University of Nottingham
UK | CHINA | MALAYSIA

University of Nottingham
Nanoscale and Microscale Research Centre

nmRC CASE STUDY

EFFECT OF EXCIPIENTS ON SALT DISPROPORTIONATION DURNG DISSOLUTION

nmRC_CS_03

University of Nottingham
UK | CHINA | MALAYSIA

University of Nottingham
Nanoscale and Microscale Research Centre

Effect of Excipients on Salt Disproportionation during Dissolution

In Situ Raman Imaging Case Study

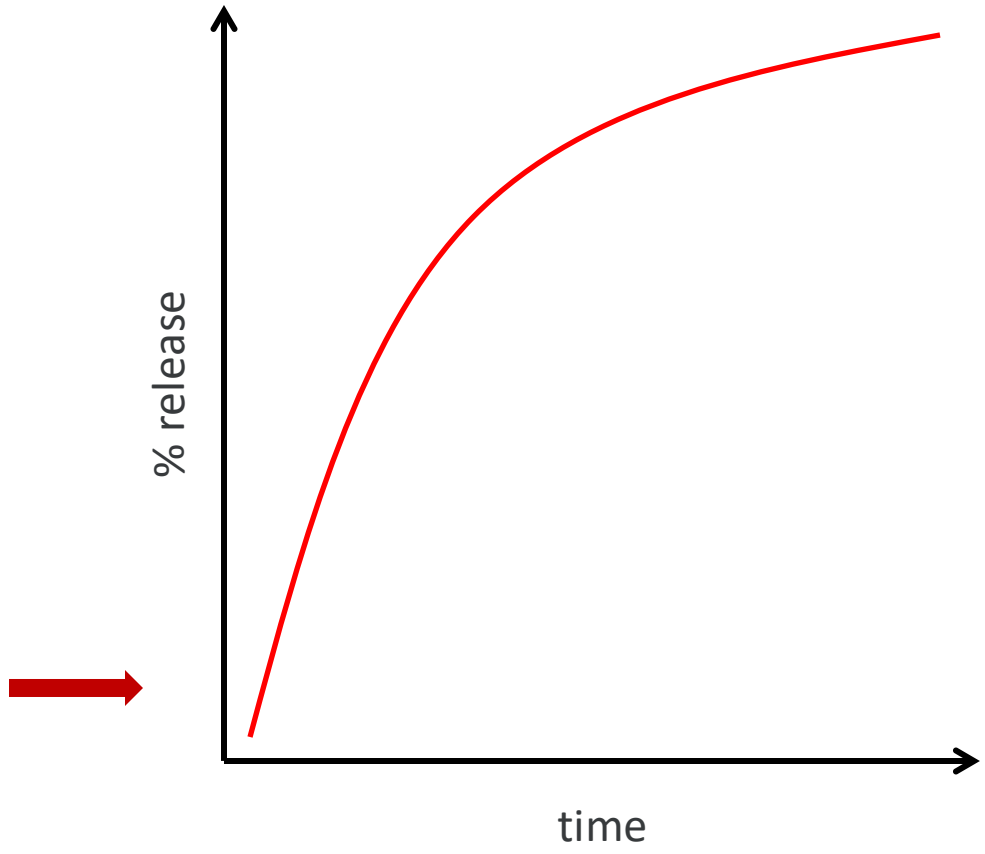
THE EFFECT OF SALT DISPROPORTIONATION

- An estimated 50-70% of all developed small molecule drugs are administered as salts.
- There is a tendency for the salt to convert back to its free (unionized) form under certain conditions via a reaction known as salt disproportionation.
- The conversion of the salt to the free form is undesirable since it may have detrimental effects on solid-state properties and pharmaceutical product performance.
- In order to understand the dissolution behaviour of pharmaceutical formulations we need to be able study them *in situ* (*i.e.*, during dissolution).

UV-VIS SPECTROSCOPY

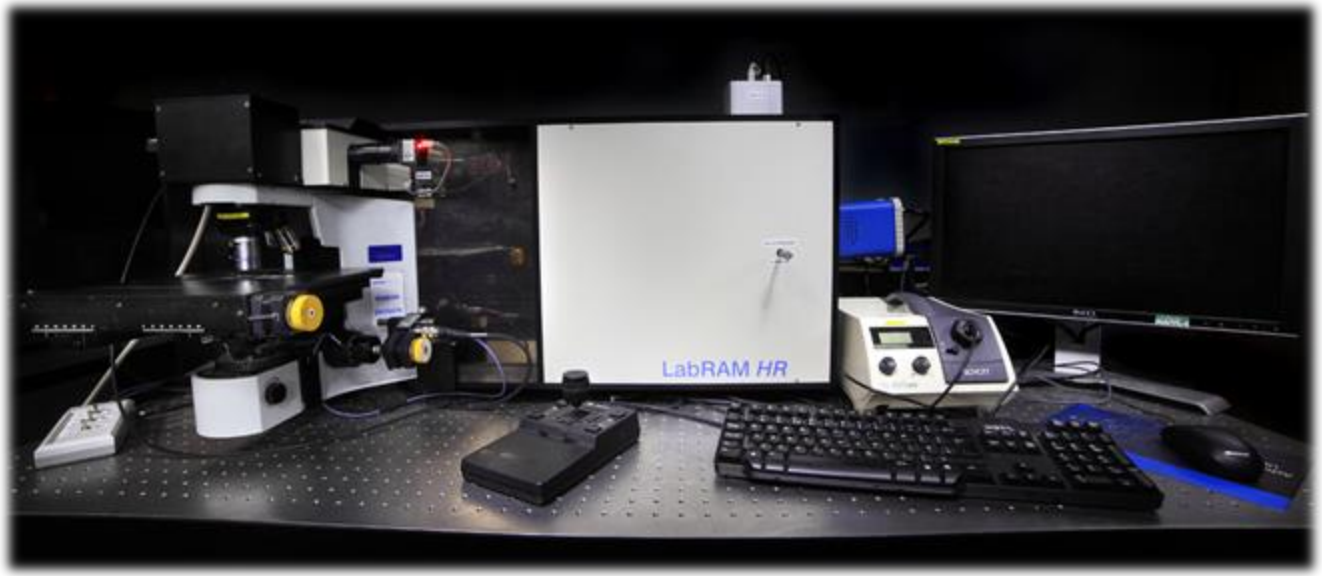
- Oral solid dosage forms are the most common way in which drugs are administered, so dissolution of the dosage form after it is swallowed, specifically the rate at which the active ingredient is released into the body, is of critical importance drug development.

- Standardised dissolution apparatus often rely upon UV-vis absorbance spectroscopy to monitor the drug release profile.



RAMAN SPECTROSCOPY

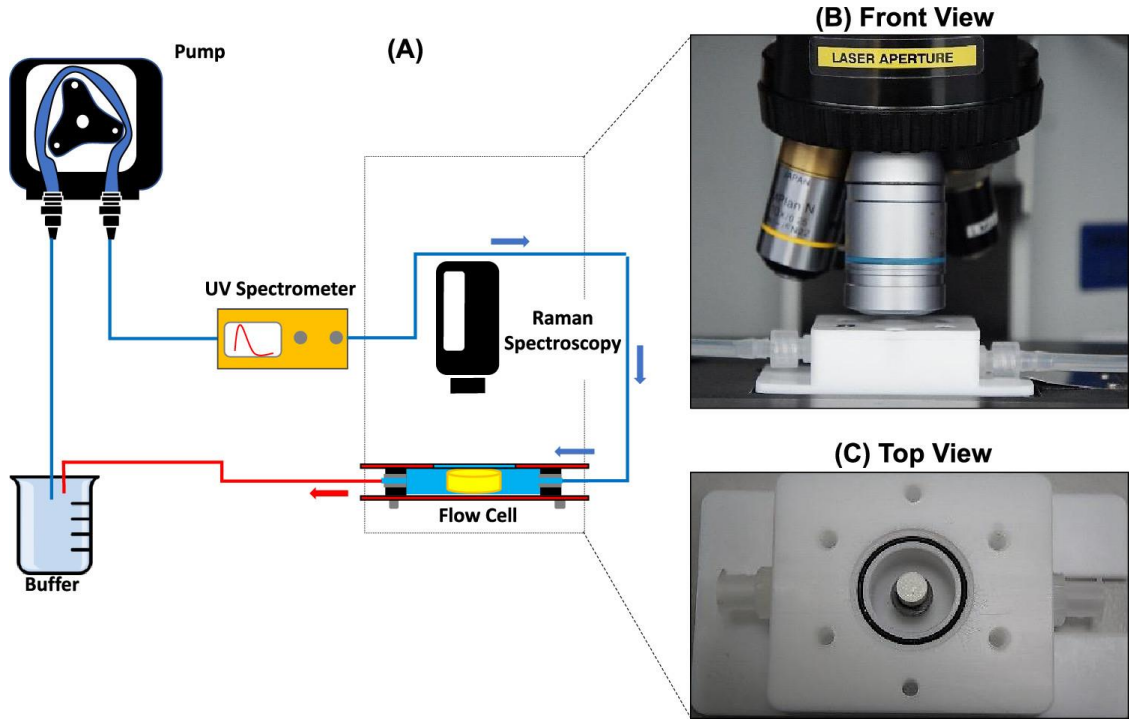
- Raman spectroscopy allows for real-time, '*in-situ*' chemical and morphological analysis that can be used to monitor dissolution dynamics.
- The technique uses the inelastic scattering of light to generate spectra unique to a material's molecular composition and state, and can be used to track changes with time.



The HORIBA LabRAM HR Raman Microscope available at the Nanoscale and Microscale Research Centre (nmRC), University of Nottingham.

RAMAN UV-VIS FLOW CELL SYSTEM

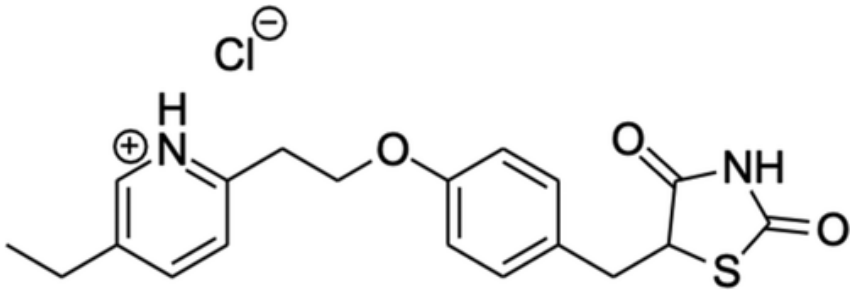
- In our study, Raman spectroscopy was used to probe the chemical composition of the tablet, whilst UV-vis spectroscopy enabled quantification of the drug release. In order to monitor both simultaneously, a novel flow cell design was used.



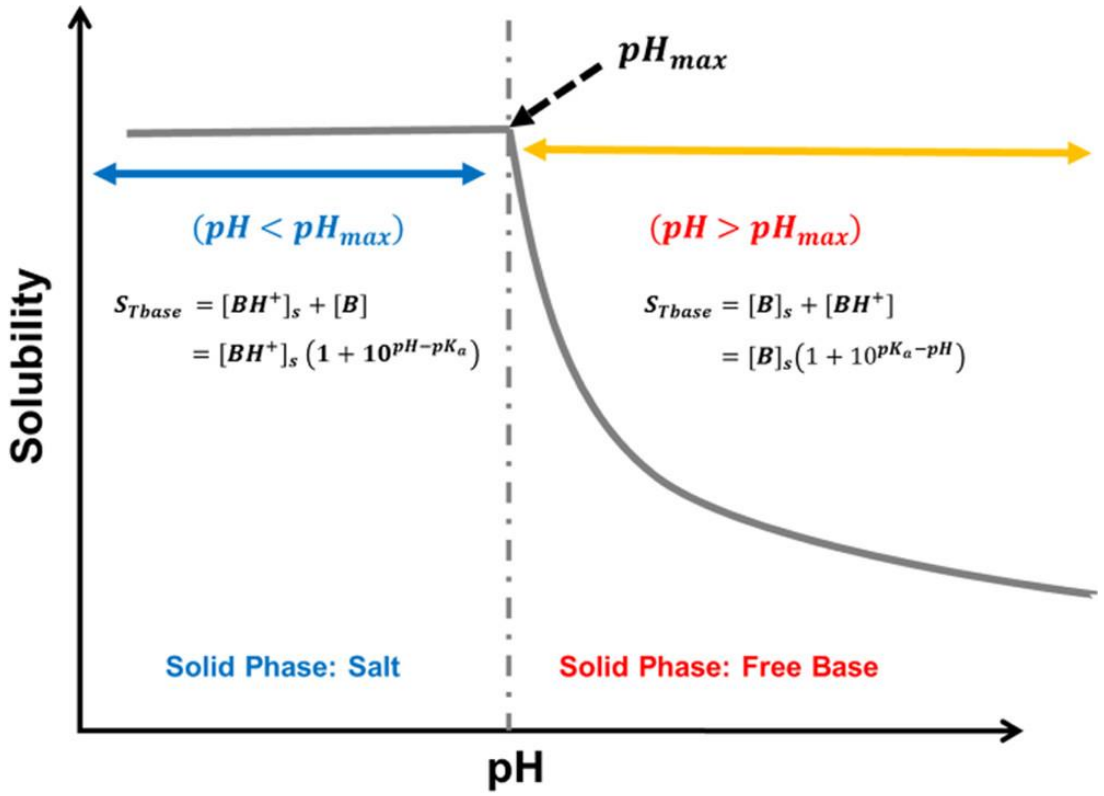
(A) Schematic diagram of the Raman ultraviolet–visible flow cell system. (B) Front view of the flow cell under the Raman spectroscopy objective. (C) Top view of the tablet placed inside the flow cell.

DISPROPORTIONATION OF PIOGLITAZONE HCL

- The challenge we have applied our novel approach to is the disproportionation of Pioglitazone HCl (PioHCl), which has pH-dependent solubility and therefore release characteristics.



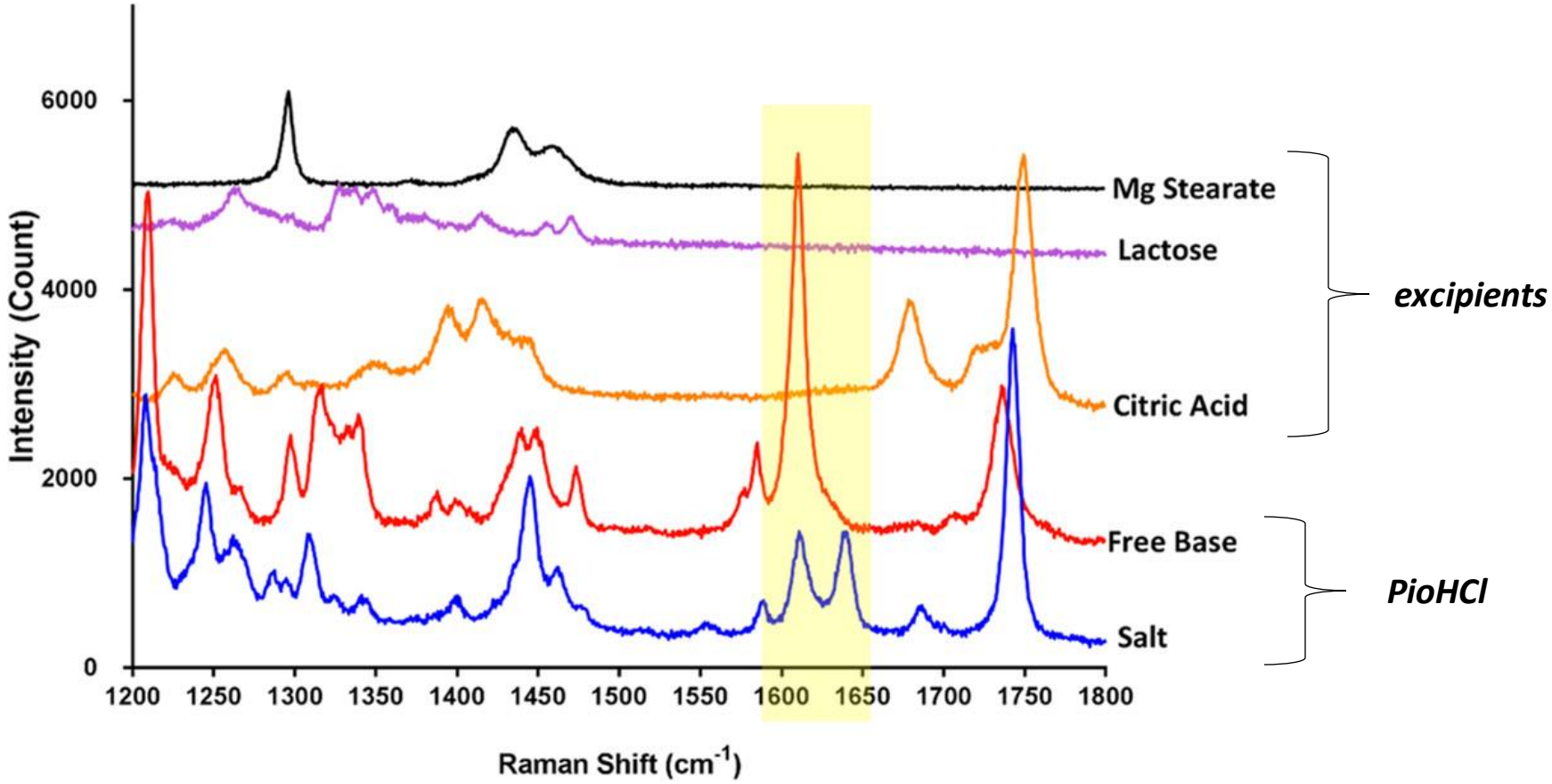
Pioglitazone HCl



pH-solubility profile of a weak base drug presenting the pH_{max} point and indicating that the solubility may be expressed by two independent regions.

FORMULATION COMPONENTS

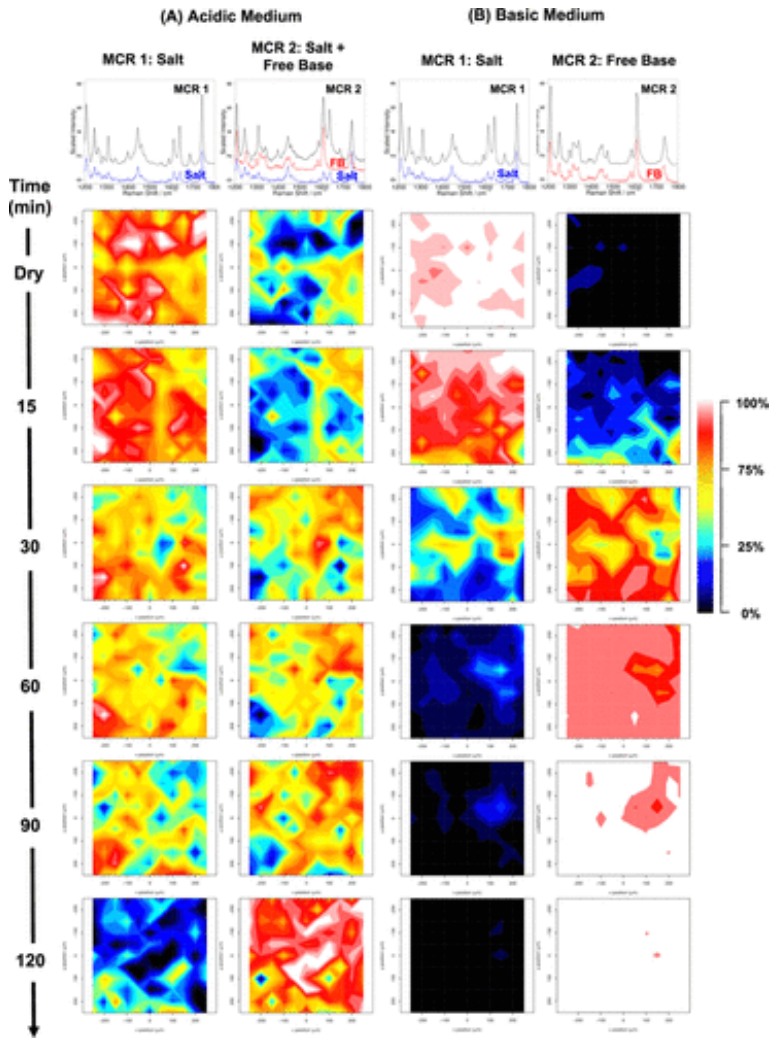
- Raman spectroscopy enables diagnosis of the composition of the tablet based on the molecular fingerprint of the components.



Raman spectra of the formulation components within the range 1200–1800 cm^{-1}.

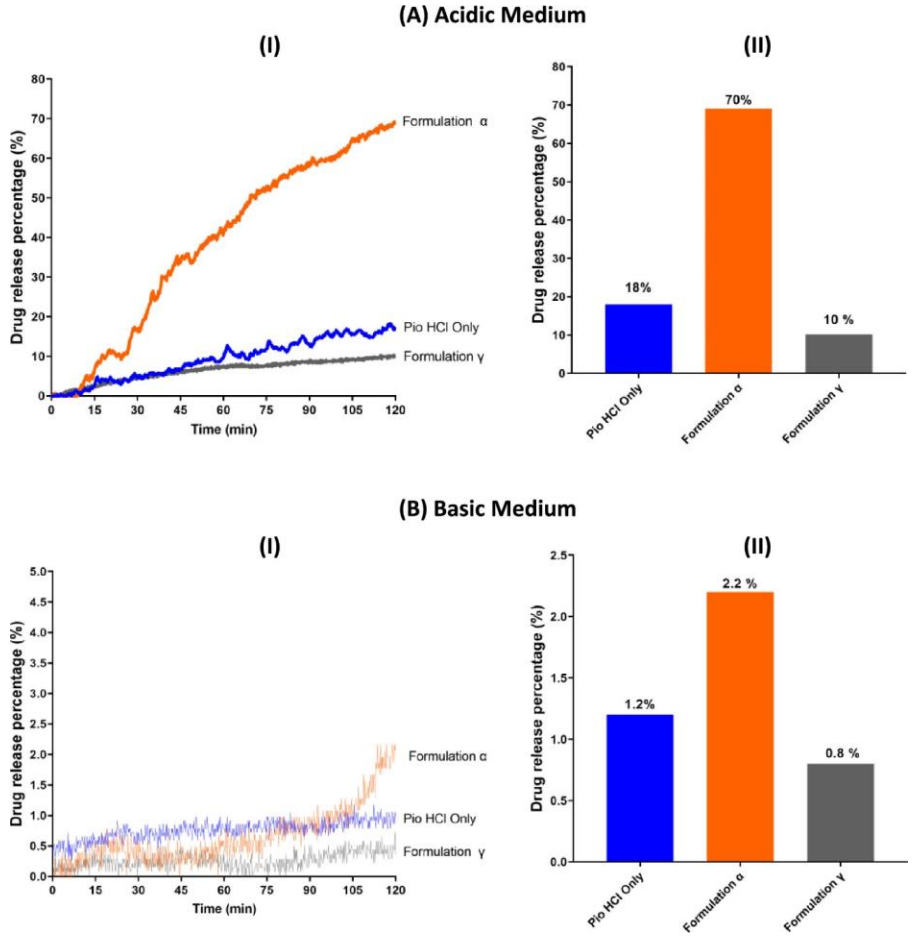
University of Nottingham
UK | CHINA | MALAYSIA

IN SITU ANALYSIS UNDER DIFFERENT CONDITIONS



Raman spectroscopy: mapping of PioHCl-only tablet during dissolution in (A) acidic and (B) basic media, as a function of time, generated by MCR analysis.

UV-vis spectroscopy: dissolution profiles in (A) acidic and (B) basic media, as a function of time, for the PioHCl-only and different formulations.



SUMMARY

- We have demonstrated the utilisation of Raman spectroscopic imaging combined with a UV-vis spectroscopy flow cell is a valuable tool for the investigation of problematic multicomponent pharmaceutical formulations, specifically where disproportionation kinetics depend on the pH microenvironment.

- This approach can enhance our understanding of the interplay between drug and excipient properties, and their influence on disproportionation kinetics, ultimately, helping to mitigate disproportionation of API salts in tablets and enabling pharmaceutical scientists to develop more reliable products with improved drug stability.

REFERENCES / ACKNOWLEDGEMENTS

For more details on the work showcased in this case study see the following publications:

A. Abouselo et al., "Effect of Excipients on Salt Disproportionation during Dissolution: A Novel Application of In Situ Raman Imaging," Molecular Pharmaceutics, vol. 18, no. 9, pp. 3247-3259, 2021/09/06 2021, doi: 10.1021/acs.molpharmaceut.1c00119.

The Raman spectroscopy analysis documented here was performed at the Nanoscale and Microscale Research Centre (nmRC) at the University of Nottingham. www.nottingham.ac.uk/nmrc

University of Nottingham
Nanoscale and Microscale Research Centre

ADDITIONAL INFORMATION

- We hope the information provided in this case study is of interest.
- If you wish to get in touch with us to discuss any of the information provided, raise a query/concern or provide feedback then please use any of the methods listed below:

nmRC Commercial Services
Nanoscale & Microscale Research Centre
University Park
Nottingham
NG7 2RD

Telephone: **+44(0)115 951 5046**
Email: nmcs@nottingham.ac.uk
Fax: **+44 (0)115 846 7969**
Website: **www.nottingham.ac.uk/nmrc-commercial**