Assessment of Fluticasone Propionate/Salmeterol Xinafoate/Lactose Particle Sizes and Co-Associations in Pharmaceutical Dry Powder Inhalation Products: A Photothermal Nanospectroscopic Study.

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Identification of Drug Distribution in Aerosols
A Nanospectroscopy and NanoThermal Analysis

Dry powder inhalers (DPIs) commonly used for Asthma and COPD treatment

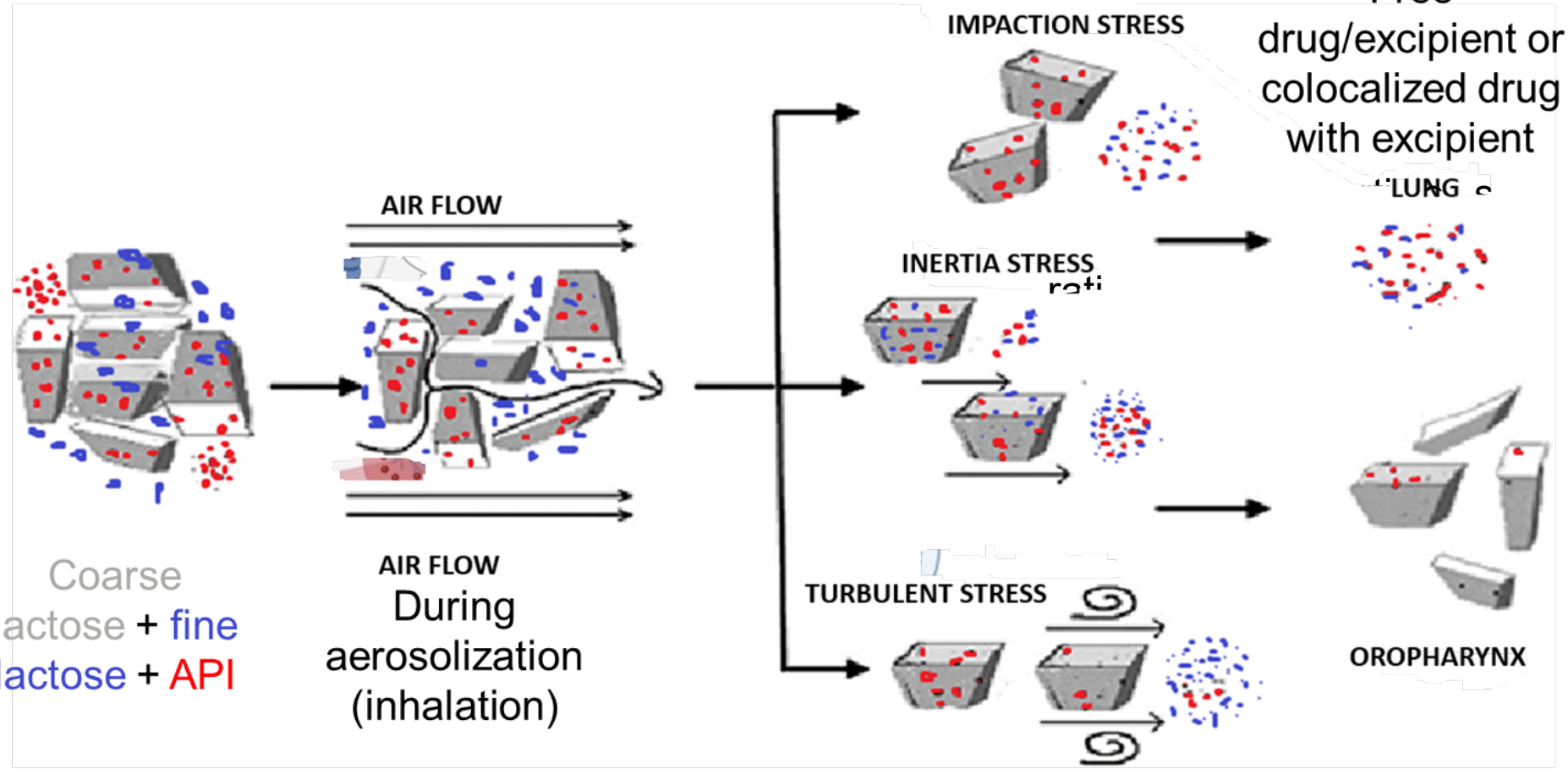
- Combination of inhaled corticosteroids (ICS) (**Fluticasone**) and long-acting beta$_2$-agonist (LABA) (**Salmeterol**) are commonly used for the treatment of asthma and chronic obstructive pulmonary diseases (COPD).
- These drugs have been proven to work synergistically at cellular level[1].

Brand Name

Generic

[1]Eur Respir J. 2002 Jan;19(1):182-91. doi: 10.1183/09031936.02.00283202.

Critical formulation aspects and therapeutic activity



- Characterisation of particle size distribution and chemical composition at the individual particle or primary aggregate level is crucial to allow quality by design of dry powder inhaler formulations.
- Optical Photothermal Infrared Spectroscopy (O-PTIR) allows for the solid-state assessment of chemical composition, morphology, crystallinity, and the evaluation of co-localization of active pharmaceutical ingredients (APIs) and/or excipients in different aerodynamic particle size fractions.[3,4]

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[3]Khanal et.al, *Anal Chem* 2020, 92: 8323–8332.

[4]Khanal et.al, *Int J Pharm* 2023, 632: 122563.

O-PTIR on dry powder inhalation formulation prepared by a blending method.

Turbula® T2G blender used for blending.

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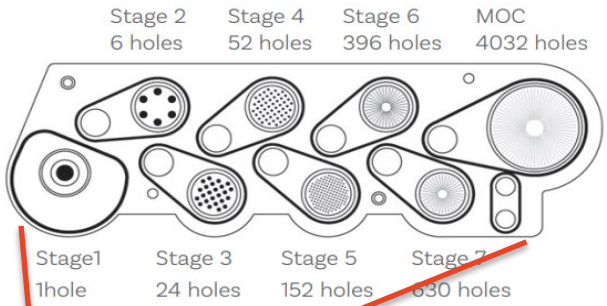
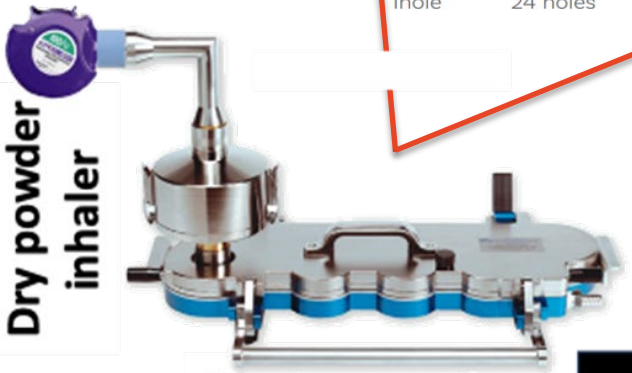
Objectives

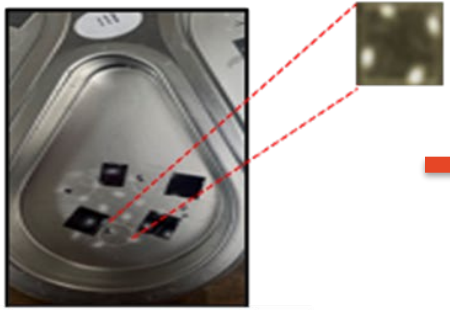
- Employ O-PTIR to characterize and compare the chemical composition of aerosolized fractions and drug-excipient agglomeration behavior of particles after the dispersion from **Advair Diskus 100/50** and **Wixela Inhub 100/50** DPIs (fluticasone propionate; salmeterol xinafoate inhalation powders).

Materials and Methods



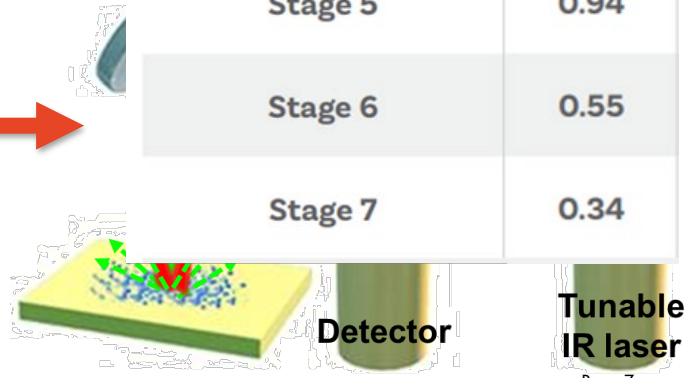


Next generation impactor

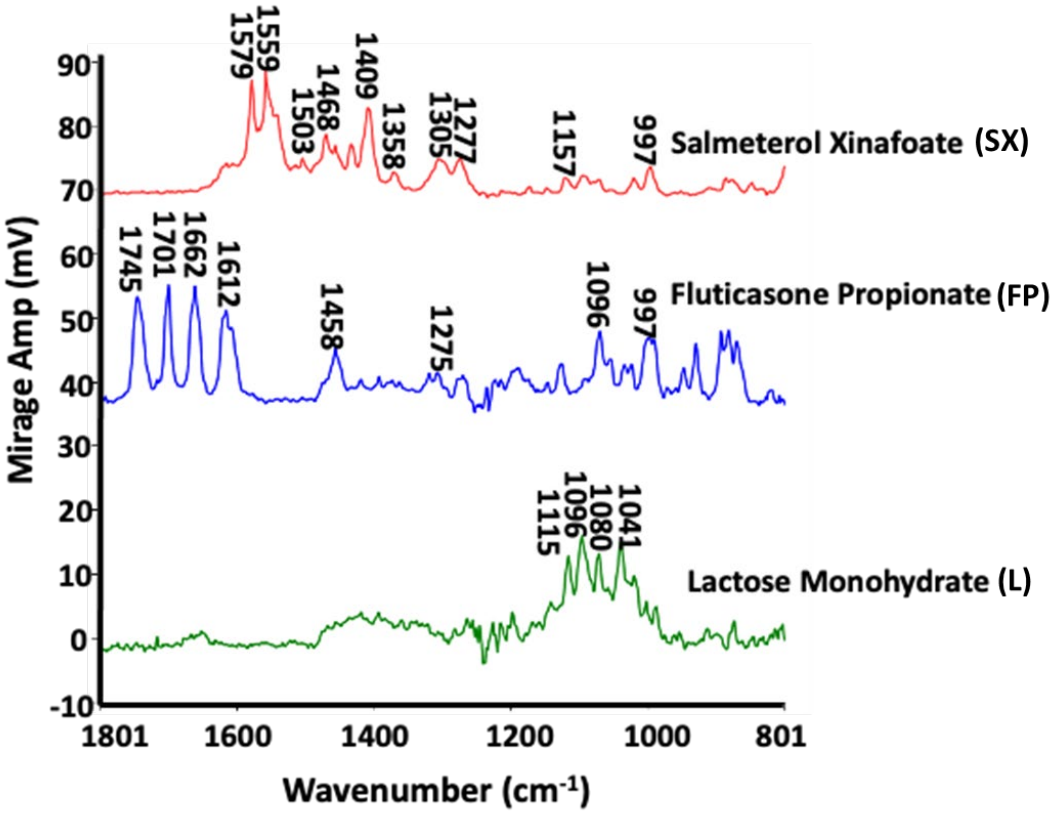


NGI cup with CaF_2 wafer after particle deposition

Stage	Cut-off Diameter (microns) at 60 L/min
Stage 1	8.06
Stage 2	4.46
Stage 3	2.82
Stage 4	1.66
Stage 5	0.94
Stage 6	0.55
Stage 7	0.34

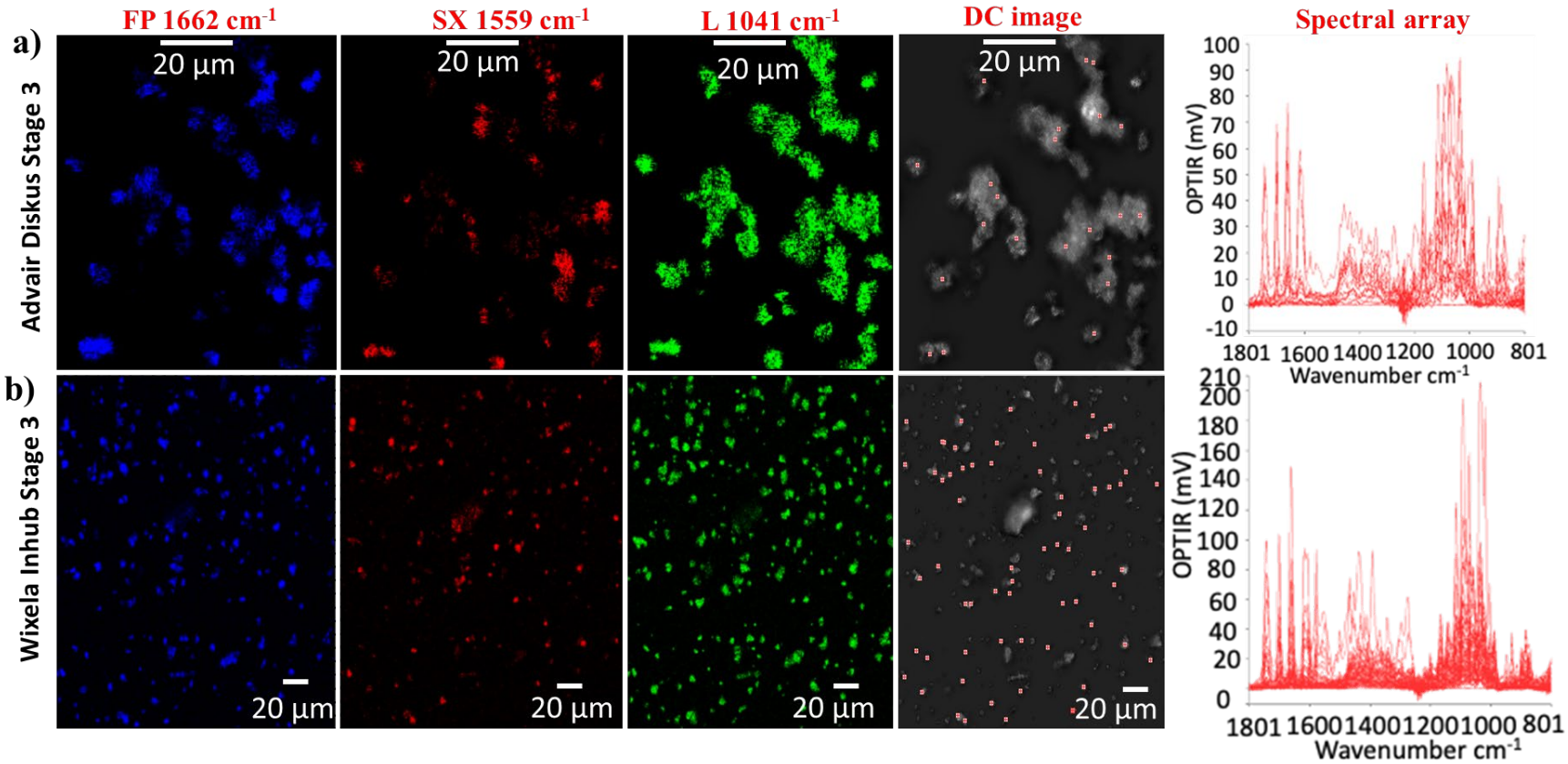


Results

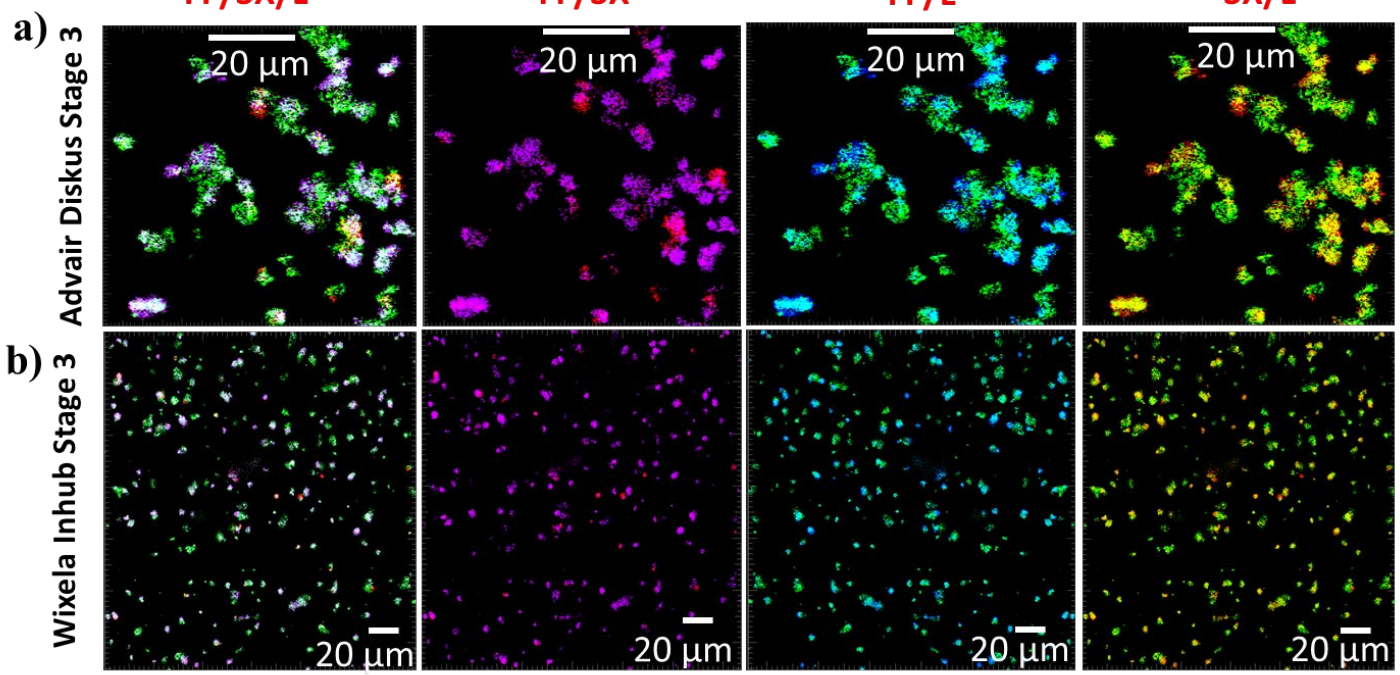


O-PTIR spectra of fluticasone propionate (FP), salmeterol xinafoate (SX), and lactose (L) raw materials.

Representative identification peaks are labelled for each component.



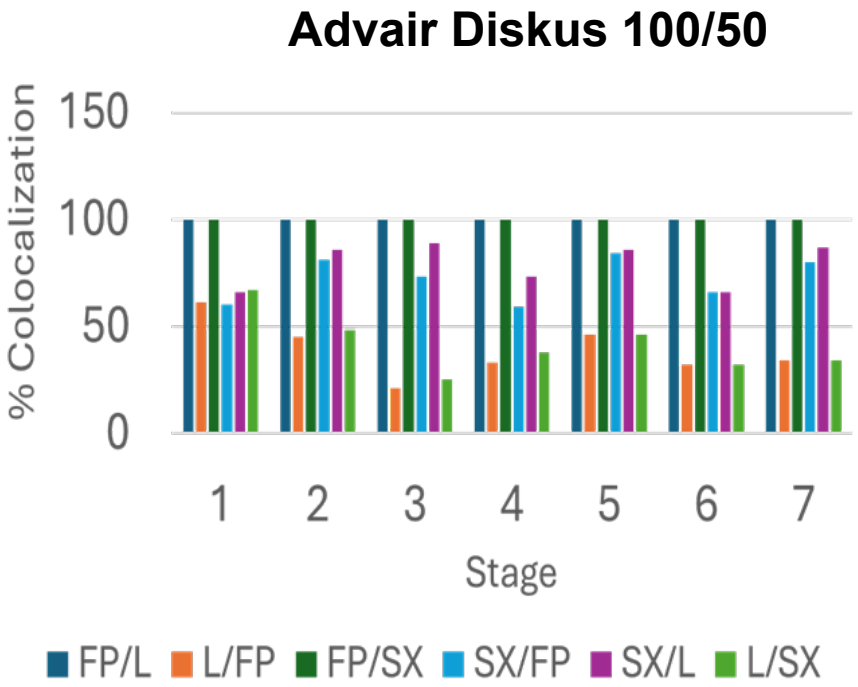
Single wavenumber chemical maps, DC image and spectral array collected from aerosolised a) Advair Diskus 100/50 and b) Wixela Inhub 100/50 particles collected from stage 3 of the NGI showing the distribution of FP, SX, and L.

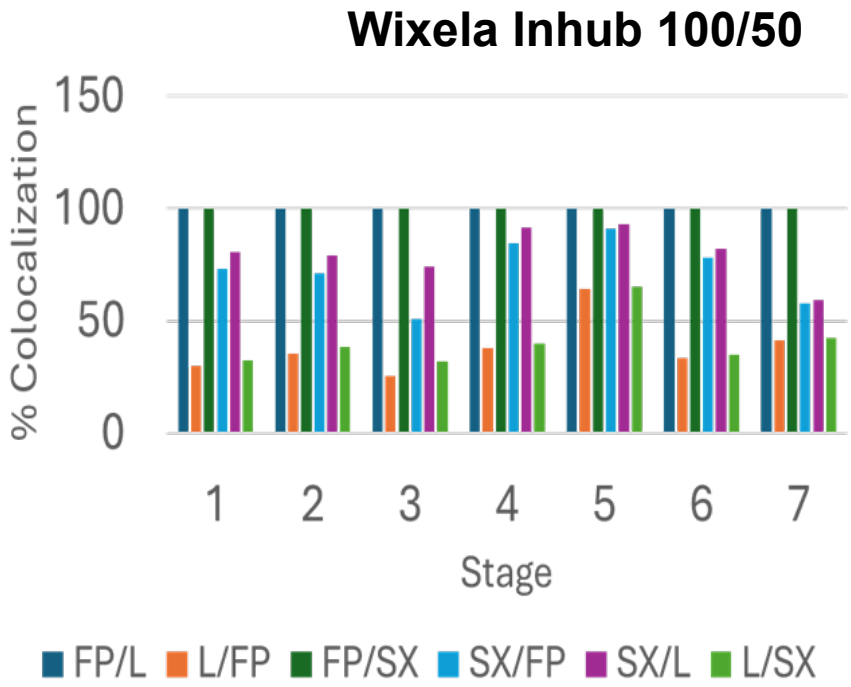


Colocalization	%
FP/L	100
L/FP	52
FP/SX	100
SX/FP	86
SX/L	96
L/SX	58

Colocalization	%
FP/L	100
L/FP	56
FP/SX	100
SX/FP	90
SX/L	94
L/SX	57

Colocalization analysis of FP, SX, and L of aerosolised a) Advair Diskus 100/50 and b) Wixela Inhub 100/50 particles collected from stage 3 of the NGI. The degree of colocalization is represented as a percentage (%) via the Manders Coefficient.

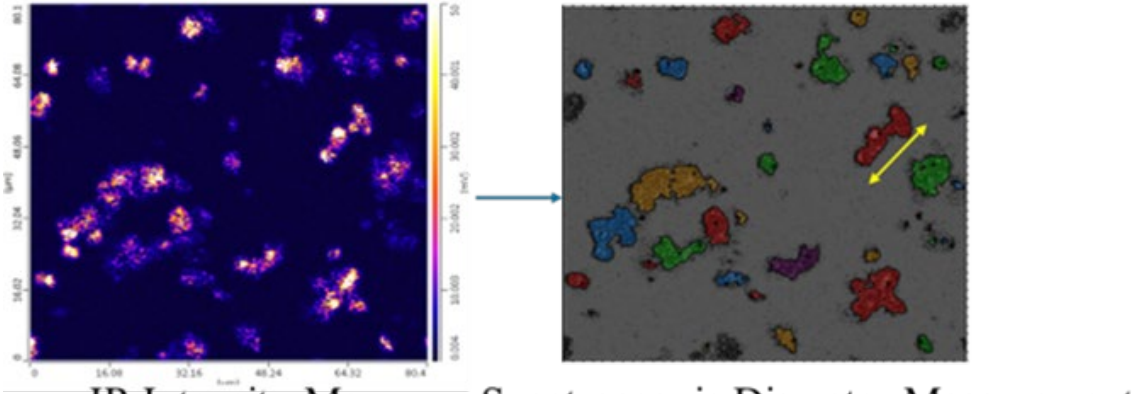




Colocalization analysis of FP, SX, and L of aerosolised a) Advair Diskus 100/50 and b) Wixela Inhub 100/50 particles collected from stage 1-7 of the NGI. Both formulations were actuated once to collect the samples on the CaF_2 substrate. The degree of colocalization is represented as a percentage (%) via the Manders Coefficient.

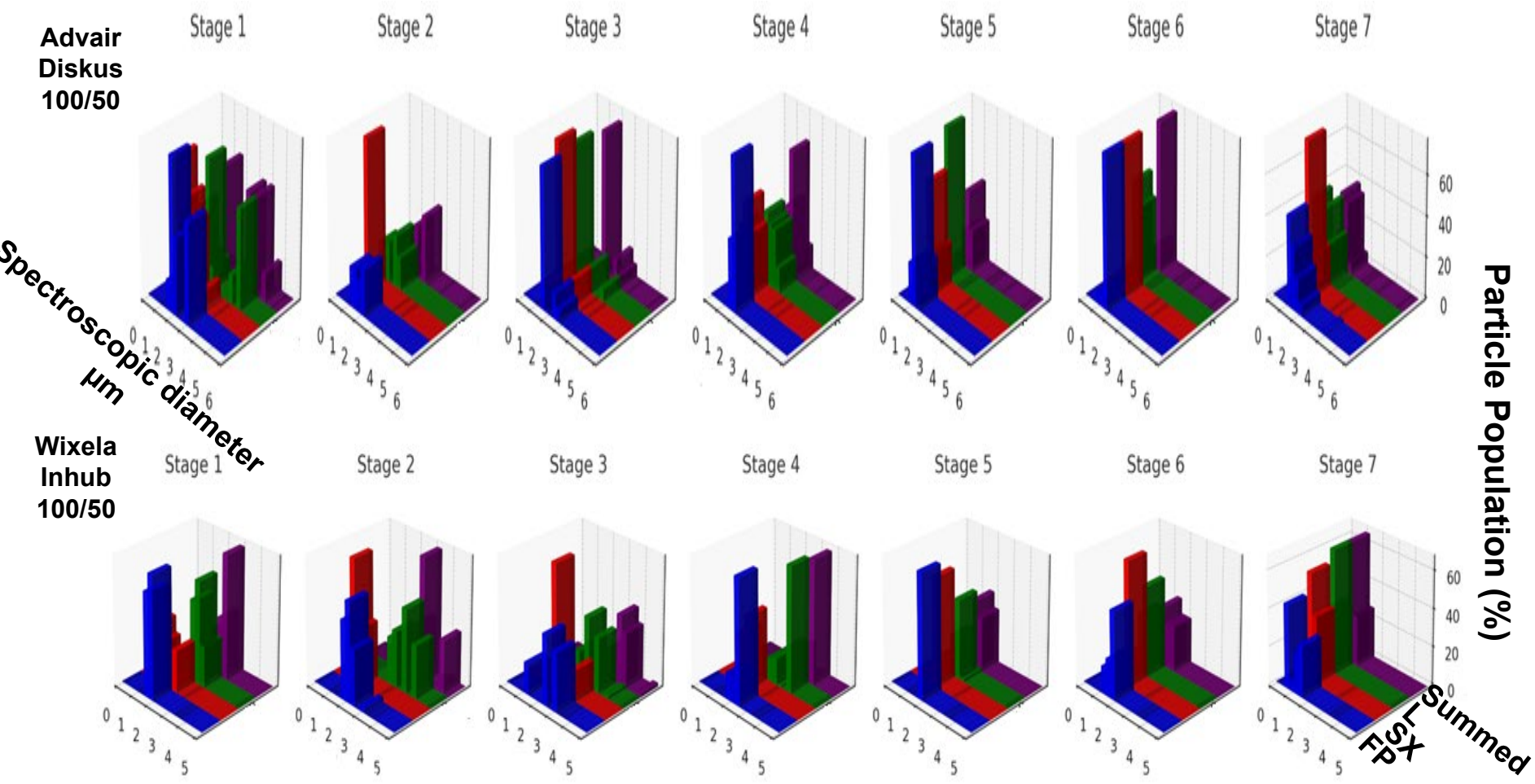
Spectroscopic diameter and integrated intensity

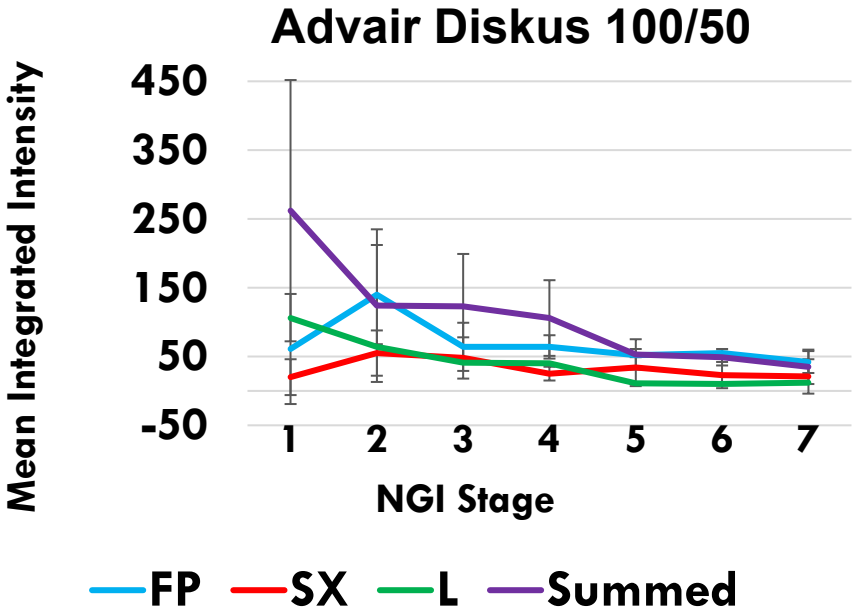
- Using the chemical images obtained at wavenumber specific to APIs (FP, SX) and the excipient (L), spectroscopic diameter was calculated using Mountains SPIP®.

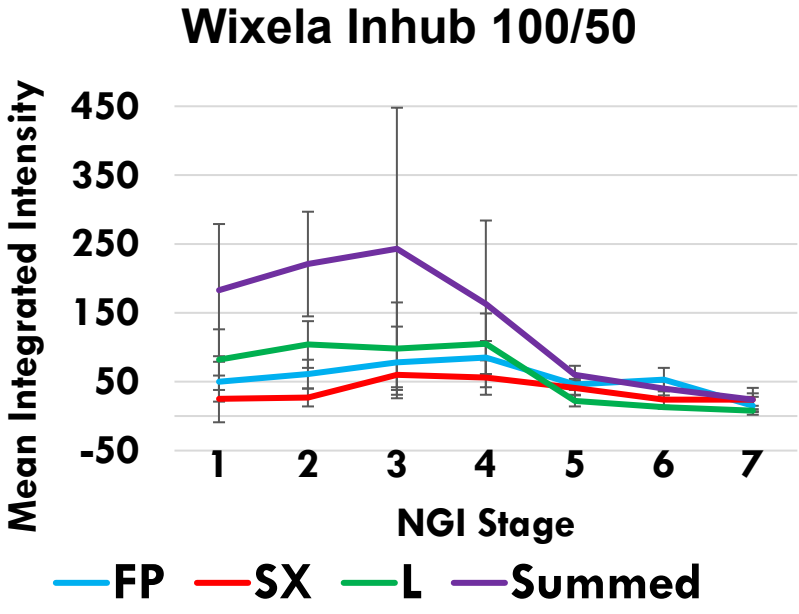


IR Intensity Map Spectroscopic Diameter Measurement

- Integrated intensity represents the summation of pixel intensities obtained from chemical images at specific wavenumbers.


Advair Diskus 100/50
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Spectroscopic diameter µm
Wixela Inhub 100/50
Particle Population (%)
Summed
LSX
FP



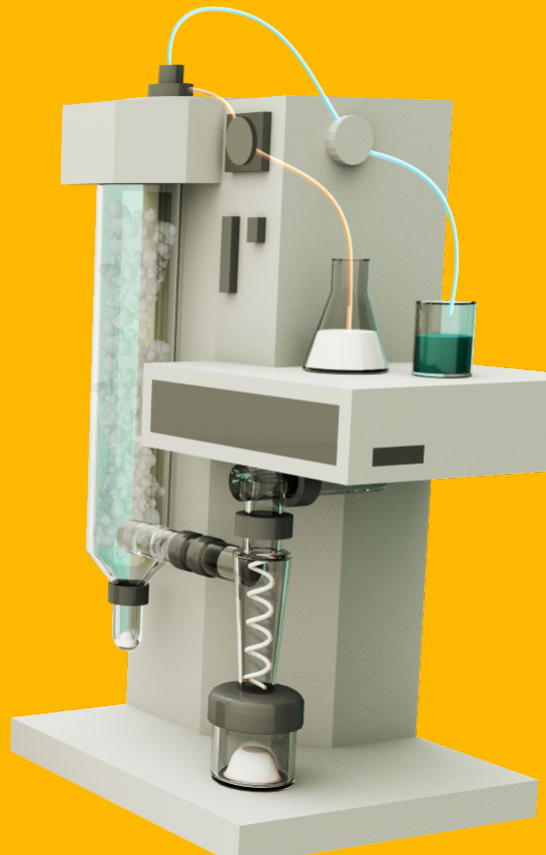


- **Both L and summed integrated intensity (summation of pixel intensities for APIs (FP, SX) and the excipient (L) decreased as a function of NGI stage.**
- **Size of APIs (FP and SX) remained constant across NGI stages.**
- **The excipient (L), affects the particle size distribution of aerosolized particles.**

Findings

- Advair Diskus had a higher percentage of lactose which was not colocalized with the APIs compared to Wixela Inhub particles.
- FP particles are colocalized with lactose and/or SX particles (100%).
- Only 66-75% of SX particles are colocalized with FP particles.
- Degree of colocalization for FP was independent of NGI stages.
- Colocalization of APIs in both commercial formulations were comparable.

O-PTIR on dry powder inhalation formulation prepared by a spray drying method.



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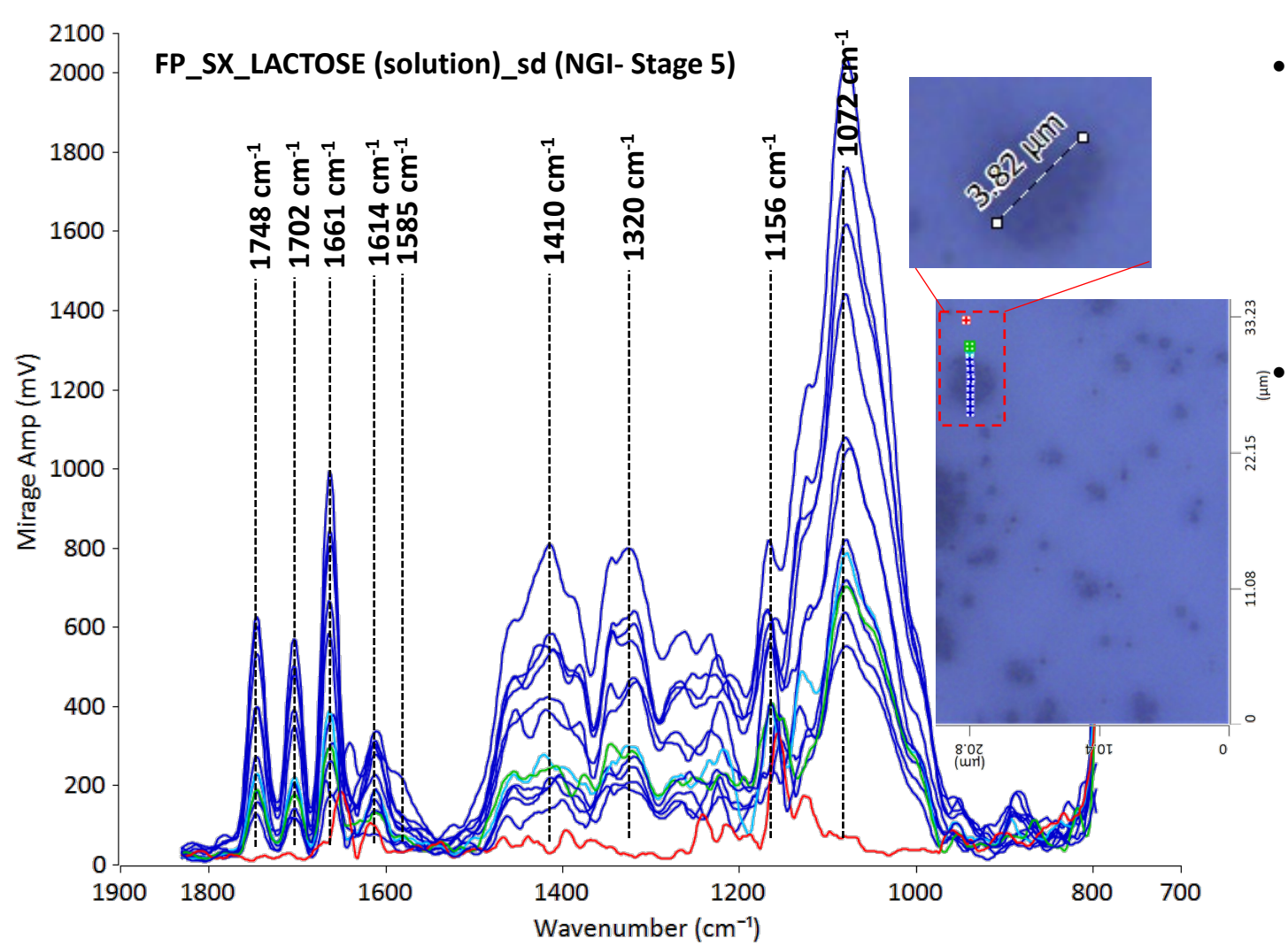
Spray drying and sample preparation method

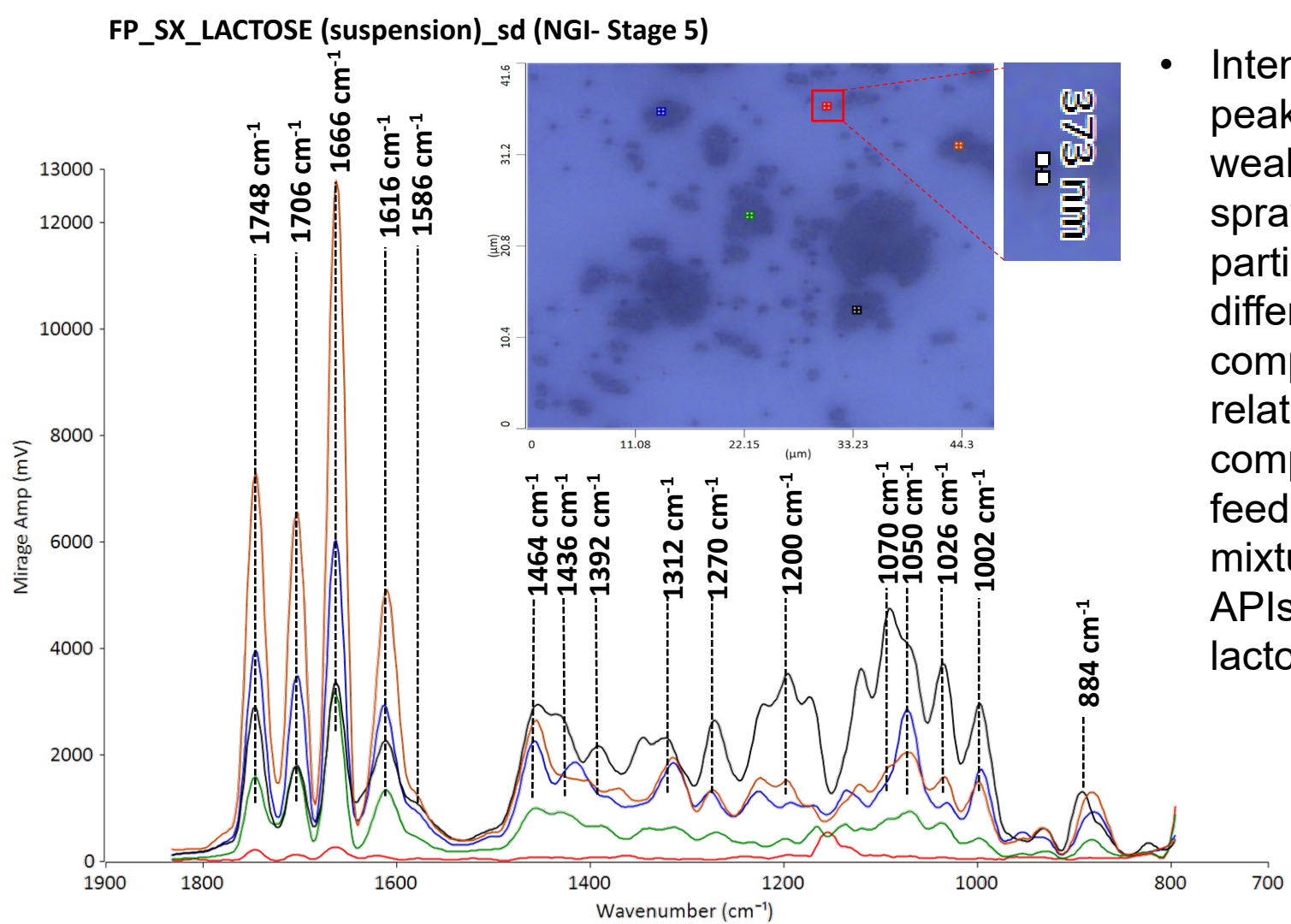
- Fluticasone propionate- 601 µg/mL
- Salmeterol Xinafoate- 86.7 µg/mL
- α-Lactose monohydrate- 6 mg/mL
- Solvent: For suspension- IPA, for solution- IPA/water (80:20)

– Spray-dried using a B-290 mini spray dryer with an inert loop (Büchi Labortechnik AG, Falwil, Switzerland) following conditions: inlet temperature of 70 C; aspirator at 38.2 m^3/h; atomizer setting at 601 L/h; feed flow of 15 mL/min.

- Each of the SD formulation powders (30 ± 0.5 mg) was loaded to hydroxypropyl methylcellulose capsules (size 3, Capsugel, NSW, Australia) and dispersed for 1.2 s using an Osmohaler into the NGI operating at a suction flow rate of 100 L/min. A silicon wafer (1 × 1 cm, ProScitech, Australia) as the substrate for spectroscopic analysis was placed on stages 4, 5, and 6 of the NGI collect the dispersed particles.

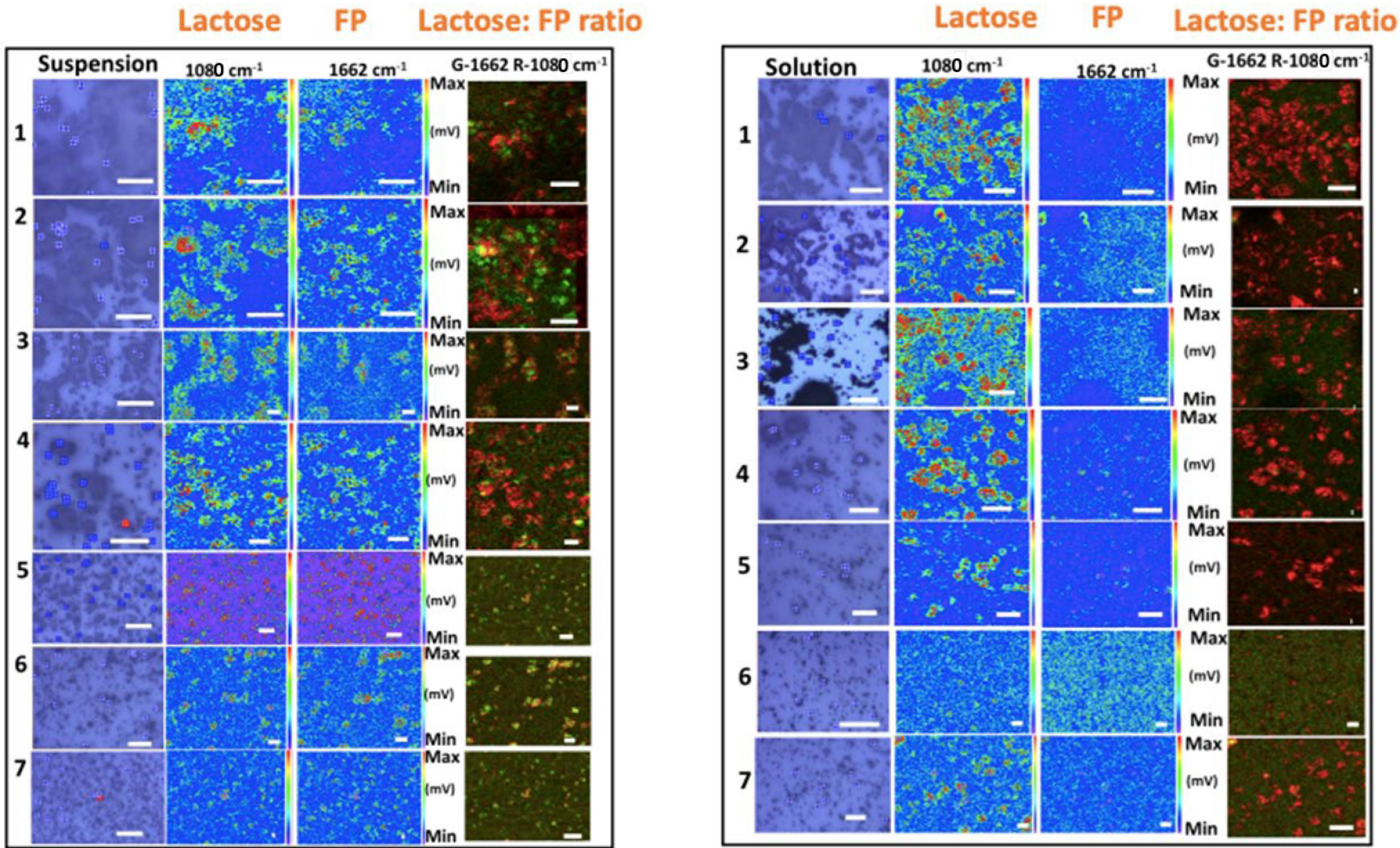


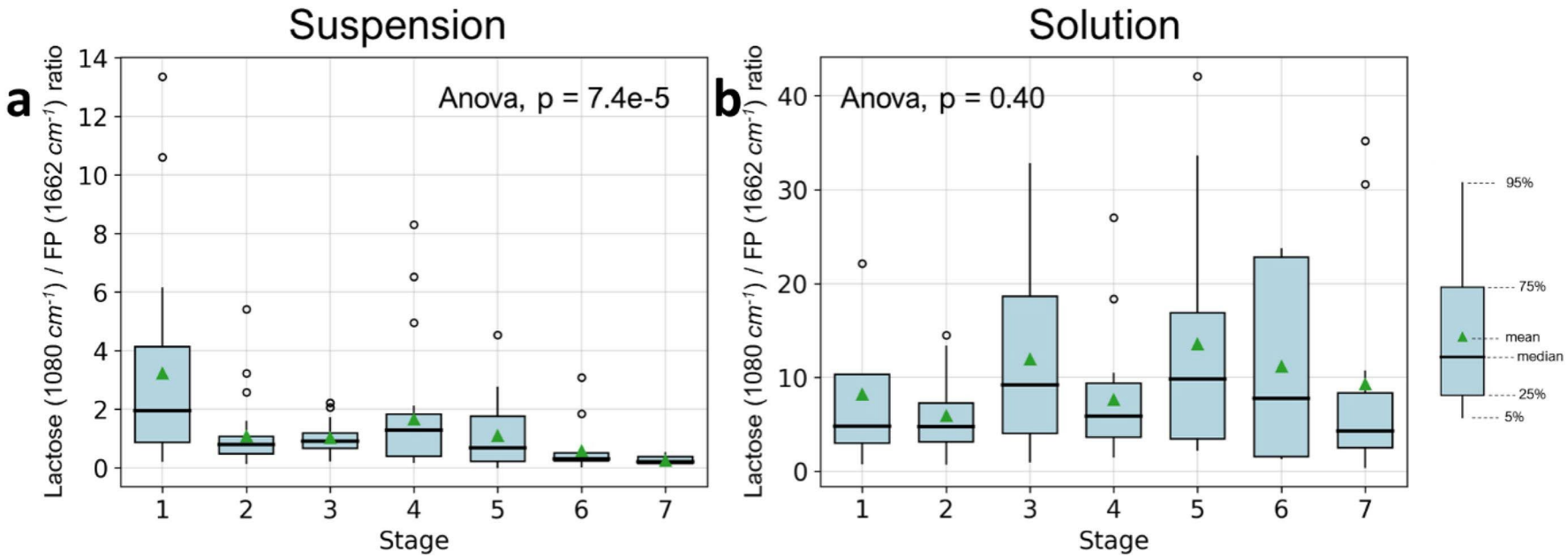
- Spectra obtained confirmed the presence of all three, FP, SX, and lactose, in the aerosol particle.
- Intensity of peak varied depending on the spatial location of spectra collection- indicating the differences in concentration of FP, SX, and lactose across the particle.



- Intensity of lactose peak is significantly weaker compared to spray-dried solution particles. This difference in chemical composition may be related to the components of the feed liquid are a mixture of dissolved APIs and suspended lactose particles.

O-PTIR chemical map collected from stages 1–7 of a NGI





Stage	1	2	3	4	5	6	7
Mean	3.2	1.1	1.0	1.7	1.1	0.6	0.3
Median	1.9	0.8	0.9	1.3	0.7	0.3	0.2
n	18	24	17	26	24	16	12

Stage	1	2	3	4	5	6	7
Mean	8.2	5.9	12.0	7.6	13.6	11.1	9.3
Median	4.8	4.8	9.2	5.9	9.8	7.8	4.3
n	5	12	20	16	12	8	11

Ratio of FP to L for particles collected from NGI stages 1-7 for spray-dried powder from a) suspension and b) solution formulations based on O-PTIR spectral analysis. (Figure from Khanal et al. Int. J. Pharm 2023)

Conclusion

- O-PTIR spectroscopy allows the solid-state analysis of distribution of APIs and/or excipient by their aerodynamic particle size collected at multiple stages of an NGI.
- It also enabled the study of an individual or primary agglomerates of inhalation powders containing two or more chemically different species to ascertain their morphology, chemical composition, and crystallinity.
- This analytical tool allows for assisting in the design and optimization of DPI formulations to achieve a desired product performance.

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– Comparison of Generic and Name Brand Dry Powder Inhalers: Advanced Insights Using Optical Photothermal Infrared Microscopy (P 66)- Sheikh Tanzina Haque

– Atomic Force Microscope-Infrared Spectroscopy as a Powerful Tool to Study the Distribution of Fluticasone Propionate/Salmeterol Xinafoate/Lactose Monohydrate in Advair Diskus 100/50 Formulations (P 59)- Blessy Joseph

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