CO-JET-MILLING WITH L-LEUCINE ENHANCES THE DISPERSION OF LEVODOPA DRY POWDER: WHAT IS THE MECHANISM?

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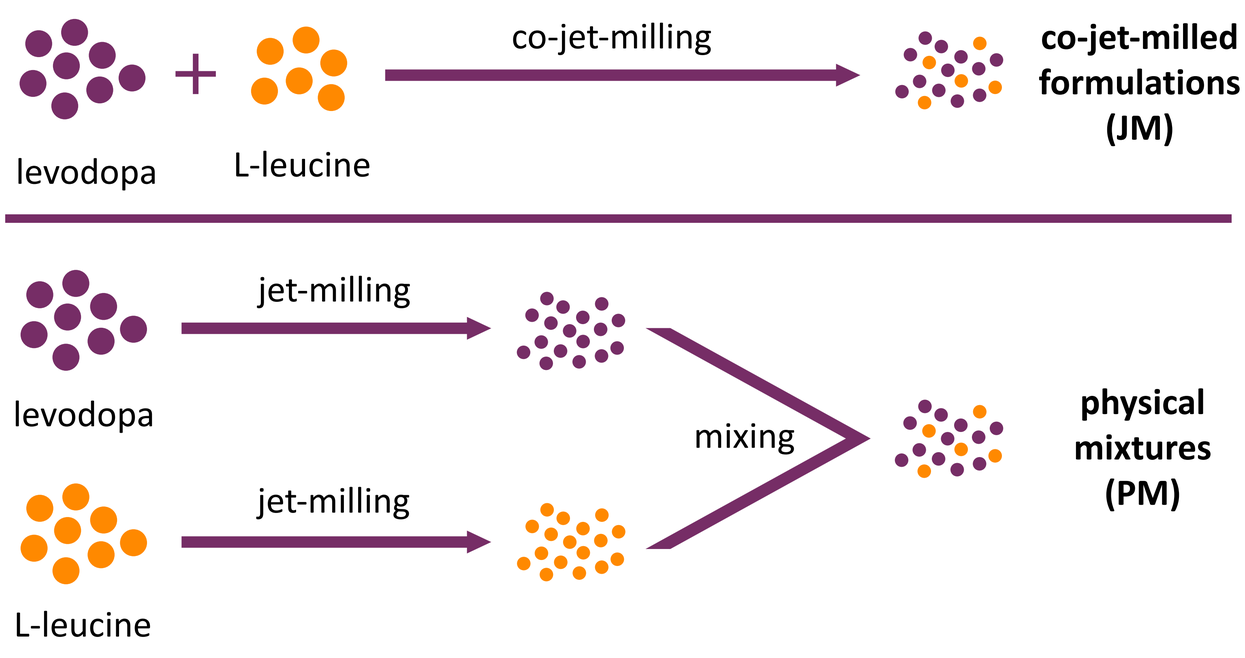
Background

- Jet-milled levodopa is highly cohesive, resulting in poor emission from Cyclops™ DPI, poor dispersibility, and poor dose reproducibility[1]
- Co-jet-milling with 2% L-leucine reduces inhaler retention and enhances dispersibility and dose reproducibility of levodopa[1]
- The mechanism by which L-leucine exerts these effects is unclear

Research question

What is the mechanism behind the effects of L-leucine on the emission and dispersibility of a jet-milled levodopa dry powder inhalation formulation?

Methods



Results

Table 1 - Primary particle size distributions and content uniformity of L-leucine

- The primary particle size distribution of the jet-milled formulations decreased upon increasing L-leucine content

	X_{50} (µm)	% <5 µm	RSD (%)
100% levodopa jet-milled	1.77	98.8	n/a
100% L-leucine jet-milled	1.94	94.8	n/a
2% L-leucine co-jet-milled	1.39	99.7	0.4
2% L-leucine physical mixture	1.77	98.3	4.6
10% L-leucine co-jet-milled	1.23	100.0	0.5
10% L-leucine physical mixture	1.93	96.9	1.5

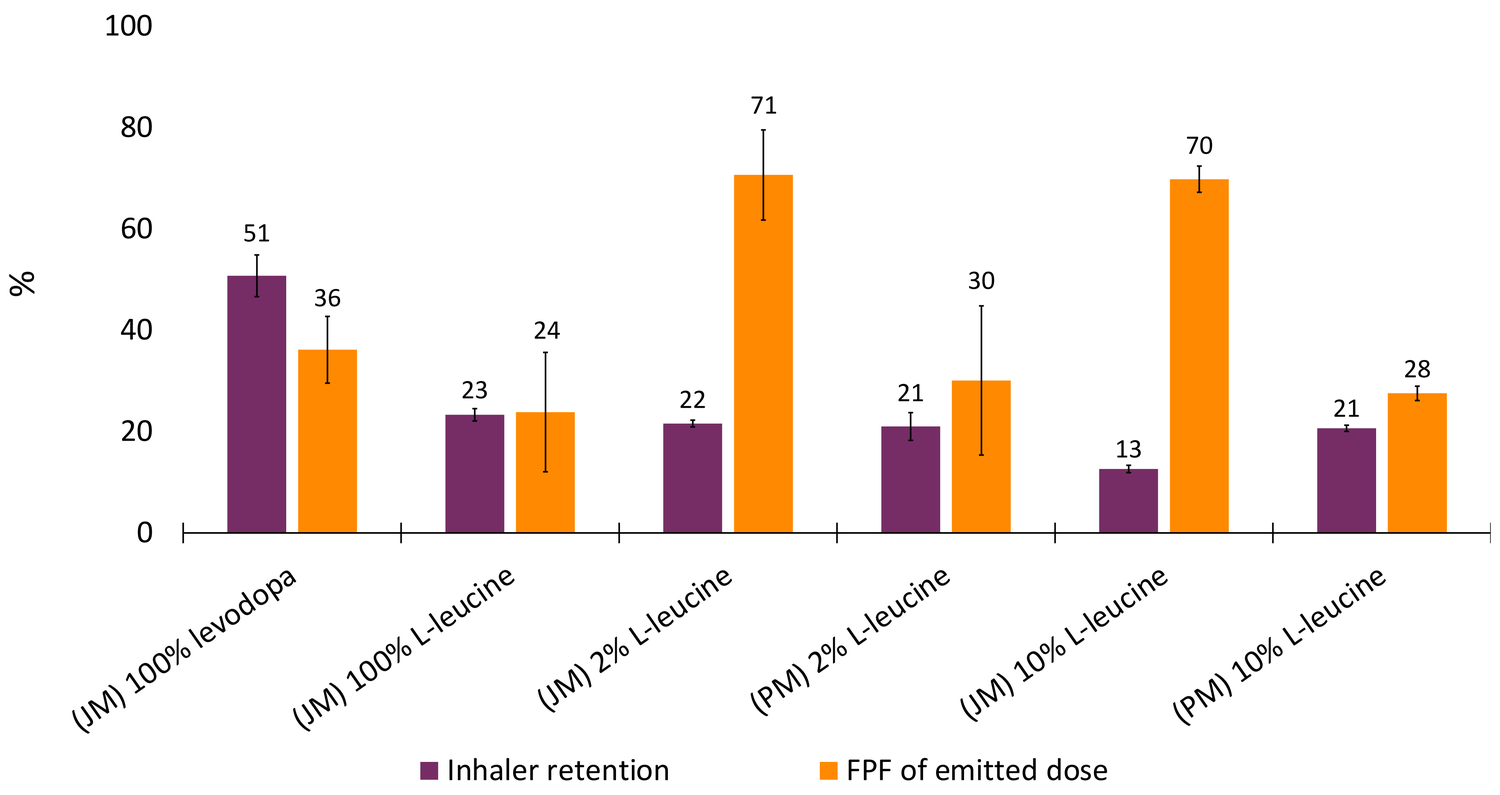


Figure 1 - Inhaler retention and fine particle fraction of the emitted dose

- Co-jet-milling with 2% or 10% L-leucine increases the dispersibility compared to pure jet-milled levodopa; physically mixing 2% or 10% L-leucine does not
- Both co-jet-milling and physically mixing levodopa with 2% or 10% L-leucine decreases inhaler retention compared to pure jet-milled levodopa
- The intrinsic dispersibility of jet-milled L-leucine is poor, implying that the surface energy of L-leucine does not play a major role in the effects of co-jet-milled L-leucine
- The intrinsic emission properties of L-leucine are good

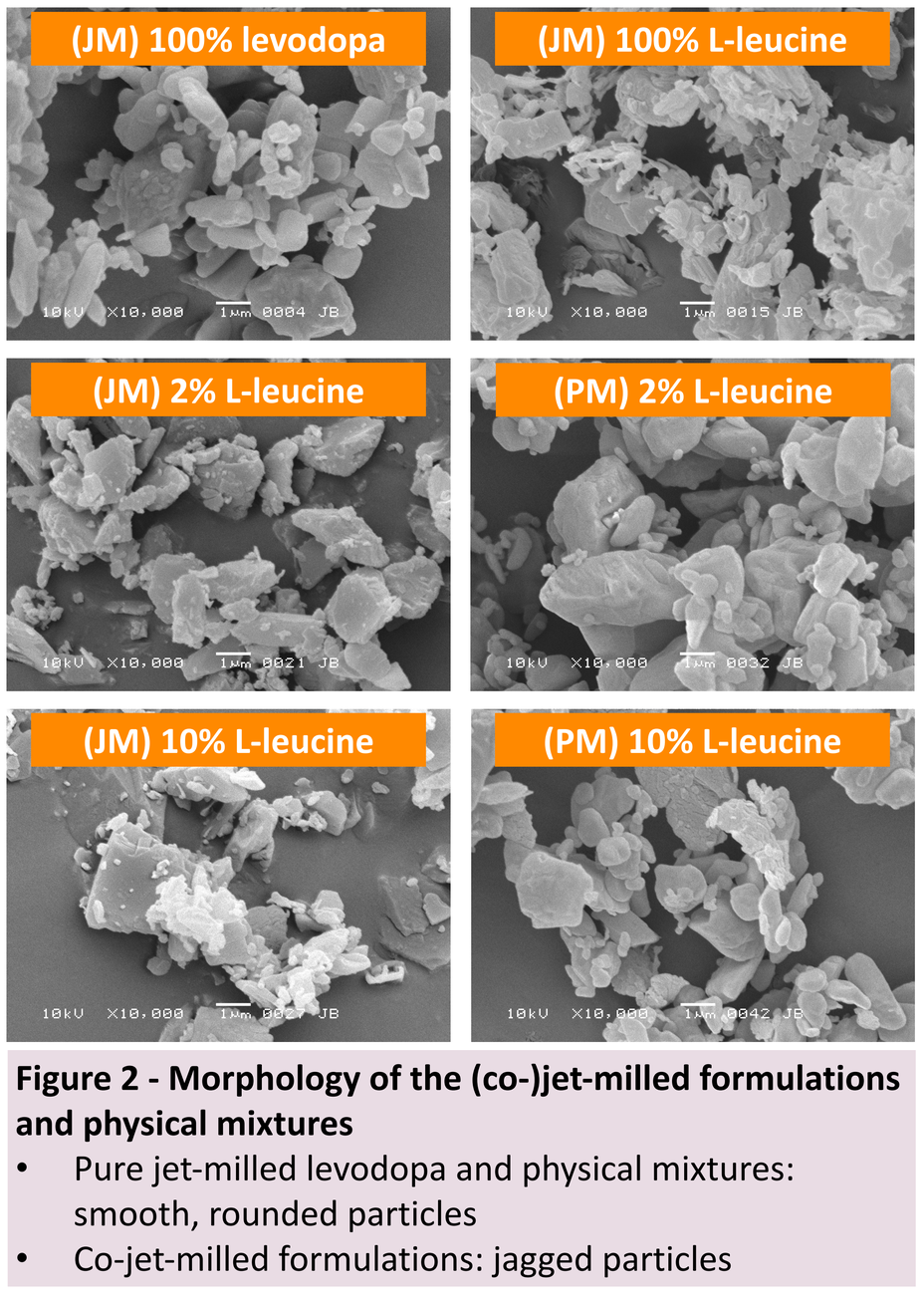


Figure 2 - Morphology of the (co-)jet-milled formulations and physical mixtures

- Pure jet-milled levodopa and physical mixtures: smooth, rounded particles
- Co-jet-milled formulations: jagged particles

Conclusions

- Co-jet-milled L-leucine may exert its effects by changing the particle size distribution and particle morphology
- The effects of co-jet-milled L-leucine on emission and dispersion can likely be attributed to at least two distinct mechanisms
- This emphasizes the importance to consider emission and dispersion separately in DPI formulation development

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Reference:
1. Luinstra M et al. (2015) *Eur J Pharm Biopharm*, 97:22-29

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