNIFER DRESSMAN
JOHANNES KRÄEMER

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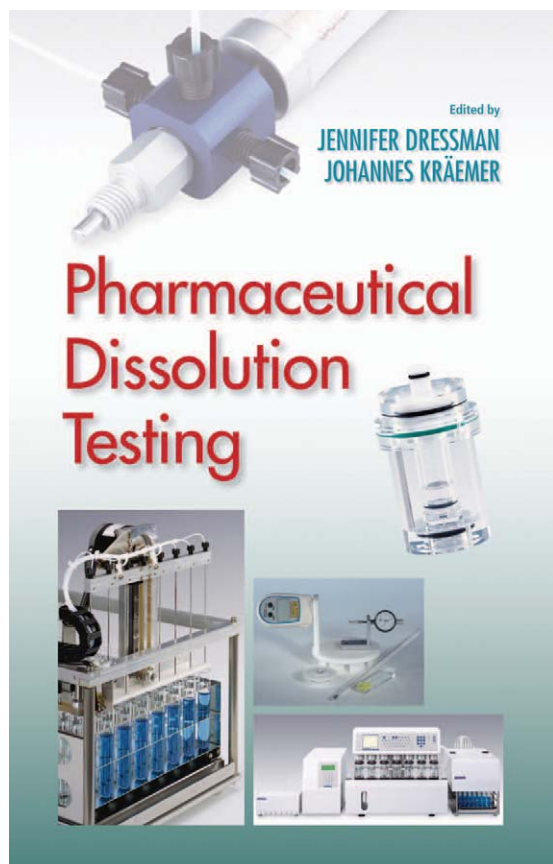
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