# David Cline, Ph.D.

## Thesis Abstract

### OPTIMIZING DRY POWDER INHALER FORMULATION PERFORMANCE USING SURFACE ENERGY AND AREA

Pulmonary delivery of active pharmaceutical agents via Dry Powder Inhalers (DPI's) has attracted much attention in recent years as an alternative to pressurized metered dose inhalers (pMDI's). DPI formulations typically consist of either drug alone or drug blended with an inert carrier as an ordered mix. Upon aerosolization the powder formulation must de-aggregate into drug particles in the 1-5 mm range for effective pulmonary delivery. This work estimates the surface energy and specific surface area of the individual powders in the formulation, proposes a model that correlates these formulation parameters to DPI/formulation performance, demonstrates the effect of jet milling and spray drying on powder surface energies, shows the influence of surface energy alterations on aerosol performance and modifies the surface energy of micronized material by coating with surfactants. Surface energy and specific surface area values were determined using Inverse Gas Chromatography (IGC). IGC is a technique that uses retention time and surface tension data of non-polar and polar probes (injected onto a packed column of the powder of interest and analyzed using a standard Gas Chromatograph) to estimate the surface energy of the powder. DPI formulation performance was examined by cascade impaction using a Multi Stage Liquid Impinger (MSLI). MSLI data from eight formulations, consisting of combinations of drug (albuterol base, ipratropium bromide) and carrier (trehalose dihydrate, lactose monohydrate, mannitol), correlated well (R2 > 0.9) with a model of particle interaction based on surface energy and specific surface area data from IGC experiments. Jet milling of albuterol sulfate caused a dramatic increase in the surface energy, which could then be reduced by spray drying a suspension of the jet-milled material in an organic solvent. A formulation containing jet milled albuterol sulfate, with a high surface energy, exhibited a lower fine particle fraction than a similar formulation containing spray dried albuterol sulfate with a low surface energy. Additionally, coating micronized drug with cholesterol or phosphatidylcholine reduced the surface energy of jet-milled albuterol sulfate. This work provides a researcher with methodology to estimate and optimize particle interactions in a DPI formulation and may potentially be expanded to other powder systems.

## Education Summary

- Aug. 1998 - Present: Graduate Student, Doctoral Program in Pharmaceutical Sciences University of Maryland School of Pharmacy Baltimore, MD. Expected Graduation, May 2003.
- Aug. 1987 - May 1990: B.S. Chemistry, Virginia Polytechnic Institute and State University Blacksburg, VA.

## Employment Summary

- Eight years of GMP / GLP experience in industry.
- Jan. 1997 - Aug. 1998: Guilford Pharmaceuticals, Baltimore, MD. Development Associate. Developed and optimized processes for incorporation of pharmaceutical compounds into novel biodegradeable polymer matrices (microspheres, films and gels). Developed and validated analytical methods (HPLC, GC, GPC) and conducted experiments to: (1) measure in-vitro release rates of incorporated drug (2) determine stability of bulk polymer under different storage conditions (3) characterize degradation of polymer (4) monitor manufacturing process (5) analyze biological samples (plasma, organ tissue extract) for released drug.

- Nov. 1994 - Dec. 1996: Guilford Pharmaceuticals, Baltimore, MD. Analytical Associate. Developed and validated analytical methods (HPLC, GC) for analysis of raw materials, in-process polymers, finished polymer products and stability testing under GMP requirements. Optimized and maintained novel, on-line flow-through dissolution system to support approved polymer product (Gliadel). Generated SOP's for instrument use, repair and calibration to comply with GMP requirements. Coordinated equipment calibration program. Trained new employees on testing methodologies and provided technical assistance.
- May 1990 - Nov. 1994: ALPharma, Baltimore, MD. Research Scientist. Developed and validated stability indicating methods (HPLC, GC) for analysis of liquid dosage form pharmaceutical products. Provided analytical support for new raw material testing, in-process/process validation batches and stability testing of development/submission batches. HPLC: Reversed-phase, Ion-exchange and Size Exclusion separation techniques Ultraviolet, Refractive Index and Electrochemical detection techniques Extensive experience with small (< 1000 mw), ionic molecules GC: Gas-liquid capillary and packed column chromatography with FID and TCD detection. Experience with residual solvent analysis, derivatizations and chemical purity. Others: FTIR, UV spec, laser diffraction particle size analysis, Karl Fisher moisture determinations, solid-phase extraction, limited mass spec experience.

## Publications

- Predicting the Quality of Powders for Inhalation from Surface Energy. Pharmaceutical Research, Volume 19(9), September 2002.

## Presentations

- Altering the Surface Energy of Albuterol Sulfate by Spray Coating, **D. Cline** and R. Dalby, Submitted for AAPS 2003 Annual Meeting, Salt Lake City, UT.
- Predicting the Quality of Powders for Inhalation from Surface Energy. **D. Cline** and R. Dalby. 2001 AAPS Annual Meeting, Denver, CO and 2002 Respiratory Drug Delivery Meeting, Tuscon, AZ.
- Predicting the Quality of Powders for Inhalation. **D. Cline** and R. Dalby. 2001 Inverse Gas Chromatography Conference, London, England.
- Controlled Release of Lidocaine Using Biodegradeable Polyphosphoester Polymers". W. Dang, **D. Cline**, Z. Zhao, G. Su, E. Aaron and E. Spicer. 1997 AAPS Annual Meeting, Boston, MA.
- Design of Novel Biodegradeable Polyphophoesters for Controlled Drug Release. Z. Zhao, G. Su, W. Dang, **D. Cline**, W. Dai, E. Aaron, E. Spicer, D. Nowotnik and J. English. 1997 AAPS Annual Meeting, Boston, MA.
- Applications of 5cm Analytical Chromatography Columns for Pharmaceutical Useage. D. Cline, R. Bell. 1993 Fourth International Symposium for Pharmaceutical and Biomedical Analysis. Baltimore, MD.

## Professional Affiliations

- AAPS, Student Member
- Pharmacy Graduate Student Association, President

## Honors and Awards

- 2002 Member, Pharmaceutical Sciences Department Chair Search Committee

- 2002-2003 Shangraw Fellowship recipient
- 2000-2001 and 2001-2002 United States Pharmacopiea Fellowship recipient
- 2001 Student Travel Award (given by conference organizers after review of abstract) to present research at the 1st International Conference on Inverse Gas Chromatography, London, UK.
- 1999-2000 Department of Pharmaceutical Sciences Merit Award recipient
- 1998-1999 University of Maryland Student Employee of the Year (Teaching Assistant)
- Lecturer for Bioanalytical Separations class on HPLC Theory and Maintenance.
- Respiratory Drug Delivery (2000 and 2002) organizational team member.
- Inhalation Aerosol Technology Workshop lab instructor (2000, 2001, 2002).