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DVS Application Note 70

Investigating Uniformity of Dry Powder Inhalation Formulations using Vapour Sorption Techniques

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Mixing and blending ingredients is critical step in manufacturing industry with an objective to get a perfectly homogenized product, especially for pharmaceutical usage. This Application note focuses on the use of DVS to study the behaviour of a formulation manufactured by two different techniques .

Introduction

The powder blending process is often identified as a challenging operation in solid dosage form manufacturing, due to the inherent properties of individual constituents, critical consideration of concentration and the precise management of the drug- to-excipient ratio. Spray drying techniques can be evaluated as an alternative to the historic ordered mix - blending techniques to minimize the effects of these variabilities. Dynamic vapour sorption studies were conducted to study hygroscopicity and the behaviour in presence of increasing humidity for an ordered mix and a spray dried formulation of Salbutamol Sulphate. Increase in hygroscopicity was observed in the spray drying formulation. This information can be used towards designing appropriate manufacturing, handling and storage process for spray dried blends. Pharmaceutical formulations are generally prepared as a homogenous physically blended mix of excipients and drug particles. Interbatch variability in particle size, shape and intrinsic nature of these excipient and drug particle interactions can lead to variability in flow properties and hence manufacturing and performance of the product. Spray drying technique can be used commercially to manufacture drug blends with consistent particle size and shape reducing the interbatch variability. The formulation blends whether an ordered mix or a spray dried formulation, need to be studied for a multiple of characteristics to ensure consistent quality in the product. Powder characterization can be broadly classified as thermal characterization and Physico-chemical characterization. Thermal characterization techniques like Differential Scanning Calorimetry and Thermogravimetric analysis provide insights to characteristics like polymorphism, crystallinity and thermal stability, whereas DVS isotherms provide information on material behaviour in presence of humidity. The data contributes in establishing processing conditions, packaging requirements and storage condition. [1,2,3,4]

Method

Salbutamol sulphate as a model drug and D–mannitol as a model excipient were used to prepare test formulations.

The surface morphology of the physical mixture and spray dried formulations was observed using scanning electron microscopy (SEM).

DVS water sorption experiments were performed by drying the samples at 0% relative humidity for 600 minutes to remove any residual moisture before being exposed to 0%RH to 95% RH using 10% RH increments to 90% RH and then by 5% RH increase to 95% RH at 25°C. The sorption cycle was followed by desorption from 95% RH to 0% RH in a similar manner maintaining the sample at the final 0%RH step at 25°C for 600 minutes. The weight change during the sorption cycle was then monitored, allowing for the hygroscopic nature of the sample to be determined. The %RH was maintained by the mixture of saturated water vapour and dry air (flow rate of 200 sccm). The percentage of mass change per minute (dm/dt) was set as 0.0002 . The rate at which the material equilibrates at each humidity level as well as the adsorption and desorption isotherm shapes for the formulations were studied.

Results

Figure 1 shows that the adsorption and desorption profiles are similar for the Physical mixture formulation and there is no significant water uptake (~ 0.5 %) at 80% humidity. Slightly higher hysteresis as compared to the spray dried formulation indicates slower release of moisture from the sample. The results indicate that the Physical mixture formulation is highly crystalline and any moisture pick up is adsorbed moisture on the surface of the formulation and does not affect its internal structure, hence this should yeild a stable formulation with respect to environmental humidity or can be defined as non-hygroscopic material.

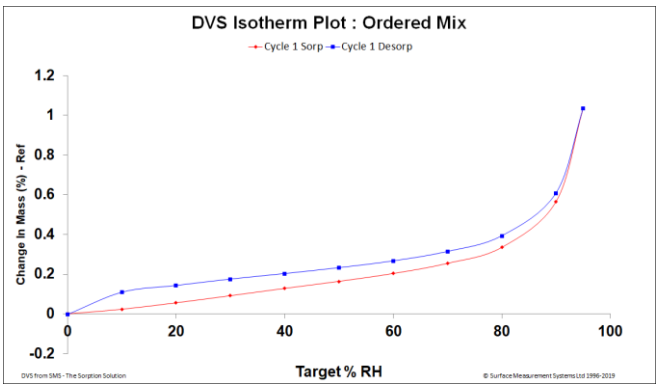

Figure 1: Physical(ordered) mixture – DVS Isotherm Plot

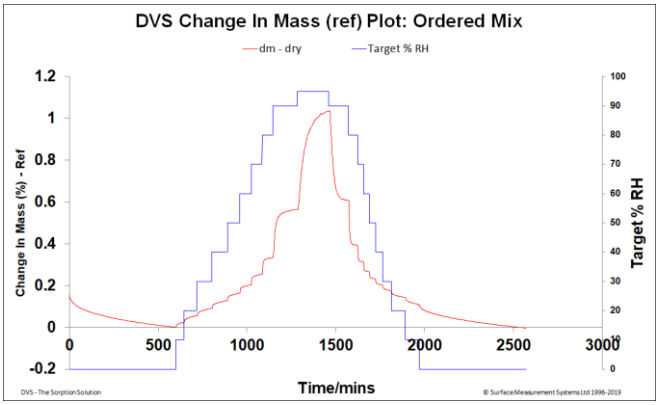

Figure 2: Physical (ordered) mixture - Change in Mass Plot

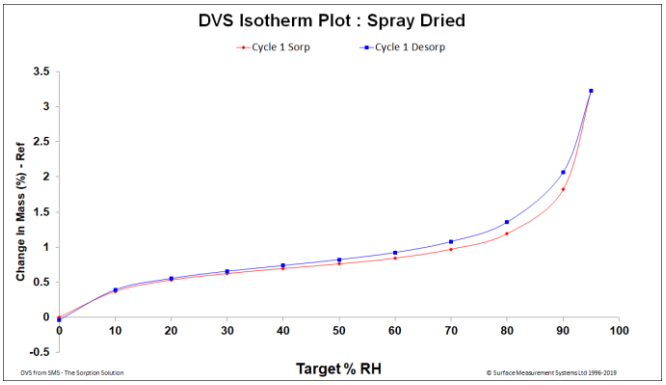

Figure 3: Spray Dried – DVS Isotherm Plot

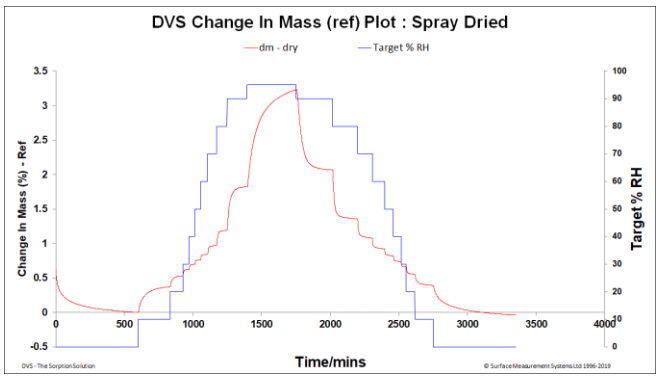

Figure 4: Spray Dried - Change in Mass Plot

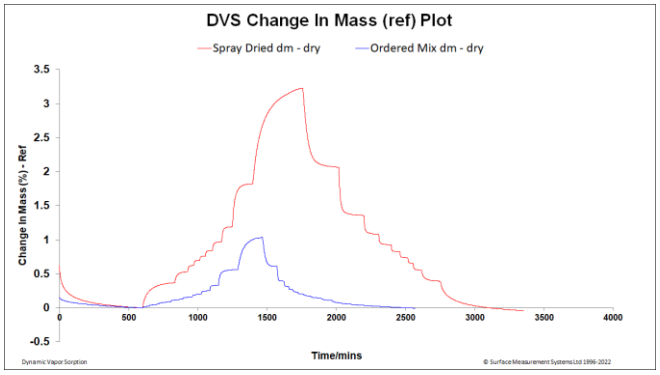

Figure 5: Superimposed DVS Change in Mass plots of Physical mixture and Spray Dried formulations.

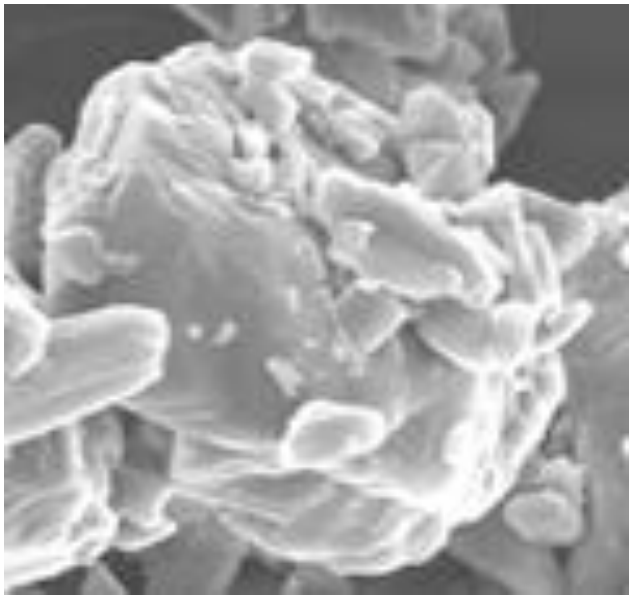

Figure 6: SEM micrographs of Physical mixture Formulation. Particles of different shapes and sizes are sticking to the larger excipient particles.

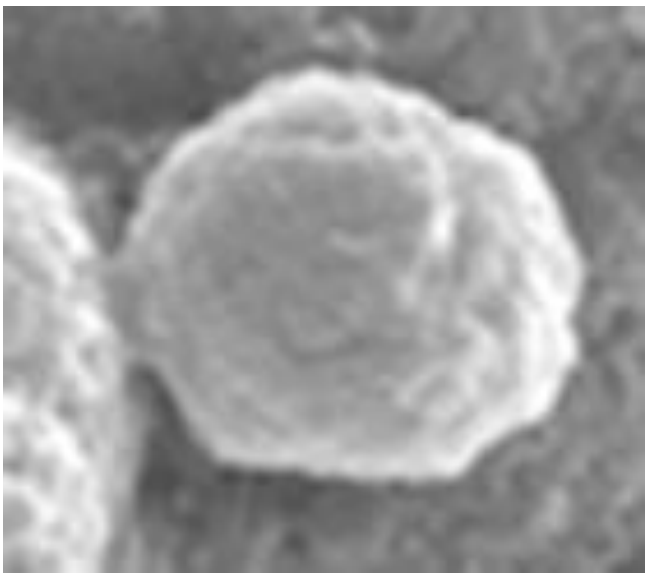

Figure 7: SEM micrographs of Spray Dried Formulation. Mostly spherical particles and smaller particle size distribution

Figure 3 shows that there is no significant difference in the adsorption and desorption profile of the spray dried formulation i.e., the water uptake was completely reversible indicating no change in formulation structure. The spray dried formulation took a longer time to stabilize at higher humidity (Figure 5) and a slightly higher water uptake ~ 1.5 is observed at 80 % humidity. However, the increase in moisture of about 3 % at 80 % humidity could potentially lead to the stability issues in the formulation due to water acting as a plasticising agent, thus significantly lowering the glass transition temperature causing spontaneous phase transitions (reference application note 101).

Figures 6 and 7 show SEM images of the Physical mixture and spray dried formulations, respectively and provide evidence on how different formulation methods affect the surface topography of mannitol formulations. While the spray dried formulation shows spherical particles with a smooth surface, the Physical mixture formulation shows crystalline structures distributed over the surface of the comparatively larger irregular structures.

The spray drying process has led to the formulation to become slightly hygroscopic and thus additional attention needs to be taken when developing manufacturing process, packaging material and storage conditions of spray dried formulations.

Conclusions

In this study the DVS was used to study the behaviour of the formulations manufactured by two different techniques. Although both the formulations obtained did not exhibit significant water uptake after the desorption cycle, an increase in water uptake was observed for the spray dried formulation at high humidity above 80%. The spray drying process has led the formulation to become slightly hygroscopic.

A future application would investigate the contribution of particle size and surface roughness to add to the results of this study. These findings would help in taking informed decisions when optimizing manufacturing and handling process, developing packaging material and storage conditions of the spray dried formulations.

References

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