Performance Advantages of Pearl Cosuspension Formulation Technology for Manufacturing of Metered-Dose Inhalers

R. Harris Cummings, Robert Schultz, Jason H. Speck, Vidya Joshi, David Lechuga-Ballesteros, Brad Flynn, Reinhard Vehring, Brian Noga, and Sarvajna K. Dwivedi
Pearl Therapeutics, 200 Saginaw Drive, Redwood City, CA 94063 (USA)

Introduction

The manufacture of Metered-Dose Inhalers (MDIs) is often difficult because of problems associated with creating and maintaining a homogeneous suspension, differential partitioning of actives and loss of active onto surfaces of the filling equipment.

The manufacture of combination products can be further complicated by differing physical characteristics of the drug crystals, such as density, solubility, surface energy, particle size and because actives can be present at very different strengths.

In addition, the development of a manufacturing process also requires scale-up from laboratory to commercial filling equipment which includes changes in the drug addition vessel, pressure vessel, stirrers and recirculation rates.

Pearl Therapeutics' cosuspension formulation allows for the rapid development of MDIs using spray-dried microparticles which are blended with micronized drug substance(s) in HFA-134a. The characteristics of this formulation technology that allow for rapid development of high performance MDIs are also evident in the manufacture of MDIs This poster presents the advantages of the cosuspension formulation for development and scale-up of MDI manufacturing processes for a variety of products, including single-component and combination MDIs.

Manufacturing Process

Pearl manufactures the spray-dried microparticles by a proprietary process on a custom built, compact, spray dryer, designed specifically for producing particles in an inhalable size range (1). The Pearl particles consist of phospholipid and calcium chloride (2), but do not contain active. The particles are blended with micronized drug substance(s) in propellant during formulation of the MDIs. The resulting cosuspension is then pressure filled into MDIs with standard MDI container-closure components using standard commercially available filling equipment. Micronized drug crystals are either purchased with the appropriate size distribution from the manufacturer or are jet milled by Pearl. Pressure filling has been accomplished using either one- or two-stage filling processes as well as sequential additions of actives, excipients and propellant. Glycopyrrolate (GP, a long acting muscarinic antagonist), mometasone furoate (MF, a glucocorticoid steroid), and formoterol fumarate (FF, a long acting β2-adrenergic receptor agonist) have been manufactured as single, double and triple combination products (3).

Methods

Several batches of single active and combination products have been filled. Total can assay (TCA) analysis is conducted to determine through-run uniformity of the filling process and TCA results are presented as percent of formulated dose. Aerodynamic particle-size distribution (aPSD) was determined using the Next Generation Impactor (NGI) at a flow rate of 30 L/min.

Results & Discussion

To date Pearl has successfully filled more than 75 batches of single and double combination products and a small number of triple combination batches. Figure 1 shows TCA results for combination batches containing GP and FF. Through run uniformity is very good, with all but a few values within ±3% of the batch average.

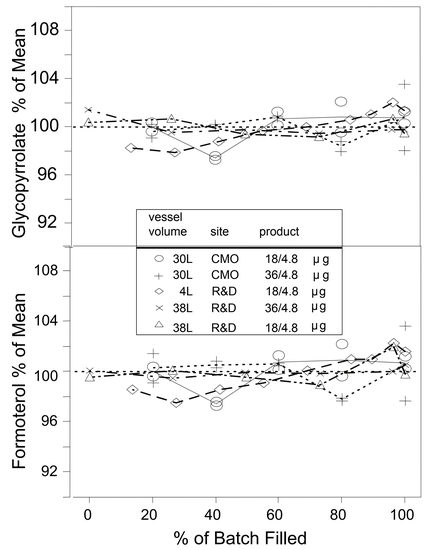


Figure 1 – Through Run Uniformity Measured by TCA for GP and FF in the GP/FF Combination Product

MDI formulations with submicrogram doses (480 ng and 960 ng per actuation) were manufactured with excellent through-batch uniformity. These data are all within ±5% of the batch mean, which demonstrates that drug loss during filling is not significant even for submicrogram products. A triple combination product containing GP, FF and MF was formulated in Pearl's R&D facility at a 4L scale (3). TCA results demonstrate that the behavior of the individual components was essentially the same in the single and double combination products regardless of manufacturing scale, with all results being within ±3% of the overall batch average, Figure 2.

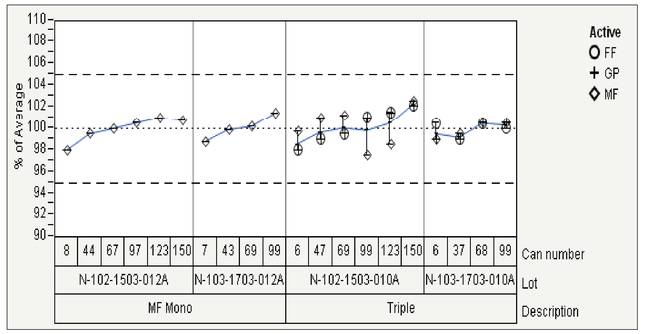
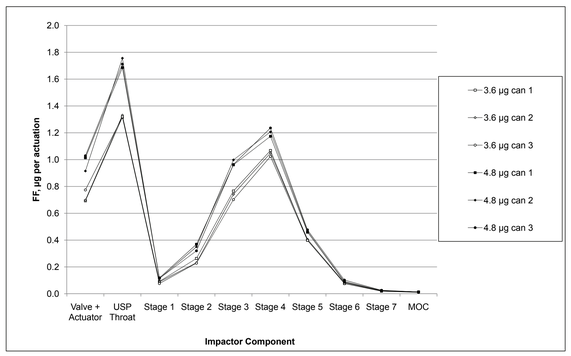


Figure 2 –TCA for MF Single and a Triple Formulation of MF, GP, and FF

In addition to inter- and intra-batch TCA data, quality of the manufacturing process can be demonstrated by comparing *in vitro* data at a variety of formulated strengths. The aPSD data for FF in 4.8 and 3.6 µg per actuation products, Figure 3a, demonstrate that the fine particle mass is clearly separated for the two strengths, suggesting that the formulations disperse readily and that there is little loss to internal surfaces of the filling equipment. Similar performance is seen for very low dose, 0.48, 0.96 and 4.8 µg per actuation, products as well, Figure 3b.



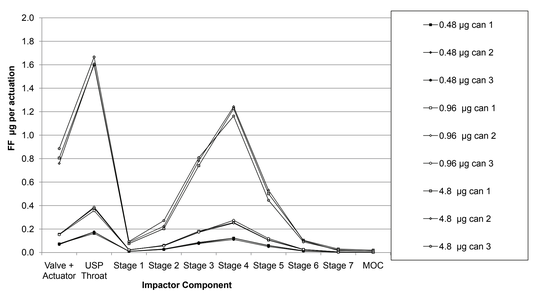


Figure 3 – Aerodynamic Particle Size Distributions of (a) 3.6 and 4.8 µg FF products and (b) 0.48, 0.96 and 4.8 µg FF

Conclusions

Those formulation characteristics which result in good physical stability and aerosol performance are also manifest in the ease and simplicity of manufacturability of Pearl MDIs.

Product Characteristics

Ability to formulate MDIs with strengths from less than 1 to at least 100 µg per actuation (highest tested to date)

- Ease of formulation of double and triple combination products with no *in vitro* drug-drug interaction
- Particle-size distribution data show that the products produced with this wide array of doses show clear separation of fine particle masses, even at the lowest doses.

Manufacturing

- Conventional manufacturing processes and filling equipment is used
- Cosuspension formulations form readily and do not require high-energy mixing
  - Stirring and recirculation sufficient to form homogeneous suspensions
- Virtually no loss of drug to the surfaces of the filling equipment
  - Little or no drug overage is needed
- Scale-up of the filling process is straightforward and predictable from laboratory to small commercial equipment

It was found that the behavior of the actives in cosuspension formulations is independent of scale, filling equipment, strength and the presence of other actives resulting in a very robust filling process.

References

1. Ivey, J., Vehring, R. (2010), "The use of modeling in spray drying of emulsions and suspensions accelerates formulation and process development," Computers & Chemical Engineering 34 (7), pp1036-1040.
2. Dellamary, L.A., Tarara, T.E., Smith, D.J., Woelk, C.H., Adractas, A., Costello, M.L., Gill, H., Weers, J.G. (2000), "Hollow porous particles in metered dose inhalers," Pharm. Res., 17, pp168-174.
3. Joshi, J., Lechuga-Ballesteros, D., Flynn, B., Vehring, R., Schultz, R., Noga, B.N., Cummings, R.H., Speck, J.H., and Dwivedi, S.K. (2011), "Development of Mono, Dual, and Triple Combination pMDIs without Coformulation Effect", Poster, RDD 2011.

Presented on May 8th, at RDD 2011, Berlin, Germany