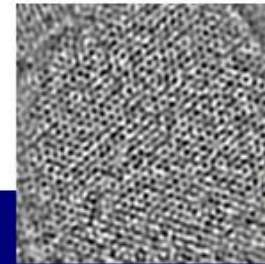
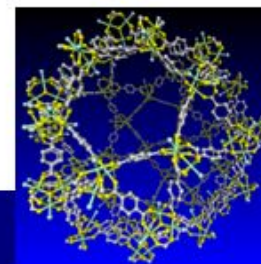
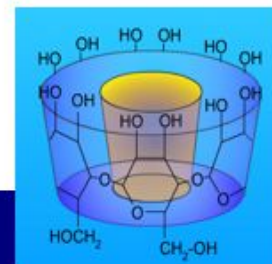
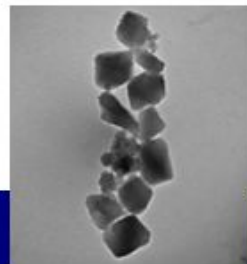


New Developments in Characterization and Process Scale Up

Ruxandra GREF

CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE



Mapping drug location and quantifying the drug loading in individual nanoparticles using AFM-IR

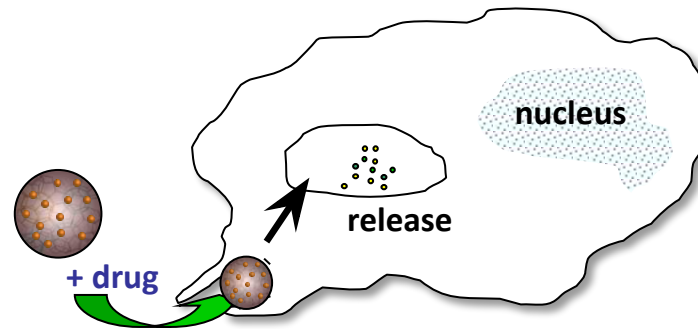
Ruxandra GREF

Institut des Sciences Moléculaires d'Orsay, Université Paris-Saclay, Orsay, France

Engineered drug nanocarriers

Requirements in terms of quality control and nanoparticle tracking in biological media :

1. Can we detect organic nanoparticles in cells without labelling them ?

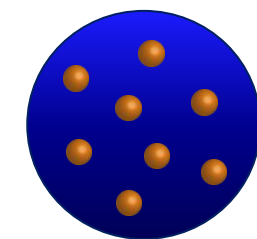


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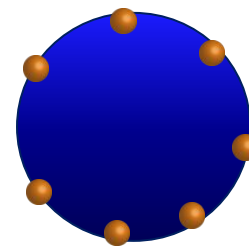
2. Where is located the drug ?



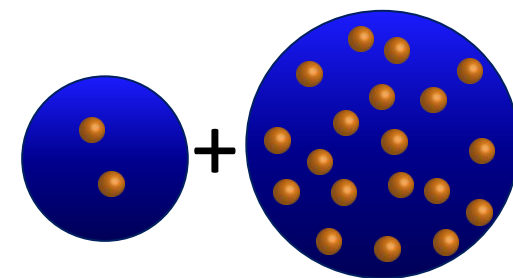
homogeneous



aggregate



surface



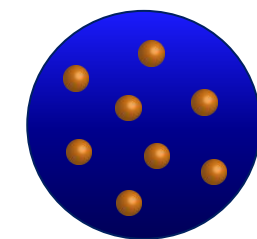
non homogeneous
distribution

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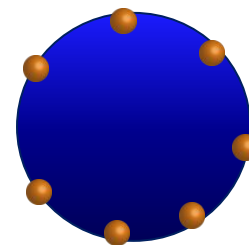
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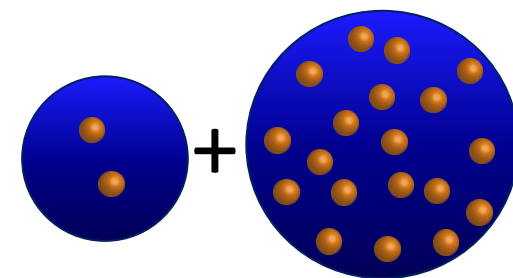
homogeneous



aggregate



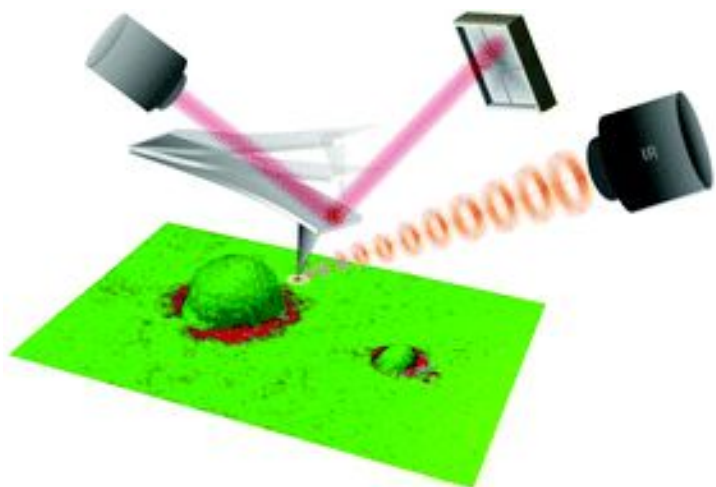
surface



non homogeneous
distribution

3. How much drug contains each nanoparticle ?

A versatile tool : AFM-IR spectromicroscopy

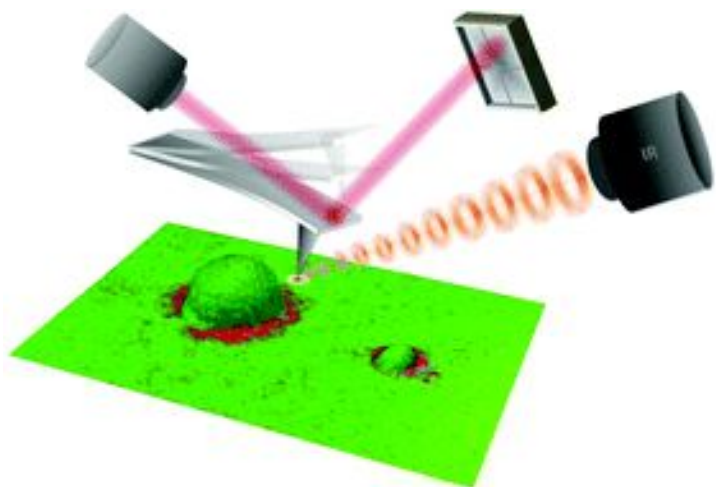


Spatial resolution 10- 20 nm

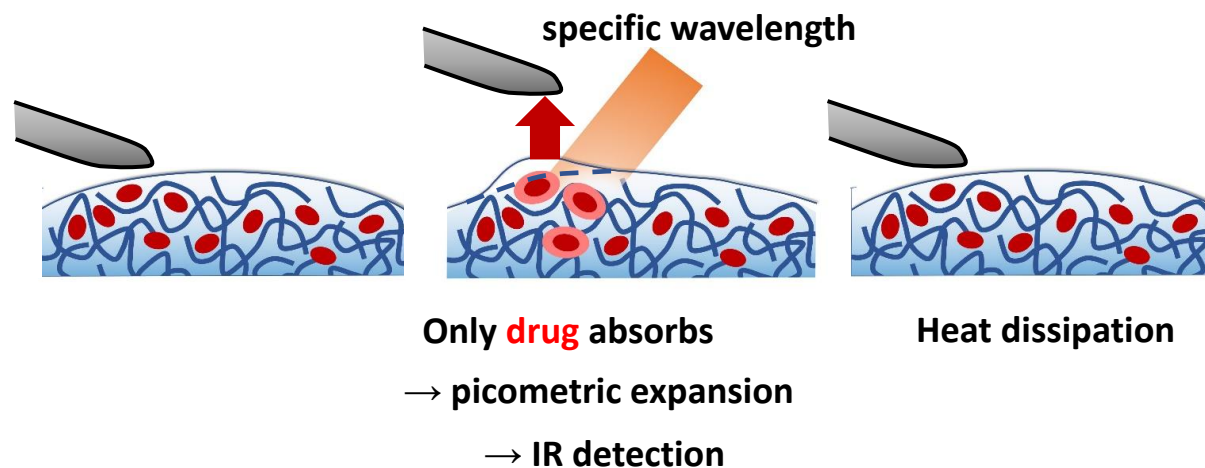
- ✓ AFM: sample topography
- ✓ Tuneable IR laser : repetition rate of the IR source synchronized to one of the cantilever
→ resonance

Dazzi, A. et al. (2010) *J. Applied Physics*

A versatile tool : AFM-IR spectromicroscopy

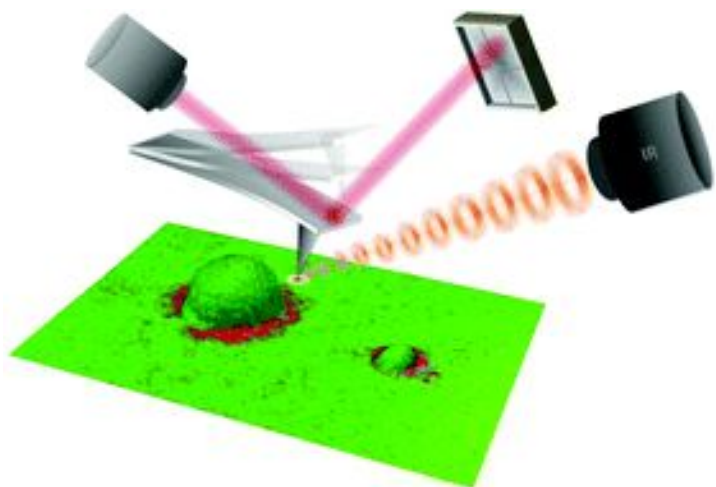


Spatial resolution 10- 20 nm

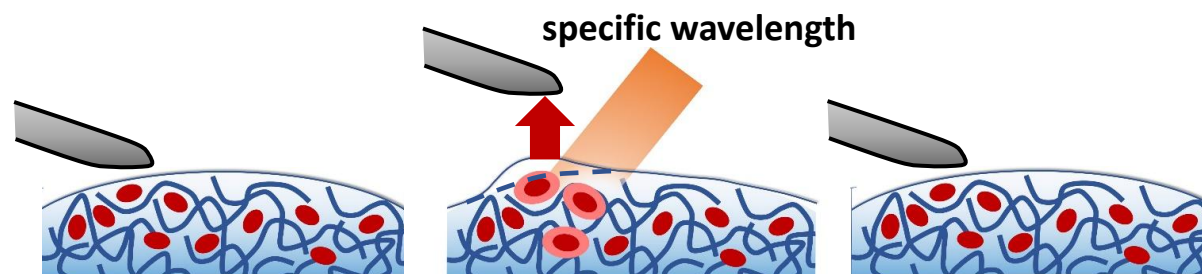


The AFM tip acts as an IR detector to locally measure the thermal expansion of a sample resulting from local absorption of the IR radiation

A versatile tool : AFM-IR spectromicroscopy



Spatial resolution 10- 20 nm

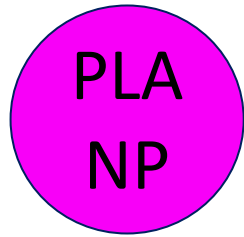


Only **drug** absorbs
→ picometric expansion
→ IR detection

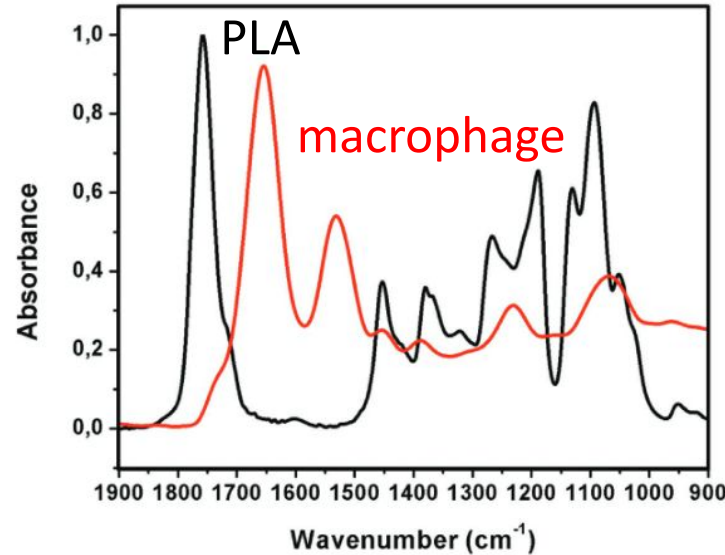
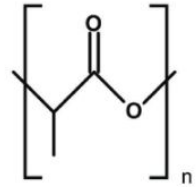
Heat dissipation

- ✓ Map the location of NP components
- ✓ Local absorption spectra
- ✓ Quantify the drug content

Label-free polymer NPs detection inside a cell

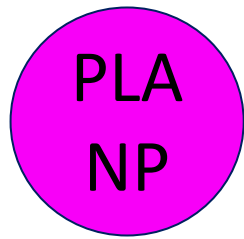


170 nm

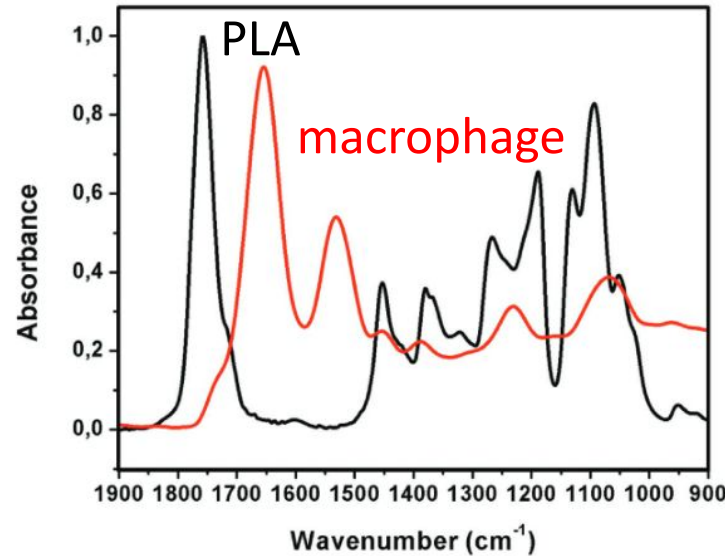
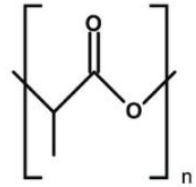


IR absorption band at 1770 cm^{-1}
(elongation vibration band of C=O of ester
functions) → **fingerprint**

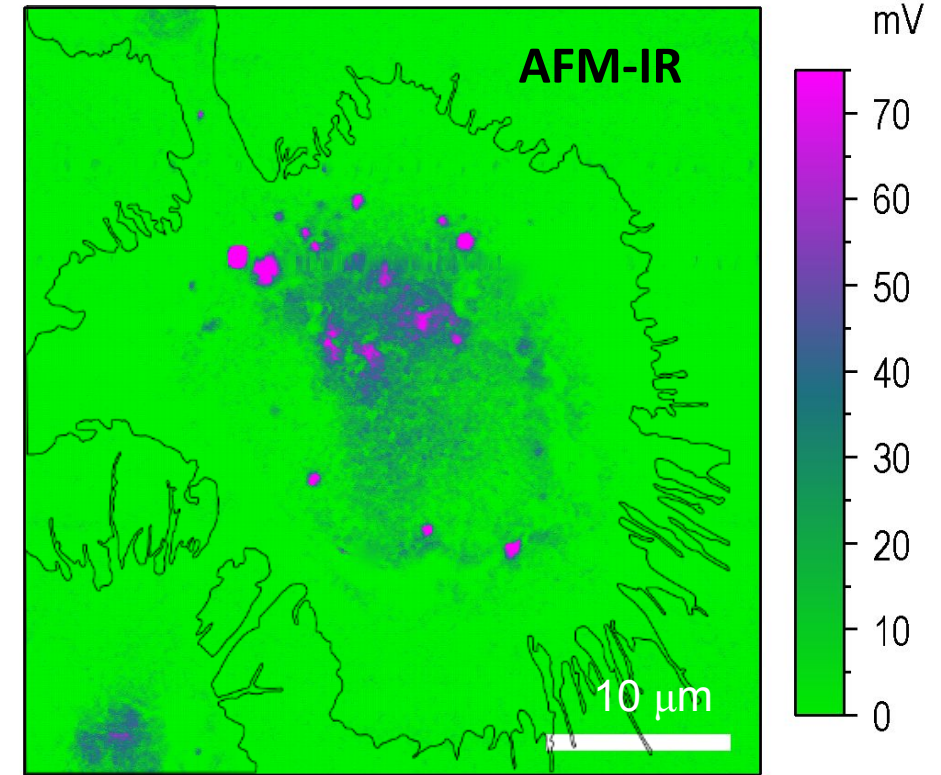
Label-free polymer NPs detection inside a cell



170 nm

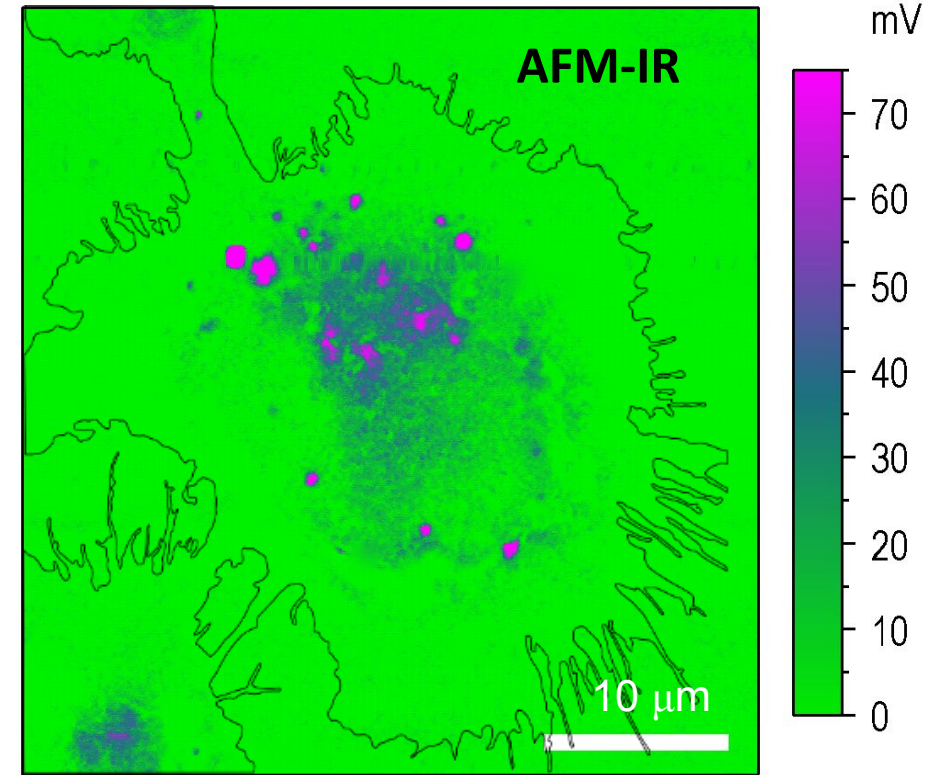
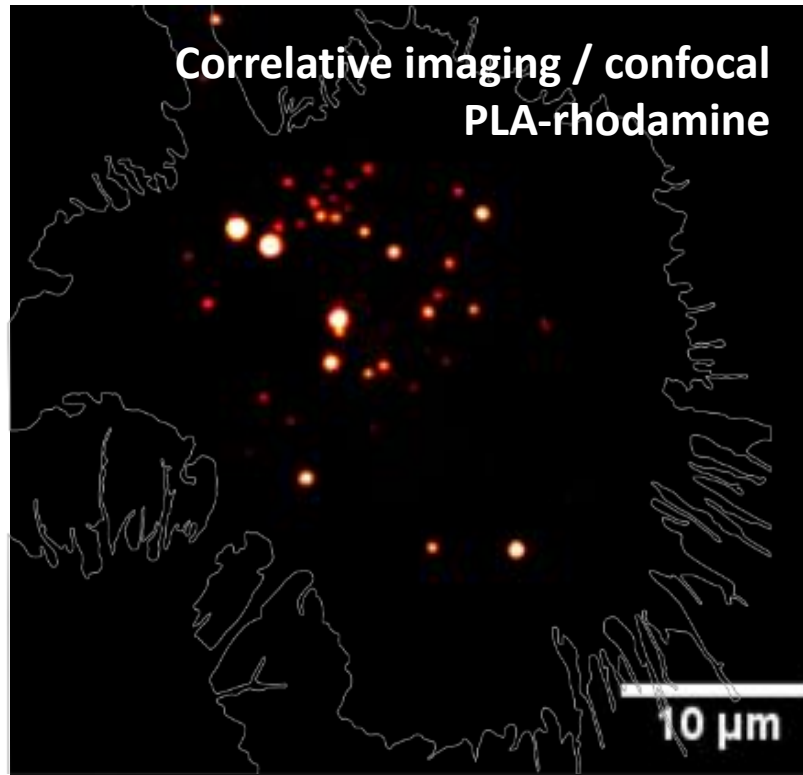


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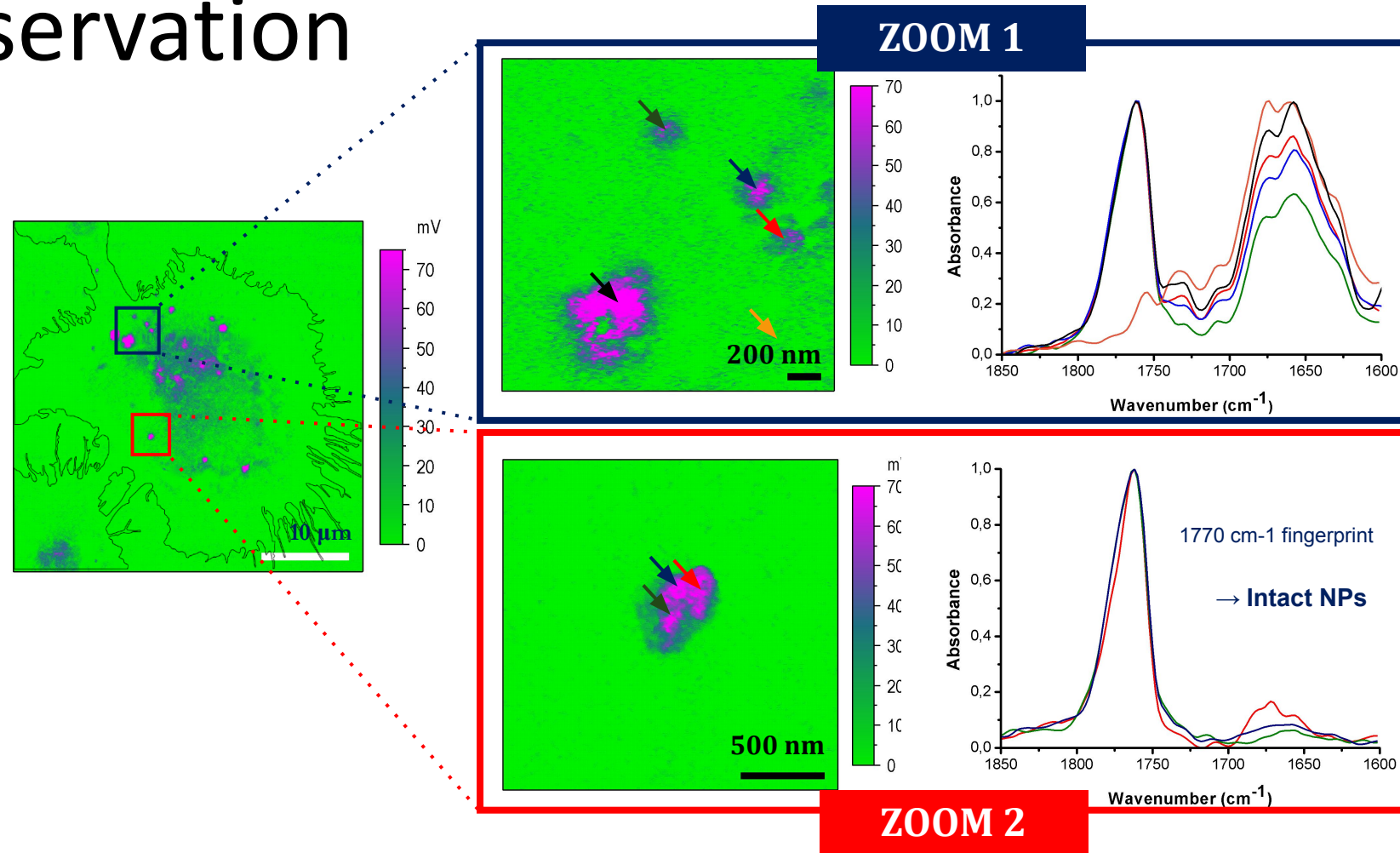
Pancani et al. *Part. Part. Syst. Charact.* 2018

Label-free polymer NPs detection inside a cell



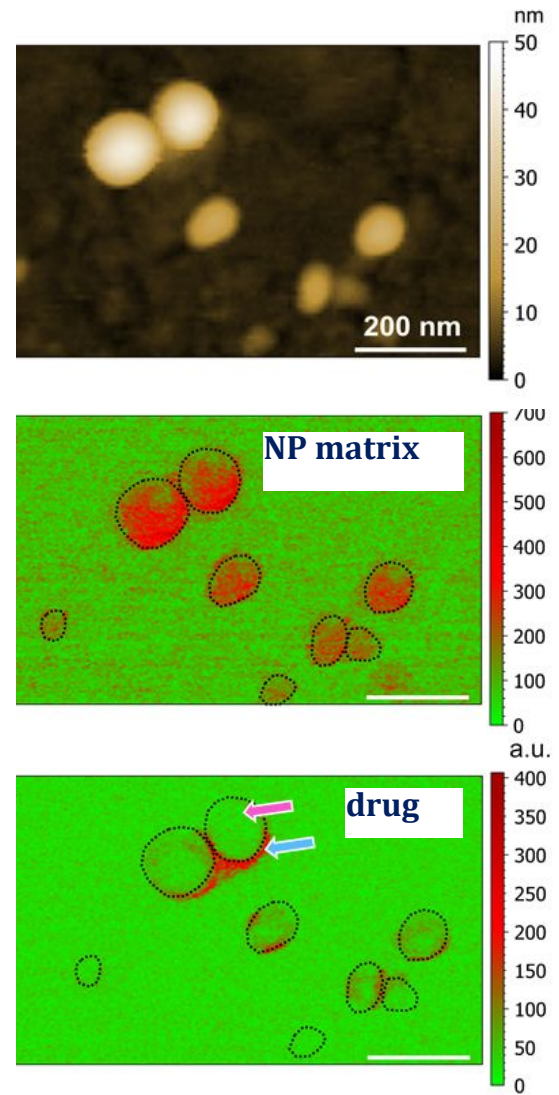
Correspondence between fluorescence and IR signals

ROI observation



Drug location ?

PLA + pipemidic acid
Drug in the corona
→ burst release

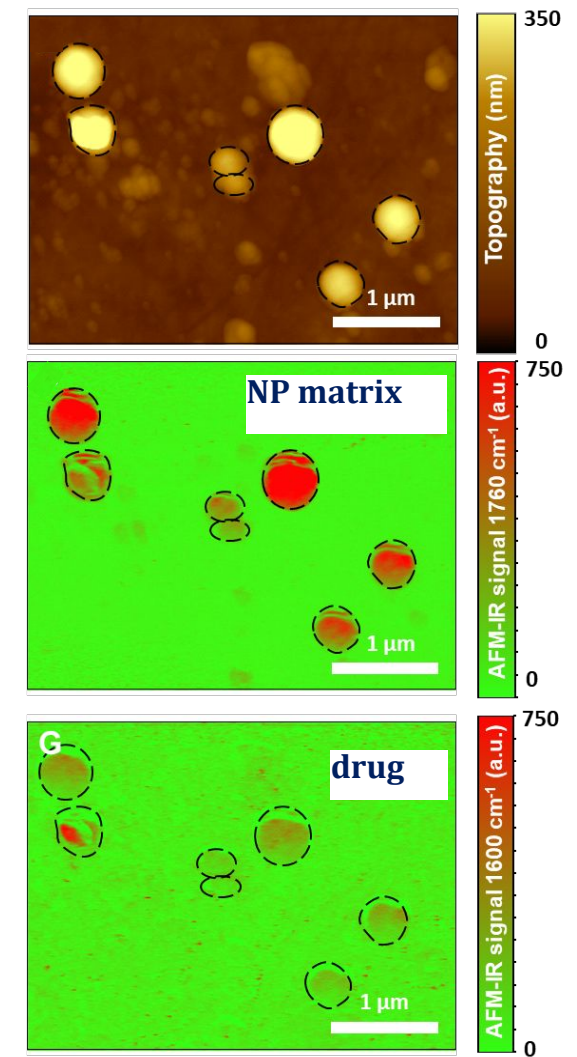
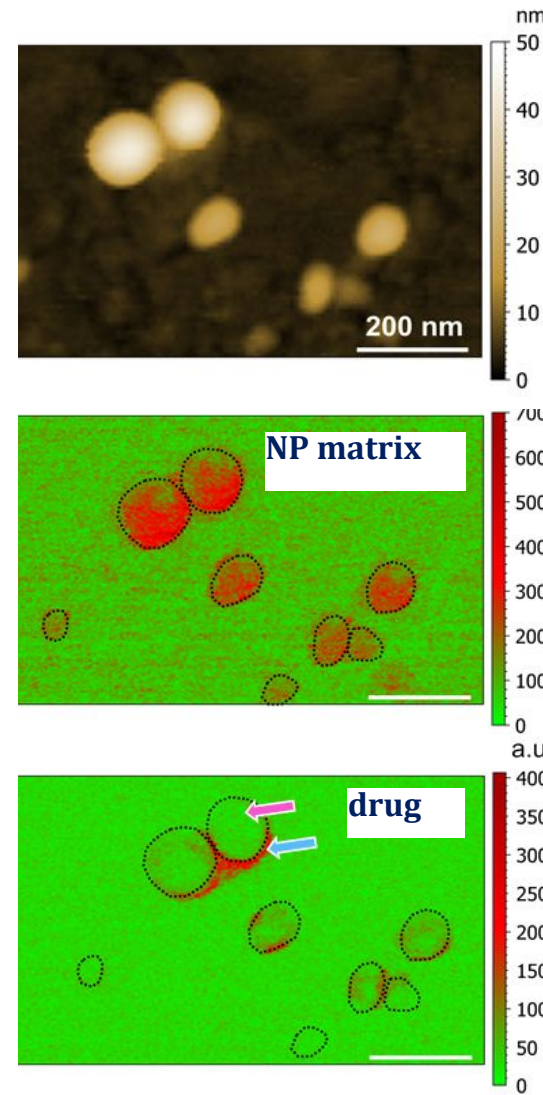


J Mathurin et al, *Analyst*, 2019

Drug location ?

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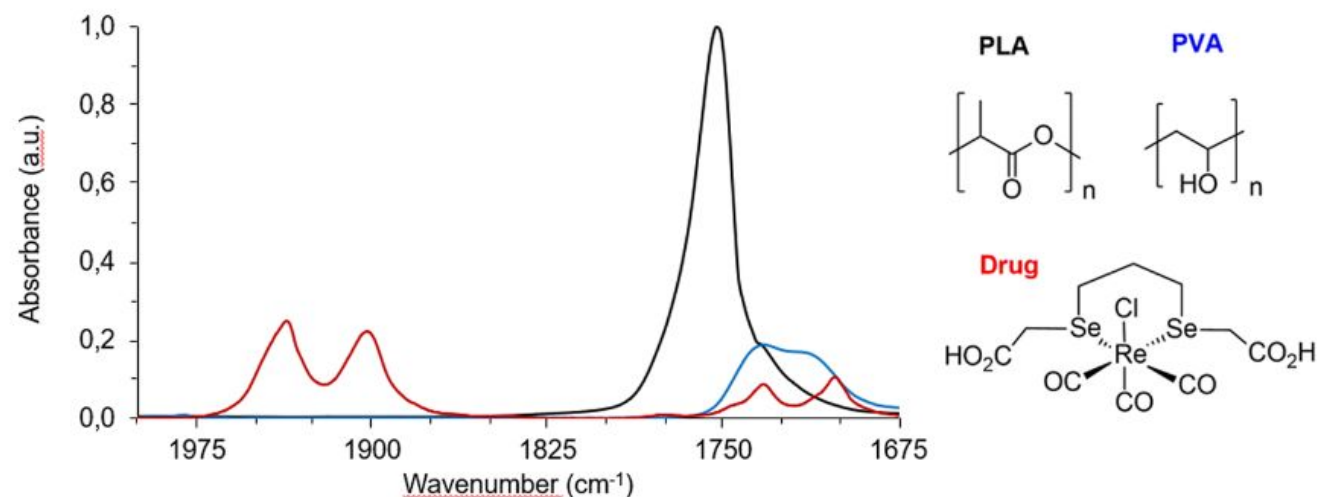
PLA + vancomycin
Drug inside the core
→ progressive release



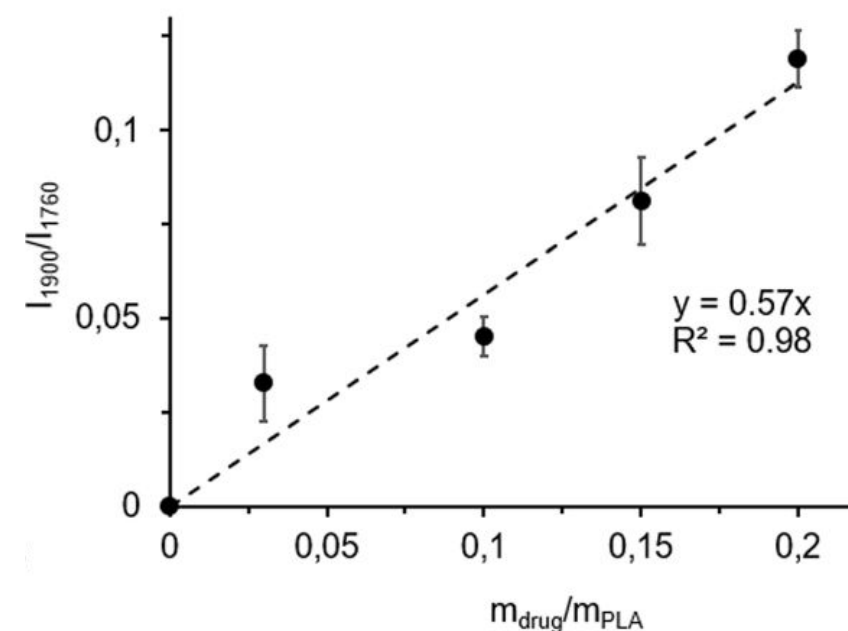
Ural et al, *Pharmaceutics*, 2021

Drug quantification

Drug, polymer and surfactant fingerprints

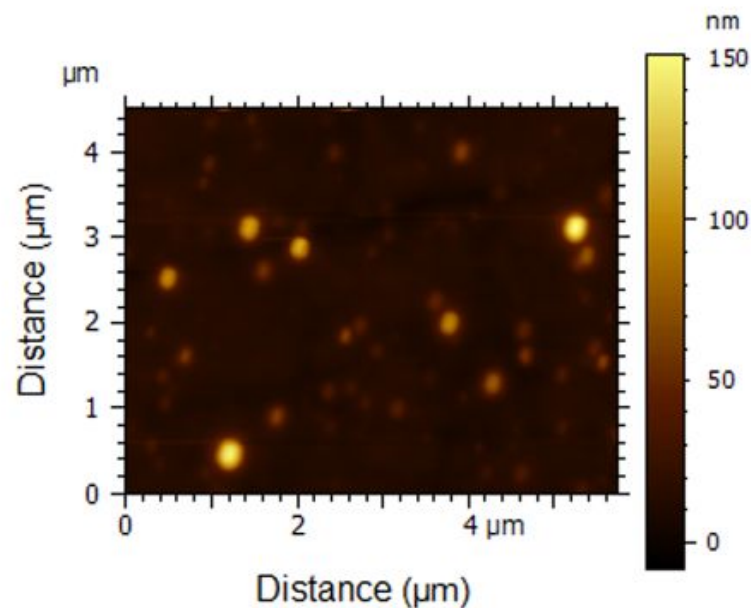


Calibration by IR microspectroscopy
using PLA-drug films

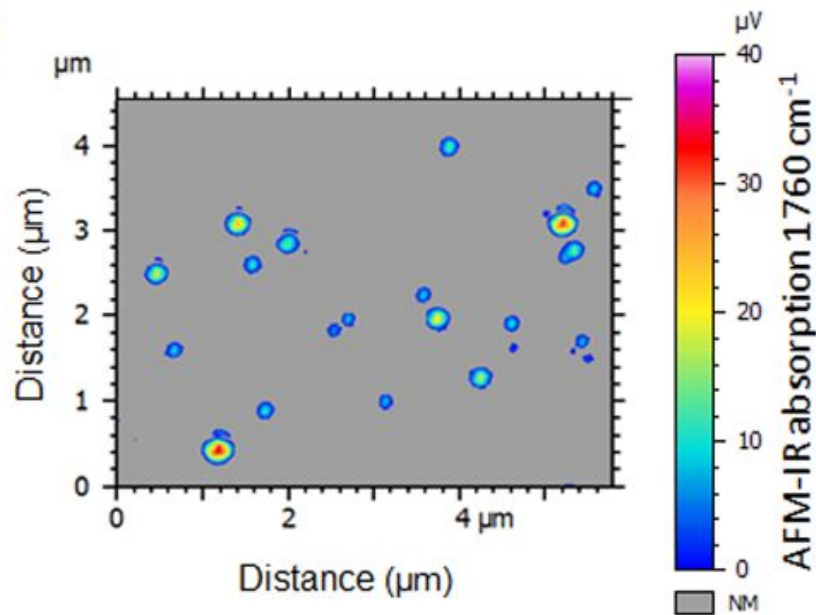


Ural et al, *Analyst*, 2022

Drug quantification – maps in tapping mode



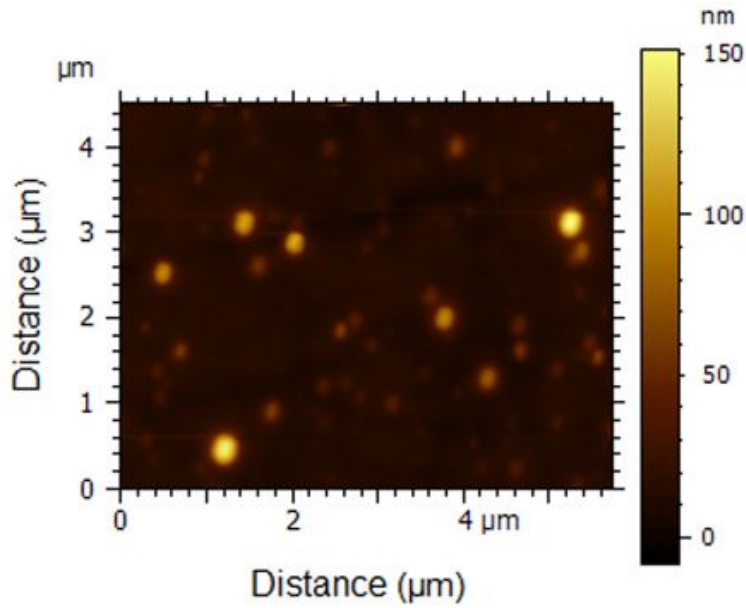
Topography



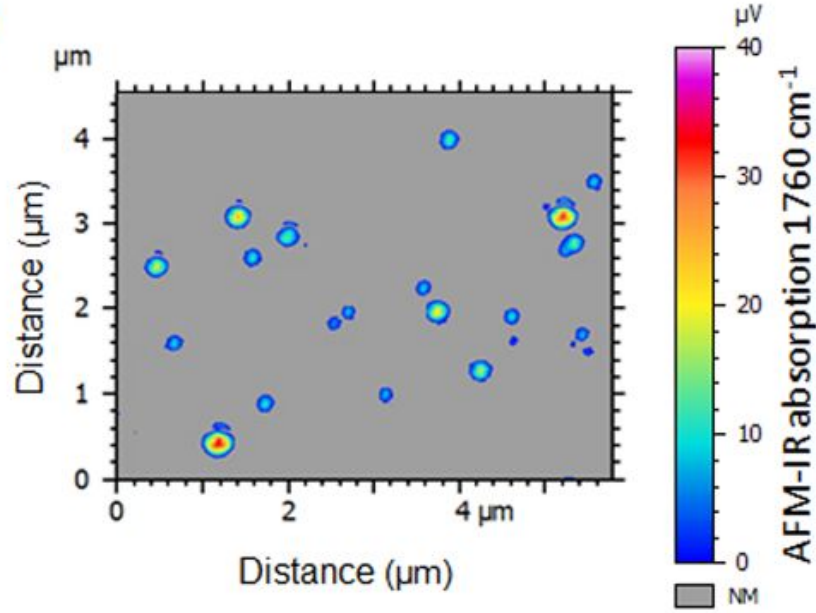
PLA nanoparticles

Ural et al, *Analyst*, 2022

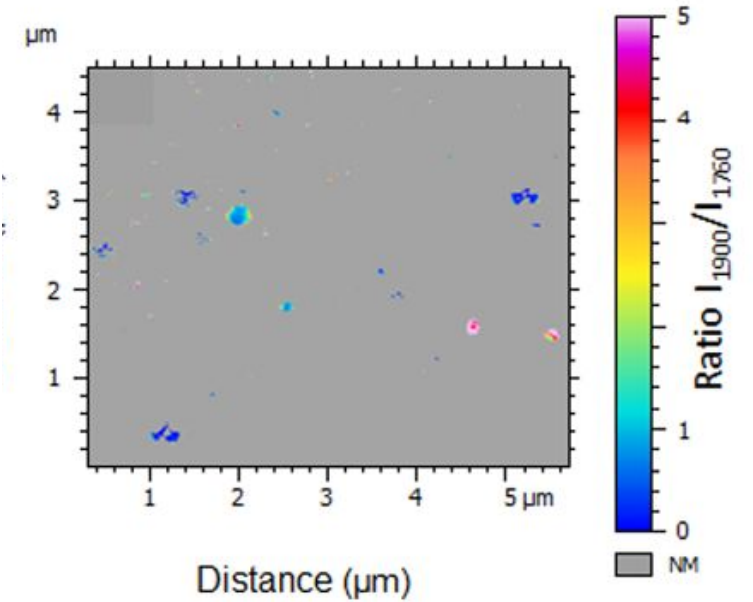
Drug quantification – maps in tapping mode



Topography



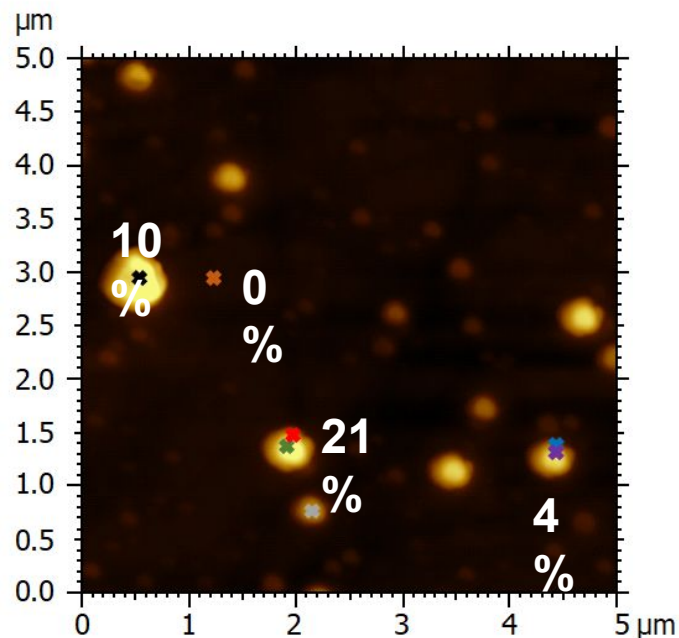
PLA nanoparticles



Drug loading map

Ural et al, *Analyst*, 2022

Drug quantification - local spectra

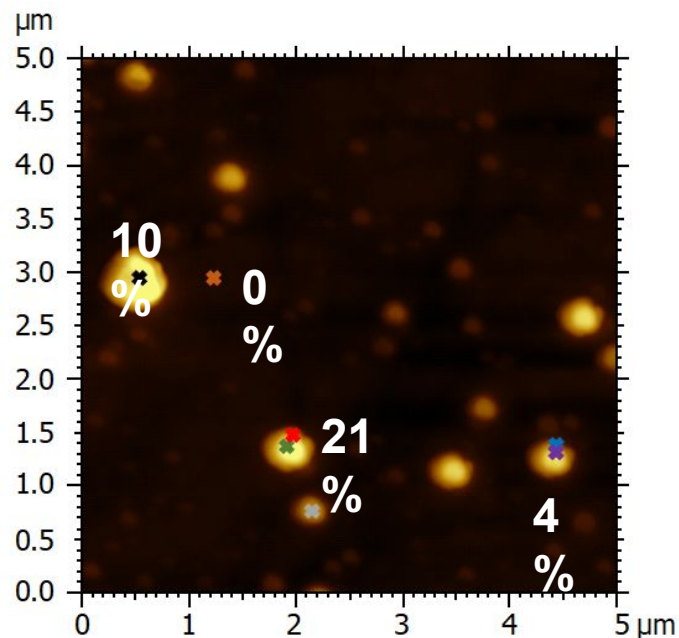


Diameter (nm)	200	320	350	570
DL (wt%)	10	4	21	10

No correlation between nanoparticle size and drug loading

Ural et al, *Analyst*, 2022

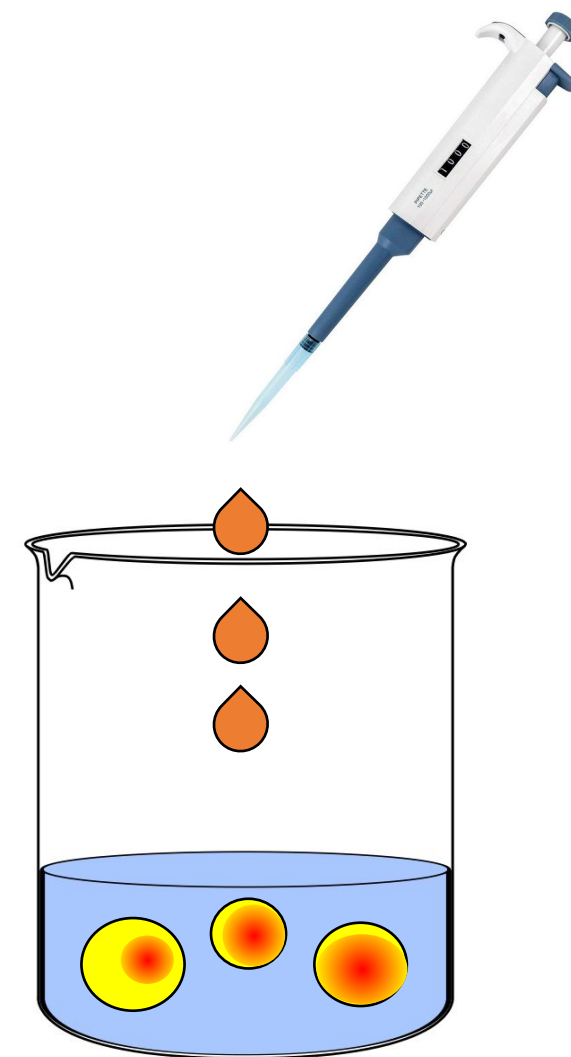
Drug quantification - local spectra



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No correlation between nanoparticle size and drug loading

Segregation during nanoprecipitation



Ural et al, *Analyst*, 2022

Conclusion

Spectromicroscopy allows to:

- Detect nanoparticles in a complex biological media
- Uncover nanoparticle morphology, component location, chemical composition
- Help in the design of the nanoparticle preparation methods

Acknowledgements

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Marie Curie Networks - Project N608407 – Cyclon Hit

