

Why is Vibration an Issue for Dissolution Testing?

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1 Introduction

It has become apparent in the recent past, that vibration within the Tablet Dissolution testing environment is a real issue.

Although this may not have been too apparent in the normal routine dissolution testing, the real impact of vibration has become a focal point as a result of the Prednisone “Calibrator Tablet” tests which generally have to be performed every 6 months on each instrument within the testing environment. Prednisone tablets are referred to as “Disintegrating” tablets as they break down in the medium very quickly to form a powdered mass, either in the basket (Apparatus 1) or as a fairly well defined cone under the Paddle (Apparatus 2). The second system validation test is made using Salicylic Acid tablets which are “non-disintegrating”, so they keep their form throughout the test and just dissolve away.

The Prednisone tablet is 10mg in active content and so has a large percentage of excipients present. The Salicylic Acid tablet is made entirely of Salicylic Acid with no excipients present.

2 What can go wrong?

The discussion will be limited to the Prednisone tablets as these are more affected by the issues under discussion.

Up to this point there were certain “anomalies” noted with these tests and a lot of the spurious results that were obtained during the performance of these tests were put down to various causes, normally the quality of the Tablets. This was a particular problem when the formulation was changed from a 50mg tablet to a 10mg tablet. Up to this point there were no influences noted with the 50mg formulation. The 10mg formulation however, presented some challenges and it became apparent that the dissolution release rate was greatly influenced by two main factors:

- Dissolved gasses, and
- Vibration.

On many occasions, the combination of poor de-aeration and vibration can work together to produce all manner of strange effects. The dissolved gasses issue can be easily resolved using a suitable de-aeration technique. At this point it is reasonable to draw a difference between “degassing” and “de-aeration”. Degassing is a technique whereby dissolved gasses with a high solubility product can be displaced by dissolving in a gas with a lower solubility product. Typically, Helium can be used to displace both Nitrogen and Oxygen in aqueous media. De-aeration, on the other hand, is a method by which we can physically remove the dissolved gasses from the medium. If we follow the USP requirements, then this can be achieved by a combination of heating, vacuum and circulation (ref.1).

A suitable level of de-aeration can also be achieved using a system as described below, the DDS Medium De-aerator and preparation System. This instrument allows the bulk preparation of suitably de-aerated medium at the correct working temperature of $37.0 \pm 0.5^{\circ}\text{C}$, delivered to the vessel. Correction can also be made for the density of the medium at the working temperature. In this case the water density at 37°C is 0.9934g/ml. This means that for a volume of 900ml at 37°C , only 894g is dispensed. The instrument is described in Fig. 1.



Fig.1: the PTDDS-4 Medium Preparation and De-aerator System.

The PT-DDS instrument can be easily adjusted and calibrated with a 1kg weight. Medium delivery can be either gravimetric (illustrated) or volumetric with a pistol grip dispenser. De-aeration quality can be easily measured using a dissolved oxygen meter (DO₂). The final Oxygen concentration should be less than 50% as seen on the instrument display.



Failure to de-aerate correctly, prior to a Prednisone test can result in an enhanced active release rate of nearly double the release rate for correctly de-aerated media. A failed test is therefore more than certain.

So this takes care of the De-aeration issue. What about Vibration?

Vibration sources can be very diverse in origin. Some of the sources are listed below.

- Internal Sources
- External Sources
- Intermittent and Operational Sources

3 Internal Sources

3.1 The Heater / Circulator

These basically arise from the instrument construction and the types of components used to manufacture the machine. The first major source is that of the heater/circulator. Some of these devices are normally of a basic design with a reasonably powered pump which takes water from the bath, circulates it through a heater element and then returns it to the bath. Unfortunately this is often one of the least developed parts of the instrument package and

therefore because of the generally “low cost” design are not in any way vibration proofed and sit on the work bench beside the dissolution bath and rumble away. These devices generate a lot of 50/60Hz noise which is transmitted through to the dissolution bath.

3.2 The Drive Motor

The next source is that of the tool rotational motor, drive belts and bearings. The rotational motor can be a source of vibration. It normally is a DC motor with a gearbox attached. The gearbox has to be maintained and checked for squeaks and rattles.

3.3 The Drive Belts

The drive belts fall into two classes. Those which are expected to drive all tool shafts from a single belt and those which have a high contact angle with the drive shaft mechanism (so multiple belt drives). Generally the quality of the belt will play a big role in the generation of higher pitched vibration which is then transmitted down the tool shaft which adds another dimension to the tablet disintegration and dissolution process. Noise generated in this way will turn the tool shaft into a type of ultrasonic disintegration probe resulting in higher dissolution rates, especially for Apparatus 1 baskets. The effect is not so profound with Apparatus 2 paddles. Using Prednisone with Apparatus 1, you can tell if there has been significant high frequency vibration transmission by the amount of “escaped” powder at the base of the dissolution vessel. Inspection of the belts will show immediately if there has been some wear and if they are shiny, then the impact on the metal or plastic drive cog wheels at the top of tool shaft will be to generate noise. You can either replace the belts or use a silicone grease based PTFE loaded spray (sparingly) which will smooth out the noise.

3.4 The Bearings

The bearings themselves can be either lubricated for life or grease packed (generally in older models). The bearings are not generally checked for wear and tear themselves but are tested as a function of the tool wobble test which is part of the OQ procedure. Of course there is the need to distinguish between tool wobble and bearing induced wobble. The bearing contribution to the overall wobble can be easily measured at the part of the tool which passes through the bearing and is located at the top of the dissolution tester head. If the tools are in a sealed bearing then this is not possible. Your only guide will then be the wobble or run out at the end of the tool shaft. However, the bearing / tool wobble may not be totally indicative of bearing noise. Wobble measurements may not show up sporadic bearing noise (typically a knocking). This can influence the dissolution rate very significantly especially with Apparatus 1 baskets. Excessive tool wobble may be indicative of distorted tools or worn bearings. An experienced investigator will be able to feel any unusual bearing behaviour.

3.5 External Sources

So this is the mechanical side, but what about the environment around the instrument? Almost no attention is paid to environmental sources. Only on some occasions there is such an influence that the lab is more or less forced to concede that there are, up to now, hidden forces at work.

A typical example was that of a 12 position bath placed in a laboratory where most of the instrument was resting on an old weighing table (so really stable) and the rest of the instrument (about the last 1/3) was resting on an extension to this weighing table which was made from “kitchen” style worktop with a thin metal frame as a support. During the Prednisone tests it was noted 3 times that vessels 5 and 6 as well as 11 and 12 were failing the test when 1, 2, 3 and 4 in the front row as well as 7, 8, 9 and 10 in the back row were well within the range. The answer was a BET Surface Area Analyser which uses a high vacuum pump to de-gas powdered samples prior to analysis. The pump runs more or less the whole time and is usually the least serviced part of the instrument system. The pump was resting on the floor but only about 0.5 metres from the base of the frame support. The vibration transmission was easily spotted in the poorly supported dissolution vessels as a series of concentric ring patterns in the surface of the media. With the pump off all was well. This is by no means, the only source. Old fridges with ancient compressors are also a good source.

3.6 Intermittent and Operational Sources

The problem with any intermittent problem is that it is just that: not always there. The best example is the slamming door. Portable A/C units can also be a problem.

Intermittent sources can also be operator generated. Some instruments have electric head drives (to raise and lower the head) and some are manually operated, either with a pneumatically assisted swing head or with a guided vertical drop. Both of these mechanisms can be sources of problems if not smoothly placed into the operating position. This again, is particularly the case with Apparatus 1 baskets. Sudden movements while the Prednisone Tablet is in the process of disintegrating can fire a shower of tablet material out of the basket and into the medium. A failed test is not far off. With swing head which opens and closes with a movement through approximately 135°, a slow gentle placing of the head in the working position will avoid problems. This situation has greatly improved with the transition to the new LOT POE203 from the previous O0C056 LOT. Values for baskets also appear to be much tighter in range.

With the vertical drop mechanisms, there is a tendency for the drive way to be a little harsh in its transition into the working position. Additional pressure to move the head can result in a hard hitting arrival which again, will drive more disintegrating formulation out from a basket than should be allowed for a successful test.

3.7 So what can Pharma Test do for you regarding Vibration?

Pharma Test instruments are designed with the dissolution user in mind. As far as the USP is concerned it has been noted that there is only a brief mention of vibration requirements consisting of the statement that “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” (ref. 3).

Other publications have also been mindful of the potential errors in terms of dissolution testing and amongst the biggest influences were vibration and medium de-aeration (ref.4).

Various studies have been carried out to try and quantify the effects of vibration on the resulting release rate of Prednisone tablets in particular. At Pharma Test we have also carried out exhaustive tests in order to investigate the effects of vibration on both older and newer instrument types and to provide definitive proof that Pharma Test Dissolution

instruments are the most developed available and that they represent a truly foresighted view of the future requirements of the dissolution user.

The total findings regarding our investigations are available from Pharma Test (ref.5).

The effects of vibration on various instruments from other suppliers has been investigated also (ref. 3). The method of vibration analysis and investigation was also reviewed by this independent body and the results make quite interesting reading. The main points are that:

1. How you measure vibration and how you quote it is important.
2. Are you measuring vibration in one axis or are some axes being “damped”?
3. It is important to use a real vibration meter which is sensitive to vibration in all axes, rather than just one which simply fixes on to the instrument surface.
4. Some newer instruments that are supposed to be state-of-the-art are more susceptible to vibration on their results than some older or less expensive units (compare VK7025 with Distek 2100 and VK7000 series units)

3.8 What is different about Pharma Test Units?

The main differences come from the quality of construction and fully researched paths to making a better all round instrument that is already prepared for all the forthcoming potential changes that may be applied to the Operational Qualification of dissolution instruments. These changes are a hotbed of discussion at the moment of going to press (ref. 6), but these issues need to be investigated and acted upon, not so much to conform to any new rules that may arise, but because we would like to strive to produce an instrument which passes any test that may be required and for the ease of the operator who has to use the instrument on a daily basis.

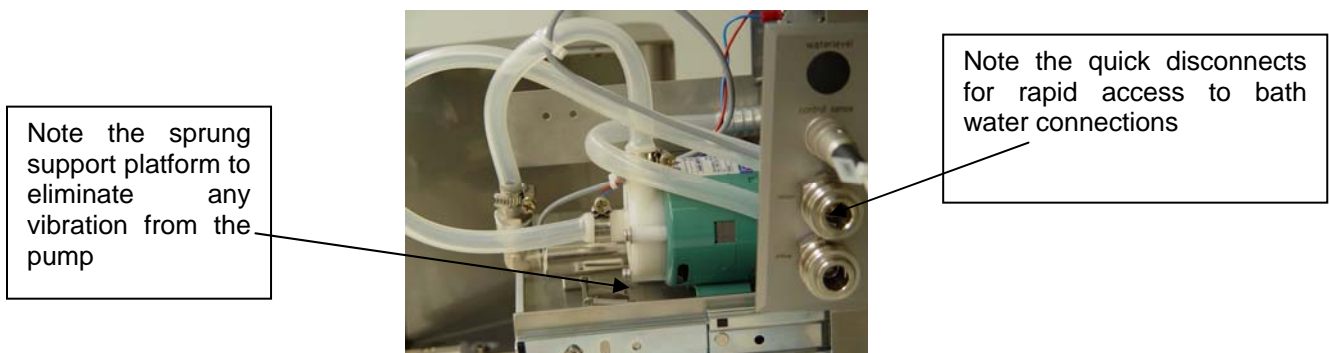
3.9 Main advantages of the Pharma Test Dissolution Tester

The main advantages are outlined below:

3.9.1 Pump and heater installation

The heating of the water bath section in a dissolution tester is normally the last point on the development list for most instrument manufacturers. This is generally limited to a “me too” type of heated circulator, which sits on the workbench just beside the dissolution tester. Most of these heated circulators have one control sensor with a fixed mounted pump mechanism. The first issue is the safety of the heating system and with Pharma Test units, we have a control sensor as well as a safety sensor after the heating element as well as a safety over-temperature switch and a thermal fuse. The second issue is the accessibility and construction of the heating elements which coincidentally contains the circulation pump. The heating system is shown below in figure 2. With the PTA Dissolution Test Series PTWS310/610/1210 it is conveniently accessed via a small drawer unit without having to disturb the positioning of the bath itself.

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3.9.2 Figure 2: Installation for the pump and heater

You can see that the pump is suspended on a sprung platform and this eliminates virtually all potential vibration sources from the pumped heating system.

3.9.3 The Water Bath installation

The water bath is also set up for vibration damping. This time we have also taken into account the impact of environmental vibration sources such as fridges, pumps, A/C systems and the like which are an intrinsic part of modern laboratory installations. The vibration damping is clearly shown in figure 3 below.



3.9.4 Figure 3: The Unique Vibration Damping Accessories

You will note from the figure above that the first line of defence against environmental vibration is the installation of metal encapsulated rubber feet. This mechanically “decouples” the dissolution tester from the work bench. These feet also allow the easy levelling of the dissolution tester prior to installation.

The second line of defence is the installation of a unique specialised polymeric vibration dampers (Vibroban™) purely for the water bath isolation from the rest of the dissolution tester. This effectively provides a second decoupling mechanism to insure that almost all vibration emanating from the working environment is eliminated. The effects of this system in

the face of external environmental vibration sources can be seen in ref. 5. The results speak for themselves.

Certainly compared to the results obtained in ref. 3, the effects of vibration in a VK7025 compared to a PT--DT8 (or PTWS310 /610/1210) are certainly important enough to take into account when choosing a new Dissolution Tester.

4 Conclusions.

- Many problems can arise within the laboratory environment to detrimentally influence the dissolution process.
- Some of these issues such as de-aeration of the dissolution medium, can be effectively handled with modern medium preparation equipment such as the PT DDS4.
- Issues such as vibration, both intrinsic and from the environment have different effects on different makes of instrument. Pharma Test, which has one of the highest R&D investment programs (as a percentage of turnover) in the instrument business today, offers a multi directional approach to eliminating factors which are detrimental to the whole dissolution process and not just certain aspects. In this way we can offer our users an unrivalled degree of security for the current, as well as some norms currently under serious discussion, which may come into practise at any time.

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