

The Next Challenge in Dissolution—Nanoparticles

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Dissolution is a crucial aspect of drug product development and characterization. It is the only pharmaceutical test which is capable of determining how a formulation will perform in a patient. Over the years, the science of dissolution has needed to adapt to advances in pharmaceuticals. At the beginning of dissolution, medicines were primarily immediate release drugs where a United States Pharmacopeia (USP) Apparatus 1 (baskets) or 2 (paddles) worked quite well at assessing how a product would perform *in vivo*.

As pharmaceuticals have advanced, a wide variety of new formulations have been developed, which all need dissolution testing. Dissolution evolved to accommodate dosage forms that required extended-release times, multiple media changes, and more. More recently, drug-device combination products

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further challenged dissolution testing by needing to test extremely low volumes for several days or weeks for implants. Now, making the APIs smaller into nanoparticles is the new challenge for dissolution testing.

Nanoparticles are becoming more prevalent to overcome two main challenges of drug design—low solubility and poor permeability. The surface area of a drug is directly correlated to the speed that a product will dissolve. Immediate-release dosage forms tend to be disintegrating tablets and powders in order to increase this surface area. Nanoparticles offer a way to further increase the surface area and allow for greater dissolution rates. The smaller size of the particles also allows for them to be more permeable through cell membranes, to more easily reach the site of action in the body.

These smaller particle sizes pose challenges, however, for *in-vitro* dis-

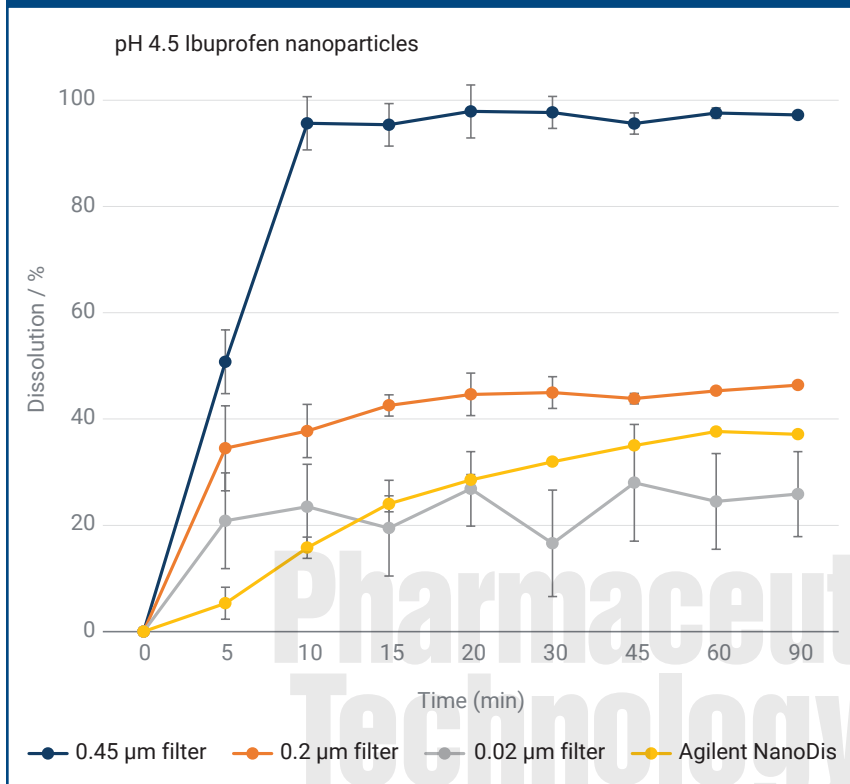
solution testing. Dissolution is essentially a three-step process: a sample preparation in a dissolution vessel or cell, the analysis of the aliquot(s), and a filtration step in between. Filtration is a critical aspect of the dissolution test as it separates the undissolved drug particles from the dissolution sample. As drug particles get smaller, the filtration of those particles becomes harder. Conventional dissolution filters are often seen as cannula tip filters or syringe filters. Cannula tip filters can vary in size from 1–70 microns, which are too large for nanoparticle formulations. Syringe filters offer finer filtration as low as 0.2 microns; however, these filters can still either be too large or face other challenges with back pressure or artificial dissolution. In addition to their size alone, these particles can also agglomerate more easily, leading to even greater filtration challenges.

Conventional dissolution filters have a variety of challenges associated with them for use with nanoparticles.

The two common ways that nanoparticles are filtered are through conventional filters and dialysis membranes. Both approaches have issues associated with them leading to either unreliable data or dissolution rates which do not correlate to *in vivo* conditions.

Conventional dissolution filters have a variety of challenges associated with them for use with nanoparticles. For filters 0.2 microns and above, nanoparticles are small enough that they can either pass directly through the filter or they can agglomerate on the filter, resulting in high backpressures which can cause the filters

Figure 1. Dissolution profiles of ibuprofen nanoparticles 200 mg/900 mL in acetate buffer pH 4.5 using different syringe filters (0.45 μm , 0.2 μm , and 0.02 μm) and the Agilent NanoDis System.



to burst. When undissolved particles reach the test tube or high-performance liquid chromatography (HPLC) vial, they continue to dissolve there. This causes higher and more variable concentrations, skewing dissolution results. Smaller conventional filters have been tried as well; however, these filters block quickly

leading to inefficient filtration and improper results (Figure 1).

Another option is to place the nanoparticles into a dialysis membrane such as a Float-A-Lyzer, and place that into the dissolution vessel. In this case, the membrane is used essentially as a filter and is effective at doing so. The challenge with use of a device

such as this, however, is that it doesn't allow for adequate mixing of the nanoparticles within the membrane, leading to an artificial slowing of the dissolution release. The data seen from many of these experiments show that the rate limiting step of the dissolution is the diffusion through the membrane rather than the dissolution process itself (Figure 2). For dissolution data to be meaningful, there must be a correlation made between the *in vivo* and *in vitro* conditions—and this is made difficult due to the diffusion barrier.

Both conventional filters and dialysis membranes can overcome some of the challenges posed by the nanoparticles.

A new option for nanoparticle dissolution testing

Both conventional filters and dialysis membranes can overcome some of the challenges posed by the nanoparticles. Conventional filters allow for a wide variety of dissolution conditions to be used to better model *in vivo* conditions but have challenges with proper separation. Dialysis membranes can effectively filter nanoparticles, although too slowly. A proper option for dissolution testing of nanoparticles requires there to be a method which has adequate hydrodynamics, media, etc. for the dissolution and filtration which is able to adequately separate undissolved particles from the sample. There is now an all-in-one solution for this using hollow fiber filters (Figure 3).

A hollow fiber filter allows for low-pressure fine filtration of nanoparticles. This overcomes the issues of back-pressure and clogging of conventional

Figure 2. Extended release testing.

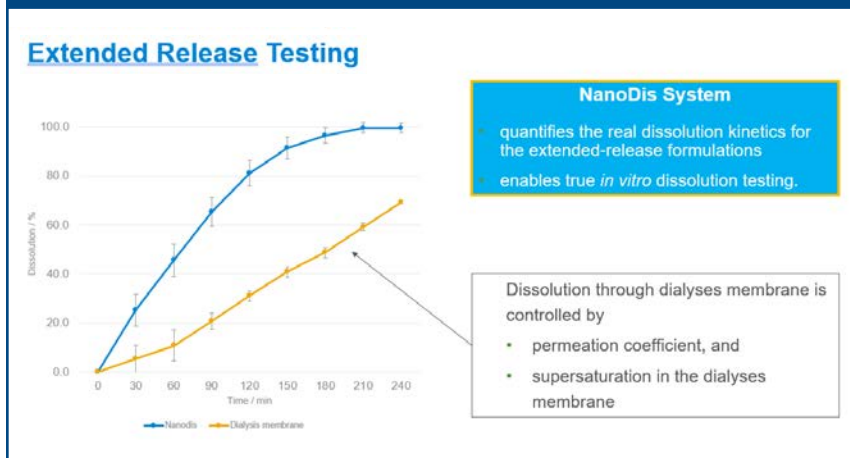
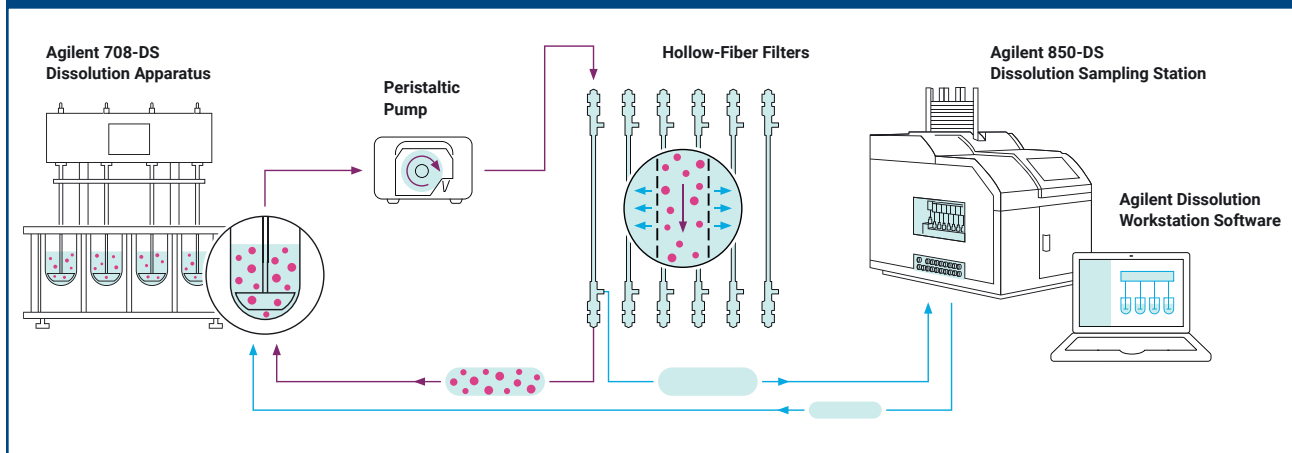


Figure 3. Diagrammatic representation of the NanoDis System showing the directional flow and separation of dissolved API and dispersed nanoparticles using the USP-compliant Agilent 708-DS Dissolution Apparatus and 850-DS Dissolution Sampling Station, operated and electronically documented using the Agilent Dissolution Workstation Software (DWS).



filters without the slow diffusion rates of membranes. A peristaltic pump cycles the dissolution media through the hollow fiber filter's core. An autosampler then processes samples perpendicularly to the flow of the hollow fiber filter, which is referred to as cross flow

filtration (CFF). This offers an effective way to properly perform fine filtration of nanoparticles at low pressure.

Conclusion

CFF can be combined with conventional dissolution apparatus, automating the

filtration and sampling process. Because CFF is an open filtration system, many common filtration challenges are overcome. Furthermore, the membrane size of the CFF filters can be chosen according to the particle size of the nanoparticles in the formulation. **PT**

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suites: the accuracy study may be done with these artificial mixtures but the precision study should be performed on the real samples of final dosage form.

Conclusion

Assay data sets of formulated liquid product, of a drug substance and of an impurity, obtained from combined accuracy-precision studies, are evaluated to calculate statistical intervals (prediction and tolerance intervals) and TAE to account for the systematic and random errors. Inclusion of either the statistical intervals or the TAE within the allowed accuracy limits is an indication of a successful validation of the accuracy and precision method characteristics.

Considering typical values of standard deviations (0.5–2.5% RSD) of chromatographic tests and typical specifications (± 2 , ± 5 , or $\pm 10\%$) of pharmaceuticals, it is shown that a substantial portion of specification tolerance is taken up by either the statistical intervals or by the TAE, particularly in cases of narrow specifications and imprecise procedures.

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