The Remedy for Pharmaceutical Tank Cleanliness

Application Note

KEYWORDS

- Active pharmaceutical ingredients
- Clean-in-Place systems
- Pharmaceutical tanks

TECHNIQUES

- Absorbance

APPLICATIONS

- Process monitoring
- Liquid tank cleaning control

Wouldn't it be nice if there was a pill for everything? Today it almost feels like there is. Indeed, just over 66% of U.S. adults take daily prescription medications[1], making pharmaceuticals yet another product of mass consumption. As the pharma industry has evolved, new and exciting technologies have emerged that can improve or entirely reinvent whole aspects of the industry, and spectroscopy is one such area of evolution.

We're all concerned about the cleanliness of where we live and the products we consume, and the level of awareness today is more than it's ever been. We pay more for organic foods without synthetic pesticides, we buy air purifiers with HE A filt ation for the home, and we filter the water coming out of our taps. So, with most Americans taking medications every day it is equally important to ensure those products are kept to proper cleanliness standards.

The two primary form factors for medications are solid (pill) and liquid (syrups, tinctures, etc.), and each has its own considerations for process cleanliness. Powders being pressed into pills may leave solid residue in the molds, and the large tanks where liquids are processed have huge surface areas that need to be meticulously cleaned. Pharmaceutical cleaning is a bit like

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checking and changing your car's oil: You check it beforehand to get an idea of how dirty things are, and then you check it afterward to ensure it looks sufficiently clean. roadband spectroscopy lets you do this on pharmaceutical molds and tanks to assess cleanliness before and after the CIP (Cleaning-in-Place) process[2].

Measurements

Most common APIs (Active Pharmaceutical Ingredients) are optically active in the UV and provide strong absorbance in that region. This may not give the specificity of NIR bands to determine exactly which APIs are present but does give a much stronger general representation of the presence or absence of the ingredient at low concentration levels. Let's take a look at an example of diphenhydramine powder (Benadryl®) on stainless steel going from an area of heavy API residue to an area of clean steel **(Figure 1)**.

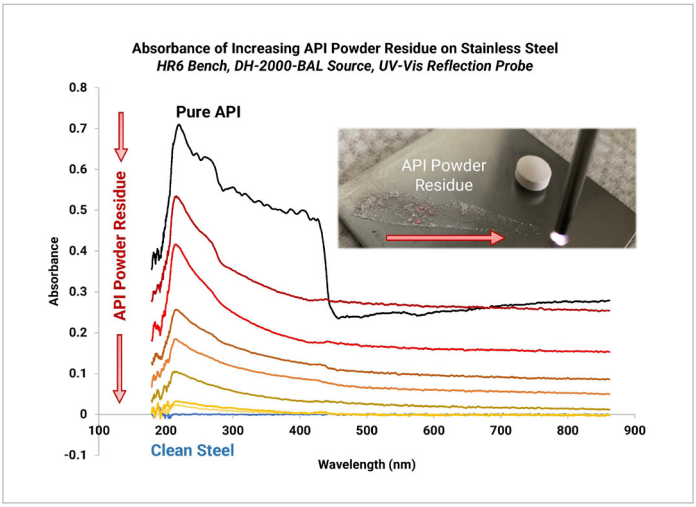

Figure 1. Broadband spectroscopy is an excellent tool for monitoring the presence of powder residues on stainless steel, comparable to what's encountered during pharma tanking cleaning.

Note the steady reduction of UV absorbance as the probe moves to cleaner areas of the steel surface, eventually dropping to a nice zero-level at the sufficiently cleaned region. By taking a light reference on a known-clean sample of the tank surface, this UV absorbance can be used as a gauge for how much solid residue may be present across other areas of the tank.

Liquids are the other common form factor for APIs. Most of us have taken cough syrup at some point in our lives, so let's look at a liquid example using common dextromethorphan cough syrup in a standard 1 cm cuvette. For liquid tank cleaning the tanks typically go through cycles of both acid and alkaline washes, and these wash solutions and subsequent rinse water can be analyzed for the presence of API as an indication of cleanliness[2]. But before we look at spectra for the various rinses we need to have some general correlation between absorbance and API concentration. **Figure 2** shows three dilution levels of the cough syrup along with a rough calibration trend in the upper-right corner. By looking at the absorbance around 315 nm we get a nice linear relationship with syrup concentration.

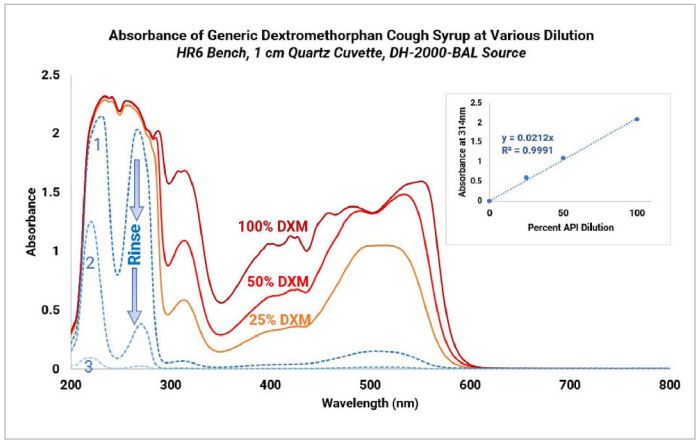

Figure 2. UV-vis spectroscopy is ideal for monitoring the concentration of liquid pharma samples including this cough syrup example.

The plot also includes an allusion to the first few rinses of the tank with each rinse giving a dramatic reduction in API concentration. But let's zoom more closely into what's happening across all seven rinses performed for this study. The plot in **Figure 3** (see next page) shows us that by the fourth rinse we are very close to zero API but still have low levels present. Even rinses five and six show some statistical non-zero level of API, but the seventh rinse eliminates traces beyond the limit of detection.

Plots are nice visual representations, but the actual absorbance numbers can be extracted from those trends and processed against our calibration correlation to give more precise figure on API residue level. **Table I** (see next page) shows the steady reduction in API concentration for each rinse, getting down to essentially 1 ppm after six washes and statistically undetectable after the seventh.

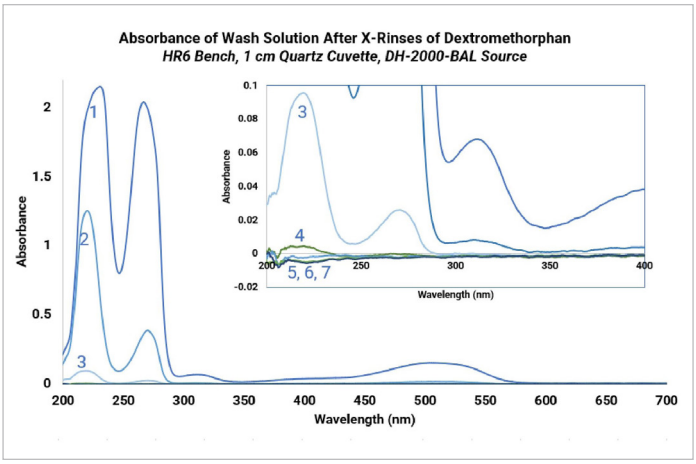

Figure 3. In these plots, absorbance measurements reveal the concentration of sample that remains after multiple rinses.

Table 1		
Rinse	**API Percent**	**API PPM**
1	*3%*	*30,000 ppm*
2	*0.4%*	*4000 ppm*
3	*0.032%*	*320 ppm*
4	*0.0025%*	*25 ppm*
5	*0.0008%*	*8 ppm*
6	*0.00016%*	*1.6 ppm*
7	*< LOD*	*< LOD*

Additional Considerations

Both sampling approaches have considerations to ensure proper measurement and to potentially enhance the limits of detection. For the solid sample approach using the reflective p obe, the repeatability of probe positioning with respect to distance and angle will determine the repeatability and accuracy of the concentration measurements.

Generally, flimsy fixturing wil lead to flimsy readings. That said, there are software techniques involving baselines and SNV normalization that can help correct for these variances in real-world settings.

For the liquid approach using a transmissive cell, an increased pathlength will proportionally improve the limit of detection.

Also, cell cleanliness will be a factor in your readings since the same difficulty of cleaning the walls of your optical cells will apply to cleaning the walls of your tanks. This leads to the decision of using either a discrete cell (liquid manually injected or removed) or a continuous flow cell linked to the wash process. The discrete option will allow easier cleaning and perhaps more confidence in the readings, while the continuous option will usually require less human interaction but may be more work in regular maintenance.

Summary

Given the financial and reputational risk of creating contaminated products, many pharma organizations opt for an over-cleaning method that has them washing out vats with solvent for hours or days longer than necessary in an effort to ensure runoff doesn't contain unexpected reagents. While this accomplishes the goal of runoff regulation, it also comes with a substantial amount of wasted time, effort, and resources.

But by implementing into their processes robust spectroscopy solutions like the HR6 spectrometer from Ocean Optics, pharmaceutical firms will be better equipped to monitor ongoing API reactions and streamline cleaning validation processes.

References

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