DPI Aerosol Robustness – Managing Impact of Environmental Relative Humidity

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ABSTRACT

It is common that binary dry powder inhalation (DPI) formulations result in variable dose quality when exposed to differences in the surrounding relative humidity (RH) during storage and/or during dose firing. The present work presents two different and complementary approaches to mitigate such general inherent features and produce formulations with robust and predictable aerosolization properties, for instance the fine particle fraction (FPF). The obtained results clearly show that it is possible to produce DPI formulations with virtually no humidity dependence by applying any of the two suggested approaches; active conditioning of API and lactose fines or adding small amount of a force control agent.

INTRODUCTION

Conventional binary DPI formulations are composed of lactose carrier particles, micron sized API particles, and sometimes also lactose fines, mixed together and thus forming an adhesive mixture. The micronisation of an API is normally done using a fluidized jet mill particle size reduction technology. This will add significant amount of surface located amorphous regions on the particles for all API types, no matter the nature, because of the continuous fragmentation process taking place. For a minor proportion of APIs, these amorphous regions will spontaneously recrystallise, providing a physically stable material, but for most substances there will be a significant amount of surface amorphicity left on the fine particles. The nature of these amorphous regions is very responsive to changes in exposed RH providing quite different properties in terms of adhesiveness and cohesiveness when surrounding moisture content changes. Consequently, the deaggregation process during inhalation will vary and provide significant changes in aerosolization behaviour with strong impact on quality attributers like FPF. The presented results illustrate two different, and complementary, approaches to reduce or even remove these phenomena; API conditioning* (i.e. restoration of crystallinity) and/or introduction of a force control agent like Mg-stearate.

*see also "***FDA draft guidance April 2018 DPIs and MDIs***"*

The crystallinity of the drug substance in MDIs and DPIs can be affected by mechanical processing, including micronization. This can lead to the generation of amorphous particles that are thermodynamically unstable, with a tendency to convert to a more stable crystalline state with time. This recrystallization of micronized material could lead to uncontrolled particle growth, thereby affecting the MDI or DPI product CQAs (e.g., APSD, DDU). Therefore, a conditioning step should be considered following micronisation to allow conversion of amorphous to crystalline form under controlled conditions of temperature and humidity.

EXPERIMENTAL

Material

Terbutaline sulphate (TBS) was donated by Cambrex (Milano, Italy). Lactohale® 300, Respitose® SV003 and Ligamed MF-2-V premium (Mg-stearate) were donated by IMCD Nordic (Malmö, Sweden). Capsugel Vcaps® size 3 was donated by Capsugel (Bornem, Belgium). Breezhaler (Novartis) was used as capsule inhaler in the NGI tests.

Formulation

TBS was micronised to an MMD particle size of 2.5 – 2.7 µm using a fluidized jet mill, either alone or comicronised with 11% Mg-stearate. The material was mixed with Lactose fines and Lactose carrier in a Diosna high shear mixer providing a final concentration of 0.5% Mg-stearate (where applicable), an API content of 4% and 6% Lactose fines.

Conditioning (where applicable) was performed at ambient temperature, using EtOH activity (micronised TBS) or RH (Lactose fines) for plasticizing effect, on TBS and Lactose fines overnight.

NGI testing

The air flow rate into the NGI during the testing was 60 L/min. The set-up was according to pharmacopeial NGI testing of DPIs. Three capsules were used per NGI test.

RESULTS

The dose quality, in terms of FPF, after provocation at elevated RH for different times are shown below in figure 1. The decrease is significant and have reached steady state after 4h (or less).

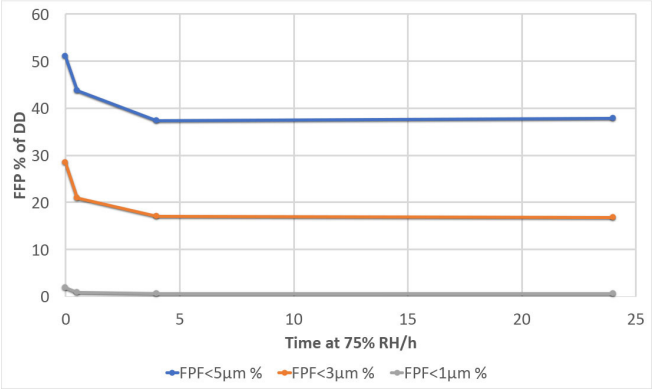

Figure 1. FPF versus time exposed to elevated RH for carrier based DPI formulation

Conditioning

The dose quality before and after provocation at elevated RH overnight are shown below in figure 2. The difference in decrease between conditioned and not conditioned is significant.

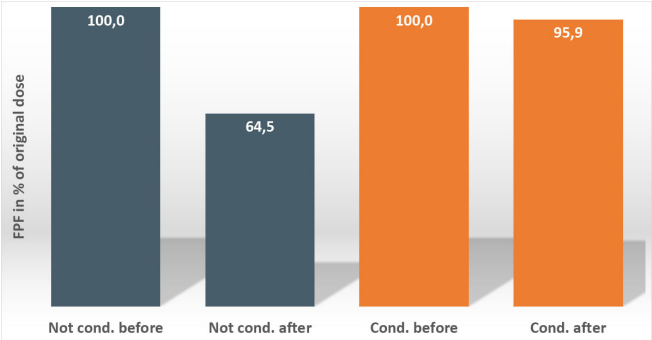

Figure 2. FPF before and after exposure to elevated RH relative to FPF (less than 5µm) before exposure. Blue – not conditioned, orange - conditioned

Force control agent (Mg-stearate)

The dose quality during dose withdrawal at different environmental RH for batches with and without Mg-stearate is shown in figure 3. The difference in RH impact is significantly reduced thanks to the presence of Mg-stearate.

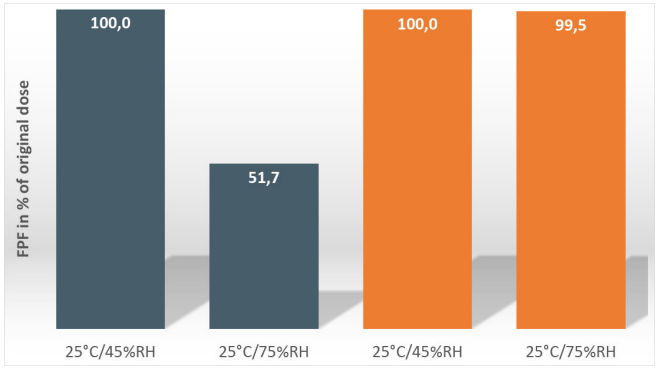

Figure 3. Impact on FPF from exposure at different RH during normal dosing. Blue – conventional formulation, orange – formulation with Mg-Stearate

CONCLUSIONS

Both active conditioning or the usage of small amount of Mg-stearate proved to be able to remove the humidity effect on fine particle fraction (FPF). The advantage of conditioning is that there is no need for an additional ingredient and that the amorphous regions are completely removed and thus providing a more stable and reproducible formulation in terms of both chemical and physical properties.

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