High-Sensitivity Analysis of Crystallinity in Respirable Powders Using Low Frequency Shift Raman Spectroscopy

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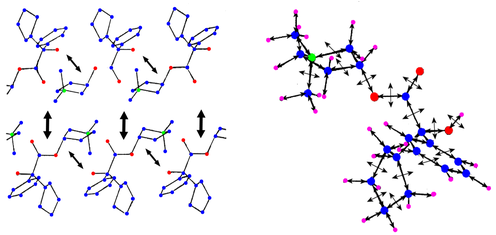
Introduction

Raman spectroscopy is a valuable technique for identification of drug components and their crystallinity in respirable combination products, which may consist of multiple excipients and drugs. Most Raman spectroscopy techniques analyze the internal vibrational modes of molecules which can be used to indirectly derive information about the solid state using secondary effects of the molecular environment on intra-molecular vibrations. It would be advantageous to make use of the much larger large differences between lattice vibrations in crystals and phonon modes in disordered matter. These vibrational modes are associated with low energy transitions in the terahertz range, which corresponds to very small frequency shifts <200 cm^{-1} in Raman spectroscopy [1]. This work uses recently developed filter technology to extend the range of a comparatively simple, dispersive Raman system into the low frequency shift range.



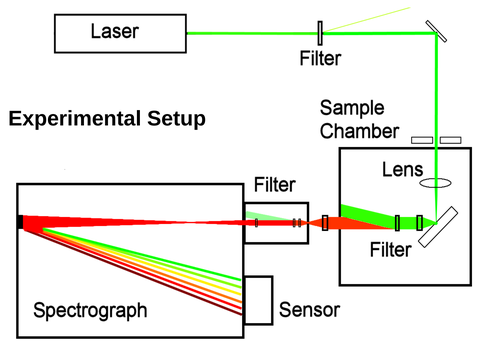
Lattice modes – **Internal modes**

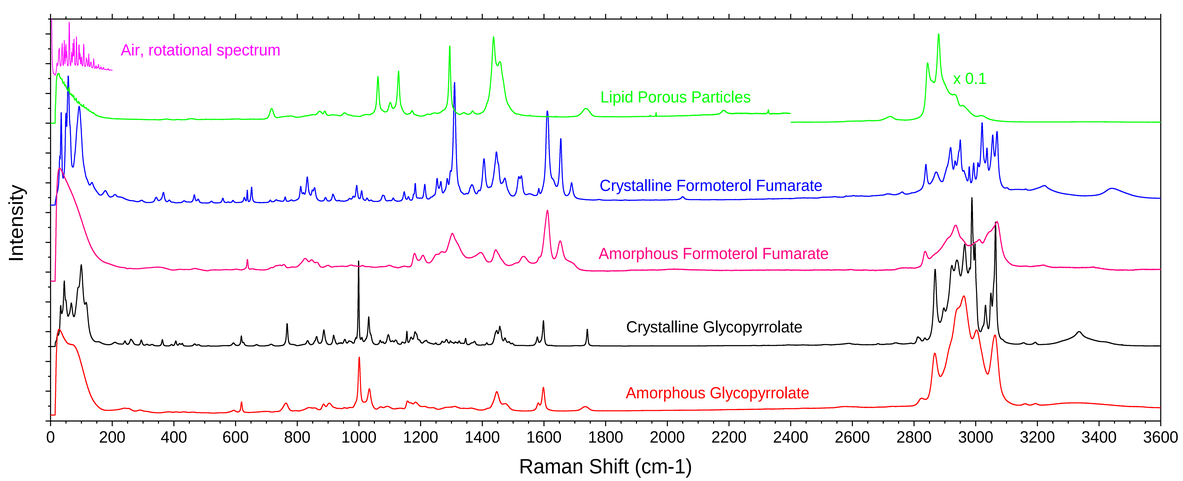
Materials and Methods

The test articles were spray dried lipid porous particles for use in pMDIs in two different configurations:

1: Lipid particles without active ingredients cosuspended [2,3] in HFA 134a with crystalline glycopyrrolate (GP) and formoterol fumarate (FF), as a physcial mixture. Powder samples were extracted from the pMDIs.
2. Phospholipid particles spray dried [4] from a feedstock in which GP or FF was dissolved. In the resulting particles the drug is present as a solid dispersion in the lipid matrix.

Raman spectra were excited with an Argon ion laser, λ= 514.5 nm. A setup using a single stage Czerny-Turner spectrograph with additional filter stage and a liquid nitrogen cooled CCD sensor [5] was modified for the low frequency shift range by adding a series of ultra narrow-band notch filters (SureBlock, Ondax, Monrovia)

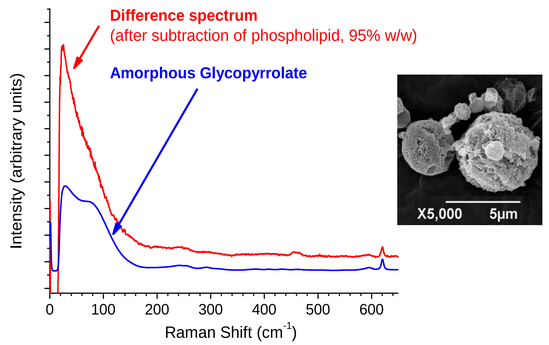




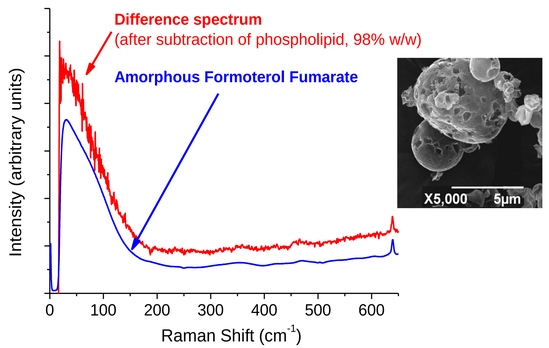
Reference spectra used in the deconvolution of glycopyrrolate and formoterol fumarate containing lipid porous particles and cosuspensions

Results

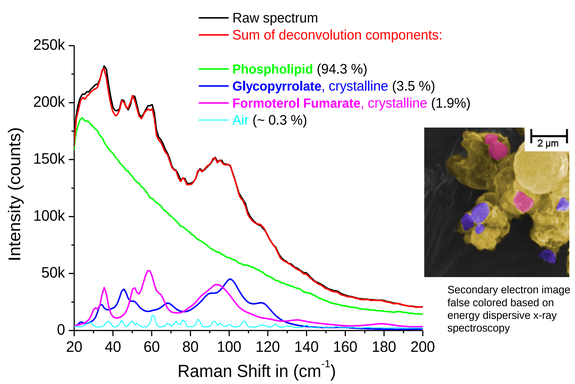
Glycopyrrolate (5% w/w) formulated into spray dried phospholipid particles is amorphous



Formoterol Fumarate (2% w/w) formulated into spray dried phospholipid particles is amorphous.



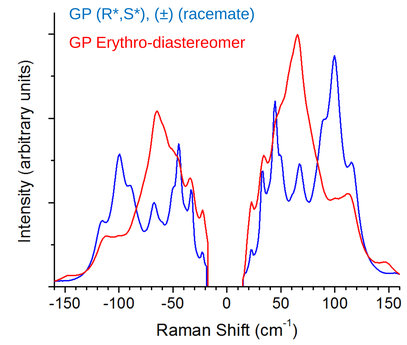
Glycopyrrolate and Formoterol Fumarate cosuspended in pMDI with phospholipid particles are crystalline



Secondary electron image false colored based on energy dispersive x-ray spectroscopy

Results

Differences in the crystal structures of glycopyrrolate diastereoisomers can be identified



Instrument Performance

Sample Requirement:	< 5 µl, ~ 0.5 - 5 mg
Sample Environment:	-50 – 300°C, 0–50 %RH, N_2 or air
Measurement Time:	1-5 min
Spectral Window:	-500 to -20 cm^{-1} (Anti-Stokes)
	15 to 4000 cm^{-1} (Stokes)
Resolution	1.5 cm^{-1}
Accuracy	0.7 cm^{-1}

Conclusions

- Low frequency shift, dispersive Raman spectroscopy can be used to identify drug components and their solid state in respirable powders.
- Small amorphous fractions (LOD ~ 0.5 %, LOQ ~ 1%) of actives in phospholipid particles can be analyzed.
- Small crystalline fractions (LOD ~ 0.2 %, LOQ ~ 0.5 %) of actives in multicomponent systems can be analyzed.
- Solid state changes, including potential enatiomeric or polymorphic changes can be detected.

References

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