Handheld Raman for quality control

CHARISMA RAMAN SCHOOL
18-19 OCTOBER 2022

Sacré P.-Y.
De Bleye C.
Hubert Ph.
Ziemons E.

Outline

- Definitions
- Design of handheld Raman system
- Spectral processing
- Specific cases

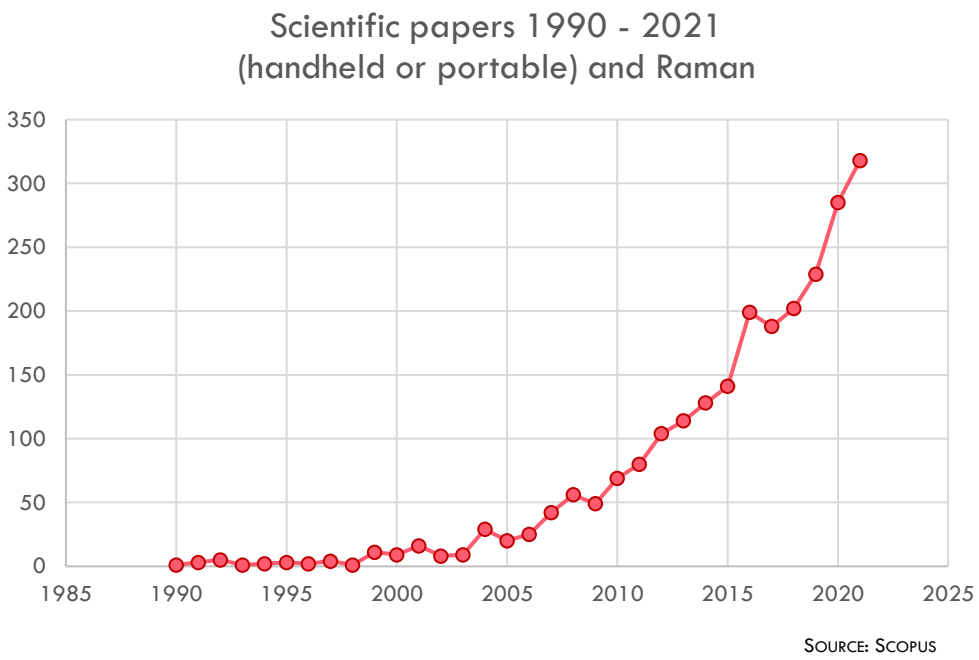
Outline

- **Definitions**
- Design of handheld Raman system
- Spectral processing
- Specific cases

Portable spectroscopy

Developments mainly driven by safety, security, terrorism, and military concerns

- Significant market presence after 9/11 attacks
  - screening and detection of explosives, chemical threats, etc…



SOURCE: SCOPUS

Nomenclature

- **Portable**
  - 3 – 20 kg, may be moved from a location to another
  - Hard waterproof case + laptop + optical fiber probes

SOURCE: TSI

- **Handheld**
  - 0.5 – 3 kg
  - All-in-one systems battery powered

SOURCE: BRUKER

- **Miniature**
  - <0.5 kg

Source: Hamamatsu

Outline

- Definitions
- **Design of handheld Raman system**
- Spectral processing
- Specific cases

Design of handheld Raman

- Design driven by the **intended application**
  - Qualitative vs quantitative

- General principle of **"good enough"**
  - Accurate answer with the required confidence level
  - Smallest measurement time
  - Lowest cost
  - Lowest power draw
  - Minimal inter-equipment variation

➔ compromises have to be made

Design of handheld Raman

- **Indoor** and **outdoor** operations:
  - Temperature
  - Shocks and vibrations
  - Humidity
  - Dust
  - Stray light mitigation

- **Users:**
  - Non expert spectroscopists (vs laboratory equipment)

Handheld Raman spectrometer

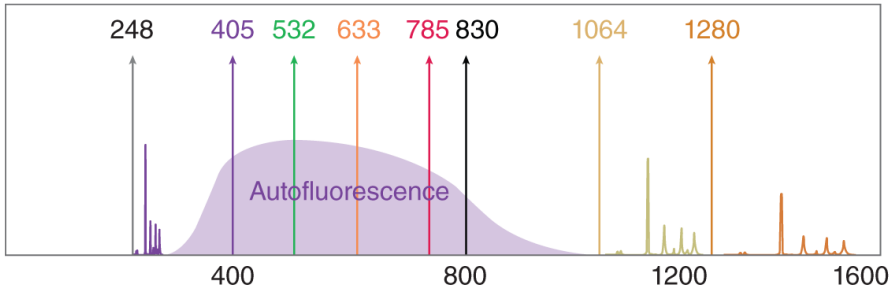
Composed of **4 main parts:**

- Laser source
- Spectrometer
- Sample interface
- User interface

Laser source

Development of **diode lasers** → key enabling technology

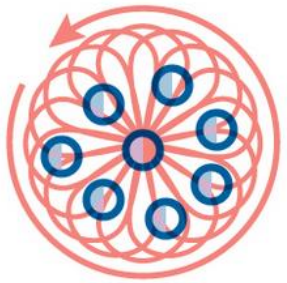
- Short warmup times
- May be switched on and off



Source: Portable spectroscopy and spectrometry 1: technologies and instrumentation

- Power of 5 – 500 mW
  - May be adjusted (→ analysis of explosives)

- Small spot size
  - May be rastered → improve representativity and less local heating



Source: Metrohm

Spectrometer

Usually a **trade-off** has to be found between:

- Spectral range
  - 200-2400 cm^{-1}
- Optical resolution
  - < 15 cm^{-1} FWHM
- Analysis throughput
  - < 5 sec / analysis

Minimal performances described in:

- Ph. Eur. 2.2.48
- USP <1858> and <858>

Sample interface

- Usually **point-and-shoot** configuration (180° backscattering)

- Analyse of samples in their **original container**
  - Should be translucid (plastic bags, blister packs, bottles/vials)

  ➔ Less manipulation
    - ↗ throughput
    - ↘ risk for analyst (e.g. high potent chemicals)
    - ↘ risk of sample contamination

Source: Metrohm

User interface

The interface should be **application dedicated**

➔ short training

➔ higher throughput

Source: Metrohm

- **Integrated module** with embedded computer + screen

- **Physically separated** module
  - Necessitates a smartphone / tablet / laptop

Source: Hamamatsu

Outline

- Definitions
- Design of handheld Raman system
- **Spectral processing**
- Specific cases

Spectral processing

- **Data collection settings**
  - Exposure time, co-adds, …
  - **Automatically selected** for the user
  - Based on **general settings** (e.g. sufficient SNR)
    - May depend on the environmental conditions (e.g. amount and nature of stray light)
  - Based on **previously acquired data**

Spectral processing

- **Conditioning of spectra**
- Make data “robust” to measurement conditions
  - Subtraction of ambient signal
  - Correction of dead pixels / spikes
  - Intensity correction
  - Raman shift calibration

- Preprocessing of spectra (derivative, baseline correction, …)

Spectral processing

- **Qualitative** objective
  - Identification
  - Confirmation
    - ➔ One-class modelling
    - ➔ Multi-class modelling

- **Quantitative** objective
  - Mixture analysis
  - Multivariate regression analysis

Spectral processing

- **Cached library** stored in device
  - Commercial or third party
  - User-defined library

- **Cloud-based services**
  - Up-to-date
  - Deployable

- IT vulnerabilities
- Needs network
- Security issues

Spectral processing

- **Display of results**
  - **User inference**
    - Rank ordered list of items with metric values
  - **Statistical inference**
    - Classification of results (pass/marginal/fail)
      - Hypothesis testing
      - Definition of threshold

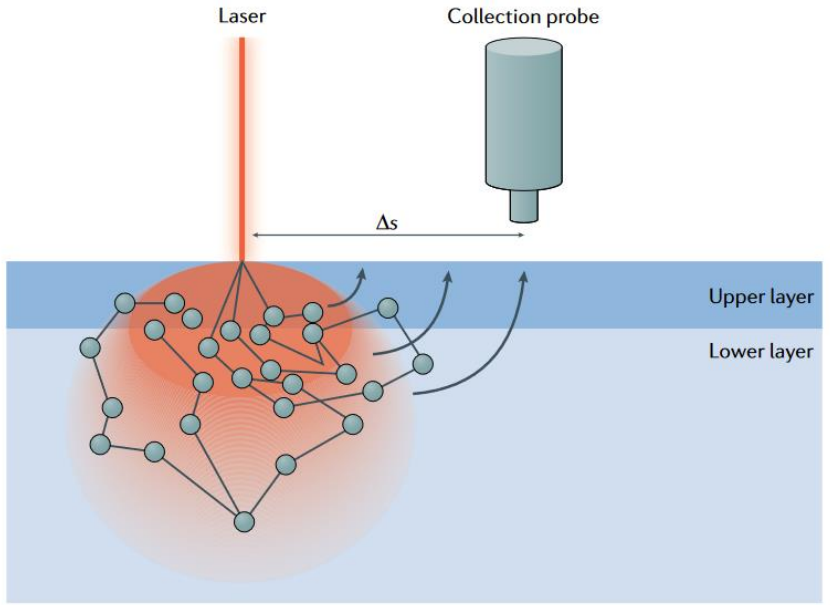
Source: Metrohm

Outline

- Definitions
- Design of handheld Raman system
- Spectral processing
- **Specific cases**

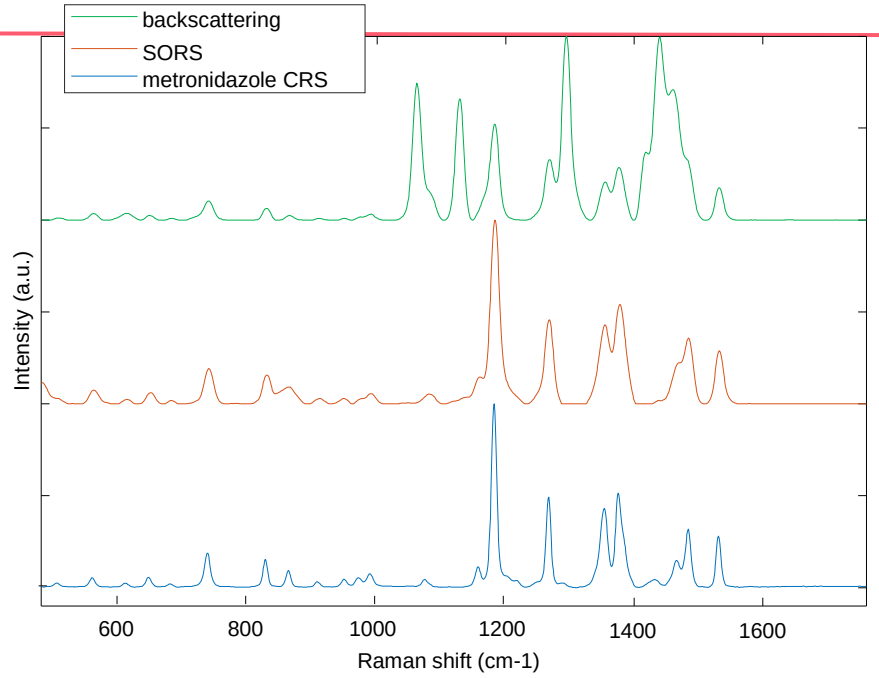
Specific cases

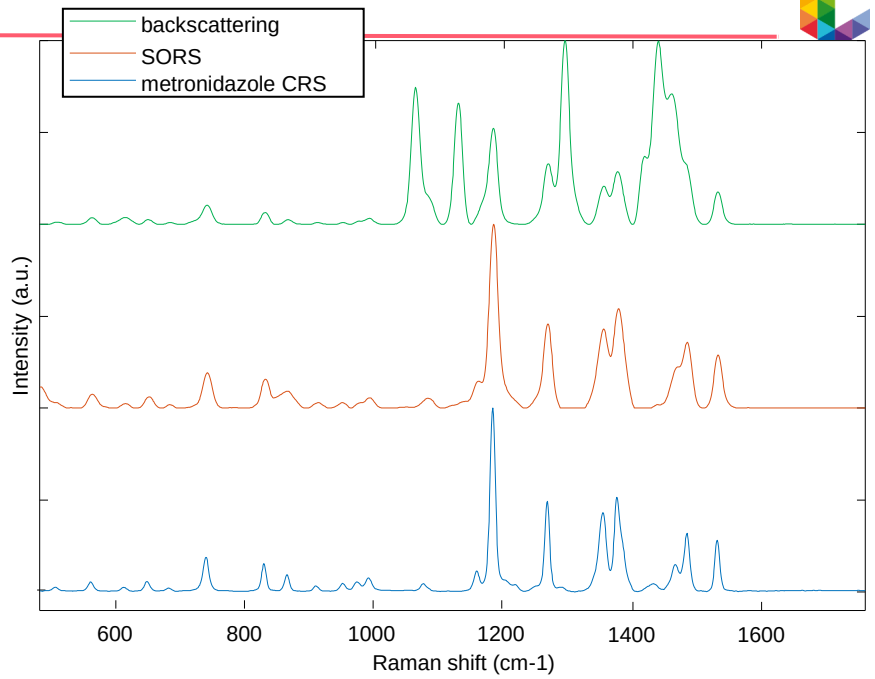
- **Through Barrier analysis**
  - Defocused lenses
    - 180° backscattering measurement
    - 1064 nm laser compatible
  - Spatially offset Raman spectroscopy
    - 830 nm laser
    - Limitations for some containers (e.g. cardboards)

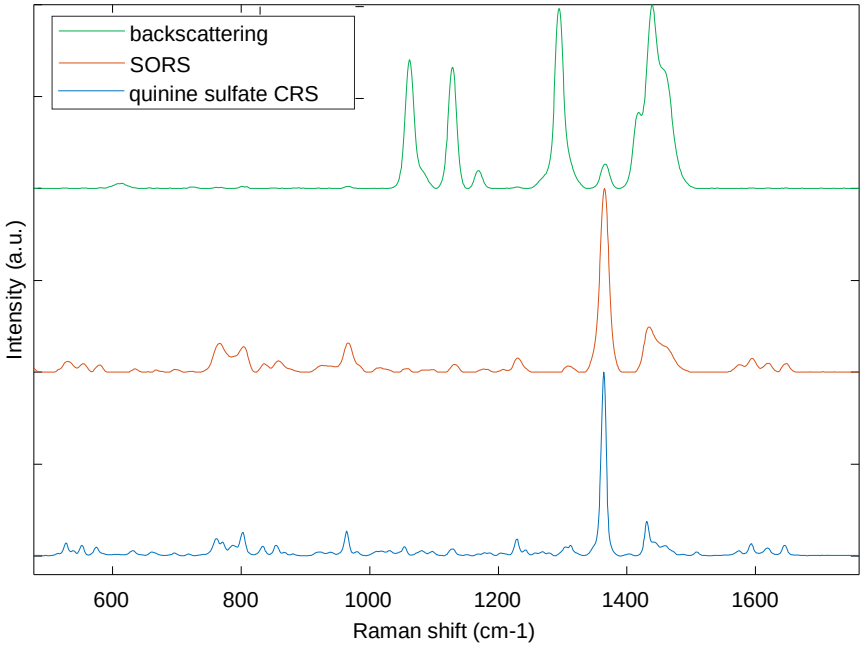


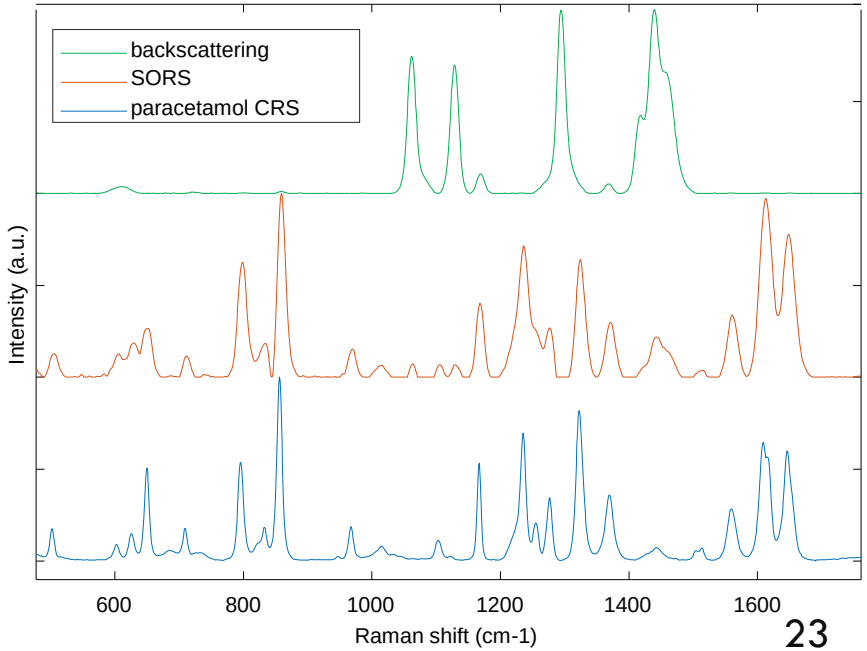

PHARMAKINA
Quinine Sulfate
500 mg
QUININE


Ammonium nitrate
Agilent
Resolve
Raman


backscattering
SORS
metronidazole CRS
Intensity (a.u.)
600
800
1000
1200
1400
1600
Raman shift (cm-1)

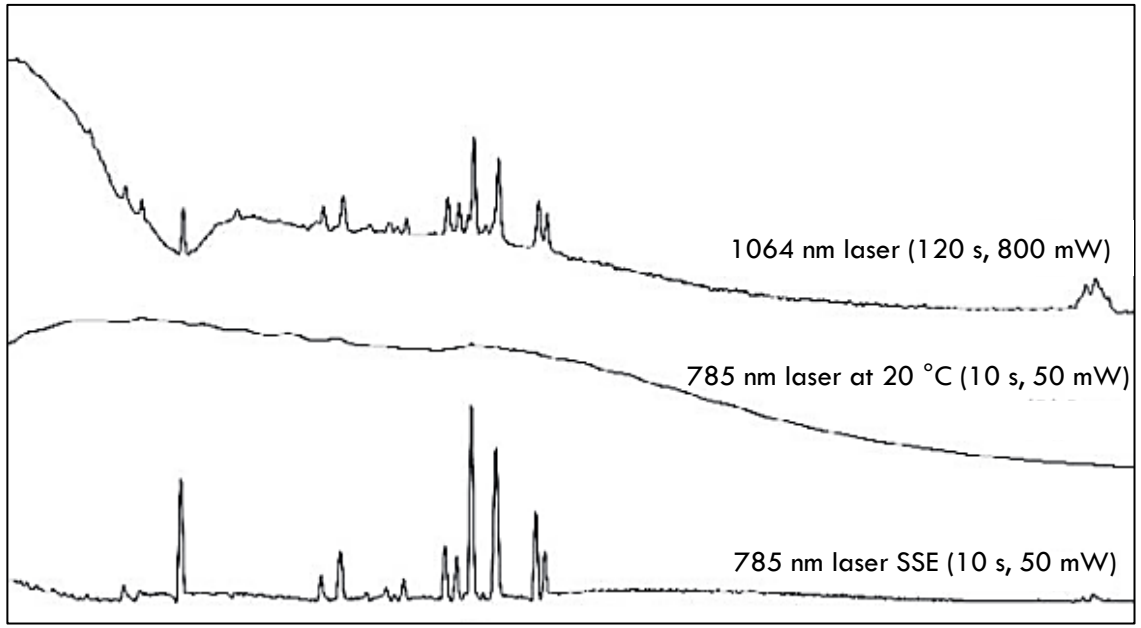

backscattering
SORS
metronidazole CRS
Intensity (a.u.)
600
800
1000
1200
1400
1600
Raman shift (cm-1)


backscattering
SORS
quinine sulfate CRS
Intensity (a.u.)
600
800
1000
1200
1400
1600
Raman shift (cm-1)


backscattering
SORS
paracetamol CRS
Intensity (a.u.)
600
800
1000
1200
1400
1600
Raman shift (cm-1)

Specific cases

- **Fluorescence** mitigation
  - Choice of laser wavelength (e.g. 1064 nm)
    - But $1/\lambda^4$ signal intensity ➔ longer acquisition time, more power needed, risk of burning
  - SERDS
  - Sequentially shifted excitation (SSE)
  - SORS
    - OK if fluorescence of packaging
    - NOK if fluorescence of investigated material



Source: Cooper et al. doi:10.1177/0003702817724164

Specific cases

- **Stand off** measurements:
  - Max 2 meters distance
  - Can be combined with SERDS and raster scanning

Source: Pendar

Source: Metrohm

Specific cases

- **Surface Enhanced Raman Spectroscopy (SERS):**
  - Enhancement of Raman signal with metallic nanostructures (Au or Ag)
  - Increasing factor up to 10^6

  - Exist as solid substrates or colloidal nanoparticles
  - Issues regarding reproducibility and stability

    ➔ **for qualitative analyses**

Source: Metrohm

Source: Hamamatsu

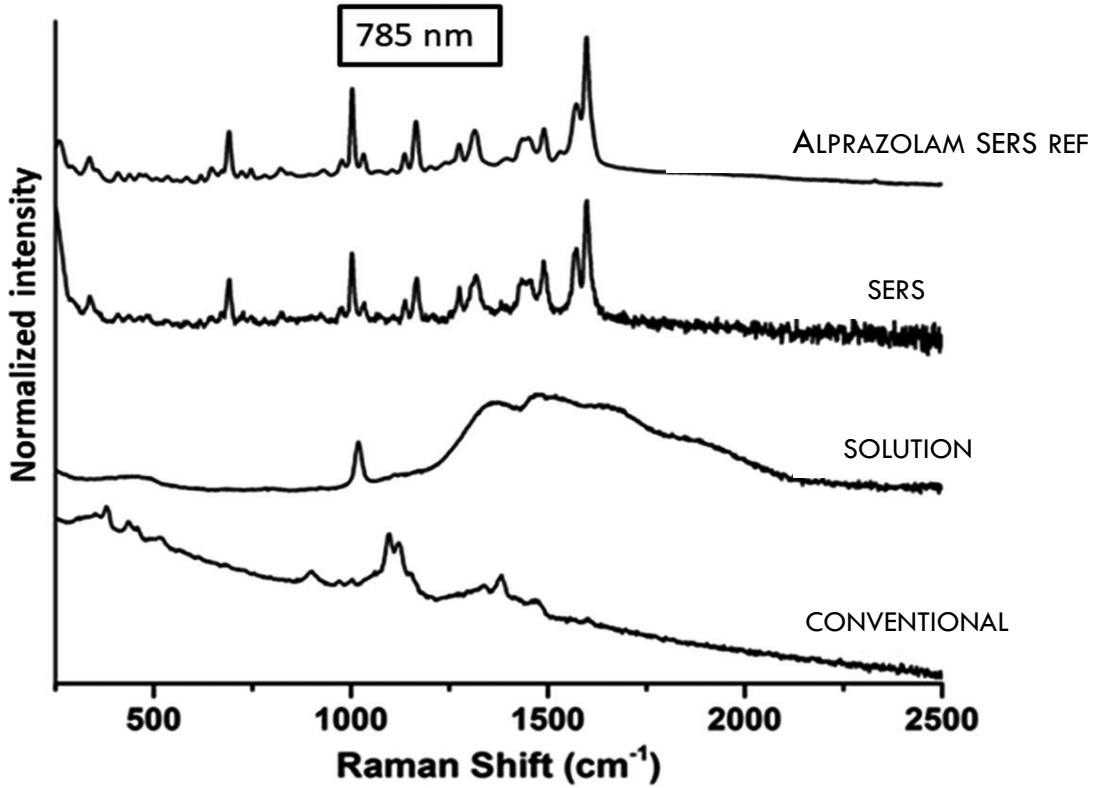
Source: Metrohm

Specific cases

SERS detection of low-dosed APIs in suspect samples (1 – 2 mg / tablet)

C_{min} ref: 0.5 µg/ml

C_{min} sample: 1 µg/tablet



Source: Kimani et al. DOI: 10.1111/1556-4029.14797

Conclusion

- Recent technology (~20 years)
- Many applications ➔ many designs and possibilities

- **Perspectives**
  - Hyphenation of techniques (MIR, NIR, XRF, LIBS)
  - Miniaturization, portability, cost
  - Algorithms, databases, calibrations

LIÈGE université
Center for Interdisciplinary Research on Medicines

Thank you for your attention

Check our publications on: https://orbi.uliege.be/

CIRM ULiège