Optimising Mixing Process Parameters for an HFA pMDI Dual Suspension Product During Early Phase Product Development

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Introduction

During the manufacture of a suspension pMDI, it is essential that adequate energy is distributed to the formulation, to disperse any API agglomerates that are present, since insufficient mixing can result in a lower and more variable respirable dose. Mixing studies are often overlooked in early phase development, where quick feasibility assessments are performed. However, during this phase, critical product decisions are often made and it is therefore desirable to employ a robust manufacturing process to reduce inherent product variability. Understanding the product's susceptibility to mixing parameters at an early phase can provide valuable information for scale-up and potentially minimise studies that have to be performed at a much larger, more expensive scale. This study investigated the impact of varying high shear mixer speed and mixing time on the pharmaceutical performance of an IBM and albuterol combination pMDI. Drug content assay and fine particle mass (FPM) were assessed for each parameter and compared to target values.

Method

Four laboratory scale batches of a dual suspension formulation containing IBM and albuterol, were manufactured by a cold fill process using a single batch of micronised IBM and albuterol sulphate (expressed as free base). The formulation was high shear mixed at the speed and for the mixing time intervals highlighted in Table 1. At the end of each mixing interval, 10 canisters were filled with formulation and crimped with a 3M valve (a magnetic stirrer was used to maintain homogeneity during filling). High shear mixing recommenced until the second mixing time point was reached and 10 further units filled. This process continued until the formulation had undergone a total of 10 minutes high shear mixing and samples had been taken at the four time points. Batch 4, an exact replica of batch 2, was included to assess the level of variability between batches.

Table 1 – Mixing speed and sample times for the laboratory scale batches

Parameter	Batch 1	Batch 2 & 4	Batch 3
Speed (rpm)	1000	4000	7000
Mixing Time (min)	0.5, 2, 5, 10	0.5, 2, 5, 10	0.5, 2, 5, 10

The first and last unit of each time interval were assessed for drug content assay, by an appropriate HPLC method, to ensue samples were homogenously mixed and on target, since an off-target result would influence the subsequent FPM value. Three of the remaining units per sample time were tested for aerodynamic particle size distribution (APSD) by next generation impactor, using a flow rate of 30 L/min, in accordance with Ph. Eur and USP guidelines[1,2]. All units were tested with a 3M actuator containing a dose counter.

Results and Discussion

Testing of batches 2 and 4 (both 4000 rpm) for drug content assay and APSD revealed minimal batch to batch variability. Consequently, data were pooled for comparison against batches 1 and 3. Figure 1 displays the drug content assay data, as a % target for IBM and albuterol for the three mixing speeds at the four mixing times. Mixing at the lowest speed of 1000 rpm did not produce a homogenously mixed, on target suspension for either API, after any of the mixing times. Similarly, 0.5 minutes mixing at the higher 4000 rpm mixing speed also resulted in unacceptably low and more variable drug content assay. On target drug content assays were achieved at 4000 rpm after 2 minutes mixing and at all mixing times at the highest mixing speed of 7000 rpm.

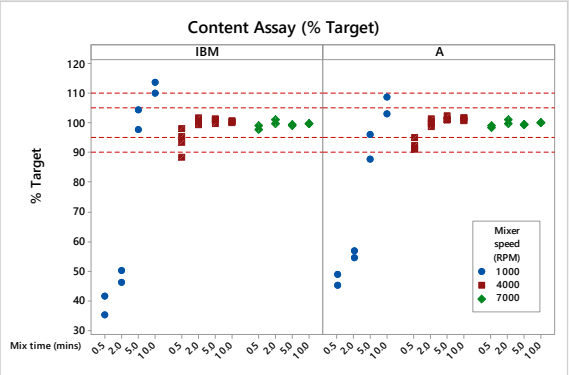

Figure 2 - Drug Content assay of IBM and albuterol in formulations mixed for increasing times at increasing mixer speeds

APSD profiles are displayed in Figure 2 for IBM and albuterol respectively across the range of mixer speeds and mixing times. Profiles generated at 1000 rpm are clearly influenced by the variability observed in the drug content assay data. At all mixer speeds, 0.5 and 2-minute mixing times produced profiles with less API deposited in the finer region and in some cases, a corresponding increase in throat deposition, suggesting that the APIs in the formulations were not fully deagglomerated. The increased variability observed between the albuterol profiles indicates that, in this formulation, albuterol is more susceptible to changes in mixing speed and mixing time than IBM and that both APIs do not behave the same.

Results and Discussion Continued

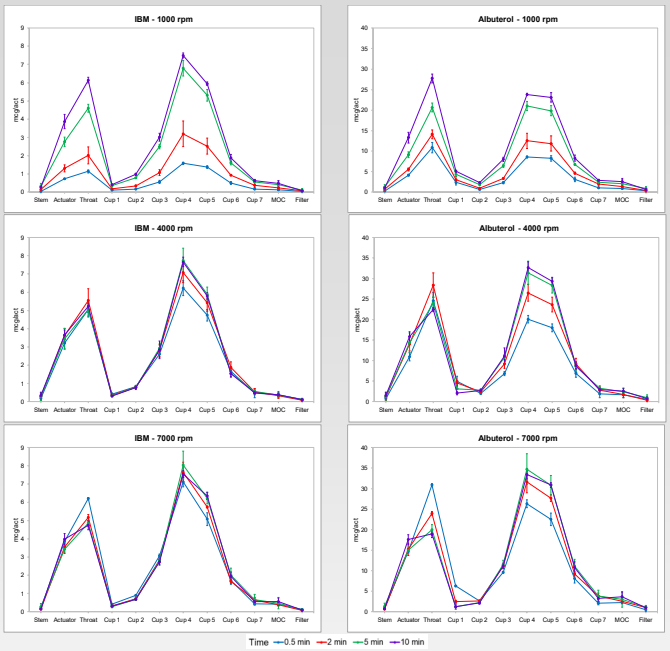

Figure 2 - APSD profiles for IBM (top) and albuterol (bottom) following mixing at 1000 rpm (left), 4000 rpm (centre) and 7000 rpm (right). Error bars represent the standard deviation.

Generally, as mixer speed and mixing time increases, the FPM also increases (Figure 3). For both APIs, target FPMs were only achieved when mixing at 7000 rpm for 5 minutes or more, despite drug content assay data suggesting that formulations were adequately mixed at lower speeds and mixing times (Figure 1).

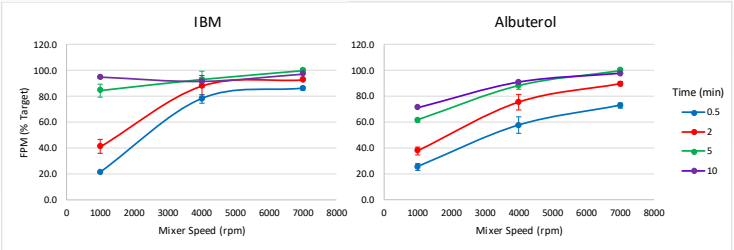

Figure 3 - Relationship between mixer speed and mixing time on the FPM of IBM (left) and albuterol (right) (expressed as a % of the target FPM). Error bars represent the standard deviation.

Mixing for 5 and 10 min at 4000 rpm generated FPM values within ±15% of the target FPM, which may be considered acceptable when developing a generic product[3]. However, for a robust process, all data would ideally sit at the target level on the plateaued part of the plots in Figure 3. Albuterol did not plateau to the same extent as IBM, implying that further deagglomeration may be achieved at higher mixer speeds. Since 7000 rpm represents the limitations of our equipment and doubling the mixing time from 5 to 10 min, at 7000 rpm, resulted in no significant change in FPM, it was concluded that these mixing parameters were sufficiently robust for an IBM and albuterol suspension pMDI in early phase development.

Conclusions

The pharmaceutical performance of an IBM and albuterol dual suspension HFA pMDI was influenced by changes in mixer speed and mixing time during manufacture. Albuterol was shown to be more susceptible to changes in the mixing process parameters investigated than IBM. Through a simple laboratory mixing study, appropriate mixing parameters were established that enabled deagglomeration and homogenous dispersion of both APIs which also resulted in optimal product performance with respect to APSD and FPM.

Furthermore, although important to confirm successful batch manufacture, drug content assay data alone may not provide sufficient information to enable optimal mixing parameters to be established for the product in question.

References

1. Ph. Eur. 8.0, Monographs on dosage forms, Preparations for Inhalation.
2. USP chapter (601): Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers.
3. CPMP/EWP/4151/00 Rev. 1. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents.