Rapid Cleaning Verification & Quality Control Instrumentation for Pharma

William F. Hug, Ray D. Reid, Michael Reid, Kenneth Nguyen, & Quoc Nguyen
Photon Systems, Inc.

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Outline

- Detection goals & methods for RCV and real-time continuous manufacturing
- Advantages of deep UV Raman & fluorescence detection
- Detection examples for pharma products
- Deep UV Raman & fluorescence instruments
- Chemical printer for NIST traceable chemical concentration calibration
Rapid Cleaning Verification

The goal
To augment or replace the present swab & test method for equipment cleaning verification with a faster and better controlled and documented method.

The solution
A handheld device that quantifies trace amounts of API in real time on manufacturing surfaces. Result: Significantly reducing production down time.
The goal
Provide instrumentation for real-time detection of the key ingredients during continuous flow manufacturing

The solution
A miniature deep UV Raman instrument that avoids fluorescence interference or obscuration and provides a high level of sensitivity and specificity for the ingredients
Advantages of deep UV
Raman & fluorescence detection
Advantages of Deep UV Detection vs Visible or IR?

- Non contact, reagentless, no sample handling or preparation
- Excitation below 250 nm separates Raman & fluorescence spectral regions to enable
  - Clear Raman spectra with no obscuration or alteration by native fluorescence
  - No alteration of the fluorescence spectra by major Raman bands
  - The ability to simultaneously detect Raman and native fluorescence
- Much higher Raman sensitivity due to Rayleigh law and resonance Raman enhancement effects
- Fluorescence detection alone has much higher specificity when excitation is below 250 nm
- Detection of concentration of pharma materials in the low ng/cm² has been demonstrated
- Detection is solar blind, enabling detection in full daylight without interferences
Why Deep UV below 250nm?

When excitation <250nm Raman and fluorescence spectral regions are separated.
Sensitivity to Excitation Wavelength
Raman Spectra with Excitation at 248 nm versus 262 nm

(Example is G Agents)

Deep UV Fluorescence Spectra of 52 Compounds
with no baseline subtraction or compensation, Ex=248 nm
Chemical Differentiability
Using Deep UV Excited Fluorescence Alone

A single deep UV laser pulse determines the location of an unknown substance in this chemometric space.

1 ring compounds incl. Tyr & Phe (A1 and A2)

2 ring aromatics (D)

3 ring polyaromatic hydrocarbons (PAHs) (F)

4 ring PAHs (G)

>5 Ring PAHS (I)

nitrogen based heterocycles (E) including tryptophan

vegetative bacterial cells (Gram + and Gram -) with cellular components (C),
bacterial spores (B)

“background” group (H), consisting of pollens, dust, minerals, and household materials (sugar, flour, corn starch, etc)
Combining the Sensitivity of Fluorescence & specificity of Raman

- Fluorescence is the most sensitive method of detection, over $10^6$ to $10^8$ times more sensitive than Raman, providing longer standoff distances and/or detection at lower concentrations.
- Raman provides information about chemical bonds and functional groups, including those that do not fluoresce (aliphatics and simple compounds).
- Fluorescence data provides information about the overall electronic structure of target & substrate components (aromatics, ketones, aldehydes).
Detection Examples for Pharm Products
OTC Benylin: dextromethorphan hydrobromide

$C_{18}H_{28}BrNO_2$

Ex=1064 nm
Ex=785 nm
Ex=248 nm

Benylin (white)
Sodium benzoate (green)
Glycerol (red)
OTC Children's Motrin (ibuprofen)—Bubblegum Flavor
Ex = 248 nm

Children’s Motrin-Bubblegum flavor

Pure Ibuprofen

[Graph showing spectroscopic data with wavenumber values for both children's Motrin-Bubblegum flavor and pure ibuprofen, with peaks at specific wavenumbers.]
OTC Children’s Tylenol (acetaminophen) w Various Flavors

Ex = 248.6 nm  Raw results. No baseline compensation.

Increasing fluorescence
Deep UV Raman & Fluorescence Instruments
Deep UV Raman PL 200

with manual or computer-controlled stage or liquid flow cell
Features of the Deep UV Raman PL 200

- A deep UV Raman and fluorescence spectrometer
- With either computer-controlled stage for mapping or liquid flow cell for continuous manufacturing quality control
- Intended for OEM applications with dramatically smaller SWAP/C than other deep UV instruments on the market
- Avoids fluorescence interference or obscuration of Raman spectra
- Enables detection and quantification of Raman bands for a wide range of pharma ingredients not possible with 785 nm or 1064 nm Raman systems due to fluorescence
- SWAP: 18 x 20 x 42 cm, 10 kg, 60 W max (100-260VAC)
Raman PL 200
with various types of flow cells or cuvette holders
Deep UV Trace Chemical (TraC) Sensor
LODs < 1 µg/cm²  Wt. 1.5 lbs
Features of Deep UV TraC RCV Sensor

- Fully self-contained RCV sensor with embedded microprocessor for instrument control, data processing, real-time data storage, and display
- Able to measure trace concentrations on curved surfaces, corners, crevices, screens, grates
- Sample rate > 10 samples/s with time-stamped real-time recording
- Hi sensitivity: able to detect concentrations of APIs < 1 µg/cm²
- Large working distance: 0 to 2 cm
- Sampling area: 0.25 cm²
- Non-contact sensing with large working distance (0 to 2 cm)
- Hand-Held: < 0.7 kg (1.5 lbs)
- Small: 7.6 x 8.9 x 19 cm
- Long battery lifetime: > 40 hours full power; > 120 hours standby
- Startup time < 10 s
- GMP & Intrinsically safe
Typical Concentration Calibration Curve & Time Stability

**Ibuprofen Chemical Concentration Calibration**

**Ibuprofen Signal Time Study**

1. **Signal (Count)** vs. **Areal Concentration (μg/cm²)**
2. **%Normalized Signal** vs. **Time After Printing (Hours)**

- **Graphs** show the concentration calibration and signal stability over time for Ibuprofen.
- The concentration calibration curve indicates a linear relationship between concentration and signal count.
- The signal time study demonstrates the stability of the signal over a period of time after printing.
STANDOFF 200 CB Surface Analyzer

Features

- **Fully integrated deep UV Raman & fluorescence surface detection analyzer**
- **Single handed operation**: 4-button plus trigger control
- **Warm-up**: < 10s from cold start, 3 s from standby mode
- **Built-in-test**: full functional test of all components on startup
- **Spectral Calibration**: Auto-calibrated on analyzer startup
- **Two Coaxial Context Cameras**: 75° wide angle image, 20mm micro image around laser spot
- **Autofocused Standoff**: 0.6 m to 5+ m
- **Materials Detected**: Chemical and Biological
- **CBE Libraries**: Built in unclassified library + SD card libraries
- **Standoff Distance**: 0.5 m to 5+ m in full daylight conditions
- **Spectral Range**: 
  - **Raman**: 250 cm\(^{-1}\) to 3500 cm\(^{-1}\)
  - **Fluorescence**: 270 nm to 320 nm
- **Context Info with Spectral Data**: Date/time stamps, GPS, azimuth, distance and two contextual photos
- **Power Supply**: User replaceable 24 V LiPO battery pack (UN/DOT 38.3 rated) or 24 V wall adapter
- **Communication**: WiFi plus Wired USB 3.0
- **Weight**: 12 pounds
- **Dimensions**: 7” W x 11” H x 16” L
- **Ingress Protection**: IP67
- **Robot compatible**: ¼ -20 camera thread or dove-tail mount
Why do you need a chemical printer?

- Test/calibrate/validate future RCV tools using NIST traceable method
- Test/calibrate/validate CURRENT cleaning tools & methods
  - Create concentration curves for swabbing.
  - Test/train swabbing personnel with accurate areal concentrations.
  - Test recovery from various surfaces/topologies with different swabbing media.
- Create coupons for visual /hotspot detection of API.
  - Hotspot detection.
  - Train personnel on visual inspection limits.
- Perform all of these with single or multiple chemicals on a single coupon or coupons.
  - Detergent + API.
  - Excipient + API.
  - Detergent + API + Excipient.
Chemical Calibration Printing

Speed
Spin Coating
Inkjet Printing
Spray Coating
Ultrasonic Piezo Printing

Uniformity
ChemCal-Printer
Manual Deposition

Known Quantity
(Pre determined)
NIST Traceable Chemical Concentration Calibration
ChemCal: A chemical printer, mapper, & calibrator

- Creates up to 16 coupons with *a priori* known, NIST traceable, concentrations of many different chemicals, including APIs, detergents, excipients, etc. on Pharma-type surfaces or quartz crystal microbalance elements for the purpose of performing calibration of hand-held trace chemical sensors for rapid cleaning validation.
- Prints and detects on curved or flat surfaces, corners, grates, screens, etc.

Operational Scenario:
- Load APIs, etc in Eppendorf rack. Up to 21.
- Load coupons onto tray.
- Press Start.
- The system prints, scans, & outputs a full calibration curve in under 3 hours. (Prints and scans 16 coupons.)
Summary

- Several opportunities exist for pharma RCV and QC instrumentation using deep UV excitation below 250 nm.

- Excitation below 250 nm provides fluorescence-free Raman and Raman-free fluorescence detection simultaneously, enabling both modes of detection to provide more accurate information about a trace substance on a surface or in a liquid.

- Combined Raman & fluorescence detection method enhance both sensitivity and specificity in identifying unknown targets.

- Detection of Raman & fluorescence in the deep UV can be accomplished using low energy lasers without major alteration or damage/ignition of targets.

- Surface detectors need a method of accurate chemical concentration calibration, common to all methods of surface detection. We call this instrument is called ChemCal.
Questions ?