Pallavi Nithyanandan, Ph.D.

Dissertation Abstract (2005)

THE ANALYSIS AND PREDICTION OF FUNCTIONAL ROBUSTNESS OF INHALER DEVICES

The reliability of inhaler devices depends on their ability to withstand the mechanical and environmental stresses encountered throughout their intended lifetime, without sustaining sufficient damage to detrimentally influence their performance. During the course of normal handling and use, these products could be subjected to accidental drops, misuse, and varying temperature conditions depending on the lifestyle of the patient. This is a critical issue in the case of devices intended to deliver potent drugs; where variability in performance could lead to adverse events or sub-therapeutic outcomes. The studies described in this thesis were undertaken to develop a rational method for the analysis and prediction of robustness of existing inhaler devices; and define a standard against which the robustness of new inhalers could be judged.

The effect of mechanical stresses alone and in combination with elevated temperatures on the in-vitro performance of pressurized Metered Dose Inhalers (MDIs) was investigated. The innovator MDI devices (Ventolin HFA and QVAR 40) tested proved to be functionally robust and rugged in response to extreme mechanical stresses, suggesting they are appropriate standards on which, acceptance criteria for new devices should be defined. Elevated temperature alone did not cause any detrimental change in performance, but made the MDIs more susceptible to damage by mechanical stress. The actuator seat where the valve stem is inserted was identified as the critical area of the MDI and functional failure in all cases was caused by damage to this region. In case of Ventolin HFA, elevated temperature caused valve leakage as well as damage to the actuator seat. However, the results revealed a large variation in the functional robustness amongst the innovator products. The results highlight the effect of the choice of materials of construction and device designs on the ruggedness of MDIs. This approach could be used by device development teams as a screening tool for rejecting prototypes likely to fail early in the development process.

A comparison of innovator vs. generic MDIs was also performed. The generic albuterol sulfate MDI manufactured by Warrick Pharmaceuticals functioned normally, while the generic albuterol sulfate MDI manufactured by IVAX Pharmaceuticals failed at 20 kg (the maximum load at which the innovator products functioned normally). The findings reveal that generic products approved as ‘equivalent’ to the innovator products by current standards; are not necessarily equivalent in ruggedness.

Finite element models of the actuator seat of Ventolin HFA (polypropylene) and QVAR 40 (high-density polyethylene) capable of predicting mechanical failure of metered dose inhalers was established. The material properties as well as the actuator design influence the operational limit of MDIs. The actuator seat design of Ventolin HFA was found (during Instron testing), and predicted by FEM to be more mechanically robust compared to that of QVAR 40. Stress analysis using finite element modeling is a useful tool which provides a scientific basis for selection of the optimal design and appropriate materials of construction; which could lead to the development of robust inhalers while shortening the product development cycle.
Expertise/Interests

Inhalation Drug delivery-Metered dose inhaler formulation. Development of methods for inhaler testing. Particle size reduction and analysis. Identifying and reducing sources of variability in standard test methods (e.g. dissolution, cascade impaction) used in the performance testing of drug products.

Education Summary

- Ph.D. Pharmaceutical Sciences, May 2005, University of Maryland, Mentor: Dr. Richard Dalby
- B.Pharm. (Bachelor of Pharmaceutical Sciences), May 2000, University of Mumbai, India
- Registered Pharmacist, Pharmacy Council of India, Dec 2001

Employment Summary

- June 2005 – Present: Chemist III- Pharmaceutical Scientist, Research and Development Laboratory, United States Pharmacopeia
- June 2001 – August 2001: Intern, Wyeth Consumer Healthcare, Studied approaches for powder flow analysis

Research Experience

- June 2005 – May 2007
  - Development of reference standards for the performance verification of inhaler testing equipment.
  - Analytical method development and validation.
  - Development of performance tests for the evaluation of dosage forms.
  - Identifying and reducing sources of variability in standard test methods (e.g. dissolution, cascade impaction) used in the performance testing of drug products.

- August 2000 – May 2005
  - Metered Dose Inhaler formulation. Project title: “Rational Selection of an Appropriate Pressurized Inhalation Formulation for an NCE.”
  - Studied approaches to controlling and manipulating particle size of aerosol formulation ingredients using a fluid-energy mill.
  - Particle size analysis.
  - In-vitro testing of metered dose inhalers and nasal sprays.

Teaching

- Instructor for Pharm. D. students Courses: Pharmaceutics, Biopharmaceutics and Pharmacokinetics, Biochemistry
Publications


Abstracts


Podium Presentations

• "Dissolution Variance Study of commercial Dosage Forms." Presentation at the USP Biopharmaceutics Expert Committee Meeting, December 6, 2006.
• "Investigation of the response of pressurized metered dose inhalers to mechanical stresses." University of Maryland Annual Graduate Research Conference, Baltimore, April 2004.
• "Analysis the response of metered dose inhalers to mechanical stresses." Biopharmaceutics and Drug Delivery Technology seminar series, School of Pharmacy, University of Maryland, April 2004.

Membership in Professional and Scientific Societies:

• American Association of Pharmaceutical Scientists, 2002 – present
• Respiratory Drug Delivery, 2002 – present

Editorial Positions:

• Reviewer, American Association of Pharmaceutical Scientists Annual Meeting, 2007
• Reviewer, Proceedings of Respiratory Drug Delivery IX, 2004

Organizing Roles in Scientific Meetings:

• Member, Organizational team, Respiratory Drug Delivery, 2002 - 2004

Honors and Awards:
- Rho Chi National Pharmacy Honors Society, inducted in 2002
- Best Podium Presentation Award in Pharmaceutical Sciences at the University of Maryland Inter-campus Graduate Research Conference, April 2004.