INVESTIGATION OF PHYSICO-CHEMICAL STABILITY OF A PURE INSULIN SPRAY-DRIED POWDER FOR INHALATION SEMI-AUTOMATICALLY FILLED IN QUALI-V®-I CAPSULES

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INTRODUCTION

The Department of Food and Drug Science of the University of Parma patented a process to produce a pure insulin pulmonary powder by spray drying [1]. This powder (Ins_SD) showed remarkable high respirability (FPF: 83.6%) and, stored in glass vials, was stable at room temperature over a period of five months [2].

In this study, the chemical stability and respirability of this insulin spray-dried powder loaded in capsules and packed in blister was investigated. In particular, the powder was semi-automatically filled in HPMC Quali-V®-I capsules using a precise micro-dosing system and they were blistered and stored at different conditions. Capsules were analyzed for respirability in a commercial DPI. Degradation products were analyzed at 0, 30, 90 and 180 days after powder production and capsule filling. Finally, the in vitro respirability of Ins_SD was compared to the one of the commercial product Afrezza®.

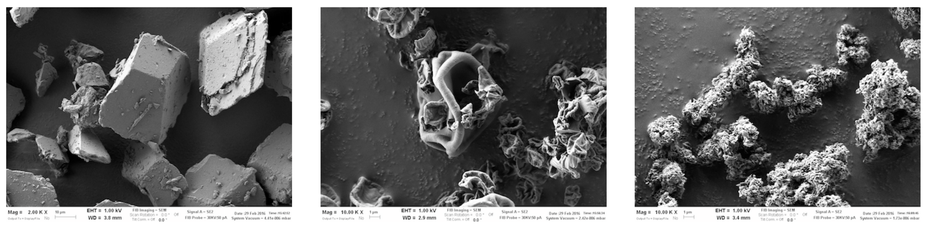

Figure 1 *SEM images of Insulin raw material, Ins_SD, and Afrezza® (10K x, from left to right)*

METHODS

- A human recombinant insulin powder for inhalation (Ins_SD) was prepared by spray drying using a mini Spray Dryer Büchi B-290 (Büchi®, CH), as previously described [1].
- Capsules Quali-V®-I size 3 (Qualicaps Europe, ES) were semi-automatically filled with 2 mg of INS_SD powder using a Omnidose TT vacuum drum filler system (Harro Höfliger GmbH, DE) and packed in PVC/PVDC 260 mm x 250 µm, 60 g transparent blister (Research Pharmaceutical Co., Ltd., Colombia) sealed with a standard 20 µm aluminum foil (Amcor Flexibles Soliera, Srl, IT).
- The *in vitro* respirability of Ins_SD was assessed using the Next Generation Impactor (NGI) (Copley Scientific, UK) inserting the capsule in a RS01® medium resistance inhaler (Plastiape, IT).
- The stability study was conducted storing the capsules in blisters at room temperature (25°C-60% RH) and at refrigerate conditions (4°C) up to 6 months. Degradation products as related proteins (A21 desamido insulin and other related proteins, ORP) and high molecular weight proteins (HMWP) were analyzed.

RESULTS

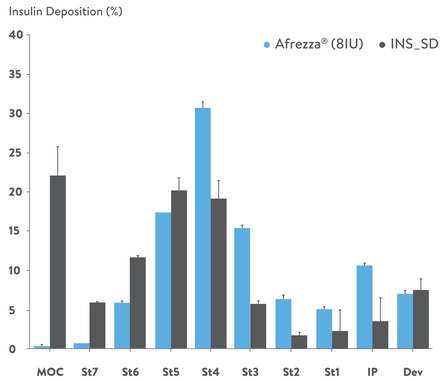

Figure 2 *Insulin stage deposition (%) of Afrezza® and Ins_SD in the NGI (n=3, ± StDev)*

	Metered Dose* (mg)	Emitted Dose (mg)	MMAD (µm)	FPD (mg)	FPF (%)
Afrezza®	0.64 ± 0.01	0.60 ± 0.01	3.19 ± 0.03	0.41 ± 0.01	68.3 ± 0.6
Ins_SD	1.62 ± 0.08	1.50 ± 0.05	0.89 ± 0.09	1.37 ± 0.04	91.5 ± 5.9
Stability at 25°C – 60% RH					
Month 1	1.86 ± 0.20	1.57 ± 0.01	0.85 ± 0.03	1.46 ± 0.02	92.7 ± 0.2
Month 3	1.75 ± 0.20	1.53 ± 0.05	0.86 ± 0.05	1.40 ± 0.06	91.6 ± 2.0
Month 6	1.64 ± 0.03	1.59 ± 0.04	0.89 ± 0.03	1.44 ± 0.04	90.3 ± 1.3

**Total amount of insulin collected in the device and impactor, quantified by HPLC*

Table 1 *Aerodynamic parameters at time zero of Ins_SD (powder loaded 2 mg corresponding to insulin 1.8 mg) and Afrezza® (powder loaded: 3.5 mg corresponding to insulin 0.7 mg) and Ins_SD stored at 25°C-60%RH*

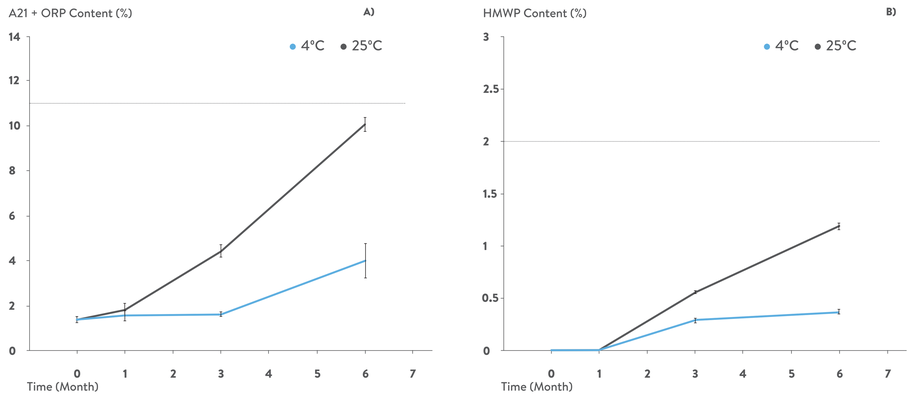

Figure 3 *Degradation products of insulin spray-dried powders INS_SD stored at room temperature (25 °C, 60% RH) for six months: (A) A21 desamido insulin + other related proteins (ORP); (B) high molecular weight protein (HMWP) degradation products; (mean ± standard deviation, n = 3), USP limits are represented by the dotted lines*

- The aerodynamic performance of both formulations Afrezza® and Ins_SD showed good emission from the device (> 90%) and high respirability, with FPF values of 68 and 92%, respectively.
- The semi-automatic filling process did not affect the aerosolization performance of Ins_SD.
- The percentage of all Ins_SD decomposition products (A21, ORP and HMWP) was found to be below the USP limits (dotted line) in both storage conditions for the 6 months of the investigation.

CONCLUSIONS

A pure insulin pulmonary powder, produced by spray drying from an acid aqueous solution of the peptide, presented high respirability and favourable flowability properties during the semi-automatic capsule filling process. The stability data have shown that Qualicaps® Quali-V®-I capsules, together with the PVC-PVDC packaging material, can provide long-term stability and mantain good aerodynamic performance, opening the possibility of a therapy less dependent on the cold storage of drug product.

REFERENCES

[1] Cagnani, S., Colombo, P., Ventura, P., 2004. Insulin highly respirable microparticles. Assignee: University of Parma; US Patent Number: 7625865 B2.
[2] Balducci AG, Cagnani S, Sonvico F, Rossi A, Barata P, Colombo G, Colombo P, Buttini F: Pure Insulin Highly Respirable Powders for Inhalation. Eur. J. Pharm. Sci. 2014, 51, 110-117.

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