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AMORPHOUS POWDER FOR NASAL DELIVERY: INTRANASAL NALOXONE POWDER FOR TREATING OPIOD OVERDOSE

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PURPOSE

The nasal route of administration has several benefits for systemic drug delivery, including non-invasive dosing, rapid absorption and no first-pass metabolism. However, liquid nasal sprays have some limitations, e.g:

- Poor chemical stability in aqueous solutions
- Requires good solubility of the API
- Suboptimal and variable absorption due to swallowing

We explored the possibility to develop a rapidly dissolving, spray-dried, nasal powder formulation to overcome limitations of liquid formulations while maintaining advantages of the nasal route of administration.

OBJECTIVE(S)

- Development and characterization of spray-dried nasal powder formulations of naloxone compared with a commercially available liquid nasal spray.
- Comparison of pharmacokinetic properties of novel powder formulations to the liquid nasal spray

METHOD(S)

Four compositions A, B, C, and D (**Table 1**) all presented as an amorphous solid dispersion (ASD) of naloxone in combination with various ingredients, were spray-dried. The powders were characterized by laser diffraction, XRPD, HPLC and the stability were followed for 12 months at long term storage (25°C/60%RH) and 6 months at accelerated storage conditions (40°C/75%RH)

Table 1: Compositions of formulation A, B, C and D (per dosage unit)

Component	A (mg)	B (mg)	C (mg)	D (mg)
Naloxone HCl	4.00	4.00	4.00	8.00
Lactose	17.72	17.50	15.56	13.54
Sucrose laurate	-	0.23	-	-
PVP	-	-	2.27	-
Residual water	0.91	0.91	0.91	0.90

Pharmacokinetics of the novel powder formulations, administered with a single dose Aptar UDS powder device, were compared with a commercial liquid nasal spray (Narcan®) in a 5-period cross-over, comparative bioavailability study in healthy volunteers (N=20).

RESULT(S)

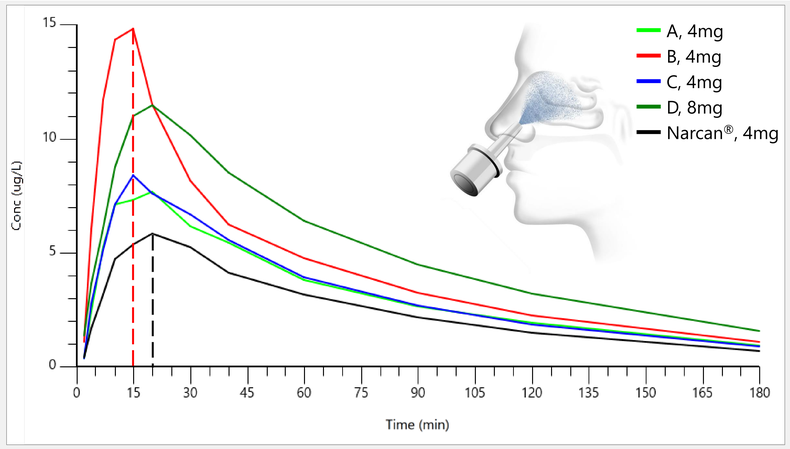


Figure 1: Naloxone plasma concentration vs time

Comparative bioavailability of powder formulations to liquid nasal spray

- Nasal powders showed *significantly* higher plasma concentrations of naloxone, sustained duration of elevated plasma concentrations and more rapid absorption when compared to Narcan® (**Fig 1**)
- Formulation B (with sucrose laurate) displayed the highest bioavailability and the most rapid absorption, with about 84% higher total and 175% higher peak exposure compared to Narcan® (**Table 3**)
- All formulations were well tolerated

Powder characterization and stability

- The spray drying process yielded free flowing powders with a narrow particle size distribution suitable for nasal administration (**Table 2**).
- All four compositions were chemically stable at long term and accelerated conditions with related substances <0.3% at the end of stability studies.
- All four formulations were physically stable under both long-term and accelerated conditions and maintained an amorphous state at the end of stability studies.

Table 2: Physicochemical and stability data. Total related substances (RS) shown.

Composition	D_v10 (µm)	D_v90 (µm)	Fines %, <5µm	XRPD	12M 25/60 (%RS)	6M 40/75 (%RS)
A	15	44	0	amorphous	0.11	0.10
B	15	55	0	amorphous	0.19	0.19
C	17	57	0	amorphous	0.14	0.28
D	17	58	0	amorphous	0.08	0.08

Table 3: Pharmacokinetic parameters. Average values (n=20) with Geo.CV%

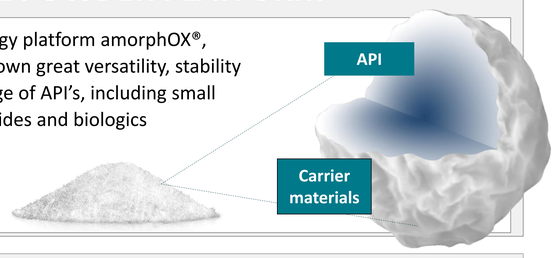
PK parameters	A	B	C	D	Narcan®
AUCt (h*ng/ml)	10.7 (24.8)	14.7 (18.5)	10.9 (27.6)	16.9 (35.9)	7.99 (44.1)
AUCinf (h*ng/ml)	10.8 (25.3)	14.8 (18.6)	11.1 (28.7)	17.1 (35.9)	8.06 (44.6)
Cmax (ng/ml)	8.43 (44.2)	15.6 (46.5)	8.94 (35.4)	12.1 (45.4)	5.67 (55.8)
Tmax (min)	20 (6.5, 40)	15 (7.30)	15 (7, 30)	20 (10, 40)	20 (7, 30)
T½ (min)	74.6 (30.0)	76.1 (22.8)	88.3 (43.6)	85.5 (20.0)	84.2 (23.2)

CONCLUSION(S)

- Amorphous spray-dried naloxone nasal powders with appropriate PSD for nasal administration, with limited risk of lung exposure, were successfully formulated
- All powders displayed excellent chemical and physical stability even after 6M at accelerated conditions (40°C/75% RH)
- Naloxone nasal powders displayed improved systemic absorption with decreased variability compared to a commercial available naloxone liquid nasal spray

AMORPHOX® – NASAL POWDER PLATFORM

The enabling powder-based technology platform amorphOX®, developed for nasal naloxone, has shown great versatility, stability and applicability for an extended range of API's, including small molecule epinephrine as well as peptides and biologics



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