

Formulation, Characterization and Optimization of Dry Powder for Inhalation using combined micronized Levo-Dropropizine and Curcumin

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Summary

Aim of the current work was to optimize process and composition of previously studied Dry Powder for Inhalation (DPI) using anti-tussive Levo-Dropropizine as Active Pharmaceutical Ingredient (API). The previous work based on Design of Experiments (DoE), was performed to select a carrier-based formulation of Levo-Dropropizine, studying different grade of Lactose, different concentration of Magnesium Stearate, Drug Load (DL) and blending procedure. However, micronized Levo-Dropropizine with selected formulation didn't give satisfactory inhalation performance. During the present work co-micronization with Magnesium Stearate and replacement of fine carrier with micronized Curcumin demonstrate to improve API inhalation performance. Surprisingly, less agglomeration between particles by co-micronization technique, shape similarity of micronized Curcumin with fine Lactose and usage of it as carrier into the formulation, improve aerosolization of Levo-dropropizine. Several formulations were produced, studying different combination and composition to better understand the impact of each component. Micronized and co-micronized APIs were characterized by High Performance Liquid Chromatography (HPLC), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM) and Laser Light Scattering (LLS). Blends and capsules were manufactured and characterized by Blend Homogeneity (BH), FT4 Rheometer, Next Generation Impactor (NGI) and Dosage Unit Sampling Apparatus (DUSA). Promising results were obtained with reduced agglomeration behaviour followed by increase of ED, FPF and FPD with reduced retention of material inside capsules, device and mouthpiece.

Key Message

Co-micronization process of Levo-Dropropizine and Magnesium Stearate reduced the micronized API agglomeration. Furthermore, thanks to shape similarity between micronized Curcumin and fine Lactose Monohydrate, Curcumin was used as carrier in DPI formulation of Levo-Dropropizine. The combination of these two approaches, permitted a deeper increase of inhalable particles of Levo-Dropropizine.

Introduction

With an increase in general understanding of physiology and illness of the lung, pulmonary drug delivery is becoming an alternative to treat local and systemic diseases. A predominant symptom in Idiopathic Pulmonary Fibrosis (IPF) is a non-productive cough that adversely affects quality of life [1]. Several treatments for cough exist on the market but, these have poor tolerability [2]. This issue for most antitussives on the market is related to central nervous system side effects. Additionally, these molecules are approved for use as syrup, oral drop and tablet forms. Thus, there is an urgent need of an alternative inhalable therapy. Levo-Dropropizine, a peripherally acting antitussive drug, has been selected for the present work thanks to good tolerability and safety profile compared to other antitussive agents that act centrally to suppress cough [3]. Clinical evidence indicates efficacy of Levo-Dropropizine to be like of centrally acting agents [4] and is also used for paediatric cough treatment [5]. In addition, Curcumin has been described as having antioxidant, anti-inflammatory, and anti-carcinogenic properties and has already been used to treat cancer, arthritis, digestive and liver abnormalities and respiratory infections [7,8]. Aim of the present work is to evaluate the performance of Levo-Dropropizine as a dry powder for inhalation (DPI) in combination with Curcumin. Curcumin was used as fine carrier into the Lactose carrier-based formulation and different co-micronization of APIs were performed to better understand the feasibility and improvement of inhalation performance of Levo-Dropropizine. The initial composition was selected using a Design of Experiments approach by Definitive Screening design, already performed.

Materials and Methods

Materials

Levo-Dropropizine and Curcumin were purchased respectively by ClaroChem (Dublin, Ireland) and CoreyChem (China). Lactose Monohydrate LH230 and SV003 were purchased by DFE pharma (Goch, Germany), Magnesium Stearate from Peter Greven (Bad Muenstereifel, Germany) and HPMC DPI capsules from Capsugel (Lonza, Switzerland).

Methods

Levo-Dropropizine and Curcumin, alone and in combination with Magnesium Stearate, were micronized using a Labo Jet-mill and analyzed by Laser Light Scattering, XRPD and DSC. Blends with micronized APIs were prepared by Procept High Shear Mixer equipped with 0.25 L bowl (50 g batch size). 250, 500 and 710 μm screens were used to sieve APIs, materials and mixtures. DPI Capsules were filled manually with 20 mg/cps corresponding to 3.0 mg dose each APIs. Manufactured blends were characterized using a FT4 powder rheometer, HPLC for blend homogeneity with evaluation of RSD %, LLS for PSD, NGI for aerosol particle size distribution (APSD) and DUSA dose delivery. One dose for each batch was tested using a Plastiap RS01 MOD7 HR device at 60 L/min using the NGI and DUSA; the powder collected was quantified by HPLC analysis. For the FT4 powder rheometer, the following measurements were conducted: Basic Flow Index (BFI), Flow Rate Index (FRI), Aeration test - Aeration Energy (AE) and Aeration ratio at minimum fluidization velocity (AR_m), and Shear Cell test studying the Flow Function (FF). All the analysis were performed in triplicates.

Results and discussion

Levo-Dropropizine and Curcumin, both micronized and co-micronized with Magnesium Stearate were prepared and fully characterized by HPLC, DSC and XRPD to understand the feasibility and the impact of high energy process as micronization. No differences were observed in terms of chemical and physical properties of both APIs. SEM pictures and PSD on micronized APIs were also performed, to compare the particles dimension and shape between the two and between different Lactose Monohydrate grade, normally used into DPI carrier-based formulation (as shown in Figure 1 and Table 2). Levo-Dropropizine micronized tends to agglomerate as shown in SEM picture (A, Figure 1) while Curcumin and fine Lactose Monohydrate present both rectangular shapes (B, C and D, Figure 1). Furthermore, co-micronization process allows to reduce the Levo-Dropropizine PSD below 5 μm .

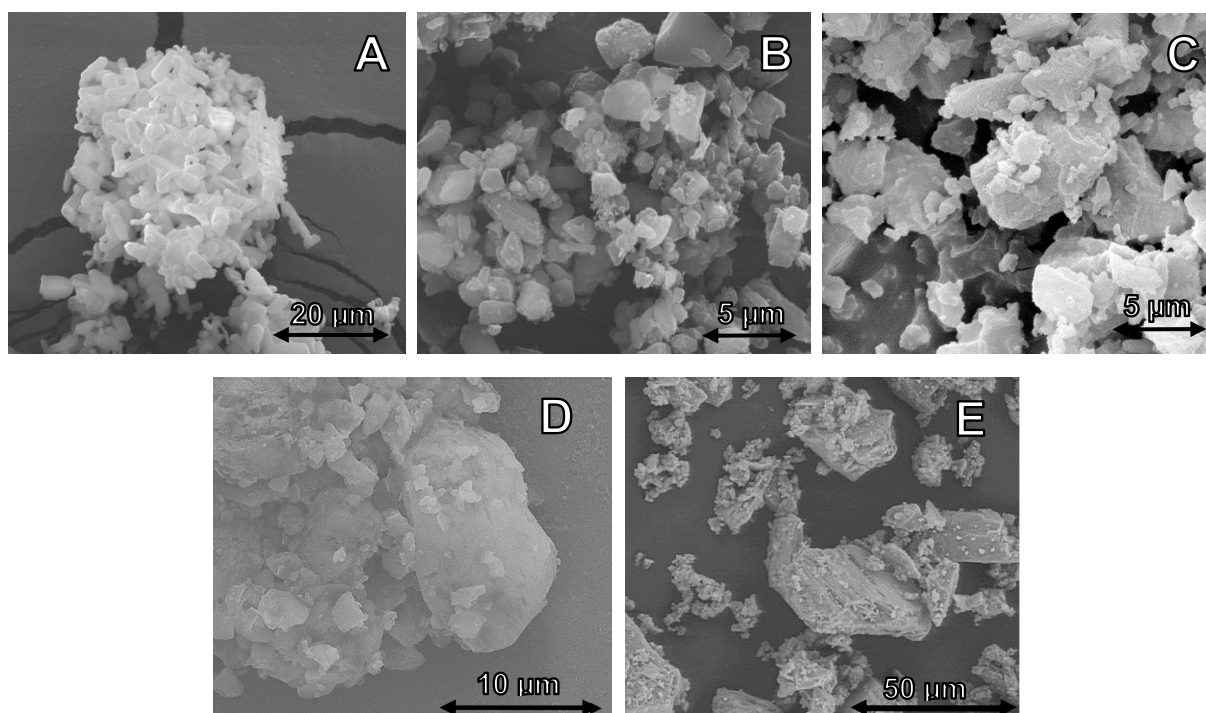


Figure 1 Micronized Levo-Dropropizine A, SEM magnification 4000x, micronized Curcumin B, SEM magnification 13000x and Lactose Monohydrate LH300 C, SEM magnification 14000x, Lactose Monohydrate LH230 D, SEM magnification 10000x, Lactose Monohydrate SV003 E, SEM magnification 2000x as reference

Table 1 PSD obtained after micronization and co-micronization of Levo-Dropropizine and Curcumin

Material	Levo-Dropropizine micronized	Curcumin micronized	Levo-Dropropizine and Mg St co-micronized	Levo-Dropropizine, Curcumin and Mg St co-micronized
D10 (µm)*	1.2 ± 0.05	0.4 ± 0.02	0.5 ± 0.07	0.4 ± 0.05
D50 (µm)*	3.7 ± 0.20	1.9 ± 0.10	2.1 ± 0.07	1.7 ± 0.02
D90 (µm)*	11.4 ± 0.40	4.5 ± 0.20	6.4 ± 0.40	4.1 ± 0.10

*Average ± Standard Deviation

Four blends and their corresponding capsules were manufactured and fully characterized. In order to better understand the impact of each components, different compositions were studied: one with co-micronized Levo-Dropropizine and Magnesium Stearate with Lactose LH230 as carrier (as per DoE formulation), one with both micronized APIs using Curcumin as carrier, one with co-micronized Levo-Dropropizine and Magnesium Stearate and micronized Curcumin as carrier and one with co-micronized APIs with Magnesium Stearate. Compositions of each blend are shown in Table 2. The composition selected by previous DoE was added as reference.

Table 2 Formulation compositions with micronized and co-micronized APIs.

Material	Initial composition by DoE (% w/w)	Composition 1 (%w/w)	Composition 2 (%w/w)	Composition 3 (%w/w)	Composition 4 (%w/w)
Levo-Dropropizine	15.00	15.00*	15.00	15.00*	15.00*
Curcumin	0.00	0.00	15.00	15.00	15.00*
Lactose Monohydrate, SV003	68.00	68.00	68.00	68.00	68.00
Lactose Monohydrate, LH230	15.00	15.00	0.00	0.00	0.00
Magnesium Stearate	2.00	2.00*	2.00	2.00*	2.00*

*Co-micronization of the material.

All blends, characterized by FT4 rheometer, exhibit always a Stability Index (SI) slightly higher than 1, indicative of powder affected by being made to flow, probably due to de-aeration and electrostatic charge of the material analysed. This tendency is confirmed also by a moderate cohesion observed by the Specific Energy (SE) results that falls into the range between 5 and 10 mJ/g. The Flow rate index (FRI) is also in agreement, since it falls above 3 meaning an average flow rate sensitivity and cohesiveness. All the data are confirmed by Flow Function (FF) values by Shear Cell. Higher cohesion was detected for trial 4 showing higher SE and FF values, probably due to smallest PSD, resulting in high electrostatic tendency. Trial 4 also, exhibits less fluidized behaviour confirming higher cohesiveness as confirmed by the Aerated Energy (AE) and Aeration Ratio (AR).

Capsules' performance results are shown in

Table 3 with APSD comparison in Figure 2. Comparing data, co-micronization of Levo-Dropropizine with Magnesium Stearate and usage of micronized Curcumin as alternative of fine carrier (composition 3), showed the best inhalation performance of Levo-Dropropizine, doubling FPD and FPF data compared to DoE formulation. Co-micronization helps to reduce the tendency of the API to agglomerate but also, the micronized Curcumin improve the aerosolization of the Levo-Dropropizine decreasing the retention of material inside capsules, device and mouthpiece. Moreover, the micronized curcumin exhibits promising inhalation behaviour itself.

Table 3 Inhalation performance of Levo-Dropropizine: results comparison between compositions 1 to 4 and initial composition by DoE

	Initial composition by DoE		Composition 1		Composition 2		Composition 3		Composition 4	
	AVG	%RSD	AVG	%RSD	AVG	%RSD	AVG	%RSD	AVG	%RSD
Delivered Dose (mg)	2.30	2.65	2.78	2.41	2.64	5.90	2.61	4.11	2.64	7.71
FPD (µg)	839.6	3.82	1562.8	3.82	794.34	7.34	1790.21	2.73	1734.53	9.22
FPF (%)	36.57	3.09	56.3	3.06	30.02	2.35	68.72	2.11	65.66	1.62
MMAD	4.00	0.72	2.70	0.70	4.77	1.59	2.25	0.65	2.50	1.00
GSD	1.80	0.90	2.00	0.49	1.58	0.97	1.71	0.58	1.87	1.14
ED (% of Label Claim)	78.80	1.12	86.47	4.02	75.35	5.43	100.07	2.97	86.87	3.58

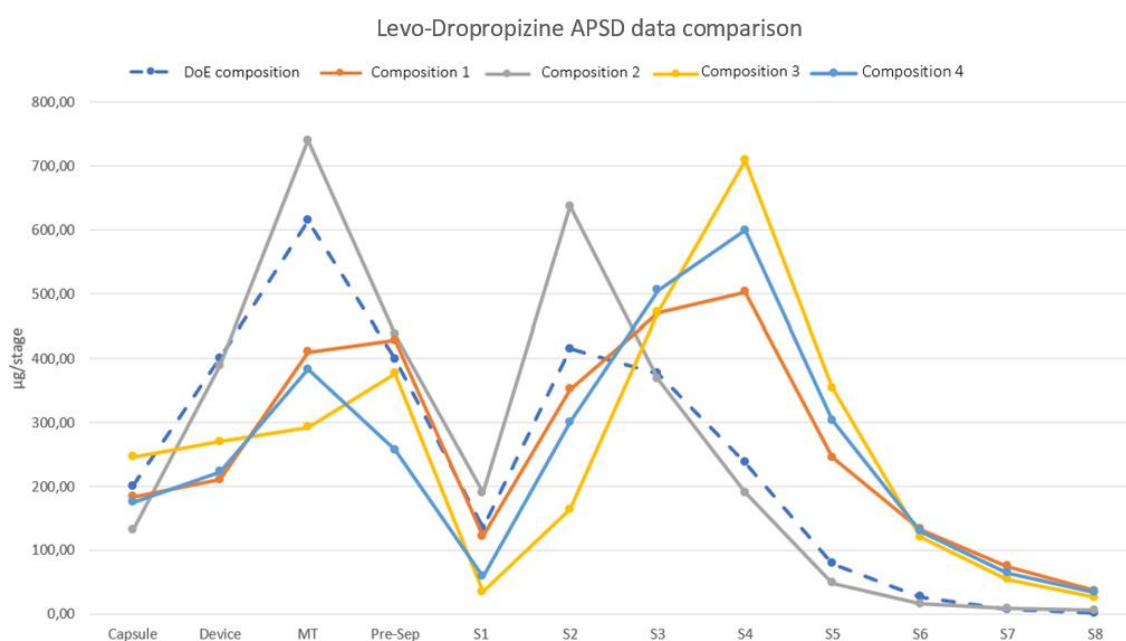


Figure 2 Levo-Dropropizine APSD: results comparison between compositions 1 to 4 and initial composition by DoE

Conclusion

The current work permitted a deeper understanding on the inhalation performance of Levo-Dropropizine administered as DPI, impacted by a strong agglomeration of the particles after micronization. The use of co-micronization technique with Magnesium Stearate and combination with micronized Curcumin as fine carrier, improve the aerosolization of Levo-Dropropizine in DPI formulation (composition 3), and decrease the retention of material inside capsules, device and Mouthpiece. Moreover, the micronized Curcumin itself exhibits promising inhalation behaviour. Furthermore, one of the advantages of Levo-Dropropizine combined with Curcumin could be to use it as treatment of different pathologies, such as Idiopathic Pulmonary Fibrosis (IPF) with both systemic and local effects exploiting the pulmonary delivery reducing side effects.

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