Spray Dried Amorphous Epinephrine Nasal Powder for the Acute Treatment of Anaphylaxis

Jonas Sävmarker, PhD; Jonas Rudén, PhD; David Öhlund, MSc; Martin Jönsson, MSc; and Robert Rönn, PhD

Orexo AB, Box 303, 751 05, Uppsala, Sweden

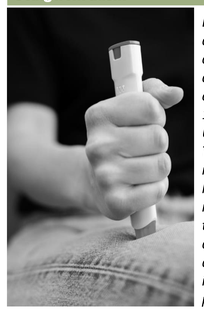
INTRODUCTION

Considering that most epinephrine products are designed for acute use, a prolonged shelf-life and enhanced overall stability is desirable. This is critical, especially considering the significant time gap that may exist between when a product is acquired by the patient or medical staff and when it is used. Existing products, such as EpiPen®, have narrow temperature storage conditions (20° to 25°C) and an expiration date of no more than two years [1]. Moreover, patients frequently subject these products to conditions beyond the recommended storage parameters, such as temperature fluctuations ranging from 15°C to 30°C, which can further compromise their integrity. Patients also require sufficient training to effectively administer the accurate dose at the right site using the injection pen. Many patients perceive this invasive therapy, which involves needle insertion, as unpleasant [2-3].

Intranasal administration is an alternative route of drug delivery that may offer several advantages, including that the peripheral blood vessels in the nasal cavity can facilitate swift absorption of the drug. In addition, some non-invasive devices now available, allow the patient or caregiver to deliver a dose of drug easily without the need for an inspiratory airflow.

We have developed a rapidly dissolving, spray-dried, nasal powder formulation that addresses the stability challenges of liquid forms while preserving the advantages of nasal administration. This was done by incorporating epinephrine into our novel drug delivery platform, amorphOX® (Orexo, Sweden), which consist of a powder composed of amorphous particles optimized for nasal deposition.

Going from this…



Epinephrine is light sensitive and should be stored in the carrier tube provided. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Do not refrigerate. Protect from light. Before using, check to make sure the solution in the auto-injector is not discolored. Replace the auto-injector if the solution is discolored or contains a precipitate.[1]

… to this

METHODS

Four nasal epinephrine powder formulations (OX640-1, 2, 3 and 4, Table 1.) containing epinephrine bitartrate (corresponding to a 1 mg dose of epinephrine base), a trehalose and maltodextrin combination (carrier material) and sucrose laurate (permeation aid) were manufactured using a laboratory spray dryer (PROCEPT, Belgium). The obtained powders were then filled Unidose (UDS) powder dose spray system devices (Aptar Pharma, France) to a fill weight of 25 mg and placed in protective storage tubes including desiccant. The products were analyzed for particle size using laser diffraction (Mastersizer 3000, Malvern) and aerodynamic characteristics using the Next Generation Impactor (NGI, aPSD), glass transition temperature (Tg) using Differential scanning Calorimetry (DSC and crystallinity using x-ray powder diffraction (XRPD). Stability was compared to the commercially available EpiPen and monitored for 12 months at 40°C and 75% relative humidity (40°C/75% RH), corresponding to accelerated conditions[4] and analyzed using high-performance liquid chromatography.

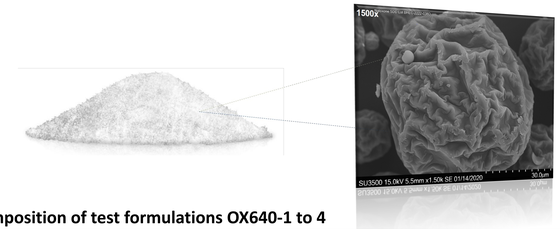


Table 1: Composition of test formulations OX640-1 to 4

Component	OX640-1 (w/w%)	OX640-2 (w/w%)	OX640-3 (w/w%)	OX640-4 (w/w%)
Epinephrine bitartrate (corresponding to 1 mg epinephrine base)	7.28	7.28	7.28	7.28
Trehalose (carrier material, chemical stabilizer)	20	40	56	75
Maltodextrin (carrier material, physical stabilizer)	65.72	45.72	29.72	10.72
Sucrose laurate (permeation aid)	3	3	3	3
Residual water	4	4	4	4

RESULTS AND DISCUSSION

The spray drying process yielded free flowing powders with a narrow particle size distribution and a low degree of fine particles fractions (FPF) and were thus suitable for effective nasal deposition with minimal risk for deposition in the lungs.[5] The lowest measurable Tg at 11% R was similar for all compositions. However, measurements at higher humidity (33% RH) showed the effect of reducing the amount of maltodextrin. The physical characteristics of the powders did not change after storage for 12 months at 40°C and 75% relative humidity (RH), see Table 2.

Table 2: Powder characteristics and physical stability at release (T0) and after 12 months (T12) at 40°C/75% RH

Composition	D_{v10},D_{v50},D_{v90} T0	D_{v10},D_{v50},D_{v90} T12	FPF <5µm T0(%)	FPF <5µm T12(%)	XRPD T0 and T12	Tg (°C) 11%, 33% RH
OX640-1	14, 30, 55	14, 29, 55	0.4	0.4	amorphous	66, 58
OX640-2	14, 30, 56	14, 30, 55	0.4	0.3	amorphous	65, 54
OX640-3	15, 31, 57	15, 31, 56	0.2	0.2	amorphous	65, 51
OX640-4	15, 30, 54	15, 30, 53	0.2	0.1	amorphous	64, 43

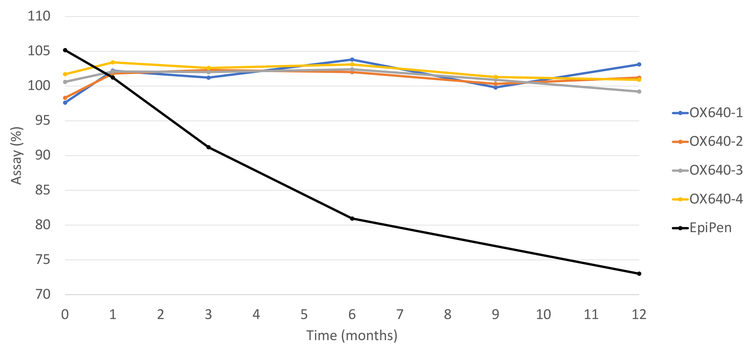


Figure 1: Assay expressed as % nominal dose of epinephrine in OX640-1 to 4 compared to EpiPen stored at 40°C/75% RH

Measuring assay, Figure 1, full dose of epinephrine remained in the powders throughout the study whereas only about 70 % was left in EpiPen.

The same trend was confirmed when analyzing related substance (Figure 2), with non of the powders having a total degradation above 1% and EpiPen measuring around 30% total degradation despite being stabilized with both chelating agents and anti oxidants. In addition, the enantiomeric proportions (Figure 3) did not change for the powders, but a clear racemization (24%) was observed for the liquid product. As R-epinephrine is the only active enantiomer the actual potency of EpiPen at the end of the study was only about 55% whereas the powders retained full potency.

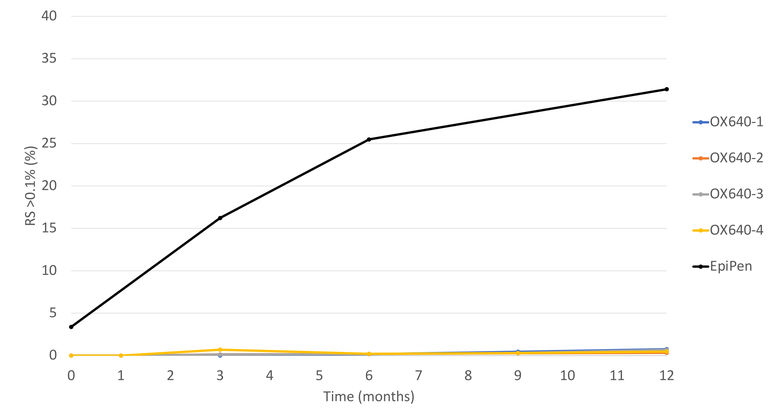


Figure 2: Related substance expressed as total amount (%) of degradation product >0.1% related to epinephrine, with powders compared to EpiPen stored at 40°C/75% RH

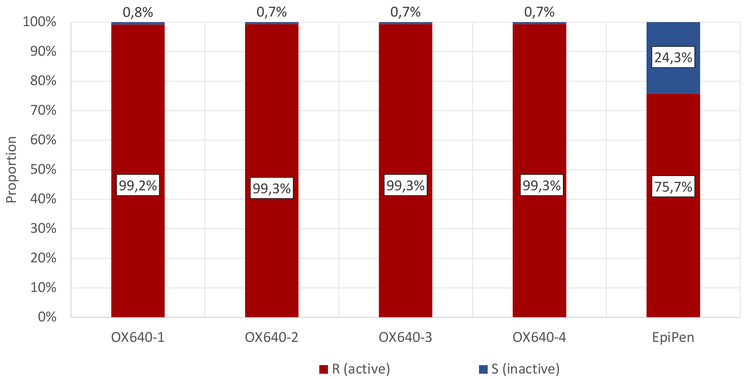


Figure 3: Enantiomeric proportions of OX640-1 to 4 compared to EpiPen stored at 40°C/75% RH

CONCLUSION

- ✓The spray drying process resulted in an amorphous powder suitable for nasal delivery
- ✓Compared to the commercially available EpiPen®, all formulations exhibited superior stability under accelerated storage conditions
- ✓These findings support the feasibility and further development of this nasal powder as a remarkably stable, non-invasive, preservative-free alternative therapy for anaphylaxis
- ✓This work also demonstrates the potential of our powder-based amorphOX® technology as a platform even for extremely unstable APIs
- ✓These formulations have been studied in humans, showing comparable PK and PD response to EpiPen. This data was presented at the AAAAI annual meeting 2024, https://doi.org/10.1016/j.jaci.2023.11.877

amorphOX®

Jonas Sävmarker, PhD
Senior Principial Scientist
Pharmaceutical Development
jonas.savmarker@orexo.com
+46 (0) 70 537 75 77

Robert Rönn, PhD
Senior Vice President
Head of R&D
robert.ronn@orexo.com
+46 (0) 18 780 88 00

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Headquarter Sweden, Orexo AB, P.O. Box 303, 751 05 Uppsala, Sweden,
E-mail: info@orexo.com, Phone: +46 (0)18 780 88 00
Subsidiary US, Orexo US Inc. 150 Headquarters Plaza East Tower Morristown,
New Jersey 07960 United States
E-mail: info-us@orexo.com, Phone: +1 (0)855 982 7658