Optical Dilution

UV Fiber Optic Dissolution Testing of a USP Monograph High-Dose API Using Sub-1mm Pathlength Probes

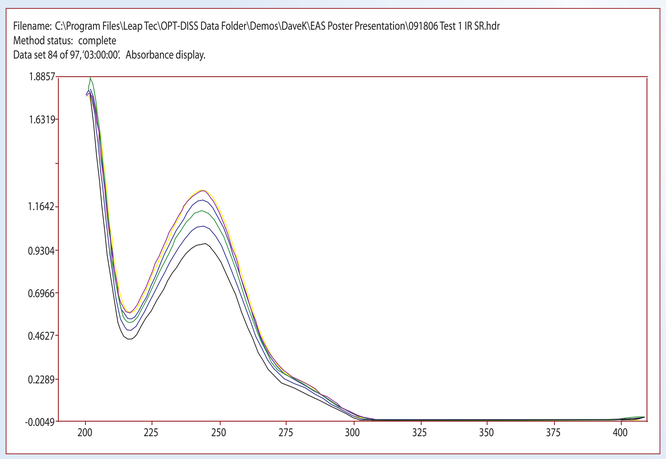
David Kwajewski - Distek, Inc.

Objectives

The purpose of this experiment was to be able to test a strong UV absorbing compound having a high API content with in-situ fiber optics. An issue with a strongly absorbing compound would be keeping the results within the linear range of the detector. Analyzing these compounds within that range can be accomplished through either an optical dilution (i.e. using a smaller pathlength probe) or through a manual dilution of the concentration of the sample. Since the objective was to perform in-situ measurement, a manual dilution was not possible. An optical dilution was employed which in theory would be more accurate than manual dilution by eliminating human error.

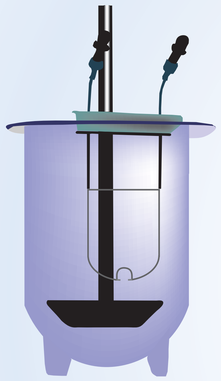
Another potential issue would be to test whether in-situ fiber optics could be used in a turbid environment. In addition to having a large API content, a large dosage form can also have a lot of excipients. Through the use of a properly designed probe and a suitable detector we hoped to be able to compensate for any scattering that might occur from the turbidity.

The fiber optic Arch probe was selected over the reflectance "dip-style" probe for two reasons. First of all it is available in small pathlengths down to 0.25 mm which was the pathlength selected for this experiment. Secondly , the Arch probe has the added advantage in design of avoiding particulate buildup and entrapment.



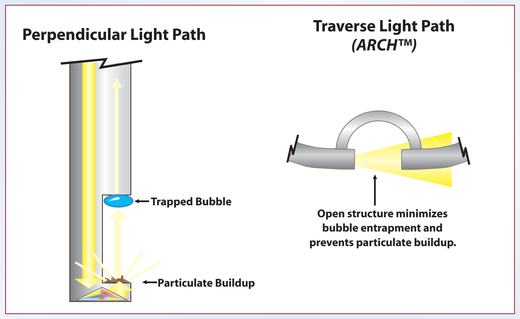
Beer's Law

- *Abs = e b c*
  - *e = constant*
  - *b = pathlength*
  - *c = concentration*
- *Linear range of detector is 0.05 to 2.1 AU*
- *A decrease in either concentration or pathlength will lower absorbance*



The Arch™

- *Direct in-situ measurements*
- *Negligible hydrodynamic effects*
- *Pathlengths from 0.25 mm to 10 mm*
- *Low stray light and wide absorbance range*
- *Designed for testing where bubbles and particulate matter exist*

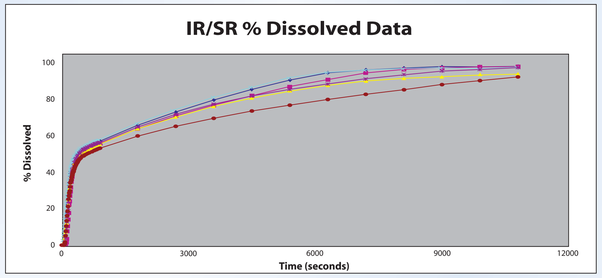


Turbidity

- *Using zero order baseline correction techniques*
  - *CCD spec allows for single point, two-point, and average over range baseline corrections*
- *Using first order baseline correction techniques*
  - *Software allows for second derivative corrections where necessary*

Experimental Method and Instrumentation

- *USP monograph for Acetaminophen Extended Release*
  - *USP Acetaminophen Standard*
  - *650 mg Tylenol IR/SR Arthritis Formula*
- *Distek 2100C Dissolution System*
- *Opt-Diss Fiber Optic System with 0.25 mm Arch probes*



Example Dissolution Curve

Time (minutes)	Max Result	Min Result	USP Spec	%RSD
15	61.4%	53%	45-65%	4.1
60	84.0%	69.5%	60-85%	5.7
180	103	92.1	>85%	2.7

Discussion

At all time points, the absorbance values are all well within the range of the detector. All of the results for the three tests met USP requirements with acceptable %RSD values (see table above). Fiber optics allowed for the detailed profiling of this product and showed an interesting release profile. There was also very little scattering even though there was a lot of turbidity.

Procedure

1. *Dissolution media prepared as Simulated Gastric Fluid without enzymes*
2. *Standard prepared at 0.66 mg/mL concentration*
3. *Probes blanked with Dissolution Media*
4. *Standard reading taken simultaneously from all six probes in standard chamber*
5. *900 ml of dissolution media equilibrated to 37.0 degrees C and RPM set to 50*
6. *Arch probes inserted in vessels 1-6 and sample blank reading taken*
7. *Tylenol introduced simultaneously with start of run*
8. *Samples taken at the following intervals:*
   Phase 1: Every 10 seconds for 5 minutes
   Phase 2: Every 15 seconds for next 10 minutes
   Phase 3: Every 15 minutes until 3 hours
9. *Test repeated three times under same conditions*

Conclusion

An optical dilution can be used to detect this strongly absorbing compound with a large amount of API. The 0.25 mm Arch probe was an appropriate choice, as the absorbance results were all within the linear range of our detector. There was very little difference between the corrected and uncorrected dissolution results due to lack of scattering. The fact that the larger particulates could not fit into the pathlength aperture was the most probable cause.

Through an optical dilution (reduction in pathlength) in-situ testing is possible for compounds where a manual dilution was once previously required.