Novel Application of an Old Excipient L-Leucine- Improving Physical and Aerosolization Stability of Spray Dried Amorphous DPI Formulations.

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KEYWORDS: dry powder inhaler; fine particle fraction; spray drying; excipients; crystallization; physical stability

ABSTRACT

BACKGROUND

Spray drying has attracted increasing interests in producing dry powder inhaler (DPI) formulations (1). However, the amorphous nature of many spray dried powders may raise concerns regarding the physical stability of such formulations (2). Our earlier study has shown moisture-induced crystallization can lead to various impact on aerosolization for spray dried amorphous DPI formulations (3). Inert excipients are often added into DPI formulations to improve stability, aerosol performance or flowability. The present study aims to evaluate the influence of various excipients (lactose, sucrose, trehalose, mannitol and l-leucine) on the physical stability and aerosol performance of spray dried DPI formulations upon storage under different humidity conditions. Ciprofloxacin (HCl monohydrate) was chosen as a model drug based on our preliminary studies.

METHODS

A feed solution (16 mg/mL total solutes) containing ciprofloxacin and excipients such as

sucrose, lactose, trehalose, mannitol or l-leucine were prepared by dissolving the ingredients in water at a mass ratio of 1:1 (and 9:1 w/w for l-leucine). Also, ciprofloxacin alone was spray dried to be used as control. The solutions were spray dried using a BUCHI B-290 mini spray dryer (BUCHI Labortechnik AG, Flawil, Switzerland). Half of the spray-dried powders were stored in a desiccator at 20 ± 2% relative humidity (RH) and the other half at 55 ± 2% RH, respectively. Crystallinity was evaluated using Powder X-ray Diffraction (PXRD), particle morphology by scanning electron microscopy (SEM), and surface analysis by X-ray photoelectron spectroscopy (XPS). In vitro aerosolization was assessed using a RS01 dry powder device (Plastiape S.p.A., Osnago, Italy) at 100 L/min (pressure drop ~3.8 kPa) and a Multi-Stage Liquid Impinger (MSLI).

RESULTS AND DISCUSSION

Co-spray dried formulations of ciprofloxacin with sucrose, lactose and trehalose were amorphous at 20% RH (Figure 1). At 20% RH the co-spray dried formulation with mannitol was crystalline immediately after spray drying; with the crystalline peaks corresponded to mannitol. The spray dried ciprofloxacin-leucine formulation was crystalline and the peaks corresponded to l-leucine (Figure 1). Thus at 20% RH, the drug ciprofloxacin was amorphous in all the formulations. The formulation with l-leucine had the highest fine particle fraction (FPF) of 74 ± 7% due to wrinkled hollow shaped particles (Figure 1).

In our preliminary data we observed a significant change (from 28% to 42%) in FPF (i.e. aerodynamic diameter $\leq$5 μm) for the spray dried ciprofloxacin alone particles upon storage at 55% RH for three days, due to crystallization and increased surface roughness (3). However, the co-spray dried ciprofloxacin with 50%w/w l-leucine resulted in no change in FPF between those stored at 20% and 55% RH (Figure 1). It is further

interesting to note that unlike the spray dried Ciprofloxacin alone powders, the co-spray dried Ciprofloxacin-L-leucine 1:1 formulation showed no major change in particle morphology and aerosolization, and also alleviated crystallization of Ciprofloxacin when stored at 55% RH for 45 days (Figure 2). Co-spray dried formulations of ciprofloxacin with lactose, sucrose, trehalose and mannitol fused upon storage at 55% RH for 10 days, as observed using SEM (Figure 1) and thus showed a drastic decrease in FPF upon storage at 55% RH. Presence of sugars in spray dried formulations has a tendency to increase powder stickiness. The sugar molecules tend to have high molecular mobility thus cause powder caking (4, 5).

Notably,10% w/w l-leucine alleviated ciprofloxacin crystallization at 55% RH in the co-spray dried formulations (Figure 3). Ciprofloxacin co-spray dried 10% w/w leucine showed no significant difference ($p>0.05$) in the FPF between powders stored at 20% RH and 55% RH (Figure 3). To elucidate the underlying mechanism of how l-leucine alleviates the crystallization of spray dried ciprofloxacin, the state-of-the-art surface analytic techniques of X-ray photoelectron spectroscopy (XPS) was employed (6). The co-spray dried ciprofloxacin-leucine formulation showed higher surface coverage of l-leucine (Table 1) (6, 7), thereby prevented changes in FPF.

Table I: Theoretical and measured (by XPS) surface compositions for the co-spray dried ciprofloxacin-leucine formulations.

Formulations	% Surface Composition (Theoretical)		% Surface Composition (Measured)	
	L-leucine	Ciprofloxacin	L-leucine	Ciprofloxacin
CiproLeu_9:1	10	90	42	58
CiproLeu_1:1	50	50	70	30

CONCLUSION

Our study demonstrated that excipients play an important role in physical stability of DPI formulations. Leucine is well-known as aerosolization enhancer, but in this study among all excipients tested, l-leucine was shown as the best excipient to alleviate crystallization of amorphous ciprofloxacin. Our study demonstrated that such enhanced physical stability is due to its surface-active properties upon spray drying as confirmed by XPS data. This study provides some insights in physical and aerosolization stability of spray dried DPI formulations for high-dose medications, which are critical for the product quality.

ACKNOWLEGEMENTS

The study is supported by NIH (R01AI132681). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

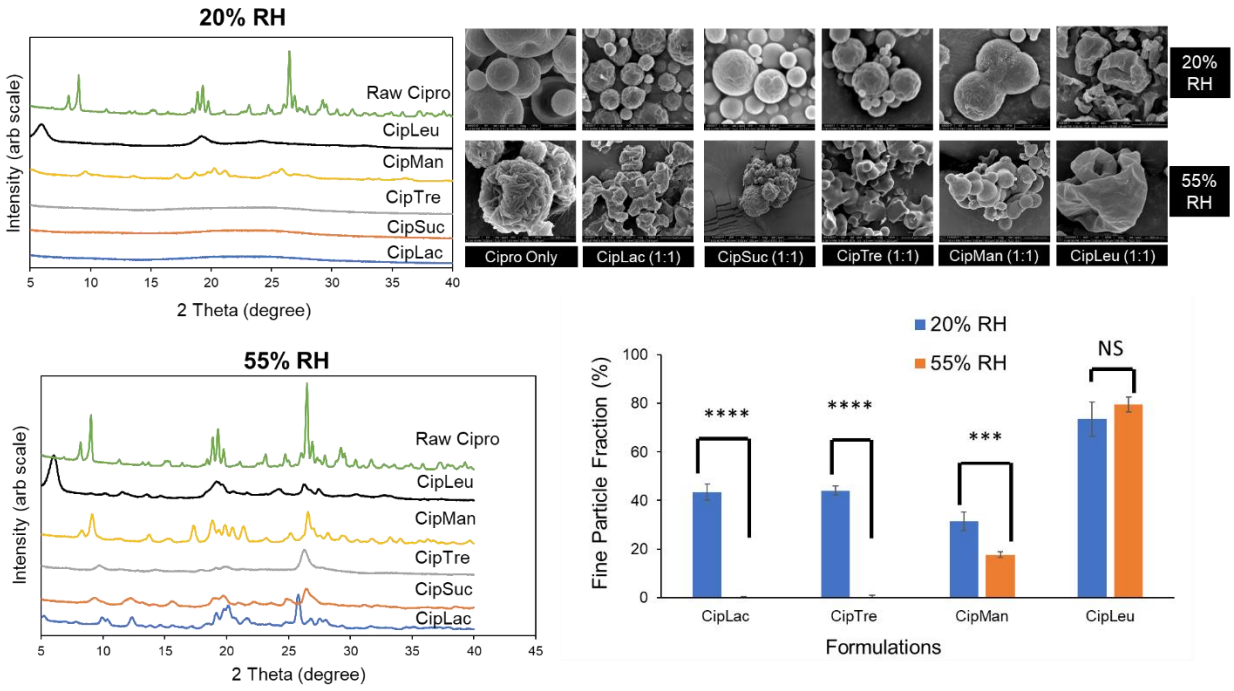

Figure 1: PXRD, SEM and in-vitro aerosol performance of ciprofloxacin co-spray dried with different excipients and stored at 20% and 55% RH. Raw Cipro: raw material of ciprofloxacin as supplied; CipLeu: spray dried ciprofloxacin formulation with 50% w/w leucine; CipMan: spray dried ciprofloxacin formulation with 50% w/w mannitol; CipTre: spray dried ciprofloxacin formulation with 50% w/w Trehalose; CipSuc: spray dried ciprofloxacin formulation with 50% w/w sucrose: CipLac: spray dried ciprofloxacin formulation with 50% w/w Lactose

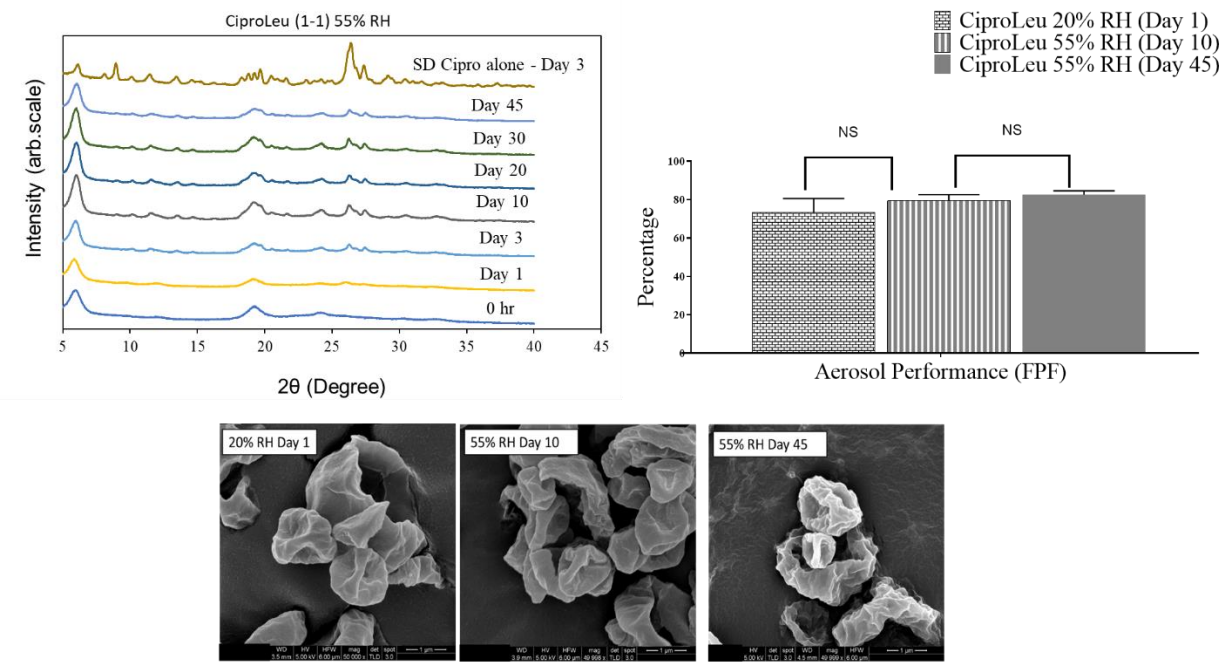

Figure 2: PXRD, SEM and dispersion for Ciprofloxacin co-spray dried with 50% w/w Leucine stored at 20% RH for 1 day and 55% RH for 10 and 45 days respectively (mean ± SD, n=4)

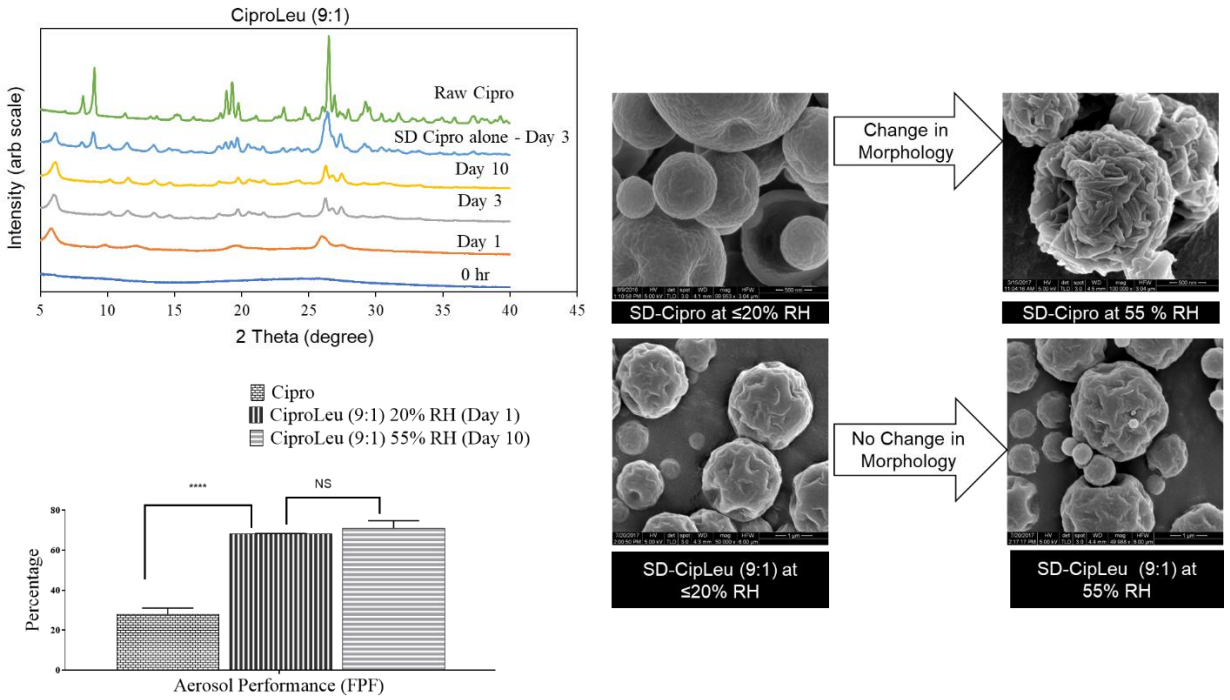

Figure 3: Ciprofloxacin formulations co-spray dried with 10% w/w leucine inhibited crystallization and improved aerosol performance

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