The Center for Structured Organic Particulate Systems (C-SOPS)
Eighth-Year Annual Report

EXECUTIVE SUMMARY

During the calendar year, 2013, the Center for Structured Organic Particulate Systems (C-SOPS) made significant progress, realizing several achievements that support the goal of understanding the effects of material properties and process parameters on the structure and functionality of pharmaceutical products, while at the same time developing transformative technologies for improving the manufacture of existing products and for the development of manufacturing methods for new products.

We understand that the ultimate stakeholder of the Engineering Research Center-Structured Organic Composites (ERC SOPS) is Society, which requires high-quality and lower-cost pharmaceutical, agrochemical and food products. During the past seven years, the Center has strategically concentrated on the pharmaceutical industry, and thus our additional stakeholders include specific pharma-related industries and their key regulatory agencies, such as the FDA.

The societal requirements have established the landscape of the system level plane, which includes all three current test beds (continuous manufacturing, stripfilms and multilayer, drop-on-demand-based printed systems). The requirements also include the workflow management framework and the real time process management infrastructure (Model Predictive Control, Real-Time Operating systems and Exceptional events Management.

Elements that serve as the main driver for the fundamental knowledge plain (SOPS delivery requirements) are expressed in terms of the FDA regulatory language as critical material attributes (CMA), critical process parameters (CPP), and critical quality attributes (CQA). Based on these requirements, we have identified the following fundamental research areas: Kinetics of particle interactions, multiphase transport, interfacial and colloid science, multi-scale modeling and structure characterization, bulk powder mechanics, reduced order modeling for design and control of manufacturing processes, and molecular dynamics.

A. Achievements in the Reporting Year

In order to overcome the barriers on informatics, property identification and prediction, functionalization approaches and an understanding of the behavior of complex fluids, we made advances in fall three planes (*Technology Integration*, *Enabling Technology* and *Fundamental Science)*. Below are outcomes at the system level and the integrated systems test beds for each level

1. Technology Integration

The key scientific deliverables include development of advanced knowledge of particle engineering techniques to develop engineered formulations and understanding of API-excipient interactions. For more information see Volume I, Pages 62-63)

- We discovered that the impact of processing parameters and stabilizer/drug loading ratio on milling dynamics in bead mills was explained by changes to the bead oscillation velocity and frequency of single bead oscillations. Micro-hydrodynamic analysis of milling experiments explain why a single high drug loaded batch (≥30%) is more efficient than multiple dilute milling batches for drug nano-particle production.

- We discovered that process intensification of the WSMM process with 100 micron beads led to sub-100 nm median size for Griseofulvin (GF) and Naproxen (NPX) particles within 30 minutes with reduced media contamination and energy consumption.

- We discovered that the use of ultrasound during melt emulsification of drugs allowed formation of stable nano- and micro-particles through enhanced disaggregation and effective adsorption of the stabilizers. (For more information, see Volume I, page 64)

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2. Enabling Technology

We identified enabling technology research areas: modeling and simulation toolbox for design, control, optimization and process validation, methods for characterization and testing of material properties, and sensing methodologies. These research activities are required to overcome the enabling technology plane barriers, which in turn are needed to deliver the function-performance engineering relationships to the system level plane. These barriers include lack of scalable techniques for sub-micron particles, lack of spatially resolved characterization methods, lack of protocols for predicting biological response, and a paucity of sensing methodologies for critical in-process material properties. (Volume I, Pages 62, 70 and 74)

- We investigated powder flow behavior and successfully installed a NIR probe in the Fette feed frame for real time determination of drug concentration.

- We discovered a novel tapping hopper feeder, which provided very accurate feeding for free flowing powders and cohesive powders down to as low as 250g/hr feed rate.

- We discovered that continuous blenders delivered superior blending performance to batch blenders for mixing strongly segregating blends having components with dissimilar properties. Such blends require much lengthier and expensive granulation processes if manufactured in batch mode.

- We discovered that we could enhance formulations for polymer film dosage forms by using super-disintegrants and different polymers. Faster disintegration and dissolution, as well as better content resulted in uniformity.

3. Fundamental Science

There are only three academic research groups in the world, including our ERC, that have been working on the pharmaceutical informatics challenge, and our ERC effort is generally recognized as the leading one. Similarly, our efforts in exceptional events management are also at the leading edge in the use of intelligent, automated, systems to address manufacturing failures in the pharmaceutical industry. This is a new, unchartered, area but the development of fundamental science-based understanding in powder feeding is very valuable.

- We discovered and designed a new microwave sensor signed for measuring blend uniformity. Whereas most microwave sensors have a single resonant frequency, the new instrument operates with six resonances over the 1-8 GHz region. We discovered that it delivered comparable accuracy to NIR probes with much more simple calibration requirements.

- In cooperation with the Purdue team, a mass flux meter was developed by En' Urga, Inc., a small business located in West Lafayette. We plan to install it on TB1. It uses a soft x-ray source (10 to 50 keV) and sensors that measure absorption through a falling powder. Velocity is measured using differential velocimetry and the extent of absorption as a measure of mass to compute the mass flow rate.

- We utilized several techniques that enhanced our understanding of powder-based feeding. These include in-line content measurement of poorly soluble active pharmaceutical ingredients (APIs) using a fiber optic Raman spectrometer during stripfilm formation in test bed 2. When we monitored moisture content by NIR, we found that we can prevent over-drying, which leads to brittle films. We also discovered that the application of microwave sensor for powder moisture content measurement and ribbon density on the dry granulation line at Purdue. NIR, webcam and microwave sensor have been integrated with the control platform for closed-loop operation.

4. Education and Workforce Development: University Education

We are continuing to educate the general public about pharmaceutical engineering through participation in organizations, campus/community events, and interactive exhibits. Nine in-service teachers participated in the Research Experience for Teachers (RET) program. They worked in project teams to advance the understanding of nano-materials' applications and to incorporate relevant STEM lesson plans into their teaching portfolios.

We expanded the recruiting database for the Research Experience for Undergraduate Students (REU) to include more than 500 applicants; special efforts were made to recruit under-represented minority students. The successful program provided more than 15 undergraduate students with an opportunity to work side-by-side with ERC research groups at C-SOPS on innovative, relevant, discovery-based projects. These students worked under the guidance of faculty, post-docs and graduate students.

The C-SOPS Engineering Projects in Community Service (EPICS) team has graduated more than 80 members during the team's eight semesters in existence. Mechanical engineering and senior design teams included the EPICS program as a part of their capstone experience. Also notable is that eight PhD students graduated during the 2013 calendar year; 36 doctoral students have graduated from the Center since its inception.

An important development in 2013 was the decision to make the courses in the Mechanical Engineering (ME) program available on line. There were six ME graduates in 2013 (three in January, two in May, one in October). The certificate program at UPRM continues to be successful; in the past six years over 12 undergraduate students have graduated (half of them women).

5. Education and Workforce Development: Pre-college education

C-SOPS has developed several projects that target K-12 students, teachers and faculty.

- <u>Governor School of Engineering</u>: At the K-12 level, the Governor's School for Engineering at Rutgers is a mechanism to get high school juniors with exceptional talent in science and engineering involved with C-SOPS researchers.
- <u>Science on Wheels</u> - This program involves a dedicated bus/van to introduce pharmaceutical concepts to middle and high school students. Currently, the Science

on Wheels Education Center provides infrastructure for a host of related programs at UPRM.

- EPICS - The Purdue Engineering Projects in Community Service has programs that target a range of students. The manufacturing line is used in K-12 outreach activities, the Minority Engineering Program Summer Engineering Workshops (for 6-8th grade students) and the Multiethnic Introduction to Engineering Program.
- Future Scholars Program - The Rutgers Future Scholars Program increases the number of high school graduates who come from less-advantaged communities for admission to colleges and universities and to provide tuition funding to those who choose to attend Rutgers University. The program won two 2013 NASPA Excellence Awards.
- PESCa - The Pharmaceutical Engineering Summer Camp engaged 24 high school students in a one-week program (180 applicants from 29 cities within Puerto Rico). To date, 68 Puerto Rican students have participated. The goal is to expand the interest in STEM fields for high school students.

6. Education and Workforce Development: General Outreach

The C-SOPS education and outreach vision has been implemented using a strategic plan developed by the core constituencies that make up the educational pipeline. The general program is shown as the fishbone diagram (see Volume I, Page 103, [Figure 3.1]). The central aspect of the strategic plan is to coordinate efforts at select programs among the partner institutions to cover the range of constituencies from K-12 through undergraduate and graduate education.

7. Education and Workforce Development: Diversity advances in the Center

The ERC-SOPS recognizes diversity as an essential component of its education and research efforts, and positively strives to maintain and increase the diversity of its participants at all levels. Diversity goals include increasing the diversity of faculty involved in the ERC-SOPS through recruitment and retention; increasing diversity of K-12 participants (students and teachers), undergraduate and graduate students participating in ERC-SOPS research and education programs; increasing diversity of students recruited to undergraduate and graduate programs in pharmaceutical engineering. (Volume I, Page 161)

Our ongoing programs include utilizing the center and its surrounding communities (six institutions) as an educational environment where learning has no boundaries. Over the past year we have increased the numbers of underrepresented minorities and women in all roles at all levels of the Center. The Center's proactive efforts in this direction have already produced tangible results, as reflected in the current make-up of the center reported in Volume 1, Page 171, Table 7f.

8. Technology transfer and commercialization: Innovation achievements

C-SOPS developed a multi-faceted strategy to speed the adoption of our technology into industrial practice and eight new companies joined this year.

The very close interaction (IAB meetings, project reports, project mentor meetings, etc.) has allowed many pieces of Center technology to be transmitted to and implemented by, our industrial partners very informally and very quickly after development (See Volume 1, Pages 131-136, Table 4-3).

The close collaboration has also led to transformative projects with industry such as the continuous manufacturing project at Janssen Ortho, LLC. ERC graduates have contributed to the Janssen Ortho project and others have been fulfilling both our mission and the terms of our membership agreement, which grants each member a NERF license for in-house use of center technology. Although most of the basic science we develop is put into the public domain fairly quickly, we make our industrial partners privy to the information many months (or years) in advance of the public.

9. International partnerships/collaborations

Two other important components of C-SOPS' configuration include the Scientific Advisory Board (SAB), and our ERC's international network of collaborators. The SAB membership broadly spans engineering and pharmaceutical technology expertise with members both from the US and Europe. We have listed the current detailed SAB roster in the Participant table (See Volume I, Page 158).

10. Center Infrastructure, including personnel (personnel diversity)

The disciplinary diversity of the research faculty is illustrated in Volume 2, Section 2.1, Page 31, for the research faculty. When considering the entire team, including colleagues that are involved in Education, Outreach, and Leadership/Administration, disciplinary distribution is as follows: 17 Chemical Engineers (Muzzio, Ierapetritou, Glasser, Ramachandran, Pedersen, Shapley, Davé, Bilgili, Acevedo, Mendez, Velazquez, Litster, Harris, Reklaitis, Beaudoin, Nagy, Cardona), six Chemists (Romanach, Mitra, Iqbal, Erenrich, Hausner, Chadwick), three Physicists (Dutt, Drazer, Tomassone), 4 Mechanical Engineers (Dave, Wassgren, Nahr, Cuitino), six Pharmacists (Morris, Chougule, Hamad, Taylor, Michniak-Kohn, Li), one Food Scientist (Takhistov), and one Social Scientist (Kaur, Lopez). As discussed later in Section 5.2, this team is also very diverse in terms of gender, ethnicity, and career stage.

See also Volume 1, Page 160, Table 6c, Country of Citizenship for ERC Foreign Personnel.

B. High-Level Response and Status to SWOT (Strengths, Weaknesses, Opportunities and Threats)

The 2012 analysis revealed potential threats and weaknesses. (For more information, see Volume I, Pages 347-354) These include:

- *The need to show tangible results to maintain interest, support and commitment from the pharmaceutical industry.*
- *The need to balance big picture commercialization with smaller technology transfer.*
- *The need to provide ongoing support for technology following commercialization.*
- *The need to develop a plan that can be implemented to survive in the event that commercialization fails.*
- *The need to overcome potential industry perception of sustainability when NSF funding ceases.*
- *The need to promote the concept that major vendors have a substantial vested (financial and otherwise) interest in C-SOPS success.*
- *The need to address competition.*

During 2013, C-SOPS took the following actions toward SWOT resolution:

Information sharing:

We adopted a new user-friendly platform in which we could manage and share project team data among researchers and industrial mentors. The C-SOPS website has been upgraded and will soon be available for reporting and dissemination of IAB materials.

Mentor Support:

We have dedicated a staff member to focus on information dissemination and a structured meeting schedule so that both companies and project teams are kept informed. We are proud of our successful project mentor program and via monthly project meetings we will ensure we and our partners maintain communication.

FDA interactions:

During 2013 we increased our direct engagement with the FDA. We held our fall IAB meeting in Maryland with the specific purpose of further engaging the FDA. In addition, we are trying to determine how we can best meet the request of our members to develop a spin-off consortium for industry to engage with regulatory authorities.

Generics:

We believe that the broad scientific focus of our research creates an attractive value proposition to generic companies and we have initiated a number of C-SOPS- supported mini-consortia with more specific focuses and services. Our goal is promote a mutual engagement so that we can grow our relationships with these companies in the future. We also believe that the market itself will be driving these companies towards our services as continuous manufacturing becomes more and more prevalent within the industry.

Competition:

We do not believe that there is undue level of competition in research associated with C-SOPS projects and test beds as we have sought to minimize duplication of activities, which could give rise to significant internal competition. Some degree of competition may arise in the initiation and execution of associated projects, which generally involves arrangements between specific ERC researchers or teams as well as industrial or other outside partners. We believe that some level of competition is healthy in this domain as it stimulates initiative and entrepreneurship on the part of the faculty and researchers in general. The leadership team will continue to make efforts to insure that opportunities which do arise are more transparent to all researchers and that the spirit of collaboration is not diminished by competition.