IMPACT Newsletter

Feburary 2006
Volume 1, Issue 1

IMPACT Technology Consultants, 9 Tabor Hill Road, Lincoln, MA 01773 Phone: (508) 951-2436

In this Edition:

Welcome to the IMPACT Newsletter

Welcome to the first issue of the IMPACT newsletter. The newsletter will be published 2-3 times per year and will cover a range of process development and scale-up projects.

Our goal is to present our approaches to developing, scaling-up, and optimizing both process and product technologies for a broad range of industries. We hope that our clients and prospective clients will find applicability within their own development programs, potentially even in new areas. We will attempt to provide as much detail as possible, within our limits of confidentiality obligations, so that the articles will be interesting to a broad audience.

We welcome your comments and suggestions on our newsletter. If you have questions or would like to hear more about any of the projects discussed in this newsletter, please contact us.

Using Lasentec® Systems for Real-Time Mixing Process Scale-Up

In early phases of process development there is significant value in having real-time feedback on the effects of input parameters on product properties. This is especially true in solid-liquid systems, for example crystallization or liquid-solid extraction processes. Real time feedback is useful for assessing and modifying the evolution of particle size distributions due to competing effects of coagulation and attrition. Typically, the controllable parameters are the system temperature, antisolvent addition rate, and shear (stirring) rate.

IMPACT has successfully scaled up and optimized several solid-liquid systems, including crystallization and extraction, using Lasentec's FBRM® real time particle size and concentration measurement system.

Lasentec® FBRM® & PVM®

A recent example is a series of tests underway at IMPACT's R&D laboratory in Devens, MA. The joint IMPACT/client team is preparing to perform a 100 liter mid-scale test.

This test follows a series of small-scale experiments performed in a 5 liter bench system at the client's laboratory.

The 100 liter tests are providing engineers with a second process scale point at 20 times the bench scale capacity and will be used to validate IMPACT's scale-up models. Once validated, these models will be used to scale the process equipment up to full commercial scale (800 liters).

IMPACT employed a Lasentec® to gain real-time particle size data during experimental runs. This gave IMPACT engineers improved insight into shear effects and potential particle size degradation during mixing. The lasentec proved to be an invaluable tool for performing these parametric studies.

IMPACT has extensive experience in process mixing studies including precipitation, crystallization and polymeric particle formation such as for microspheres.

IMPACT technology consultants™

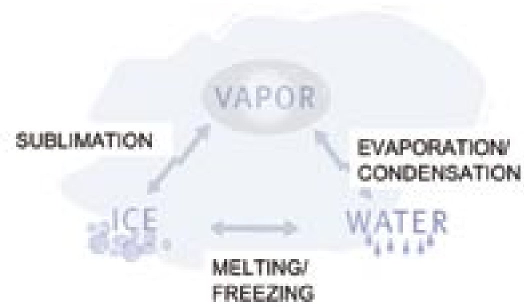
What is Lyophilization and when is it used?

Lyophilization, or freeze drying, is a means of drying, achieved by freezing a wet substance and causing the ice (or solid for non-aqueous applications) to sublime directly to vapor by exposing it to a vacuum.

Biological materials often must be dried to stabilize them for storage or distribution. Drying always causes some loss of activity or other damage. Lyophilization is a method of drying that significantly reduces such damage. Because lyophilization can be the most complex and expensive form of drying, its use is usually restricted to delicate, heat-sensitive, high value materials.

Substances that are not damaged by freezing can usually be lyophilized so that refrigerated storage is unnecessary. Many microorganisms and proteins survive lyophilization well, and it is a favored method of drying vaccines, pharmaceuticals, blood fractions, and diagnostics. Some specialized food products are also lyophilized. They rehydrate easily and quickly because of the porous structure left after the ice has sublimed.

Occasionally materials are lyophilized to achieve a porous, friable structure rather than for preservation. Lyophilizers are sometimes used for concentration of delicate materials.



Technology Highlight: Lyophilization

IMPACT Offers Lyophilization Cycle Development Services

In May of 2005, IMPACT installed a 4.7 ft^2 lyophilizer at its R&D laboratory in Devens, MA and began offering cycle development and optimization services. This unit operation expands IMPACT's capabilities in offering hands-on process development and scale-up services into the science of lyophilization.

The unit is being used to perform feasibility studies, cycle optimizations, small-scale manufacturing, and formulation development for pharmaceutical and specialty chemical clients.

The IMPACT team has a long history in lyophilization; and not only with process development and scale-up activities, but also in the design and construction of lyophilization equipment. IMPACT spent over two years helping a major lyophilization equipment manufacturer improve the reliability and design of their products starting with a process known as FMEA, or Faliure Modes and Effects Analysis (see page 3 of this issue for more on Six Sigma tools such as FMEA).

IMPACT has also developed close relationships with academic leaders in the field of lyophilization, in particular Professor Mike Pikal at the University of Connecticut. IMPACT collaborates with Dr. Pikal to perform fundmental characterization, e.g., DSC and freeze drying microscopy, of materials prior to developing lyophilization cycles. These tests provide critical freeze drying parameters such as glass transition points and collapse temperatures, which are necessary to accurately determine optimal freeze drying cycle parameters.

IMPACT's freeze drying system is capable of processing some solvents in addition to aqueous solutions. Please call to discuss specialized applications.

Modeling Particulate Nucleation, Condensation, and Coagulation

An understanding of nucleation, condensation, and coagulation kinetics is necessary to predict particle size when scaling up a crystallization or precipitation process.

Typically, the approach to developing this understanding is purely empirical, requiring a large number of experiments that are system-specific and provide little true insight into the governing mechanisms. When system scale up is subsequently performed, the process technology developed on the small scale must often be replaced by "scalable" technology on the larger scale, and a new set of experiments must be performed in order to achieve the targeted product properties. If a fundamental understanding of the key parameters has been developed on the small scale, then the number of experiments that must be performed at larger scales and the time and cost to market are reduced.

The key parameters affecting nucleation, condensation, and growth are degree of supersaturation, temperature, shear rate, and solute concentration. Growth of particles from a nucleation pool can be through particle agglomeration or condensation – as determined by the process physics. Interestingly, the physics governing aerosol formation are very similar to the mechanics of small particles forming in solution.

IMPACT has developed a general numerical simulation model for predicting the evolution of particle size distribution (PSD) in solid-liquid and solid-gas systems based on the general dynamic equation of Smoluchowski. This model includes terms for Brownian, gravitational, and shear coagulation; nucleation, condensation, and attrition.

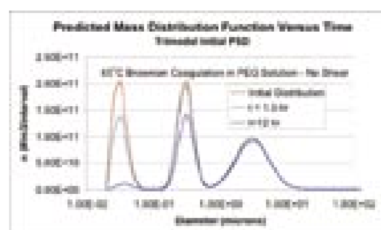
The model has been employed for process development, scale up, and optimization. The biggest value of the model has been to provide a quantitative framework based on fundamental principles for designing experiments, interpreting data, and developing processes.

Use of the model in combination with the experimental techniques described in the article on Page 1 for dynamically measuring particle size distributions results in effective and efficient process development.

Coagulation General Dynamics Equation

$$
\begin{aligned}
\frac{\partial}{\partial t} n(v,t) = \frac{1}{2}\int_0^v \phi(s, v-s)\, n(s,t)\, n(v-s,t)\, ds \\
- n(v,t)\int_0^\infty \phi(v,s)\, n(s,t)\, ds \\
- \frac{\partial}{\partial v}\left[I(v)\, n(v,t)\right] \\
- n(v,t) R(v) + S(v,t)
\end{aligned}
$$

where $\phi(v,s)$ = agglomeration kernel between particles of volume v and s,
$n(v,t)dv$ = number density of particles with volume between v and $v + dv$,
$R(v)$ = removal rate for particles of size v,
$S(v,t)$ = source rate for particles of size v,
$I(v)$ = condensation growth rate



Six Sigma at IMPACT

To survive in today's competitive environment, companies must continually improve quality and productivity. Many leading companies have implemented a proven methodology called "Six Sigma."

Six Sigma is more than a metric; it is a cultural change that puts tools and processes in place to drive continuous improvement. Continuous improvement is measured by its economic effect on the company. Six Sigma initiatives must be economically viable; an improvement in quality that does not increase profits does not fit the Six Sigma philosophy.

Six Sigma enables companies to reduce costly defects and uses data and logic to drive process improvements and measure success. By using it, companies can determine how quickly they are eliminating waste and reducing defects and variations in their processes.

Six Sigma teaches a specific, structured, technique for implementing process improvements to ensure that economic benefits are realized and maintained. The acronym to describe this technique is DMAIC:

- Define
- Measure
- Analyze
- Improve
- Control

(story continued on back page)

Contact: Bill Cox

Phone
(508) 951-2436

Fax
(508) 529-2390

E-mail
bcox@impact-tc.com

Website
www.impact-tc.com

Hands-On Process
Development & Scale-Up

Six Sigma at IMPACT (continued from page 3)

The Six Sigma discipline includes a group of tools, including:

- Quality Function Deployment (QFD)
- Failure Mode and Effects Analysis (FMEA)
- Fishbone diagrams
- Gauge repeatability and reliability (GR&R)

Gary Graves, the newest member of the IMPACT team, has over 20 years of industrial experience leading process development and improvement initiatives employing the tools used in the Six Sigma discipline.

Gary is currently a Green Belt in Six Sigma. He is performing his final project to complete his Black Belt Certification.

Gary also has experience in the development and delivery of training programs to support six sigma teams and Green Belt Certification.

About our Organization

IMPACT Technology Consultants is a team of experienced, advanced-degree chemical engineers with extensive backgrounds in chemical process technology development, scale-up, commissioning, and optimization.

Our mission is to provide process development, scale-up and engineering assistance to all industries including specialty chemical, pharmaceutical, biotech, metallurgical, and medical equipment/devices.

IMPACT also operates a scale-up and process development laboratory located at 88 Jackson Road, Devens, MA. The facility responds to frequent requests from clients to provide an off-site capability in performing process or product research, scale-up, optimization, and troubleshooting experiments.

IMPACT Technology Consultants

9 Tabor Hill Road
Lincoln, MA 01773