Development of a Novel Dry Powder Inhaler for Semaglutide: Freeze-Drying Micronization and PK study

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Abstract #488

Objective

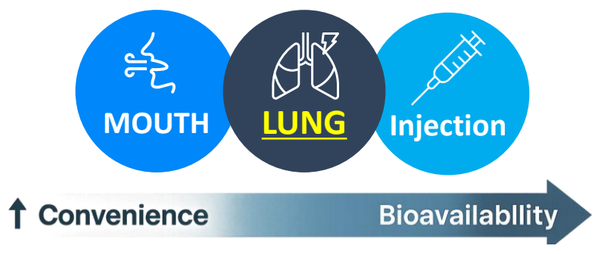
The objective of this study was to develop and optimize a novel semaglutide-loaded dry powder inhaler (DPI) formulation using freeze-drying technology, with the aim of enhancing pulmonary delivery and systemic bioavailability of semaglutide while overcoming the limitations associated with injectable and oral administration.

Specifically, the study sought to:

- Compare the physicochemical properties and aerodynamic performance of micronized semaglutide powders produced by freeze-drying methods
- Investigate the effects of various excipients (lactose, sucrose, mannitol) and carrier quantities on particle morphology, stability, and lung deposition efficiency.

Introduction

- **Injection-related limitations**
  - ▸ Current subcutaneous route reduces patient adherence due to injection discomfort and systemic exposure.
- **Oral formulation challenges**
  - ▸ Semaglutide tablets exhibit poor bioavailability due to enzymatic degradation and limited intestinal absorption.
- **Enhanced compliance and broader therapeutic utility**
  - ▸ Inhaled formulation may improve convenience, efficacy, and clinical outcomes in patients with metabolic-pulmonary overlap.
- **Advantages of pulmonary drug delivery**
  - ▸ Enables targeted lung deposition, faster onset of action, and minimized systemic exposure.
- **High burden of pulmonary comorbidities in obese and diabetic patients**
  - ▸ COPD and interstitial lung disease are prevalent in this population, requiring dual-targeted therapy.
- **Emerging pulmonary benefits of semaglutide**
  - ▸ Preclinical studies suggest anti-inflammatory and anti-fibrotic effects in lung tissue.



Method

Manufacturing

Freeze-drying

- ▸ Manufacturing equipment: **LP03** (Ilshin Bio, Korea)
- ▸ Freeze-drying conditions:
  - Temperature: -15 ~ 40°C
  - Pressure: 5 mTorr

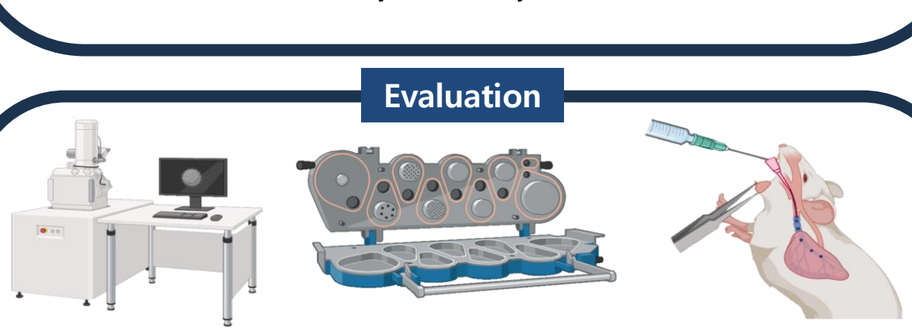
Blending & Capsule filling

- ▸ Manufacturing equipment: **GKF-702** (Syntegon, Germany)
- ▸ Equipment imformation:
  - Output: 42,000 caps/h
  - Cycles: 140 cycles/min

DPI (Proprietary DPI platform)

- ▸ Inhaler information:
  - Air Flow Resistance (kPa/L/min): 0.024
  - Capsule: Size 3

Evaluation



Properties Analysis

- ▸ Scanning Electron Microscopy (SEM):
  - Model: TM3000 (Hitachi, Japan)
  - Voltage: 15 kV.

***In vitro* Aerodynamic performance test**

- ▸ Measuring equipment: next generation impactor (Copley, UK).
- ▸ Measurement condition:
  - Flow rate: 100 L/min for 2.4s following USP<601>

***In vivo* animal test**

- ▸ Animal model: Male Sprague-Dawley rats (8 weeks, 280-300 g)
- ▸ Intratracheal Administration: Using a insufflator (DP-4; Penn Century Inc.,USA)

Images were created using BioRender (www.biorender.com)

Result

Table 1. Compositions of semaglutide-loaded DPI

Process	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Freeze-drying	Semaglutide	-	0.71	0.71	0.71	0.71	0.71	0.71	0.71
	Sugar	-	-	-	-	2.0	2.0	4.0	6.0
Blending	Semaglutide	0.71	-	-	-	-	-	-	-
	ML003	21.753	21.753	10.503	4.203	2.203	19.753	17.753	15.753
	LH300	2.5	2.5	1.25	0.55	0.55	2.5	2.5	2.5
	Magnesium stearate	0.037	0.037	0.037	0.037	0.037	0.037	0.037	0.037
Total weight (mg)		25.0	25.0	12.5	5.5	5.5	25.0	25.0	25.0

Fig 1. Scanning electron microscopy (SEM) images

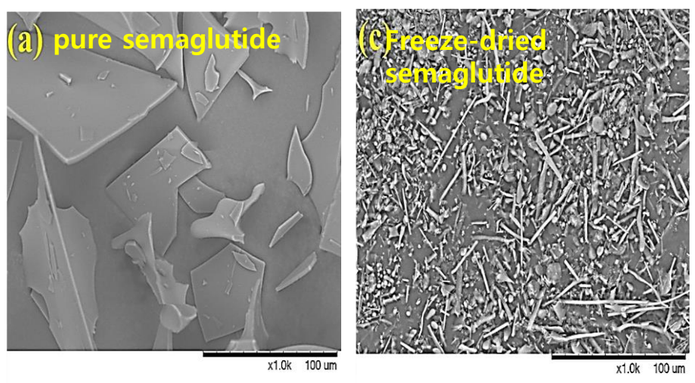


Fig 2. Aerodynamic performance of sema.-loaded DPI

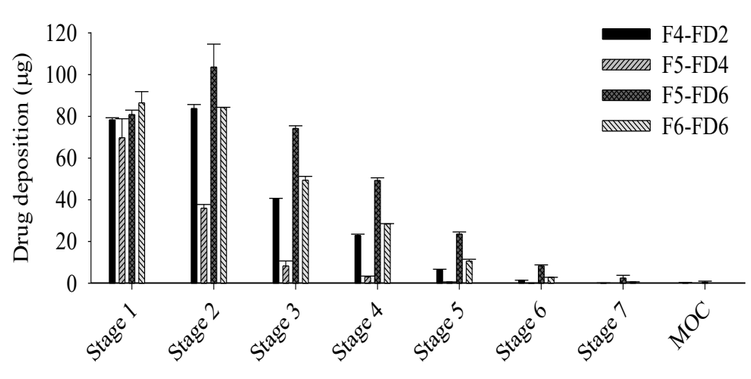


Table 2. Emitted dose (ED) and fine particle mass (FPM) of semaglutide-loaded DPI.

	Semaglutide	Total weight (mg)	ED (μg)	FPM (μg)
F1	Pure semaglutide	25.0	643 ± 73	4 ± 1
F2-SD	Spray-dried	25.0	533 ± 5	51 ± 1
F2-FD1	Freeze-dried	25.0	543 ± 63	137 ± 15
F2-FD2	Freeze-dried	25.0	622 ± 33	136 ± 13
F2-FD3	Freeze-dried	25.0	557 ± 1	97 ± 36
F3-FD2	Freeze-dried	12.5	657 ± 24	138 ± 4
F4-FD2	Freeze-dried	5.5	642 ± 9	155 ± 3
F5-FD4	Freeze-dried with sucrose	5.5	543 ± 5	48 ± 5
F5-FD6	Freeze-dried with mannitol	5.5	595 ± 11	262 ± 11
F6-FD6	Freeze-dried with mannitol	25.0	611 ± 5	176 ± 3
F7-FD7	Freeze-dried with mannitol	25.0	596 ± 14	172 ± 8
F8-FD8	Freeze-dried with mannitol	25.0	597 ± 30	159 ± 29

Table 3. The total impurities and aggregates of semaglutide

	Total impurities (%)	Aggregates (%)
Pure semaglutide	0.05 ± 0.02	0.07 ± 0.05
Freeze-dried semaglutide	0.06 ± 0.03	0.09 ± 0.03
Freeze-dried semaglutide with mannitol	0.07 ± 0.02	0.11 ± 0.02

Fig 3. Pharmacokinetic profile of animal model

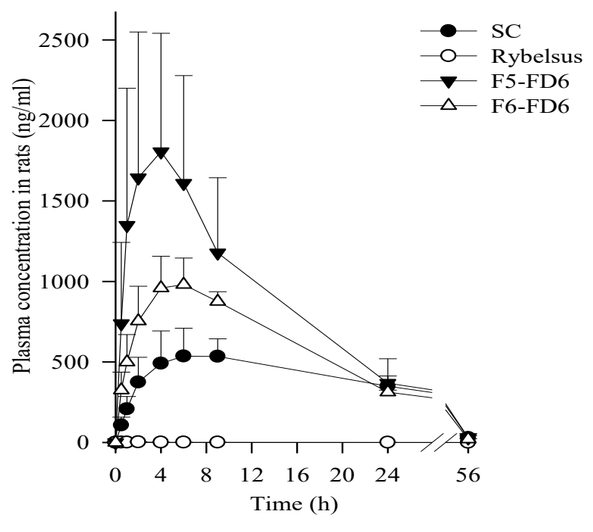


Table 4. Pharmacokinetic parameters after the subcutaneous, oral and intratracheal administration to rats.

	SC	Rybelsus®	F5-FD6	F6-FD6
Dose (mg/kg)	0.2	2.4	2.4	2.4
AUC (h•ng/mL)	16568.39 ± 1618.11	18.24 ± 10.97	31202.93 ± 12534.42	21590.87 ± 1629.90
C_{max} (ng/mL)	535.66 ± 165.17	2.36 ± 1.51	1805.94 ± 829.60	980.83 ± 181.65
T_{max} (h)	7.75 ± 2.50	1.50 ± 0.87	4.00 ± 1.63	6.33 ± 2.52
$t_{1/2}$ (h)	11.57 ± 3.52	19.65 ± 11.77	8.81 ± 0.77	8.58 ± 0.46
K_{el} (h^{-1})	0.06 ± 0.02	0.04 ± 0.12	0.08 ± 0.01	0.08 ± 0.00
F_{rel} (%)	-	**0.01**	**15.7**	**10.9**

Conclusion

Semaglutide-loaded DPI: a promising pulmonary delivery platform for peptide therapeutics

Micronized DPI formulation successfully developed

- ▸ Freeze-drying with mannitol produced elongated, fine semaglutide particles suitable for deep lung deposition.

Enhanced aerosol performance

- ▸ Optimized formulation achieved high FPM and met pharmacopeial content/dose uniformity standards.

Marked improvement in semaglutide bioavailability

- ▸ Pulmonary delivery via intratracheal route resulted in ~15.7% bioavailability in rats, markedly higher than oral Rybelsus® (<1%).

Maintained drug stability and purity

- ▸ No adverse iDermpact on impurity or aggregation profile observed after freeze-drying.

Non-invasive alternative to injectable/oral semaglutide

- ▸ The pulmonary route overcomes injection-related discomfort and low oral absorption, providing a viable platform for systemic delivery of GLP-1 analogs and other peptide therapeutics.

Reference

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