Comparative evaluation of powder delivery devices for nasal administration in rat

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Introduction

- Intranasal administration is an increasingly important route in toxicological testing, enabling direct exposure of the nasal mucosa and associated lymph nodes.
- While snout-only inhalation procedures results in nasal exposure, the approach is less efficient and less accurate when only the nose is the target.
- Powder insufflation, while more technically demanding than liquid instillation and often associated with greater variability, allows delivery of higher drug concentrations and reduces nasal runoff.
- Nonclinical delivery of dry powder has posed a challenge for nonclinical testing because of device availability and suitability. Delivery efficiency and dose reproducibility can significantly influence study outcomes.
- Therefore, Labcorp developed a nonclinical device for nasal powder dose administration that would cover a range of dose levels and compared it to other commercially available options.

Methods

- Three nasal delivery devices were evaluated across key performance parameters: the Penn-Century® Dry Powder Insufflator, a second commercially available device (Device #2), and a Labcorp dry-powder delivery device.
- Powder was loaded and dispensed using either 1 mL or 2 mL of pressurized air.
- Efficiency of each device was determined by calculating the difference in weight between the loaded and discharged device.
- **Phase 1**
  - Lactohale® LH200 (pharmaceutical grade) was selected as a model powder (d50: 50-100 µm) for nasal-targeting therapeutics.
- **Phase 2**
  - Animal care and use was performed in accordance with applicable animal welfare regulations at an AAALAC International accredited animal program and was IACUC approved.
  - Wistar Han rats (Crl:WI[Han]), 7 to 9 weeks of age, were anesthetized with isoflurane and manually restrained for dose administration. There were 3 males per dose level.
  - A proprietary dry powder blend containing 4% trypan blue was administered using the Labcorp device. Dose levels were escalated, using 0.5, 1, and 5 mg.
  - Animals were sacrificed immediately postdose (5 mg) or at 0.5h, 1h, and 2h postdose (0.5 and 1 mg). Deposition in the nasal cavity was assessed macroscopically as quickly as possible.
  - To further study nasal deposition, a dose (5 mg) was delivered postmortem to 1 animal. In addition, following an examination for the 1 mg dose, the powder was placed on the tissue with a spatula to observe the rapid absorption.

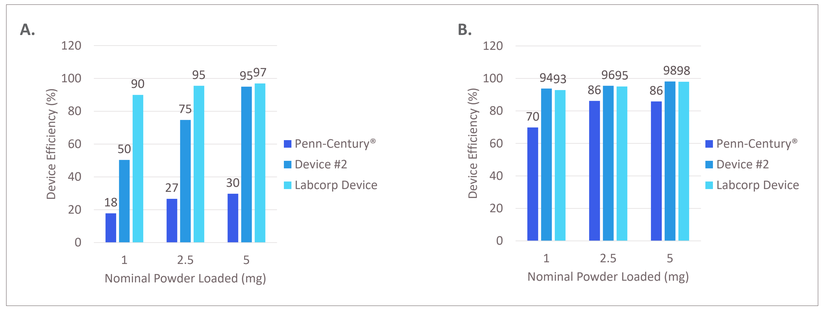


Figure 1. Comparison of device efficiency at different syringe pressures. A) Device efficiency using 1 mL syringe pressure. B) Device efficiency using 2 mL syringe pressure.

	Penn-Century®			Device #2			Labcorp Device		
Mean powder loading (mg)	1.16	2.63	5.10	1.29	3.08	5.61	1.16	2.90	5.74
SD	0.17	0.36	0.47	0.26	1.16	0.66	0.19	0.18	1.07
% CV	15%	14%	9%	20%	38%	12%	16%	6%	19%
n	10	5	5	10	5	6	10	10	10

Table 1. Device efficiencies at 1 mL syringe pressure.

	Penn-Century®			Device #2			Labcorp Device		
Mean powder loading (mg)	1.18	2.44	5.33	1.37	2.68	5.63	1.14	3.21	5.50
SD	0.11	0.47	0.61	0.59	0.12	0.9	0.19	0.32	0.59
% CV	9%	19%	11%	43%	4%	16%	17%	10%	11%
n	10	5	5	10	6	6	10	10	10

Table 2. Device efficiencies at 2 mL syringe pressure.

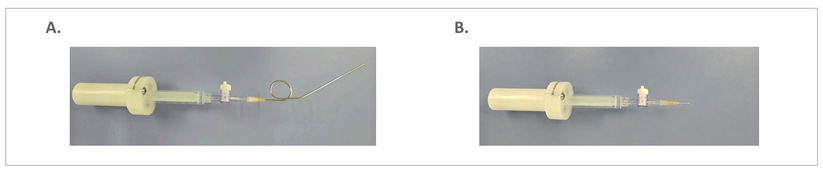


Figure 2. Pictures of the Labcorp devices used for testing and dose administration in rat. A) Device used to generate data in Figure 1, Table 1, and Table 2. B) Device used to generate data in Table 3 and Figure 3.

Nominal dose (mg)	Pressure (mL of air)	Efficiency/accountability (%)
Prestudy qualification, 1 mg	2	83% (85, 77, 86, 12*, 35*)
0.5	2	81% (64, 122, 58)
1	2	80% (81, 8*, 79)
5	2	91%
5	1	41% (54, 21, 47)

Table 3. Phase 2 device efficiency and dose accountability with LH200 (prestudy) or the proprietary trypan blue dry powder blend using the Labcorp device. Means (individual animal data) are shown. *The device misfired and is not included in the mean; based on prestudy qualification results, the stopcock was tested for stickiness prior to animal dosing to prevent this from recurring.

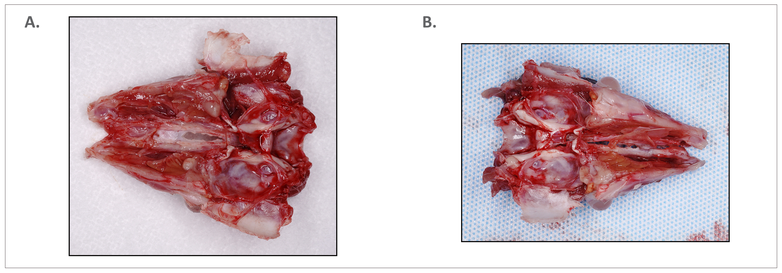


Figure 3. Photographs of absence of trypan blue staining of the nasal cavity. A) Nasal cavity at 5 min postdose at 5 mg using 2 mL pressure (R0201). B) Nasal cavity when 5 mg (1 mL pressure) was delivered postmortem (R0301).

Results

- At 1 mL of pressurized air, the Labcorp device demonstrated the highest delivery efficiency across all tested powder loadings (95%), compared with Device #2 (74%) and Penn-Century® Dry Powder Insufflator (25%).
- At 2 mL of pressurized air, the Device #2 and Labcorp devices demonstrated comparable mean delivery efficiencies (96% and 95%, respectively), across the tested powder loadings. In contrast, the Penn-Century® device exhibited a lower mean delivery efficiency (81%).
- Rats tolerated the dosing procedure with no clinical observations. There was visual expulsion of the powder from the nostril at 5 mg (at both 1 mL and 2 mL) but not 0.5 or 1 mg.
- The proprietary trypan blue blend (up to 5 mg) was rapidly absorbed by the nasal mucosa and could not be visualized following conscious administration in rat. No dye was observed in the larynx or trachea.

Conclusions

- At two settings (1 mL and 2 mL pressurized air), the Labcorp device and Device #2 demonstrated higher delivery efficiency than the Penn-Century® Dry Powder Insufflator across nominal powder loadings of 1 to 5 mg.
- Device #2 showed notably lower output efficiency at 1 mL syringe pressure compared with the Labcorp device; however, at 2 mL syringe pressure, output efficiencies were comparable across all powder loadings up to 13 mg (data at 10 and 13 mg not shown since inapplicable to rodents).
- The proprietary trypan blue powder was successfully delivered with 83% efficiency and rapidly absorbed by the nasal mucosa in rat.
- Further refinements to the Labcorp device and procedure are being made to minimize expulsion during dose administration.

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