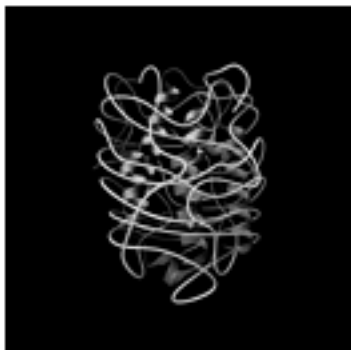


Raman Spectroscopy Combined with Cascade Impaction

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AAAR 2004 Annual Meeting
Atlanta, Georgia



NEKTAR[™]
Transforming Therapeutics

Assessment of Powder Composition by Raman Spectroscopy

1. Introduction

- Pulmonary drug delivery
- Methodology

2. Results

- Blended powder
- Homogeneous powder

3. Summary



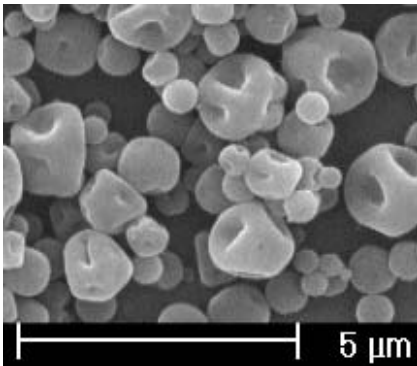
Pulmonary Drug Delivery

Surface area of the lung = area of a tennis court

- Good target for local and systemic delivery



Respirable range ≤ 5 microns



Dry Powder Technologies

Active pharmaceutical ingredients can be formulated in different ways for lung delivery:

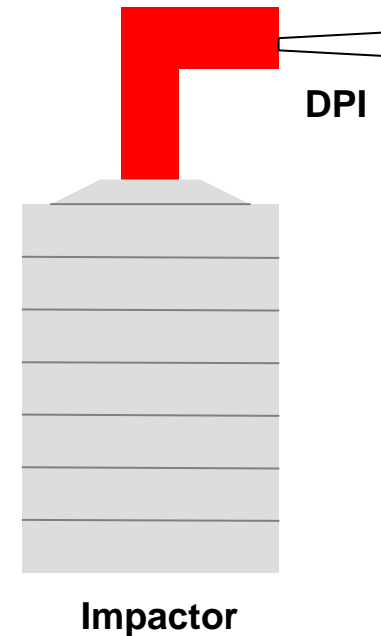
1. Blended with larger sized, carrier particles (e.g., lactose)
 - Heterogeneous particles
 - High surface energetics (cohesiveness) result in poor dispersibility through inhalation devices
2. Spray-dried (Nektar) formulation
 - Homogeneous particles
 - Low surface energetics result in good dispersibility



Need for characterization

Aerodynamic particle sizing is necessary for dose assessment in the lung

- Gravimetric
 - Cascade impaction
 - Total powder delivery
- Chemical
 - drug specific dose

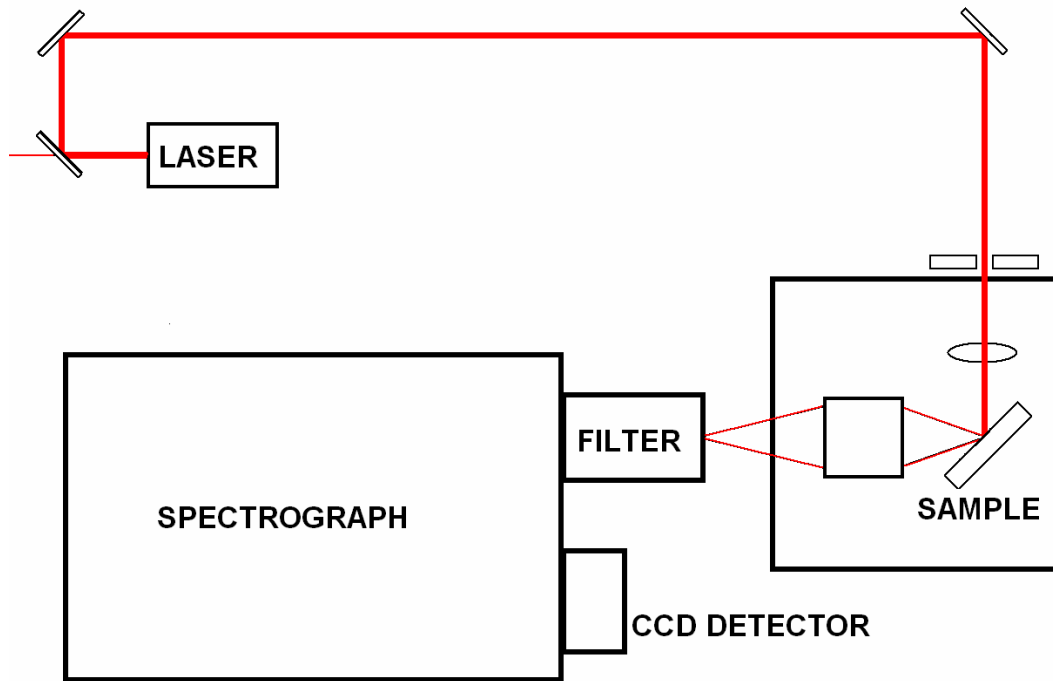


Use of Raman Spectroscopy for Analysis

- Advantages of Raman spectroscopy
 - Specificity
 - Polymorphs, crystallinity, protein conformation
 - Low water interference
 - Minimal sample preparation
 - Fast
- Disadvantages of Raman Spectroscopy
 - Low scattering cross-section requires good instrumentation



Raman instrumentation



Custom instrument

- Better control of samples

Red excitation laser

- Increased sensitivity
- Minimal laser/sample interaction

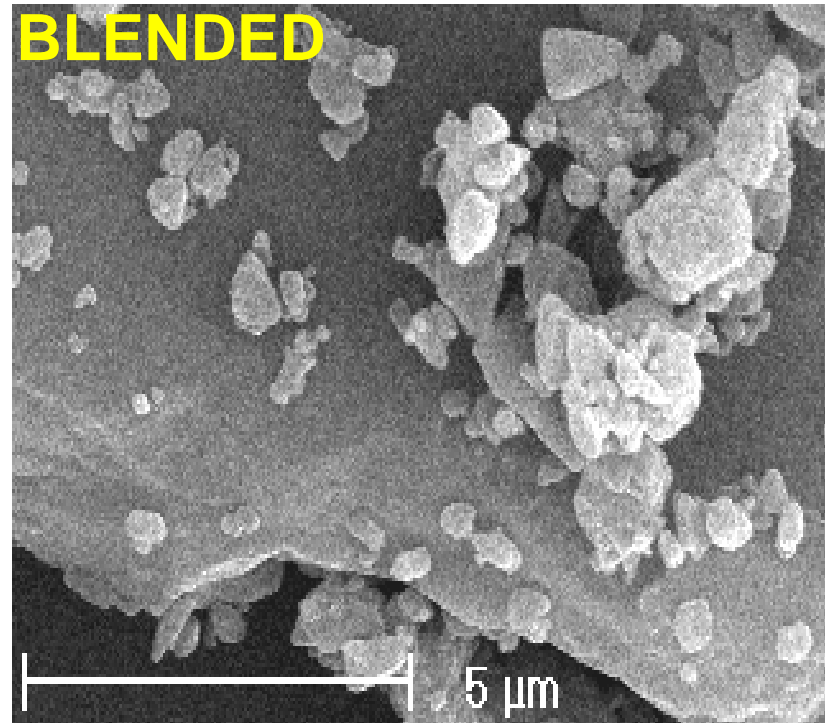
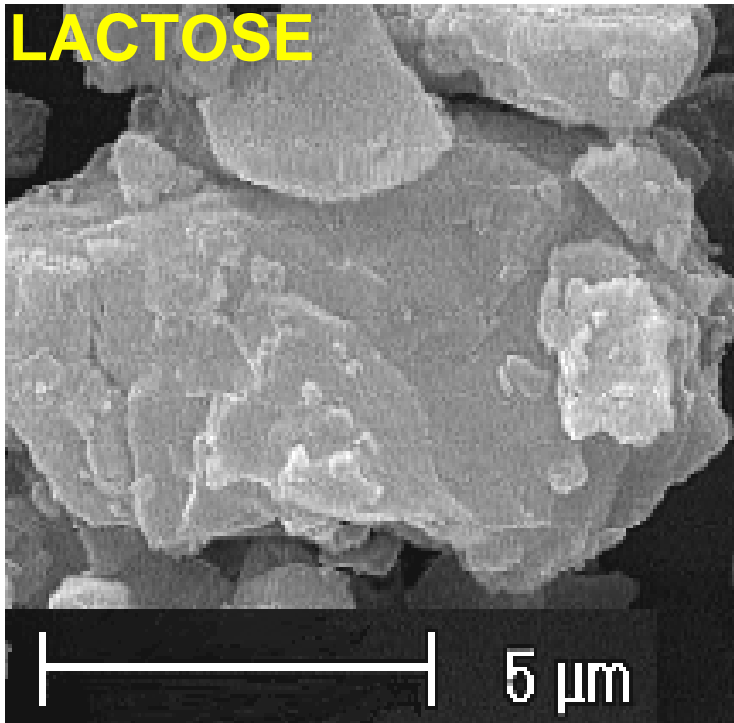
Advantages

- RH and temperature control in sample chambers

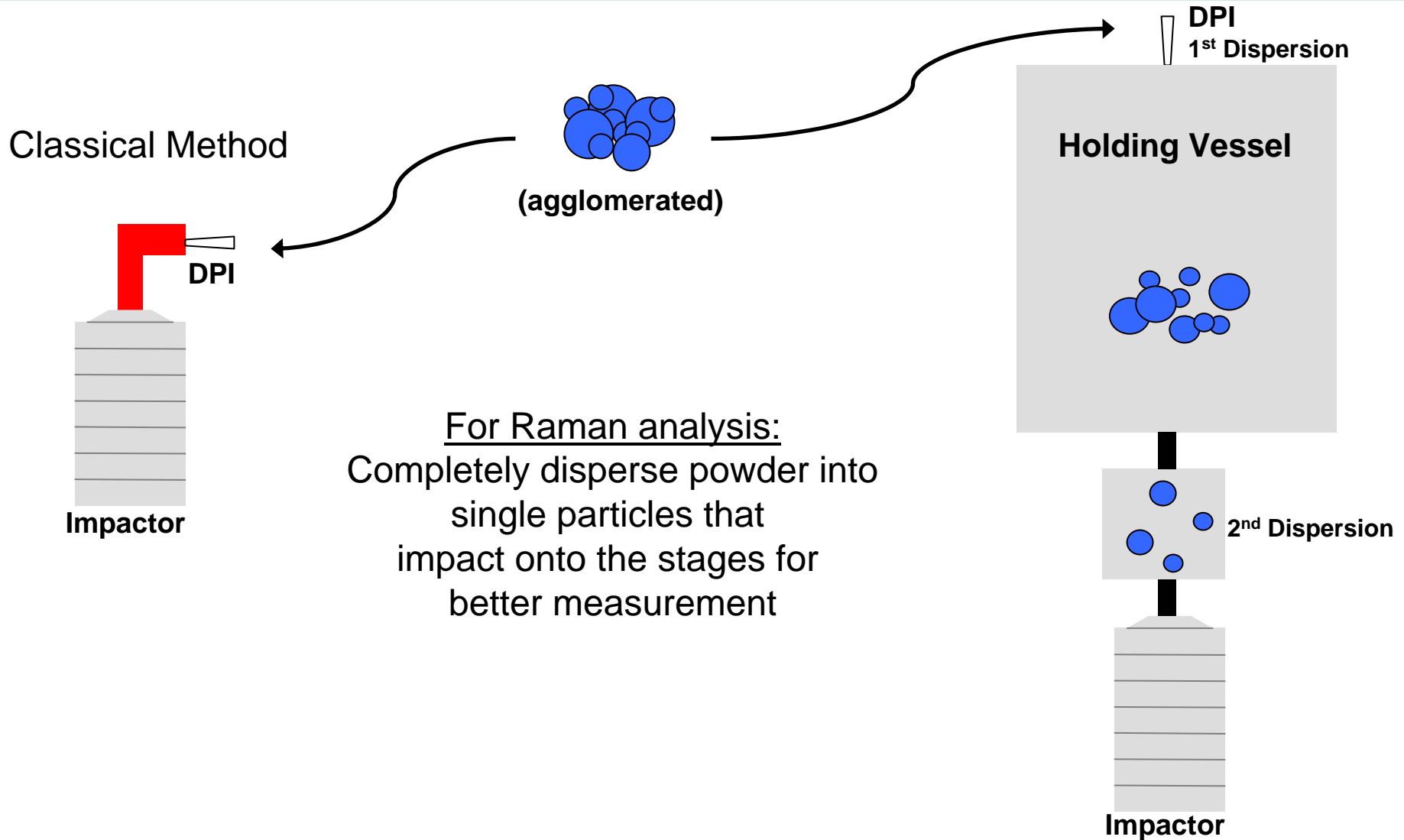


Conventional technology: *BLENDED POWDER*

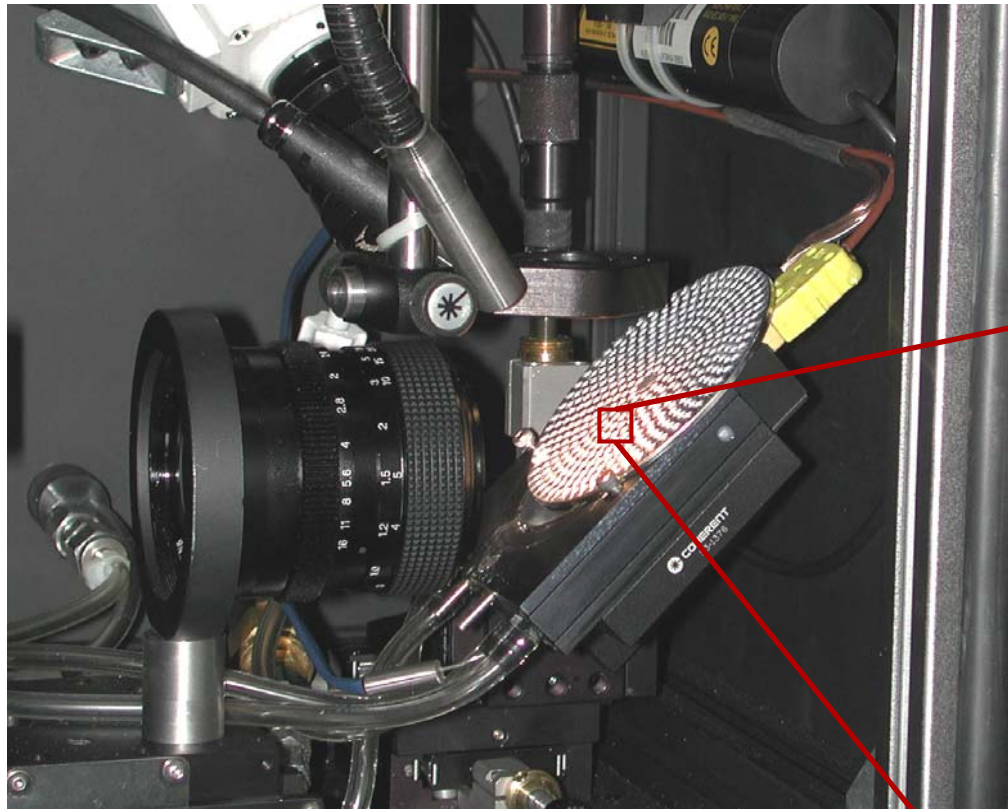
- Small molecule and (α)-Lactose carrier system
 - 1:4 formulation ratio
 - (α)-Lactose, 10 μ m primary particle size



Powder dispersion methodology



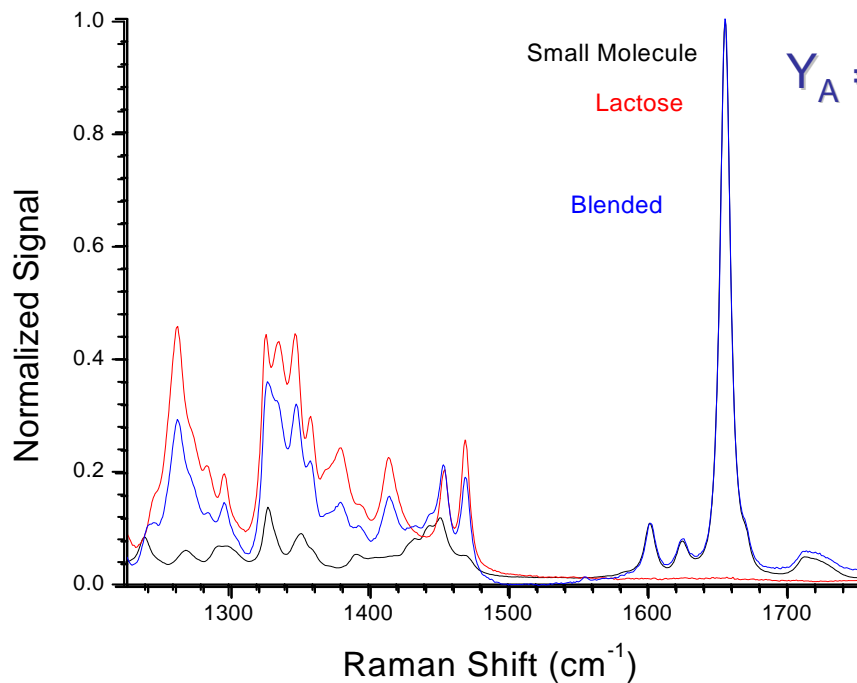
Low sample mass on impactor stage



Sample mass range
1 – 20 μg



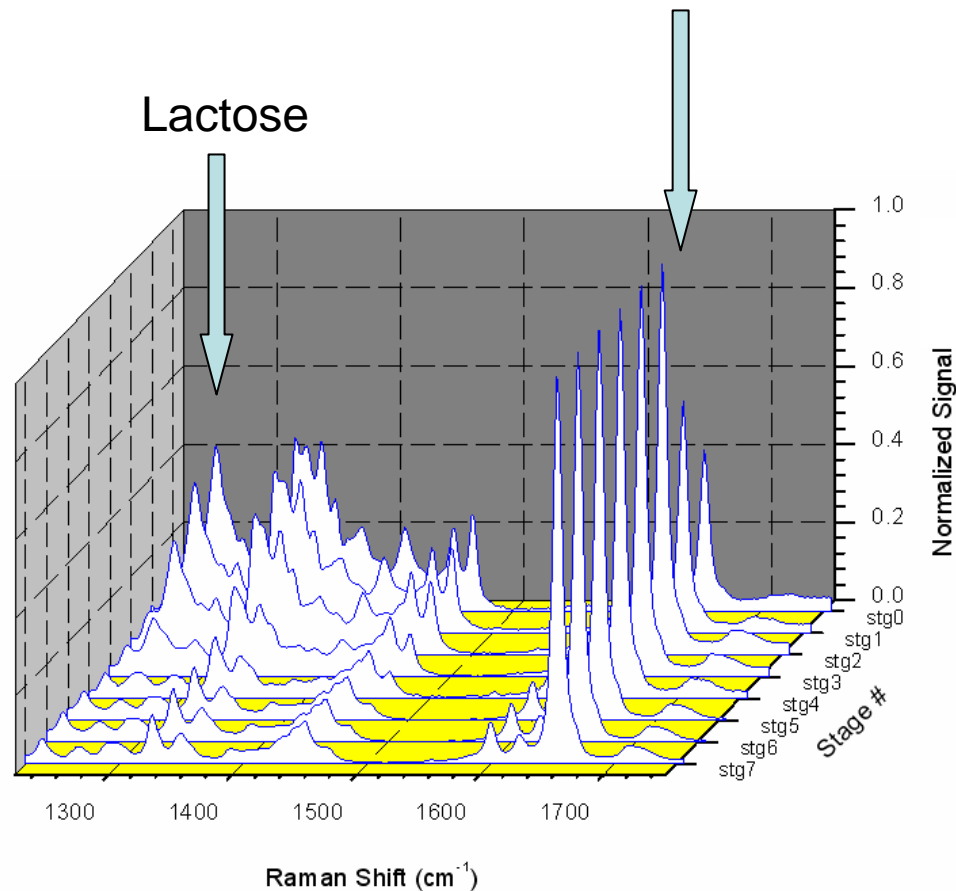
Raman analysis of dispersion



$$Y_A = Y_{Ref} \cdot k_{A,Ref} (S_A/S_{Ref})$$

Small Molecule

Lactose

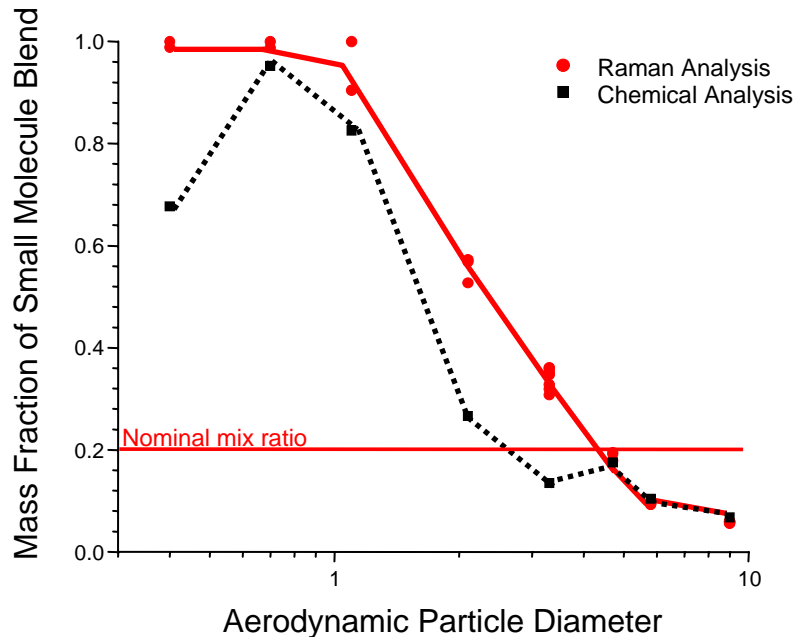


Intensity ratio changes from stage to stage indicating different blend ratios across size fractions

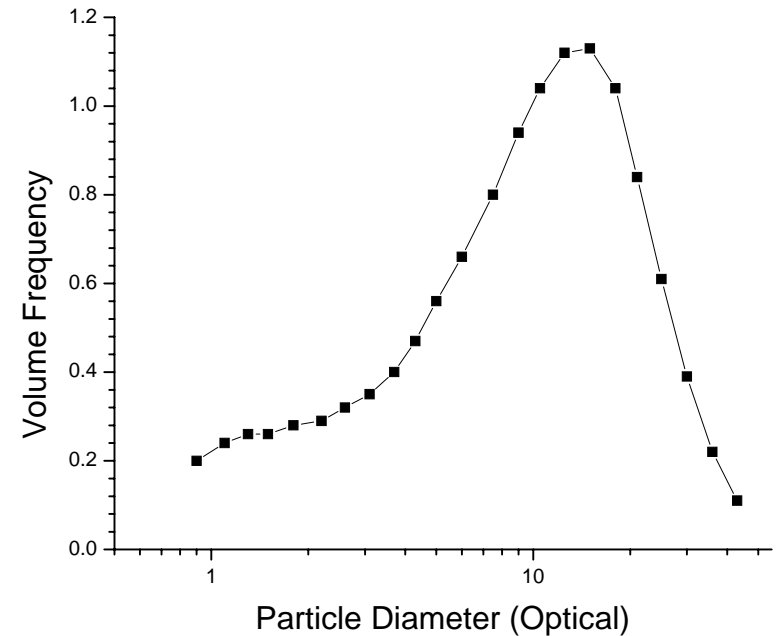


Quantitative results

Chemical & Raman Analyses



Size Distribution of Lactose

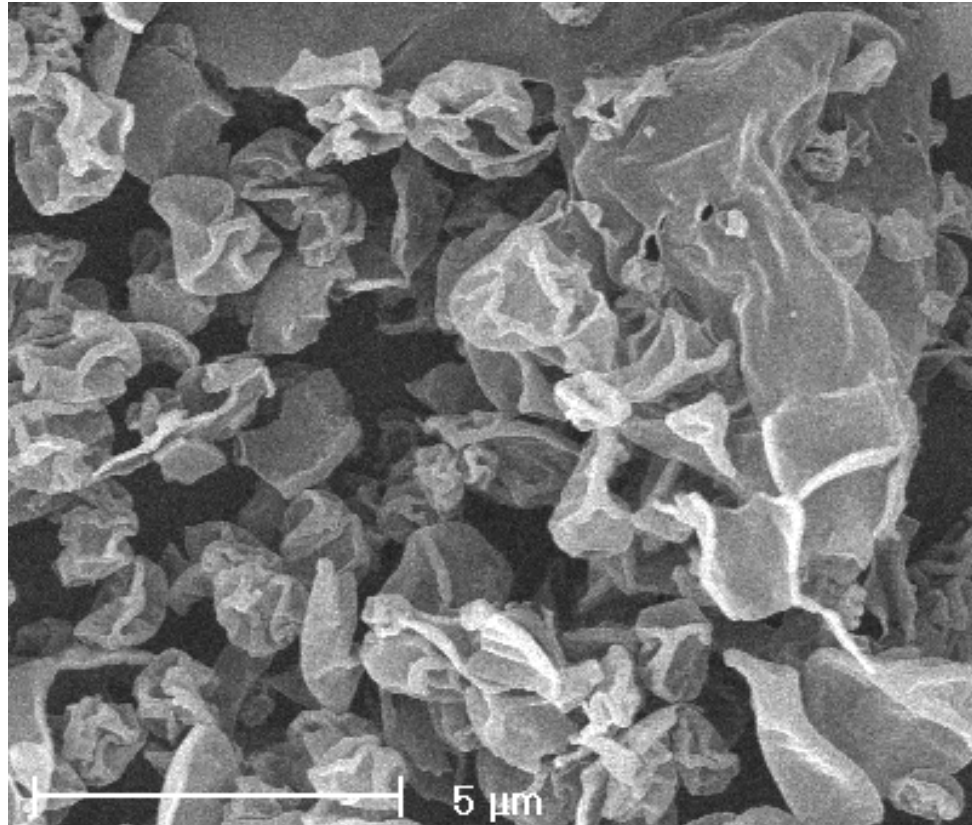


- Good reproducibility of Raman analysis
- HPLC data misleading

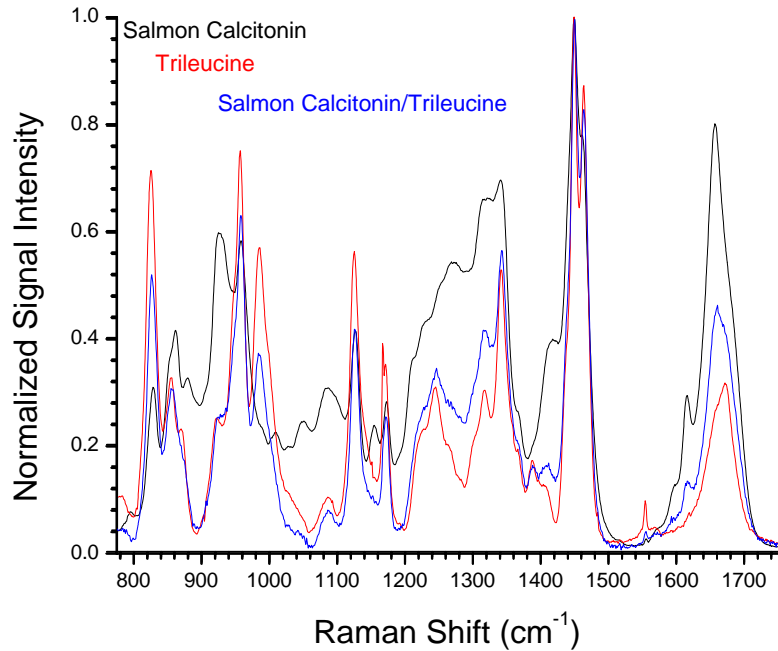


Nektar's Homogeneous *SPRAY-DRIED* powder

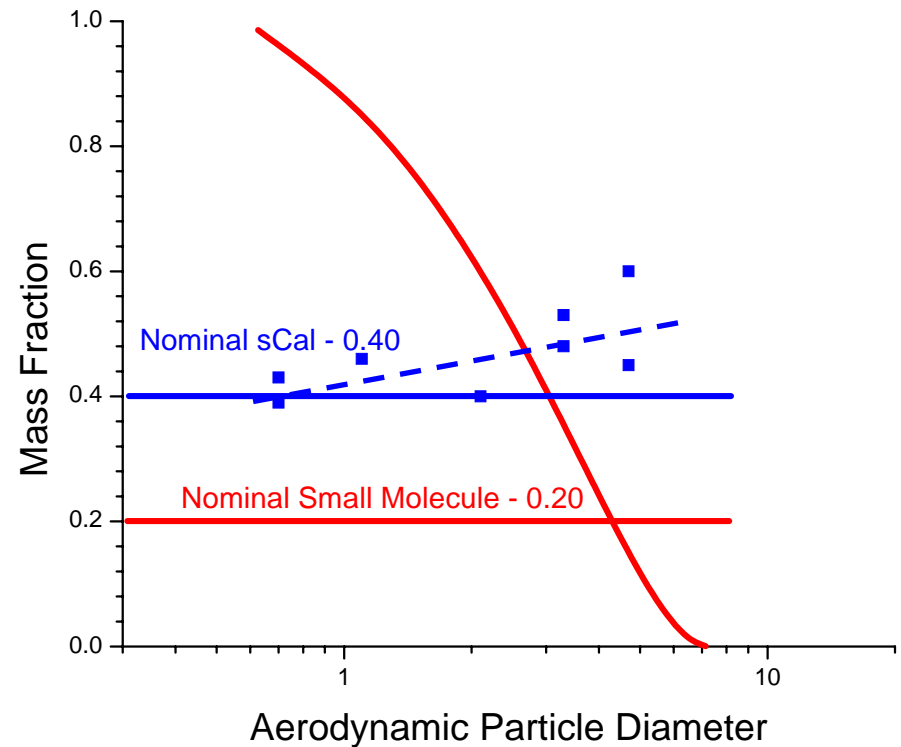
Salmon Calcitonin (sCal) and Trileucine
2:3 formulation ratio



Powder dispersion analysis via Raman



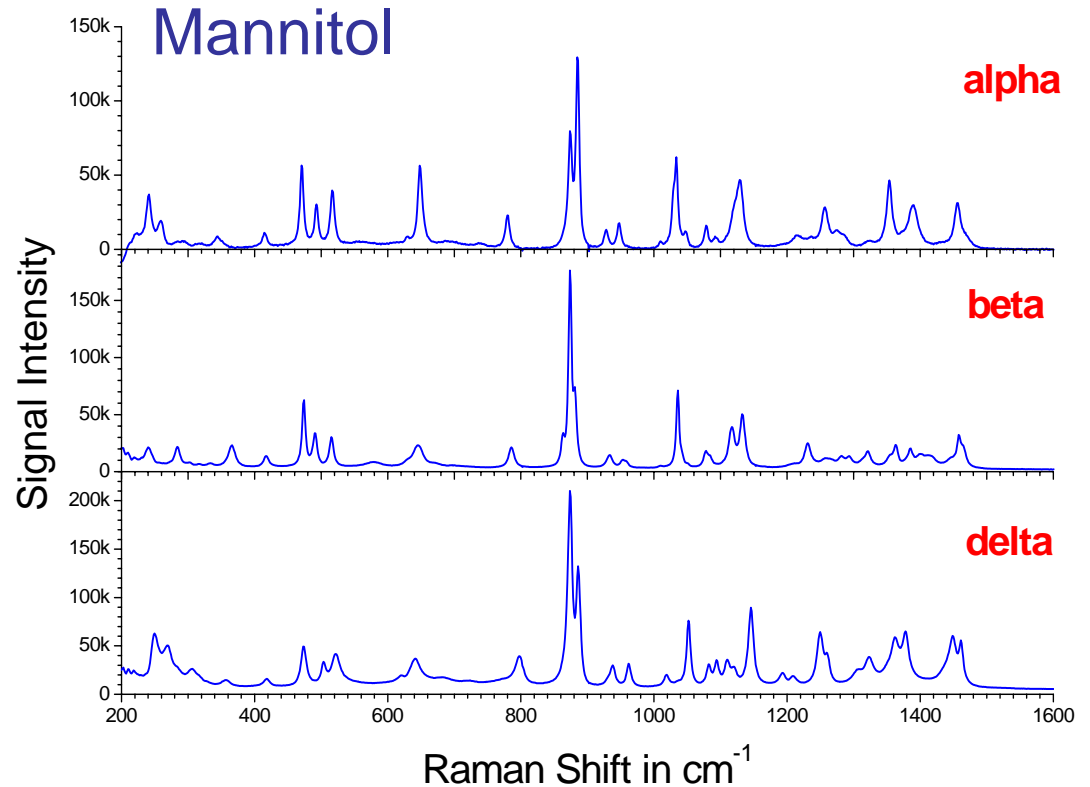
$$Y_A = Y_{\text{Ref}} \cdot k_{A,\text{Ref}} (S_A/S_{\text{Ref}})$$



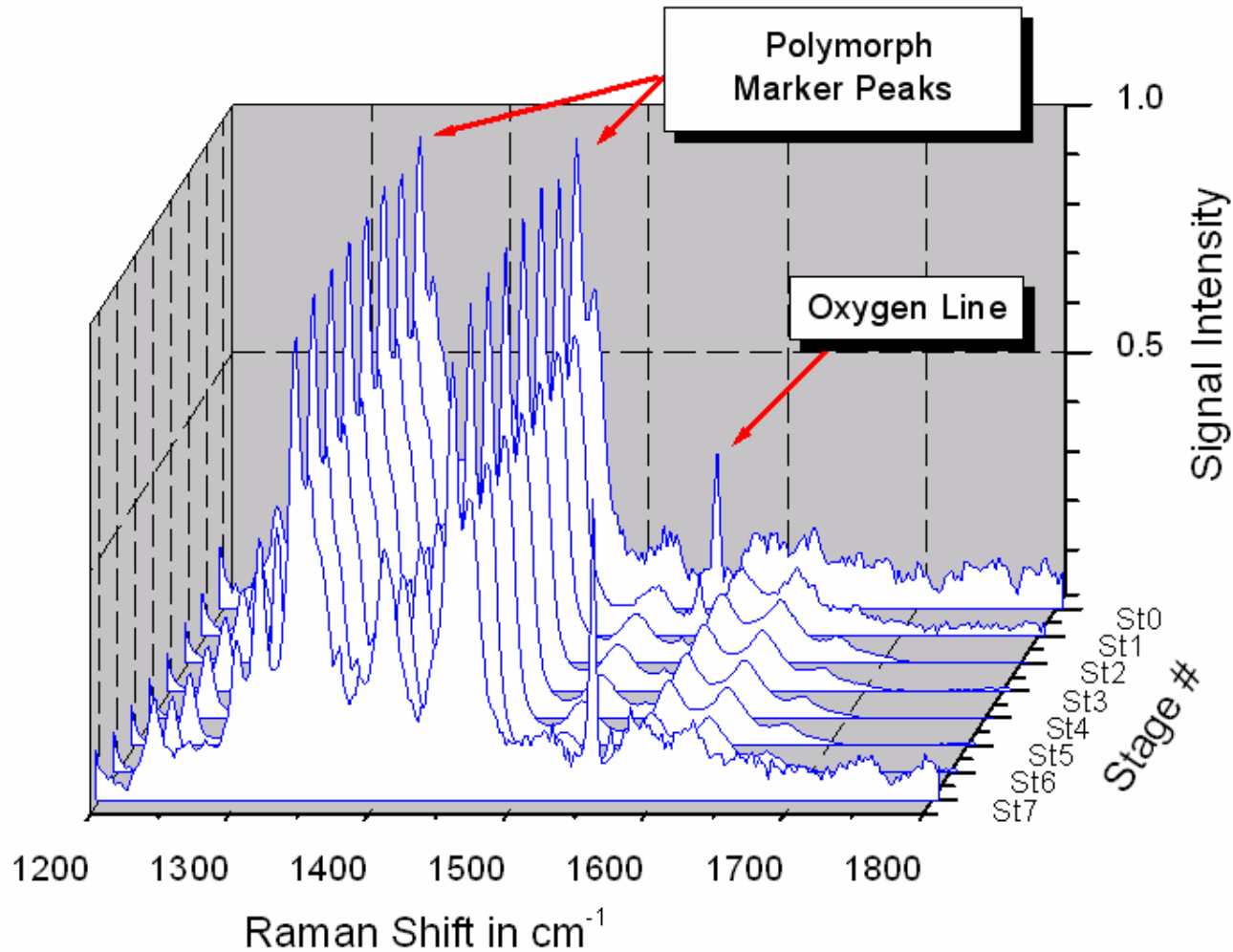
Raman spectroscopy

Improved specificity

- Polymorphism
- Crystallinity



Size selective polymorph analysis



Summary

- Raman spectroscopy can be used to
 - Quantitate composition
 - Detect changes in polymorphism or crystallinity on size fractionated powder in combination with an impactor
- Application:
 - Spray-dried powder for pulmonary delivery was found to be homogeneous across different particle sizes
- Advantage:
 - Less analytical work necessary

