Development of High Shear Homogenization Parameters for Production of Budesonide Inhalation Suspension

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Problem Definition

There are currently 16 million Americans who have been diagnosed with Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death in the United States, encompassing two chronic illnesses: emphysema and bronchitis. Various treatments are available, with medication preferred for daily treatment of exacerbations and inhaled corticosteroids (ICS) the preferred administration route. When inhaled corticosteroids are inhaled, aerosols open up the lungs, but the extent of delivery depends on drug formulation. Inhalation suspensions provide adequate delivery but may have low stability due to the tendency for the dispersed phase to settle out of medium. Suspension stability depends on particle size and homogeneity, which are influenced by manufacturing methods. High shear homogenization is preferred since it is fast, generates lower heat, and energizes particles, preventing particle growth.

Solution

Pulmicort, the reference listed drug (RLD) for COPD, is expensive and has the propensity for agglomeration. The generic, however, is more affordable but has high production costs due to tedious methods for suspension formulation, machinery operation, and sterility. Generic formulations cannot be altered, thus manufacturing methods must be adjusted. Varying rotor-stator configuration and homogenization duration allows for control of energy input and thus the stability of the suspension. The proposed solution is to determine ideal parameters of high shear homogenization for budesonide production to achieve an ICS suspension with an increased long-term stability at reduced cost compared to the RLD.

Methodology

Formulation and homogenization
- Four 0.5 mg/2 mL budesonide batches of varying homogenizer rotor-stator configuration:
  - Batch 1 (1P:2G), Batch 2 (4M/4G), Batch 3 (1P:2G & 4M/4G), and Batch 4 (1P:2G & 6F/6F)
- Preliminary testing of batches 1, 2, 3, and 4
- Particle Size Distribution (PSD) to determine specific surface area and particle size
- Select samples to place under accelerated conditions (40°C, 25% relative humidity) for stability testing
- Stability testing at times 0, 1, and 3 months
- Acrylamide Particle Size Distribution (aPSD)
  - UPLC to ensure particles deposited in lower respiratory tract after inhalation
- Label Claim Assay
  - Ensures final product meets mean drug content using UPLC
- Related Substances
  - Uses UPLC to determine impurities against the standard to assess stability and shelf life
- pH and Osmolality
  - pH recorded at 25°C, for equilibrium using pH probe
- Bondancy determination product freezing point
- Analysis of data for batches 1, 2, 3, and 4
- Cost analysis to determine manufacturing cost reduction
- Mean comparison and one sample t-test statistical analysis
- Determine optimal configuration and duration

Results

Figure 1. Diagram of Suspension Homogenization Through a Rotor-Stator Generator. The rotor spins inside the stator as product travels through, creating high shear force and coercing the product into a suspension. Rotors and stators may have teeth of varying numbers and thickness.

Figure 2. Components of the IKA Process Pilot 2000/4 Homogenizer. Panel A depicts the overall interior setup of the IKA Process Pilot 2000/4 Homogenizer. Panel B depicts the rotor-stator configuration used in the project.

Figure 3. Comparison of Batches 1 and 2 by Percent Difference for Stability Testing. Stability testing includes label claim assay, related substances, particle size distribution (PSD), and acrylamide particle size distribution (aPSD). PSD testing is represented by volume mean method (VVM) and aPSD testing is represented by fine particle size.

Figure 4. Comparison of Batches 1 and 2 by Average Percent Difference for Stability Testing at the Three Major Time Points. Time point 1 represents 0 months, time point 2 represents 3 months, and time point 3 represents 6 months. The bars indicate the results of high shear homogenization for budesonide suspension coverage may increase and patients will be able to have greater access to therapeutic treatments. After completing all of the stability testing protocols, TRC will ultimately scale up the batch size from a 0.0 mL batch to a 4000 mL batch for bulk production of budesonide inhalation suspension to further reduce the costs associated with the manufacturing process.

Future Directions

For the timeframe, TRC will be completing this project. TRC will complete 3 month accelerated conditions stability testing for batches 3 and 4 as well as 6 month accelerated conditions stability testing for all four batches. TRC will analyze the data and determine if the homogenizers’ prediction of the optimal homogenization parameters is consistent with the homogenization parameters designated by the final results. The optimal homogenization parameters will be implemented into the manufacturing methods at TRC to reduce the time and cost of creating the product. The reduction in manufacturing costs will be further reduced by increasing quantities of the batches that are run each time, such that budesonide inhalation suspension coverage may increase and patients will be able to have greater access to therapeutic treatments. After completing all of the stability testing protocols, TRC will ultimately scale up the batch size from a 0.0 mL batch to a 4000 mL batch for bulk production of budesonide inhalation suspension to further reduce the costs associated with the manufacturing process.

Conclusion

Conclusions: Since all data passes testing specifications, the optimal homogenization configuration and duration is determined by the batch closest to the RLD. Based on data obtained for the four batches, batch 1 (1P:2G) at 12 volumetric turnovers (NT) has the most similar physicochemical properties to the RLD distinguished through percent difference analysis of stability tests. Mean comparison and t-test statistical analysis demonstrated a trend of batch 1 at 2NT producing results that are least different from the RLD. Significance was not proven from statistical analysis due to the small sample size used in this study.

Limitations: Complications led to alterations in the original methodology, goals, and objectives. Zeta potential was originally used as the method to select samples for stability testing, but after attempts to refine the protocol it was determined that the population of particles sized greater than 10 µm lead to inaccurate readings by the ZetaSizer. Although zeta potential testing was originally important, the removal of zeta potential testing did not affect sample selection because PSD testing was used to assess sample stability. Other limitations were project timeframe, fixedexcipient concentrations in drug formulation for generic drug production, and small sample size limiting the ability to determine statistical significance.

Implications: This study attempts to lower manufacturing costs associated with budesonide inhalation suspension production by altering homogenization parameters to allow the product to be covered by insurance companies and make the product more readily available to patients. In addition to lowering cost, the generic has increased product stability compared to the RLD, making it a more efficient product.

References: