Bulk composition analysis of microparticle-based pharmaceutical dosage forms by macro-Raman spectroscopy

Hui Wang[1], Lisa Williams[2], Susan Hoe[2], David Lechuga Ballesteros[2], Reinhard Vehring[1,2]

[1]Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada

[2]Pearl Therapeutics, Inc., Redwood City, CA, USA

Introduction

Bulk composition analysis of pharmaceutical dosage forms is important for quality control during manufacturing and shelf life of the product, e.g., to monitor potential transformations of actives and excipients into other forms or states [1]. However, non-representative sampling may be an important quantification error source, especially for techniques analyzing very small samples, like micro-Raman spectroscopy [2]. Larger sample volumes have been intentionally pursued using various methods [3]. A quantitative description of the minimum sample volume required for representative sampling of microparticle based powder samples is presented here.

Materials and Methods

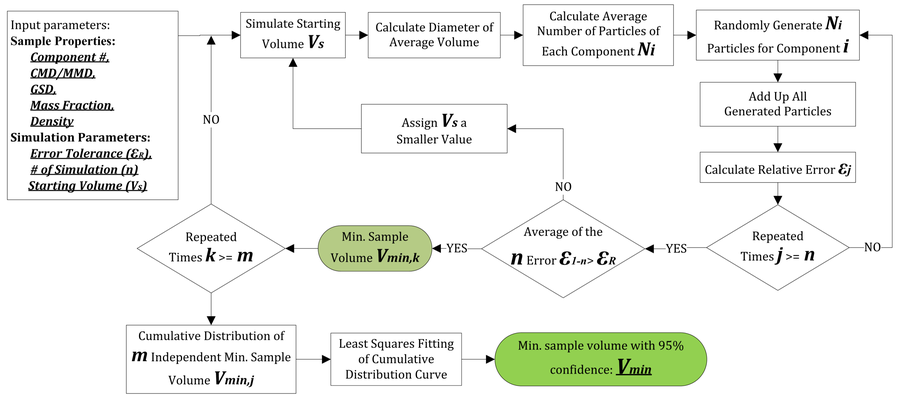
❖ **Materials:**

1) Seretide® 50 Evohaler®: pMDI, 50µg fluticasone propionate (FP), 25µg salmeterol xinafoate (SX).
2) Seretide® Accuhaler®: lactose carrier-based DPIs, 50µg SX and 100, 250, or 500µg FP.

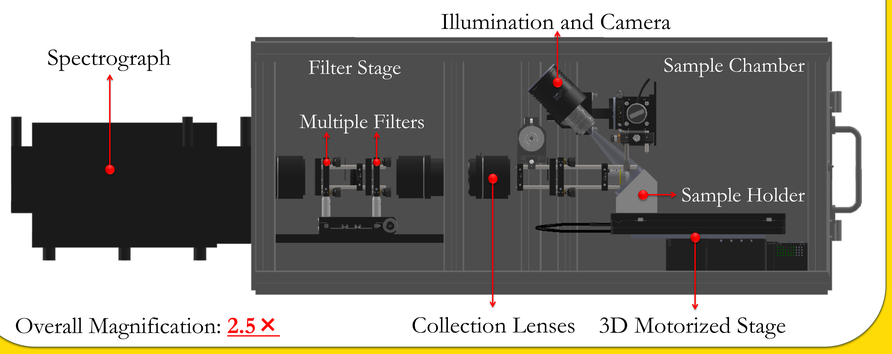
❖ **Methods:**

1) Particle size distributions of lactose carrier particles were measured by a laser diffraction system (HELOS BF, Sympatec GmbH) with an attached powder disperser (OASIS/M).
2) A stochastic model was developed to simulate the random sampling process of multi-component micro-particle based powder samples to predict the minimum sample volume required for representative sampling.

Monte-Carlo simulation



3) A dispersive macro-Raman system [4] with a large sample volume was developed to quantify compositions of powders extracted from the three DPI devices. Quantification was realized by separating the spectral contributions of each component and correlating the deconvoluted spectral intensities with mass fractions using a calibration factor.

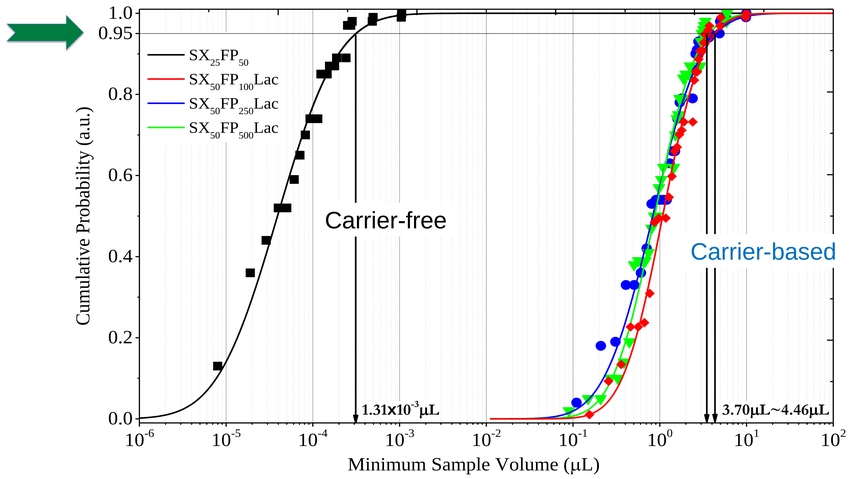


Results

Simulation results:

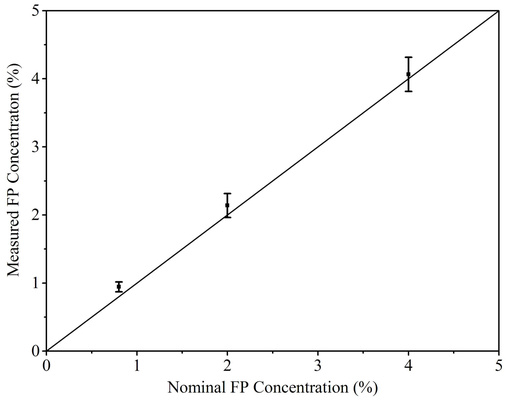
For < 3% relative error (95% confidence) after 5 independent sampling events:

1) The sample volume for a carrier-free product, e.g., Seretide® 50 Evohaler®, must be ≥ **10^{-3}µL**.
2) The sample volume for carrier-based products, e.g. Seretide® 100, 250, and 500 Accuhaler®, must be more than three orders of magnitude greater in the **microliter** range (due to the dominant presence of large lactose particles).



Predicted minimum sample volume distributions of commercial pMDI and DPI products

Measured FP mass fractions agree well with nominal values **even for a FP fraction < 1%.**



Error distributions for macro-Raman analysis: (Including instrument variations, quantification methodology error, and sampling error. The large error for the sample with the lowest FP strength shows that the effective sample volume needs to be increased for this case.

Formulation	Nominal FP mass fraction %	Measured FP mass fraction (±S.D.) %	Relative Error %	Relative Error % (±)		
				Spectral noise and imperfect reference	Predicted Sampling error for 0.16µL (±S.D.)	Quantification method
50µg SX + 100µg FP + Lactose	0.8	0.94(±0.07)	17.5±8.8	2.4	4.7(±4.6)	7.4
50µg SX + 250µg FP + Lactose	2.0	2.14(±0.18)	7.0±9.0	2.0	4.3(±3.8)	8.4
50µg SX + 500µg FP + Lactose	4.0	4.07(±0.25)	1.8±6.3	1.8	6.0(±5.6)	6.1

Conclusions

❖ To consistently achieve a small relative sampling error (<3%) with high confidence (>95%) in the analysis of powders from carrier-free MDI or DPI products, millions of particles must be sampled, corresponding to sample volumes on the order of 10^{-3}µL.

❖ Products with non-respirable large carrier particles or containing small mass fractions of one component, e.g. combination products with high potency actives, further increase the required sample volumes to the microliter range.

❖ These sample volume requirements are impractical to meet for Micro-Raman systems.

❖ Macro-Raman spectroscopy is suitable for representative composition analysis of inhomogeneous bulk powder samples frequently encountered in respirable dosage forms.

❖ The numerical results can also be applied to any other technique measuring bulk properties of particle based samples.

References

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Acknowledgements

Pearl
NSERC CRSNG
UNIVERSITY OF ALBERTA

Respiratory Drug Delivery 2015, Antibes, France