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In this Edition:

IMPACT Newsletter Well Received!

Scaling Down to Scale-Up

Technology Highlight: SMART Freeze-Drying®

FMEA: A Simple, Yet Powerful Quality Improvement Tool

Coagulation of Nanoparticles – the “Self-Preserving” Size Distribution



IMPACT Newsletter Well Received!

Earlier this year, we launched the first edition of the IMPACT Newsletter, the goal of which is to present our approaches to developing, scaling-up, and optimizing both process and product technologies for a broad range of industries.

We were pleasantly surprised by the number of positive responses we received from the readership about the usefulness and utility of having a forum like this for specifically discussing process development issues.

We actually received a number of specific topic requests for future editions and we encourage other readers to do the same.

We are also proud of our recently published article on process scalability in the December/January issue of Pharmaceutical Formulation and Quality (PFQ). Full text of this can be found at our website.

Again, thanks for your support and please keep up with the feedback!

Scaling Down to Scale-Up

A recent IMPACT client needed to perform an 8X scale-up of a reaction/ washing process involving suspended particles. A supplier of mixing equipment recommended equipment and operating conditions based on their standard calculations and orders were placed to meet tight time constraints.

However, the client was concerned with how the recommended large-scale mixing conditions would affect the particles. Would attrition lead to yield losses or poor product quality? In addition, the existing 1X pilot system had been dismantled and was no longer available for parameter testing.

One option for studying mixing parameters for a commercial process is to scale the process down to a volume that can be accommodated by readily available equipment and using small quantities of materials.

In this case, the process was scaled down to 0.05X in the laboratory. This allowed the recommended operating conditions from the mixer vendor to be studied and

optimized if necessary prior to plant startup.

Particle attrition was studied through mathematical modeling and using a Lasentec FRBM in-line particle monitoring device. Mixing was determined to contribute to a significant yield loss (~30%) at the operating conditions and resulting shear rates proposed by the vendor.

Optimal conditions were subsequently determined at the small scale that resulted in reduced attrition at lower shear rates, while still maintaining other process requirements, such as full off-bottom suspension of particles and foam re-entrainment.

These new operating conditions were later tested and confirmed during 0.75X scale pilot runs at IMPACT's Scale-up and Development laboratory.

These scale-down and pilot experiments proved valuable by giving engineers a platform to study the process and gain an understanding of the fundamental parameters that govern process scale-

up for their system. The outcome enabled insightful changes in operating conditions at full scale, which minimized particle attrition while achieving process objectives.

This know-how will insure both a smooth start-up of the commercial process and allow the client to achieve significantly higher product yields and profitability.



100 Liter Mixing Vessel at IMPACT's R&D Laboratory

Technology Highlight: SMART Freeze-Drying®

As outlined in our previous newsletter, lyophilization or freeze drying is a method of drying, via sublimation, heat-sensitive materials under low temperature and pressure conditions. It is a fairly expensive process, in both capital and operating costs, and is usually applied to high value products that are available in relatively small volumes (e.g., pharmaceutical actives).

This often places conflicting restraints on development engineers who need to perform a comprehensive process optimization study to minimize production costs yet are limited by material available for testing and/or the associated costs.

Time is often another constraint as a typical development program to optimize a freeze drying cycle can take 3 to 4 months and involve 8 or more runs or batches on an R&D scale freeze dryer. The process involves varying rates of freezing/drying, temperature, pressure, and time in order to achieve a stable, efficacious product in the least amount of processing time.

Experience and skill in this field is a large factor in the total effort and cost required to optimize a freeze drying cycle. Sometimes the lack of material, resources, or time forces development groups to by-pass this critical effort and proceed to production scale with an un-optimized, overly conservative cycle (sometimes twice as long as should

be required). Validation can then lock-in this process inefficiency and cost the company hundreds of thousands of dollars annually in unnecessary operating costs.

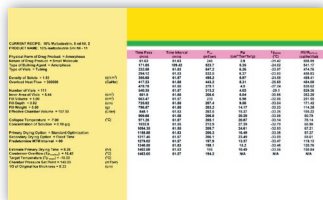
FTS Systems (Stone Ridge, NY and supplier of the R&D scale freeze dryer, LyoStar II) has recently launched an interesting new product for optimizing freeze drying cycles call SMART Freeze-Dryer™ Technology.

SMART is a control platform that utilizes sophisticated control algorithms developed by leading experts in freeze-drying technology at the University of Connecticut and Purdue University to automatically optimize freeze drying cycles often in a single run.

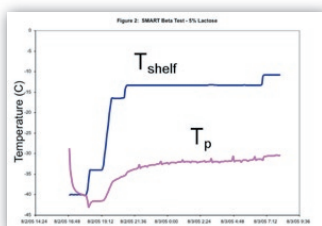
This significantly streamlines freeze drying optimization efforts and saves time, development costs, and material requirements. The advanced level of process monitoring and data also lays the groundwork for SMART to be an effective PAT tool in the future.

For more information on SMART, contact Leslie Mather of FTS Systems at (845)687-5315 or visit www.ftssystem.com. FTS Systems has been a long term client of IMPACT, our involvement including helping to develop and implement the commercialization of SMART Freeze-Dryer Technology.

Step 5
Smart cycle ends and outputs a superior data/calculation set of process knowledge.



Step 4
SMART detects the end of primary drying and automatically proceeds into secondary drying (at higher temperatures)

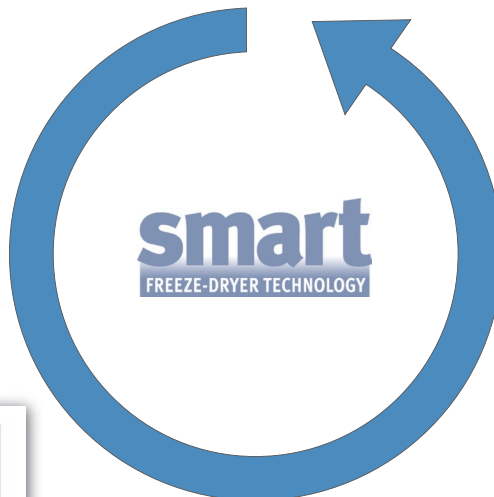


Step 1
Initial Temperature and Pressure are automatically chosen by SMART

Step 2
Once stabilized, MTM measurements and SMART's complex algorithms accurately determine product temperature (Tp)

$$\left[\dots P_{ice} - (P_{ice} - P_o) \cdot \exp\left(- \frac{(N \cdot A_p \cdot 62.3 \cdot T)}{18 \cdot V \cdot R_p \cdot 3600} \dots \right) \right]$$

Step 3
SMART automatically adjusts shelf temperature to achieve optimal product temperature



FMEA: A Simple, Yet Powerful Quality Improvement Tool

Failure Mode and Effect Analysis (FMEA) is a quality improvement tool that has become a mainstream technique in preventing defects, enhancing safety, and increasing customer satisfaction in many industries.

The technique, designed to identify and prevent product and process failures before they happen, is a systematic approach that can be used to improve the quality of product designs and manufacturing processes.

In addition to preventing failures and improving processes, the FMEA methodology also brings order and prioritization to the often numerous competing projects facing companies. This helps direct a finite set of technical resources to work on projects that have the largest impact, which is not always intuitive without proceeding through a structured analysis like FMEA.

Having an extensive prioritized action plan also has some benefit for regulatory inspections such as the FDA or for ISO 9001 audits. Reacting to auditor's recommendations can often be disruptive and cause resources to "scramble".

The FMEA, which is a living document, allows organizations to have set plans for improving operations, including meeting regulatory compliance issues, in a deliberate and structured manner and avoids continual changing of priorities.

How does an FMEA work?

The objective of an FMEA is to identify all possible ways that a process or product can fail or not function as intended. To accomplish this, a cross-functional team (4-7 people) is assembled to provide input and representation from all areas within a company (e.g., engineering, service, manufacturing, marketing).

The team reviews the product or process being studied, analyzing the function of each component or process step and brainstorming, "What could possible fail or go wrong?" All possibilities, no matter how small or seemingly insignificant, are documented.

FMEA Rankings

For each possible failure mode, the team then considers all of the possible effects of the failure and assigns a Severity Ranking for each effect. This ranking, from 1 to 10, is an estimation of how serious the effect would be if the failure occurred.

Next, the team assigns an Occurrence Ranking. The Occurrence Ranking, also on a scale of 1 to 10, is based on how likely or how often a particular failure mode may occur.

Finally, the team assigns a Detection Ranking. The Detection Ranking, again on a scale from 1 to 10, looks at how likely is it that a failure would be detected and possibly prevented.

At this point the three rankings are multiplied to establish a Risk Priority Number (RPN) ranging from 1 to 1000.

Prioritize Failure Modes and Take Action

Once the RPN numbers have been calculated, failure modes are prioritized based on the highest values. Typically, once a company adopts the use of FMEA's as standard practice, a cut-off RPN value is established (e.g. 120). All failure mode RPN's must be under this cut-off, or an action plan is developed to reduce the severity, occurrence, and/or lack of detection to reduce the RPN value. Once the action plan is implemented, the resulting RPN number is recalculated.

THE FMEA Process

1. Review the product or process
2. Brainstorm potential failure modes
3. List potential effects for failure modes
4. Assign a Severity Ranking
5. Assign an Occurrence Ranking
6. Assign a Detection Ranking
7. Calculate Risk Priority Number (RPN)
8. Prioritize failure modes for action
9. Take action to reduce RPN number
10. Recalculate resulting RPN numbers

Coagulation of Nanoparticles – the "Self-Preserving" Size Distribution

Many processes of interest in pharmaceuticals, specialty chemicals, water treatment, and nature are coagulation processes. These include many crystallization processes, aerosol formation, and flocculation-based water purification. A key quality control parameter is normally the particle size distribution, or a related measurement, such as the quartile ratio, the polydispersity ratio, etc.

In cases where coagulation by Brownian motion dominates, small particles will quickly aggregate and form a "self-preserving" size distribution, as described by Friedlander and Wang (1965). A self-preserving size distribution is also predicted by similarity solutions to the Smoluchowski Equation (see our last newsletter). The self-preserving particle size distribution forms regardless of the initial particle size distribution.

Over the years, IMPACT has worked on many coagulation processes, and we have developed a general purpose computational model for simulating collision/coagulation in well-stirred or continuous flow systems in transient or steady-state operations. The basis of the solver is a discretized version of the Smoluchowski equation solved using cubic splines and with added terms for particle break-up and coagulation due to shear,

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Modeling Story (continued from page 3)

thermophoresis, and other important interparticle forces.

Figure 1 provides a comparison of our model predictions with the well-known self-preserving size distribution. In our modeling, we assumed an initial particle size distribution that was normally distributed around 5 nm. As seen in Figure 1, the predicted particle size distribution is developing and is clearly far from self-preserving. By $6.01E-03s$, the distribution almost matches the similarity solution of Swift and Friedlander. By $6.0E-01 s$, the size distribution is fully self-preserving. It is evident that IMPACT's model matches the published similarity solution well at both ends of the distribution.

Near the center of the distribution, the asymptotic similarity solutions are less accurate than our model, resulting in the differences that can be seen in the figure.

A much more difficult test of our model is provided in Figure 2, where combined Brownian and shear-based coagulation of latex particles in water are modeled at two shear rates: 20 and $80s^{-1}$.

Excellent agreement between experimental results and predictions is obtained.

IMPACT has customized this model to address many industrial particle growth,

settling, and attrition problems. Combined with CFD and targeted experimentation, the model is a powerful scale-up and process development tool.

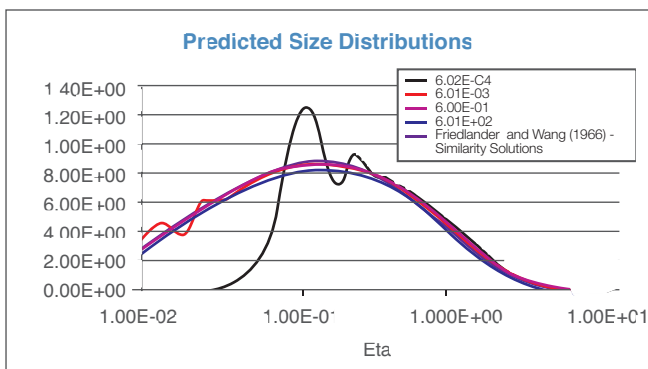


Figure 1: Self-preserving particle size distributions.

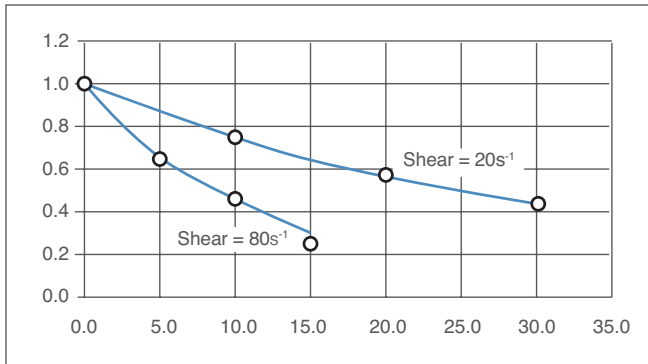


Figure 2: Experimental and predicted normalized particle number density

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.