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# **Optical Photothermal Infrared Spectroscopic Assessment of Fluticasone/Salmeterol/Lactose Co-association in Advair Diskus 100/50 and Wixela Inhub 100/50**

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Identification of Drug Distribution in Aerosols  
A Nanospectroscopy and NanoThermal Analysis**

# Introduction

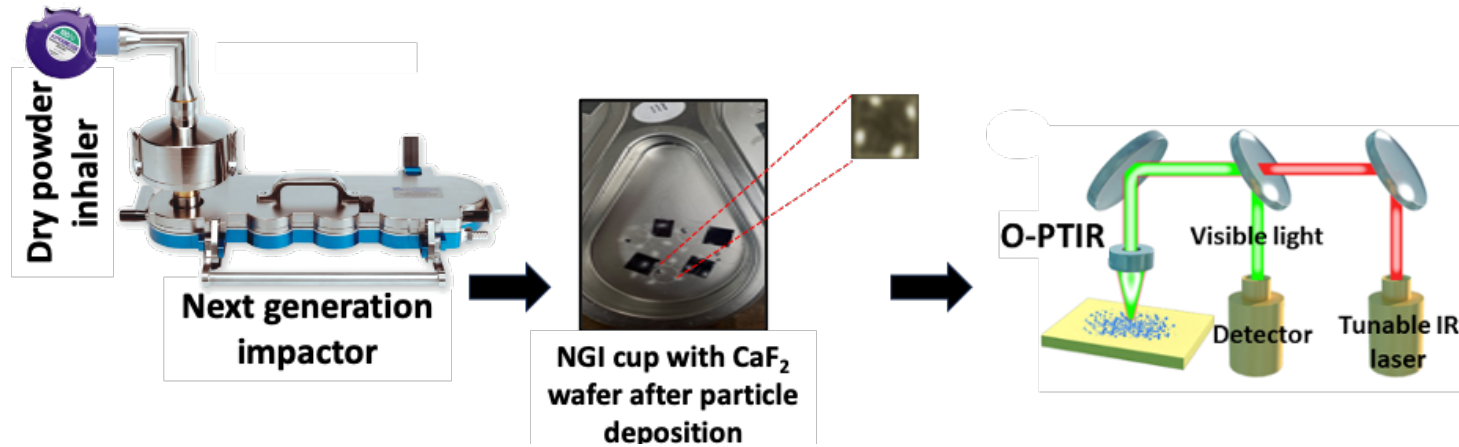
- Submicron characterization of the physicochemical properties of dry powder inhaler (DPI) particles is critical to gain an understanding of the formulation attributes that can affect the aerosol performance of a DPI.
- Optical Photothermal Infrared Spectroscopy (O-PTIR) is a pump-probe technique that utilizes **photothermal expansion** for infrared and Raman imaging with a spatial resolution of **~300-500 nm** for the solid-state assessment of chemical composition, morphology, crystallinity, and the evaluation of co-localization of drugs and/or excipients in different aerodynamic particle size fractions.<sup>1,2</sup>

# 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).

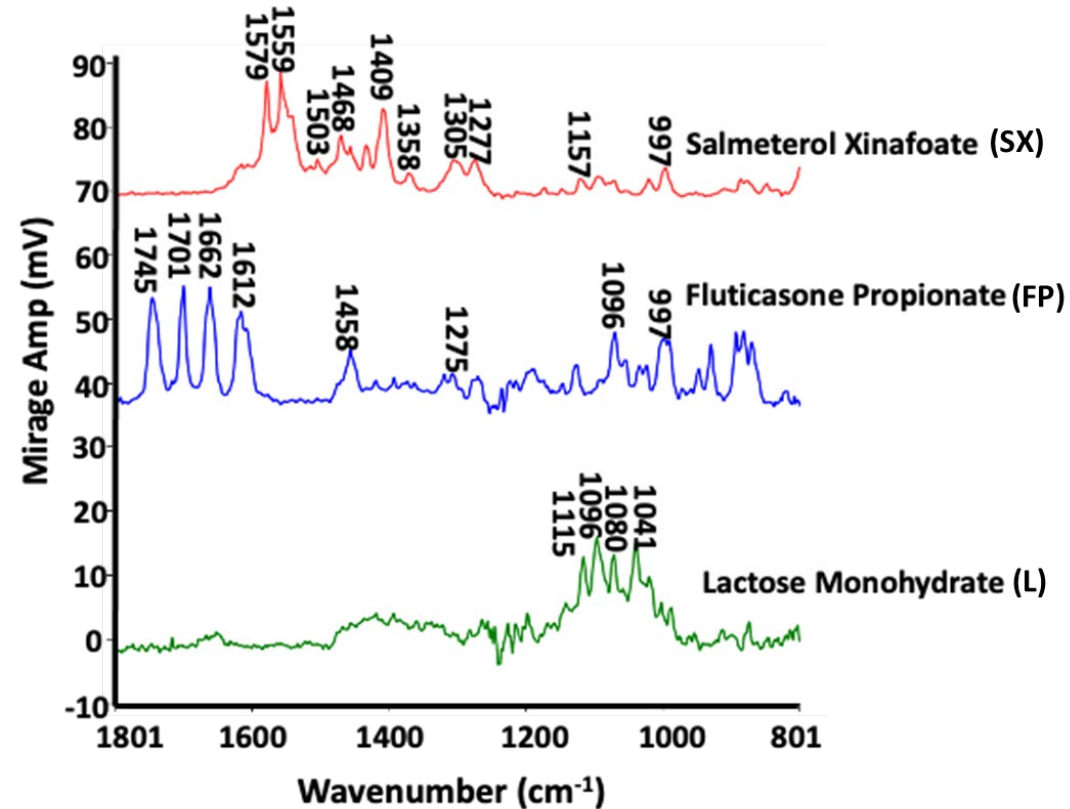


# Materials and Methods



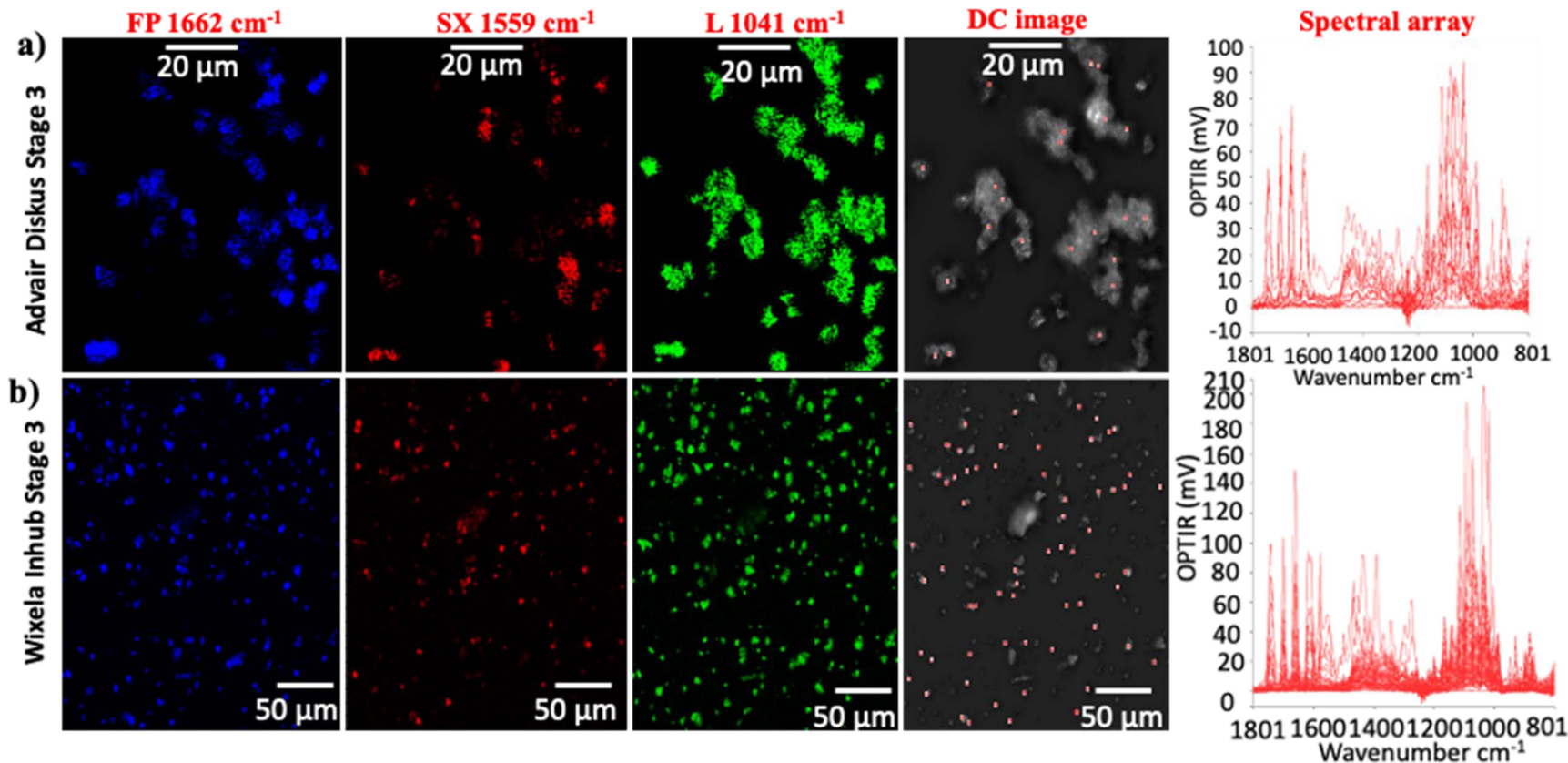
- Aerosolized fractions (**60 L/min**) of Advair Diskus 100/50 and Wixela Inhub 100/50 were collected on calcium fluoride (CaF<sub>2</sub>) placed at different stages of a Next Generation Impactor (NGI) followed by O-PTIR measurements using mIRage-LS (Photothermal Spectroscopy Corp.).
- IR power of 4 % and probe power of 4.7 % were used for spectra acquisition and chemical imaging at a pixel of 0.3  $\mu\text{m}$ .

# Results

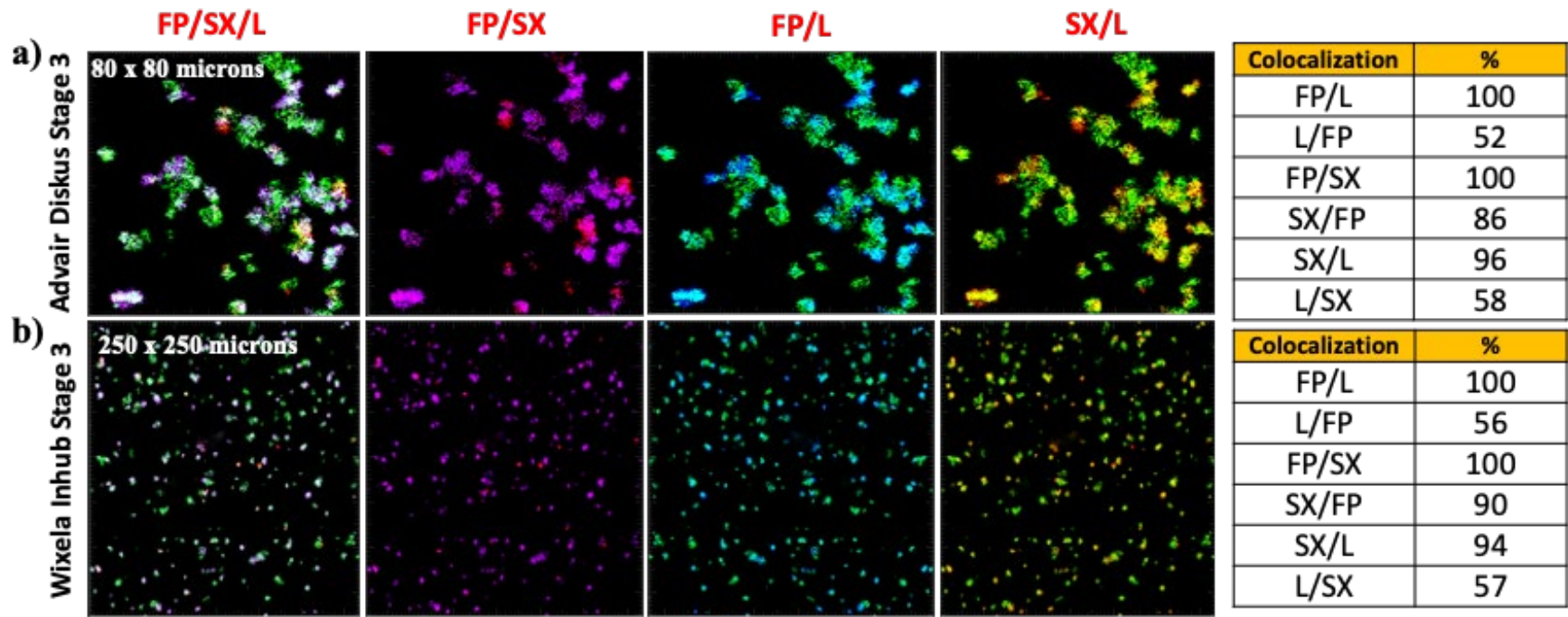


O-PTIR spectra of fluticasone propionate (FP), salmeterol xinafoate (SX), and lactose (L) raw materials.

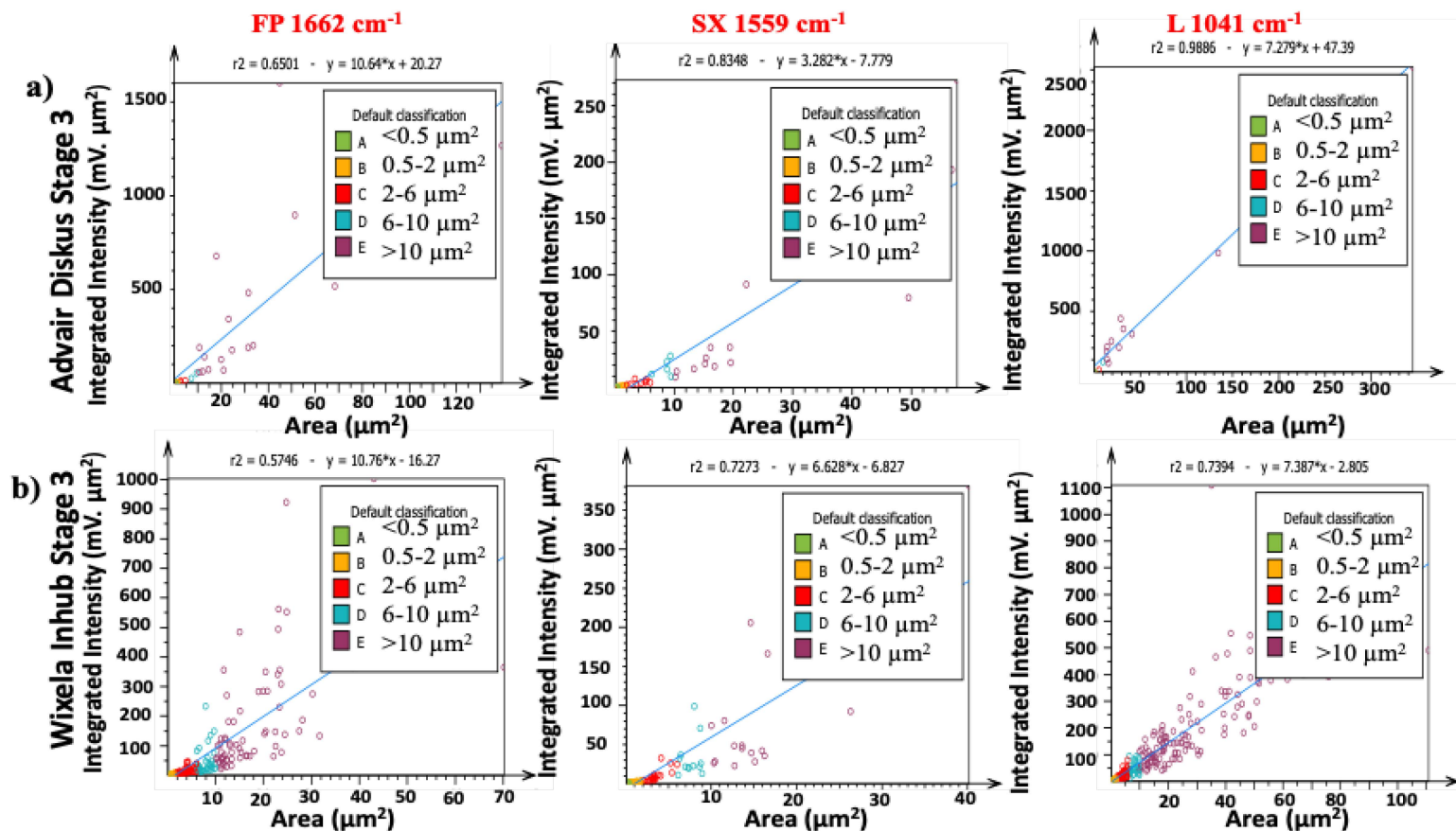
Representative identification peaks are labelled for each component.



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



**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.**



**Scattered plot of integrated intensity vs area of particles demonstrating the particle size distribution of FP, SX, and lactose.**

| Colocalized components | Percentage of colocalization<br>Weighted Average<br>(Multiple Region of Interests) (%) |              | Composition of the particles | Average particle diameter ( $\mu\text{m}$ )<br>Weighted Average<br>(Multiple Region of Interests) ( $\mu\text{m}$ ) |               |
|------------------------|----------------------------------------------------------------------------------------|--------------|------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------|
|                        | Advair Diskus                                                                          | Wixela Inhub |                              | Advair Diskus                                                                                                       | Wixela Inhub  |
| FP/L                   | $100 \pm 0$                                                                            | $100 \pm 0$  | FP                           | $2.1 \pm 1.1$                                                                                                       | $2.5 \pm 0.7$ |
| L/FP                   | $29 \pm 20$                                                                            | $47 \pm 17$  | SX                           | $1.4 \pm 0.6$                                                                                                       | $1.5 \pm 0.4$ |
| FP/SX                  | $100 \pm 0$                                                                            | $100 \pm 0$  | L                            | $2.9 \pm 2.0$                                                                                                       | $2.9 \pm 0.6$ |
| SX/FP                  | $66 \pm 28$                                                                            | $75 \pm 18$  | FP/SX                        | $1.9 \pm 1.2$                                                                                                       | $2.0 \pm 0.5$ |
| SX/L                   | $78 \pm 28$                                                                            | $83 \pm 11$  | FP/L                         | $1.9 \pm 1.1$                                                                                                       | $2.0 \pm 0.2$ |
| L/SX                   | $34 \pm 26$                                                                            | $51 \pm 13$  | SX/L                         | $1.4 \pm 0.6$                                                                                                       | $1.7 \pm 0.3$ |
|                        |                                                                                        |              | FP/SX/LH                     | $2.6 \pm 1.4$                                                                                                       | $2.5 \pm 0.6$ |

**Summary of colocalization of FP, SX, and L along with the spectroscopic diameter of individual FP, SX, L particles and colocalized multicomponent particles for Advair Diskus 100/50 and Wixela Inhub 100/50 particles across multiple regions of interest on Stage 3 of the NGI. Analysis was based on the single wavenumber chemical mapping followed by colocalization analysis. (N= >>10,000 pixels across all ROIs, each pixel size is 300 nm).**

# Conclusions

- Advair Diskus 100/50 had a higher percentage of lactose which was not colocalized with the active pharmaceutical ingredients (APIs) compared to Wixela Inhub 100/50 particles.
- Fluticasone propionate particles are colocalized with lactose and/or salmeterol xinafoate particles (100 %).
- Only 66-75 % of salmeterol xinafoate particles are colocalized with fluticasone propionate particles.

- Both formulations contain fine lactose particles.
- O-PTIR allows the solid-state chemical analysis of the distribution of drugs and excipients within DPI formulations at a resolution of 0.5 microns which may not be possible using conventional chemical imaging techniques with a resolution of 5 microns.
- This analytical tool allows for the design and optimization of DPI formulations to achieve the desired product performance.

# Acknowledgments

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# Thank you all for your kind attention



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