

**Chiesi**

Use of Resonant Acoustic Mixing to produce dry powders for lung delivery

Cristina Rey-Blanes

Resodyn Technical InterChange 2025, 17th September 2025



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Introduction - Types of Inhalers



Pressurized Metered Dose Inhalers (pMDIs)



Dry Powder Inhalers (DPIs)



Nebulizers

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Introduction - Types of Inhalers



Pressurized Metered Dose Inhalers (pMDIs)



Dry Powder Inhalers (DPIs)



Nebulizers

Advantages of DPIs:

- Ease of use
- Lack of propellant
- Enhanced stability compared to liquid forms
- Larger amount delivered for poorly soluble drugs

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### Introduction - Anatomy of the Lung

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Chaurasiya & Zhao, *Pharmaceutics*, 2020

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### Introduction - Challenges of Formulating DPIs

- The main challenge when formulating DPIs arises from the **small particle size required (1-5 µm)**.
- This requirement results in high surface areas and interparticulate interactions, which lead to a high degree of cohesion and adhesion between particles.
- This has been traditionally handled by using larger particles (~100 µm) as carriers. The main carrier used is Lactose Monohydrate, which can come in different morphologies and sizes in order to optimise the product's performance.
- In addition, force control agents, such as Magnesium Stearate, are often added to the formulation in order to improve aerosolization.

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### Introduction - Traditional Blending Methods

- Two of the most used traditional blending methods are low shear and high shear mixing:

<p>Low shear mixing</p>	<p>High shear mixing</p>	<p>Medium shear mixing</p>
<ul style="list-style-type: none"> <li>Low speed mixing.</li> <li>Low energy.</li> <li>Longer mixing times (hours).</li> <li>Often requires several middle steps, such as sieving, and mixing at different speeds.</li> </ul>	<ul style="list-style-type: none"> <li>High speed mixing.</li> <li>High energy.</li> <li>Shorter mixing times (~30 mins).</li> <li>Chance of breaking down the larger carrier into smaller particles - generation of fine particles needs to be monitored.</li> </ul>	<ul style="list-style-type: none"> <li>Mixing happens through longitudinal acoustic pressure waves.</li> <li>Medium energy.</li> <li>Shorter mixing times (~1 to 5 mins).</li> <li>Uniform mixing over the entire volume of the mixing vessel.</li> </ul>

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**Introduction - Questions**

- Is RAM technology capable of producing homogeneous and aerosolizable DPI blends in a short mixing time?

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**Introduction - Questions**

- Is RAM technology capable of producing homogeneous and aerosolizable DPI blends in a short mixing time?
- Can RAM be used to manufacture blends with a good manufacturing repeatability?

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**Introduction - Questions**

- Is RAM technology capable of producing homogeneous and aerosolizable DPI blends in a short mixing time?
- Can RAM be used to manufacture blends with a good manufacturing repeatability?
- How does the homogeneity and aerodynamic performance profile of blends manufactured with RAM compare with other traditional blending methods?

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**Introduction – Questions**

- Is RAM technology capable of producing homogeneous and aerosolizable DPI blends in a short mixing time?
- Can RAM be used to manufacture blends with a good manufacturing repeatability?
- How does the homogeneity and aerodynamic performance profile of blends manufactured with RAM compare with other traditional blending methods?
- Are the blends produced by RAM scalable at a lab scale?

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**Materials & Methods**

- The New Chemical Entity (NCE) was provided by Chiesi (Chiesi Farmaceutici S.p.A., Italy). For the DPI formulations, Carrier 1 (containing coarse and fine lactose, and a force control agent) and Carrier 2 (coarse lactose) were used. For confidentiality reasons, further details about these compounds cannot be disclosed.
- **Design of Experiments 1 + scale up:**

		Level 1	Level 2	Level 3
X1	Blending Time (min)	1	3	5
X2	Acceleration (g)	30	60	90
X3	Vessel Fill Volume (%)	40	60	80
X4	API Concentration (%)	5	15	25
X5	Carrier Type	Carrier 1	Carrier 2	



- This design of experiment was designed to explore a suitable working space within the RAM technology that would generate homogeneous and aerosolizable DPI blends.
- A LabRAM II ResonantAcoustic® Mixer was used.
- 25 experiments were planned and executed.
- A 54.6 mL stainless-steel vessel was used.
- The total amount of NCE to be added was sandwiched between two equal layers of the desired carrier.
- No extra steps such as sieving or conditioning of the vessel were carried out.
- 4 out of the 25 blends were selected and scaled up to two different batch sizes using two larger stainless-steel vessels (242.2 and 730.9 mL).

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**Materials & Methods**

- **Design of Experiments 2:**

		Level 1	Level 2
X1	Blending Time (min)	10	25
X2	Speed (rpm)	400	800
X3	API Concentration (%)	5	25
X4	Carrier Type	Carrier 1	Carrier 2



- This design of experiment was designed based on previously obtained data with the used NCE in order to obtain DPI blends for a performance comparison with RAM manufactured blends.
- A Mini Cyclomix Lab Mixer (Hosokawa Micron Ltd, UK) was used.
- 8 experiments were planned and executed.
- A 100 mL stainless-steel vessel was used, filled to 70% capacity.
- The total amount of NCE to be added was sandwiched between two equal layers of the desired carrier.
- No extra steps such as sieving or conditioning of the vessel were carried out.

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### Methods - Analytical Methods

- The impact of the different parameters on the process yield (%), API recovered assay (%) and homogeneity (Relative Standard Deviation, RSD (%)) was evaluated.
- Aerodynamic Particle Size Distribution (APSD) was studied using a high resistance R501 (Plastape S.p.A, Italy) as a model device, actuated at a flow rate of 65 L/min for 3.7 s. White size 3 HPMC capsules (Lonza, Switzerland) were filled by hand with 20 mg of each formulation.
- A Next Generation Impactor (NGI, Copley Scientific, UK) was used to evaluate the aerodynamic performance. This allowed understanding of the impact of the different variables studied on the Delivered Dose as a percentage of Metered Dose (DD%MD), Fine Particle Fraction as a percentage of Delivered Dose (FPF%DD) and shot weight (mg).
- All the quantification was performed using UV High Performance Liquid Chromatography.



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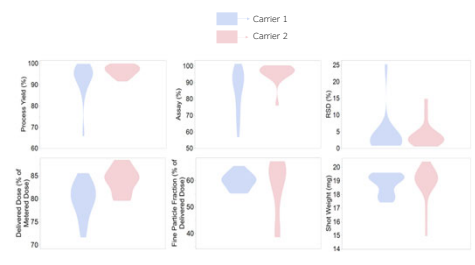
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### Results - RAM DoE

	Level 1	Level 2	Level 3
X1	30	60	90
X2	30	60	90
X3	10	40	90
X4	5	15	25
X5	Carrier 1	Carrier 2	



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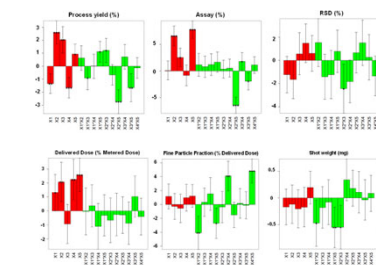
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### Results - RAM DoE (Statistical Analysis)

	Level 1	Level 2	Level 3
X1	30	60	90
X2	30	60	90
X3	10	40	90
X4	5	15	25
X5	Carrier 1	Carrier 2	



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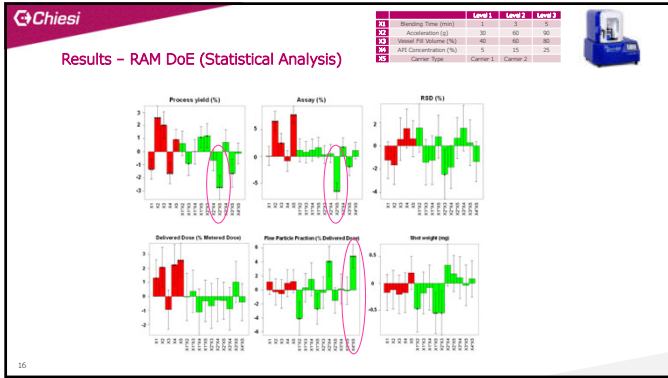
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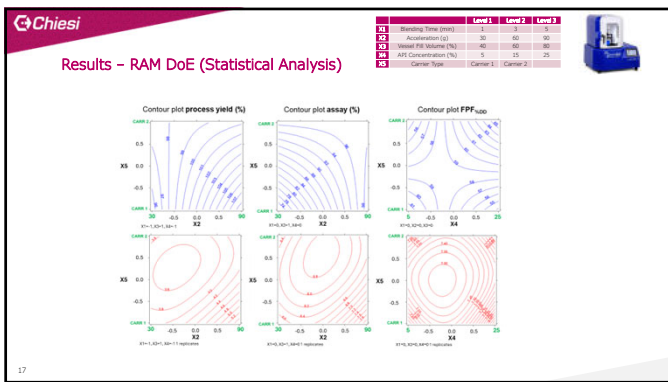
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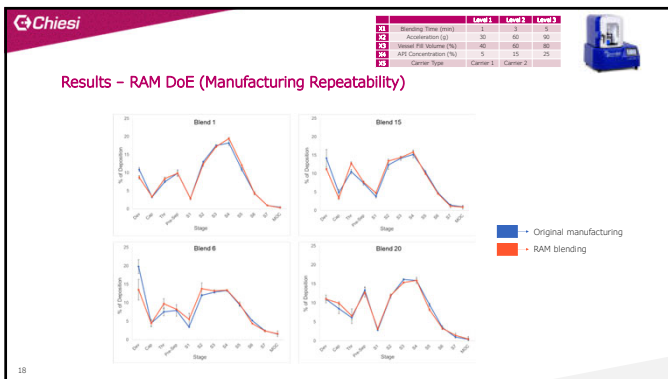
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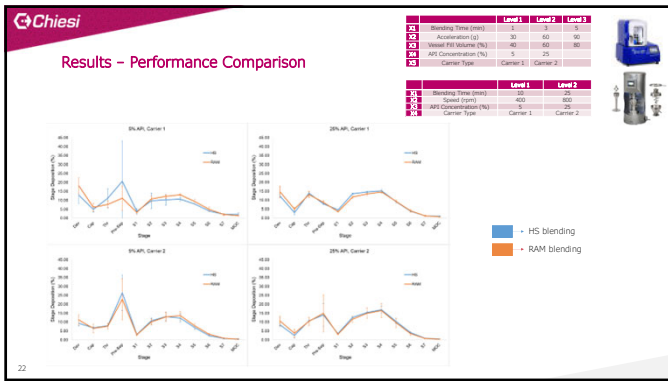
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### Conclusions

- RAM technology is capable of producing homogeneous and aerosolizable DPI blends in a short mixing time.
- RAM manufactured blends present good manufacturing repeatability.
- Blends manufactured using RAM show enhanced homogeneity and similar aerodynamic performance profile when compared with blends manufactured using HS mixing, in a shorter manufacturing time.
- The blends produced by RAM are mostly scalable at a lab scale, however careful considerations in terms of vessel fill volume and acceleration must be taken into account in order to prevent a too tight binding of the API molecule to the carrier lactose.

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### Next Steps

- Further scale up of the most promising blends (4-8 kgs).
- Study the manufacture of marketed blends using RAM.

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### Acknowledgements

Big thank you to our colleagues in the Chippenham Lab and Parma Lab who helped us with the DoE generation and experiments:

- Katrina Zalokoski
- Neil Anderson
- Richard Friend
- Gareth Hardwell
- Diego Copelli

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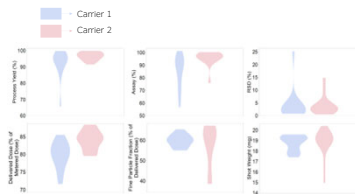


### Results - RAM DoE

	Level 1	Level 2	Level 3
13 Blending Time (min)	30	60	90
14 Acceleration (g)	30	60	90
15 Blend #/Volume (%)	100	60	100
16 API Concentration (%)	5	15	25
17 Carrier Type	Carrier 1	Carrier 2	



- Most of the blends were homogeneous (RSD < 5%), regardless of the blending parameters or carrier selected.
- Process yield and assay above 90% for the different blending conditions.
- Most of the blends presented an optimal aerosolization profile.
- The  $D_{p0.5}$  results ranged from around 70 to 90%.
- The  $FF_{50\%}$  obtained was from around 50 to 70%, with a couple of blends around 35%.
- The shot weight, more variable, was around 17 to 20 mg (20 mg loaded per capsule).



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Results - Performance Comparison

	Level 1	Level 2	Level 3
Blending Time (min)	1	3	5
Acceleration (g)	30	60	90
Initial PEI Volume (mL)	40	50	60
API Concentration (%)	5	25	
Carrier Type	Carrier 1	Carrier 2	

	Level 1	Level 2
Blending Time (min)	30	24
Speed (rpm)	400	600
API Concentration (%)	5	25
Carrier Type	Carrier 1	Carrier 2



- The aerodynamic performance obtained by blends manufactured with both mixing techniques was comparable, except for one formulation identified as an outlier obtained with HS mixing for the 5% API, carrier 1 group.
- The Delivered Dose and the Fine Particle Mass obtained as an average of the different blends manufactured either by HS or RAM with a fixed concentration of API or carrier used did not present any statistically significant differences.

