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.[1,2]

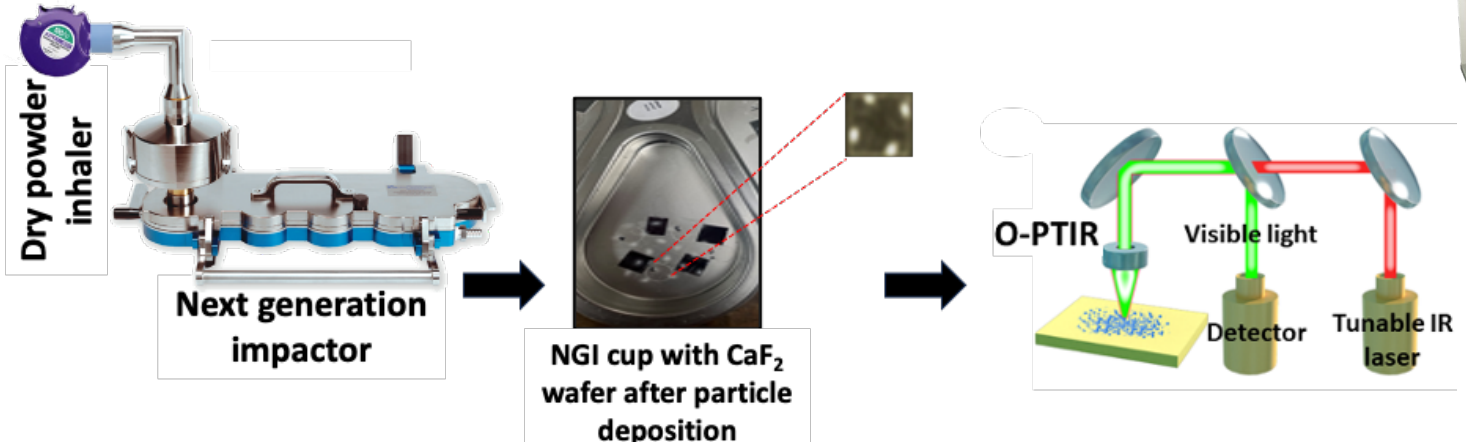
[1]Khanal et.al, *Anal Chem* 2020, 92: 8323–8332.

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

Objectives

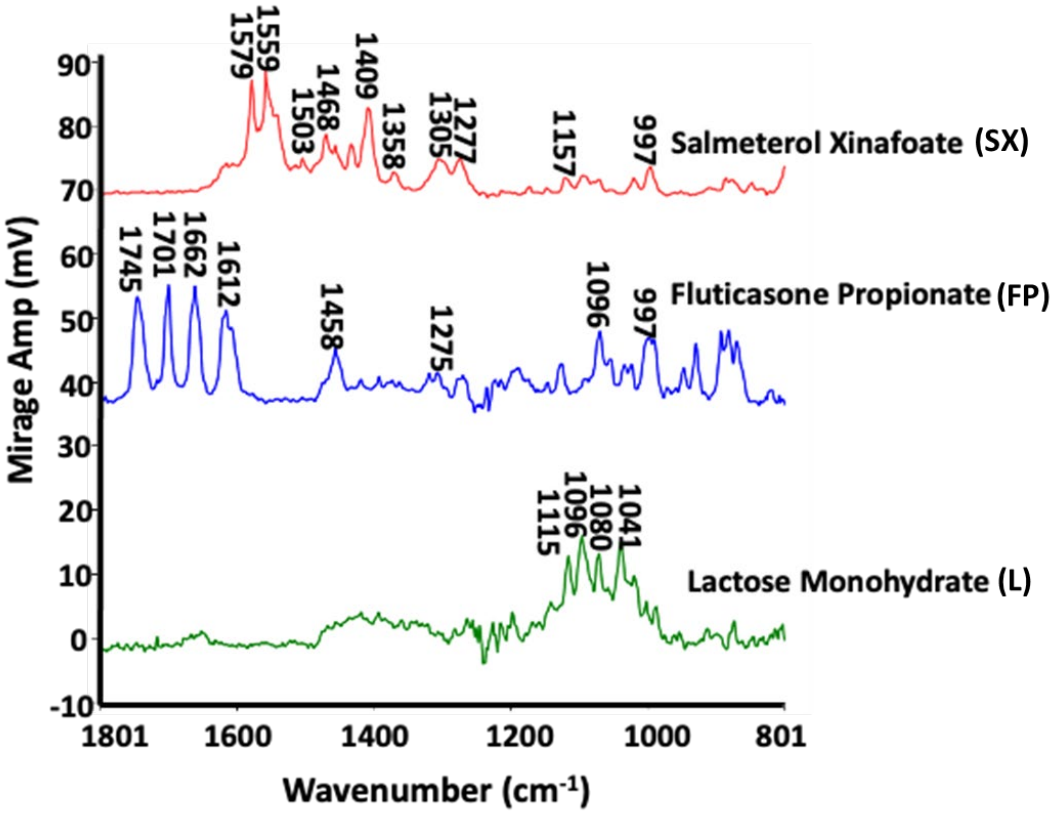
- Employ O-PTIR to characterize and compare the chemical composition of aerosolized fractions and drug-excipient agglomeration behavior of particles after the dispersion from **Advair Diskus 100/50** and **Wixela Inhub 100/50** DPIs (Fluticasone Propionate; Salmeterol Xinafoate Inhalation Powders).

Materials and Methods



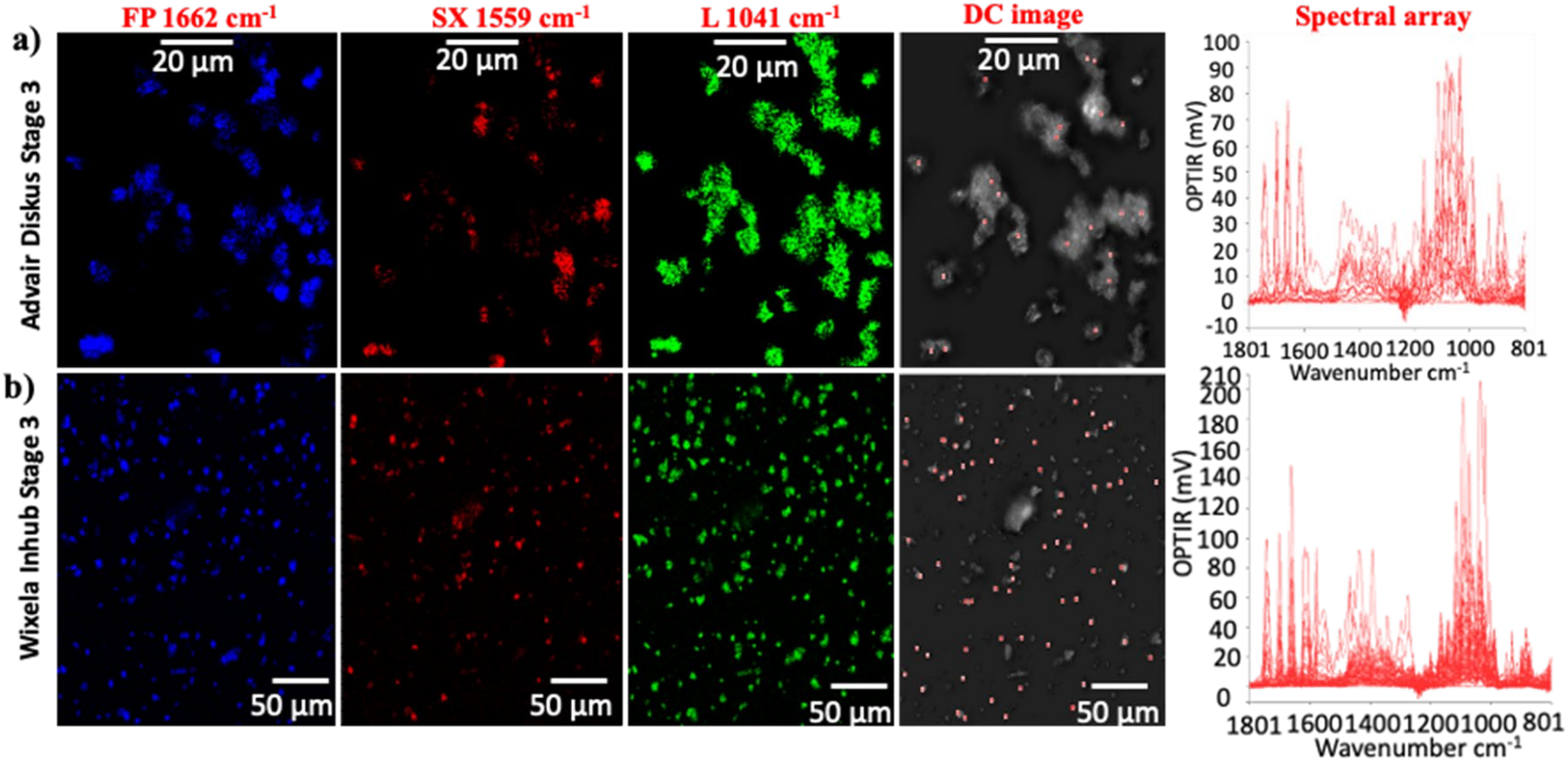
- Aerosolized fractions (**60 L/min**) of Advair Diskus 100/50 and Wixela Inhub 100/50 were collected on calcium fluoride (CaF_2) placed at different stages of a Next Generation Impactor (NGI) followed by O-PTIR measurements using mIRage-LS (Photothermal Spectroscopy Corp.).
- IR power of 4 % and probe power of 4.7 % were used for spectra acquisition and chemical imaging at a pixel of 0.3 µm.

Results

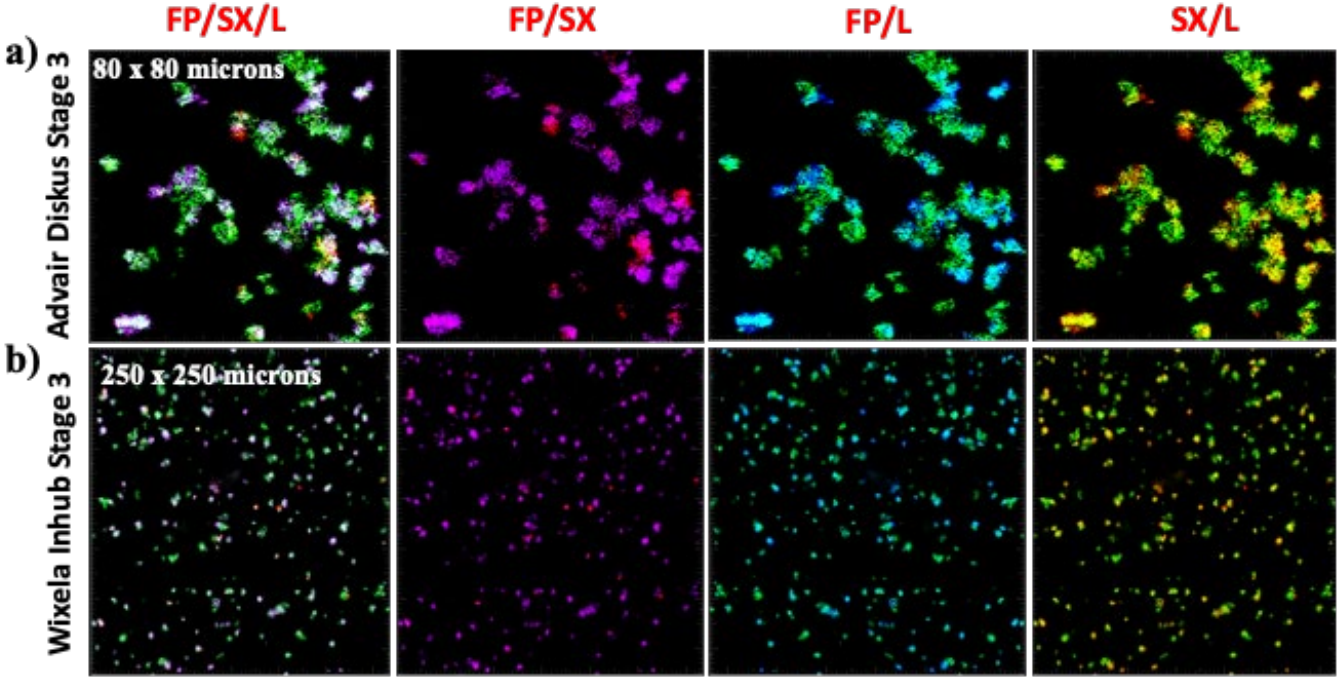


O-PTIR spectra of fluticasone propionate (FP), salmeterol xinafoate (SX), and lactose (L) raw materials.

Representative identification peaks are labelled for each component.



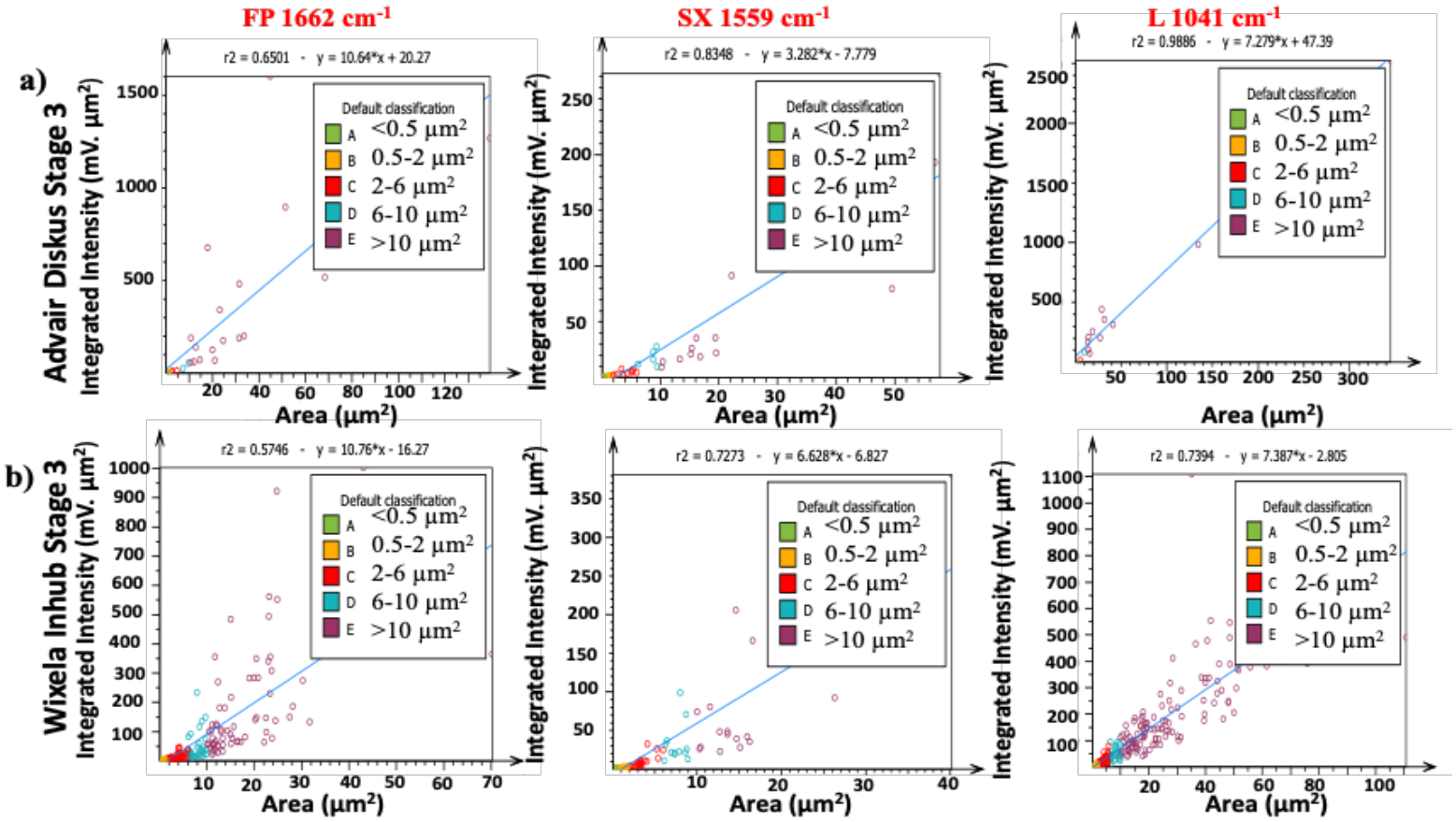
Single wavenumber chemical maps, DC image and spectral array collected from aerosolised a) Advair Diskus 100/50 and b) Wixela Inhub 100/50 particles collected from stage 3 of the NGI showing the distribution of FP, SX, and L.



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.



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

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