Investigation of Powder Blend Uniformity and Deposition in a Nasal Cast Using a Unit Dose Nasal Device

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INTRODUCTION

There is a growing interest in delivery of powders to the nasal cavity for applications such as vaccines, pain management, and central nervous system (CNS) disorders, e.g., Parkinson's, Alzheimer's, etc., using the nose to brain route [1, 2]. This study investigated the effect of different powder blends of sumatriptan (a highly selective ligand for 5-HT1B/1D serotonin receptors, used as an anti-migraine drug) and their deposition in a nasal cast, using a proprietary unit dose nasal device.

MATERIALS AND METHODS

Sumatriptan succinate (Dr Reddy's Laboratories, Hyderabad, India) was micronized using an MC One Jet Mill (DEC Group, Balerna, Switzerland) at a grind pressure of 4 bar and Venturi pressure of 7 bar. Powder blends of sumatriptan were manufactured with lactose as carrier using Respitose ML001 (DFE Pharma, Vehgel, Netherlands) and Lactohale 200 (DFE Pharma, Borculo, Netherlands). These blends were prepared by low shear Turbula blending for 20 minutes at 22 RPM (Willy A. Bachofen AG, Muttenz, Switzerland). Two additional blends were manufactured, which incorporated 1% w/w magnesium stearate (MgSt, sourced from Peter Greven GmbH, Bad Münstereifel, Germany), with ML001 and LH200. These ternary mixtures were prepared by high shear processing of MgSt and lactose, using a GEA Microgral blender at 500 RPM for five minutes (GEA, Collette, Belgium), followed by low shear Turbula blending with the active pharmaceutical ingredient (API). All formulation blends were prepared to obtain 5 mg of sumatriptan succinate in 12.5 mg of powder. The blend content uniformity (BCU) was assessed after seven days using a validated HPLC method. Powder permeability measurements were performed by measuring the pressure drop across the powder blends at an applied load of 15 kPa using a FT4 Powder Rheometer (Freeman Technologies, Malvern UK).

The nasal cast used has been validated *in vivo* and *in vitro* [3] (Figure 1) and is separated into the following anatomical regions: nose, nasal valve, frontal sinus, floor of cavity, turbinates, maxillary sinus, olfactory region, sphenoids, and rhinopharynx.

Prior to testing, devices (unit dose nasal device, Aptar Pharma, Le Vaudreuil, France) (Figure 1) were filled either with 5 mg of pure micronized sumatriptan or with 12.5 mg of blends, so that 5 mg of sumatriptan was delivered in each case. For the dosing in the nasal cast, the following parameters were used: no airflow, device angle of delivery ~60° (from horizontal), one dose in each nostril. Samples from the nasal cast were collected and analyzed using a suitably validated HPLC method.

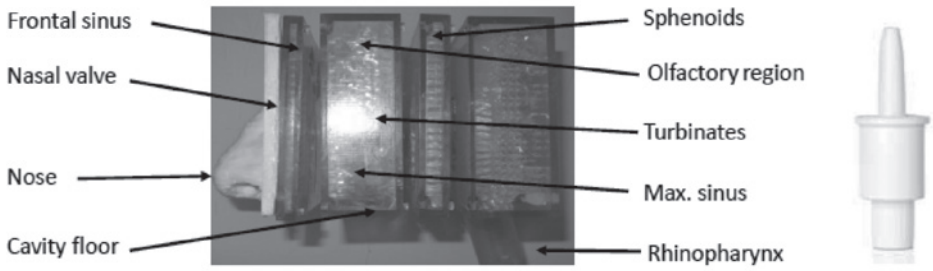

Figure 1. Left: nasal cast model with various anatomical regions – nose, nasal valve, frontal sinus, floor of cavity, turbinates, maxillary sinus, olfactory region, sphenoids and rhinopharynx. Right: Aptar Pharma unit dose powder device, UDS.

RESULTS AND DISCUSSION

The particle size of the sumatriptan before and after micronization is presented in Table 1, and shows the micronized sumatriptan to have a D_{50} of approximately 10 μm. The particle size was targeted to be larger than 10 μm to avoid lung deposition and less than 80 μm, as most commercial products are in this range [4]. Data suggest that the micronization process resulted in significant particle size reduction. Blend content uniformity data and powder permeability measurements at 15 kPa of the blends are shown in Table 2. All blends had an acceptable BCU (<5%), which suggested the blending processes were successful in preparing homogenous binary and ternary blends of the micronized API. Powder permeability measurements can be used to understand bulk powder cohesive properties, since materials that produce the largest pressure drop upon a defined compression are indicative of cohesive materials. Powder permeability measurement suggested the following rank order of bulk powder cohesion (greatest to least):

ML001>ML001/MgSt>LH200>LH200/MgSt

These data suggest that the ML001 formulations were more cohesive than the other batches and LH200/MgSt was the least cohesive. These data show that the inclusion of MgSt resulted in a decrease in the cohesive properties of LH200 and ML001.

Deposition in the nasal cast was studied using unit dose powder devices filled with sumatriptan or with sumatriptan blends with LH200, LH200/MgSt, ML001 or ML001/MgSt. Typically, conventional nasal sprays deposit a large fraction of the API delivered dose in the nasal valve or the nasal cavity floor [5]. Irrespective of the physical properties of the powder blends,

results suggested that measurable quantities of the powders were deposited in the regions of interest, such as the turbinates and the olfactory region (Figure 2). High quantities were also measured in the nose and the nasal valve, which can be explained since the nasal valve is a very restricted anatomical region. Furthermore, there was no significant difference between the deposition of API aerosolized from the different blends in the olfactory region of the nasal cast (ANOVA, confidence level 5%, p-value of 0.062).

Table 1.

Particle size distribution of as received and micronized sumatriptan (n = 3, ± StDev).

	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
As received API	4.69 (0.18)	45.76 (0.12)	143.92 (0.23)
Micronized API	1.87 (0.05)	10.25 (0.08)	33.96 (0.58)

Table 2.

Blend content uniformity and powder permeability measurements at 15 kPa of the different powder blends (n = 10 for BCU, n = 3 for pressure drop, ± StDev).

	BCU - % RSD	Pressure Drop – 15kPa
LH200	3.05	1.90 (0.04)
LH200/MgSt	3.65	0.74 (0.05)
ML001	4.89	3.05 (0.08)
ML001/MgSt	4.72	2.06 (0.05)

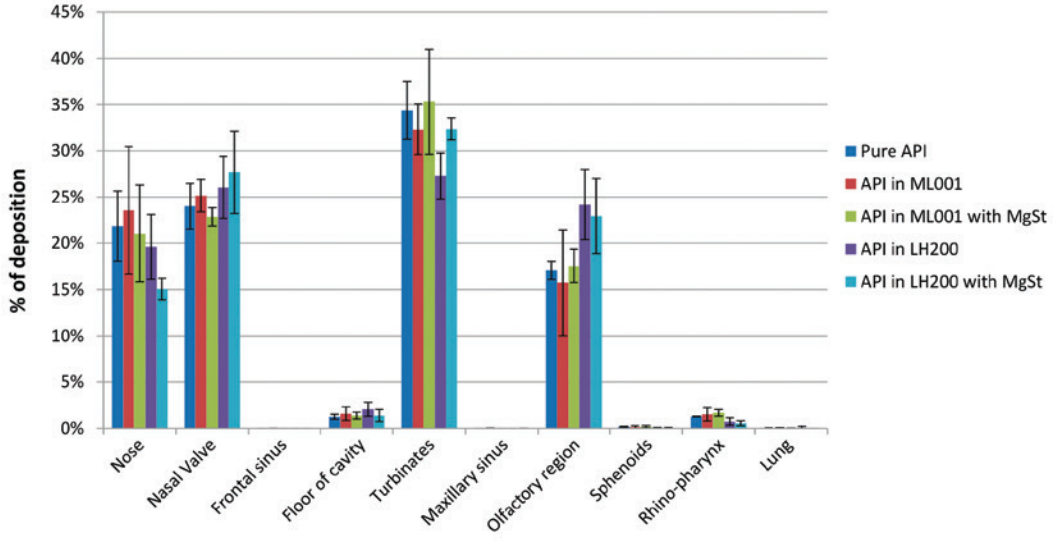

Figure 2. **Deposition of sumatriptan succinate (API) using a unit dose nasal device with different powder blends, (n = 3, ± StDev).**

CONCLUSIONS

Blends of sumatriptan powders were prepared with different flow properties, with ML001 being the most cohesive and LH200/MgSt being the least cohesive. Powder blends were successfully delivered using a unit dose nasal device to regions of interest in a nasal cast, such as the olfactory region and turbinates. Powder formulations offer many advantages such as solid-state stability, no cold chain issues, delivery of insoluble compounds, and no need for preservatives. Unit dose nasal devices in combination with powder formulations offer the opportunity to deliver drugs to the nasal cavity in order to treat many disorders and hold future promise for unmet medical needs in diseases difficult to therapeutically target.

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