

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
 - Thesis title: "The Analysis and Prediction of Functional Robustness of Inhaler Devices."
 - 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, Laboratory Sessions on "Inhaler testing using pharmaceutical impactors", and "Formulation of Metered-dose Inhalers" at the: Inhalation Aerosol Technology Workshop (2002-2004). Attended by 40-50 participants from the Industry, Academia and Government.
- Instructor for Pharm. D. students Courses: Pharmaceutics, Biopharmaceutics and Pharmacokinetics, Biochemistry

Publications

- "Analysis and Prediction of Functional Robustness of Inhaler Devices". **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby, Journal of Aerosol Medicine, Vol. 20, No. 1, March 2007.
- "Dissolution Variability: Comparison of Commercial Dosage Forms with USP Lot P Prednisone Reference Standard Tablets". **Pallavi Nithyanandan**, Walter Hauck, Jimmy Munoz, Gang Deng, William Brown, Ronald Manning, and Samir Wahab. To be submitted to AAPS PharmSciTech (2007).
- "Analysis of robustness of inhaler devices: Response of pMDIs to mechanical stresses." **Pallavi Nithyanandan**, Stephen Hoag, and Richard Dalby. Respiratory Drug Delivery IX, DHI Publishing, pp 789-792, 2004.
- "Evaluation of the Sensitivity of USP Prednisone Tablets to dissolved Gas in the dissolution Medium Using USP Apparatus 2". **Pallavi Nithyanandan**, Gang Deng, William Brown, Ronald Manning, and Samir Wahab. Dissolution Technologies August 2006 Vol. 13 No. 3.
- "The USP Performance Verification Test, Part III: The USP Performance Verification Test, Part III: USP Lot P Prednisone Tablets— Quality Attributes and Experimental Variables Contributing to Dissolution Variance". Gang Deng, Alyssa J. Ashley, William E. Brown, Joseph W. Eaton, Walter W. Hauck, Loice C. Kikwai-Mutua, Mark R. Liddell, Ronald G. Manning, Jimmy M. Munoz, **Pallavi Nithyanandan**, Maria J. Glasgow, Erika Stippler, Samir Z. Wahab, Roger L. Williams. In review, Journal of Pharmaceutical Sciences.

Abstracts

- "Dissolution Variability: Comparison of Commercial Dosage Forms with USP Lot P Prednisone Reference Standard Tablets ". **Pallavi Nithyanandan**, Walter Hauck, Jimmy Munoz, Gang Deng, William Brown, Ronald Manning and Samir Wahab. Annual meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 2007.
- "Comparison of the Efficiency of Deaeration Techniques for Dissolution Media Using Two Orthogonal Methods". **Pallavi Nithyanandan**, Johanna Smeller, Gang Deng, William Brown, Ronald Manning and Samir Wahab. Annual meeting of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
- "Sensitivity of USP Prednisone Tablets Reference Standard Lot P0E203 to Dissolved Gas in the Dissolution Medium". **Pallavi Nithyanandan**, Gang Deng, William Brown, Ronald Manning and Samir Wahab. Annual meeting of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
- "Validation of a Dissolved Gas Meter for the Determination of Dissolved Air Content of Dissolution Medium". **Pallavi Nithyanandan**, Gang Deng, William Brown, Ronald Manning and Samir Wahab. Annual meeting of the American Association of Pharmaceutical Scientists, San Antonio, TX, October 2006.
- "USP Prednisone Dissolution Calibrator Variability Study on USP Dissolution Apparatus 1 And 2". G. Deng, A. Ashley, W. Brown, J. Eaton, M. Liddell, R. Manning, J. Munoz, **P. Nithyanandan**, H. Rowe, S. Tan, S. Wahab. 8th US-Japan Symposium on Drug Delivery Systems, Maui, HI, December 2005.
- "Prediction of mechanical failure in metered dose inhalers (MDIs) using Finite Element Analysis (FEA)." **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby. Annual meeting of the American Association of Pharmaceutical Scientists, Nashville, TN, November 2005.
- "Characterization of Metered Dose Inhaler Robustness: A Stress Analysis and Mechanical Failure Study." **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby. Annual meeting of the American Association of Pharmaceutical Scientists Conference, Nashville, TN, November 2005.

- "Development of a rational test method for the analysis of robustness of inhaler devices." **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby. Annual meeting of the American Association of Pharmaceutical Scientists Conference, Baltimore, November 2004.
- "Analysis of robustness of inhaler devices: Response of pMDIs to mechanical stresses." **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby. Respiratory Drug Delivery IX conference, Palm Desert, California, April 2004.
- "Determination of the operational limit and mode of functional failure of Metered Dose Inhalers." **Pallavi Nithyanandan**, Stephen Hoag and Richard Dalby. Philadelphia Pharmaceutical Forum, Philadelphia, March 2004.
- "Manipulation of particle size of aerosol formulation ingredients using a fluid-energy mill." **Pallavi Nithyanandan** and Richard Dalby. Annual meeting of the American Association of Pharmaceutical Scientists, Toronto, Canada, November 2002.
- "Powder flow analysis using a novel approach." W. Mark, **P. Nithyanandan**, A. Usayapant, A. Goldberg, W. Bubnis, T. Koch. Annual meeting of the American Association of Pharmaceutical Scientists, Toronto, Canada, November 2002.
- "Assessing drug-drug interactions via moisture sorption analysis." W. Mark, D. Theim, K. Gladysz, H. Akin, T. Koch, **P. Nithyanandan**, S. Pinnamaneni. Annual meeting of the American Association of Pharmaceutical Scientists, Denver, CO, October 2001.

Podium Presentations

- "Dissolution Variance Study of commercial Dosage Forms." Presentation at the USP Biopharmaceutics Expert Committee Meeting, December 6, 2006.
- "Measurement of Dissolved Gases in Dissolution Media." Presentation at the USP Biopharmaceutics Expert Committee Meeting, March 21, 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.
- "Powder flow analysis using a novel approach." Wyeth Consumer Healthcare, Richmond, Virginia, August 2001.

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.