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Lonza
Pharma & Biotech

Science of Scale for Spray-Dried Intermediates

INTRODUCTION

Speed to market is a critical aspect of developing new pharmaceutical products and scale-up—or scale-down—can play a key part in that process. Significant interest has been focused on the science of scale for spray drying, since this process is the leading technology for formulating drugs with slow dissolution rates or poor solubility, which can lead to poor bioavailability. Compounds with these challenging properties—estimated at 70% of the compounds in drug pipelines today—have a narrow window of absorption in the small intestine, reducing the amount of drug absorbed into the body and significantly decreasing efficacy.

Spray drying effectively addresses this challenge, improving the dissolution, solubility, and, hence, bioavailability of these compounds that might otherwise have to be abandoned, resulting in lost economic and therapeutic opportunities. Spray-dried dispersions (SDDs) have been produced as drug-product intermediates for a wide array of final dosage forms including tablets and capsules.

More than 20 products containing spray-dried intermediates have been brought to market, most within the last 10 years, and dozens more are currently advancing in pharmaceutical pipelines. As a result, substantial pressure has built to develop process understanding and science of scale tools so these promising compounds can rapidly and seamlessly progress from prototype preclinical and clinical formulations directly to commercial scale.

SMOOTHING THE DEVELOPMENT PATH

Based on more than 20 years of experience in developing SDDs, Lonza has identified some critical steps that can smooth the development pathway, eliminating scale-up headaches down the road.

The first step, identifying the optimal formulation, is grounded in a thorough understanding of the problem statement to determine if spray drying is the best approach. The critical question that must be answered is what mechanisms are causing poor drug absorption? To provide answers, proprietary screening methods have been developed that require milligram quantities of active pharmaceutical ingredient (API), which is often expensive and in short supply, particularly in early phase programs. These methods include an amorphous solubility test and a membrane flux test, both of which can be conducted for API combinations with different crystallization-inhibiting polymers, allowing rapid formulation identification.

The second step is to use our laboratory-scale spray dryer, specifically designed in-house based on scale-down analysis, with custom heat- and mass-transfer models to identify the preferred spray-drying process. Again, this modelling work requires only small quantities of API to assess feasibility quickly. Modelling results provide a firm basis for process scale-up to larger spray dryers, eliminating time-consuming formulation and/or processing rework as the product advances to clinical and commercial scales. An example of formulation progression and spray-dryer scale-up is shown in Figure 1.

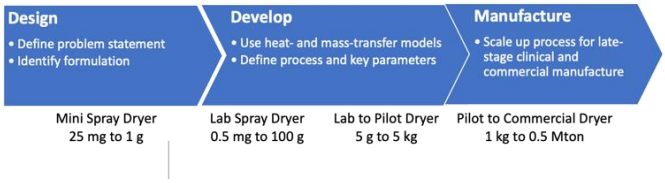
IS BIGGER ALWAYS BETTER?

In the past, scaling of a spray-drying process has involved scaling up to large commercial spray dryers. However, science of scale must address smaller scales as well to provide fundamental knowledge for successful scale-up. This can be especially relevant for the growing number of specialty drug applications where commercial volumes are typically low. Particularly in early feasibility assessment work, scale-down knowledge is vital, addressing the question of how robust the formulation and process is that's developed for preclinical assessment of the API and formulation.

Lonza has designed and built its laboratory spray dryers around the smallest pressure-swirl atomization nozzles commercially available. This allows preclinical development work to proceed with as little as a few hundred milligrams of API and results in similar SDD properties that are targeted at large scale. Based on our extensive experience, the process can then be translated directly into larger dryers with significantly larger batch sizes. The data generated by our modelling work in the preclinical runs make replicating these results in larger-scale production runs straightforward.

Figure 1

Example formulation progression and spray-dryer scale-up



In response to market trends of smaller-volume, more-patient-centric and higher-value products, we are also developing an alternative scale-up strategy involving the use of a series of smaller, high-throughput dryers. To show the relative market need for efficient scale-up of these specialty applications, 44% of the U.S. FDA's Center for Drug Evaluation and Research (CDER) drug program approvals in 2019 were for rare and orphan diseases, i.e. conditions that affect fewer than 200,000 patients.

This approach—known as "numbering up"—accommodates smaller batch sizes, adding flexibility during the development process and reducing capital expenditures and space requirements for larger equipment as production runs become larger. This numbering up scale-up strategy is an effective approach for addressing the smaller batch sizes needed for specialty and orphan indications, provides significant manufacturing flexibility if commercial demands fluctuate significantly.

MORE PROCESSING INNOVATIONS

Science of scale work has also resulted in another innovative spray-drying process, aimed at delivery of compounds with low solubility in both water and the organic solvents that are typically used for spray-drying. If an API is poorly soluble in a spray solvent, it results in a low-concentration spray solution that requires longer processing times and larger equipment.

To overcome this challenge, Lonza has developed a proprietary heated spray-drying process. A suspension of API in spray solvent is pumped through an in-line heat exchanger immediately before the spray nozzle. By elevating the temperature of the spray solvent (sometimes to more than 100°C), we can attain API concentrations that are often more than 10 times those using conventional processes operating at room temperature. This approach improves efficiency, reduces processing time, and reduces the size of equipment needed.

NEW TOOLS FOR OTHER PROCESSES

Science of scale work has provided the impetus needed to ensure that process engineers have the right equipment available at the right scale at all stages of development. Using the science of scale approach has resulted in equipment innovation across other pharmaceutical technology areas used extensively in specialty and enhanced drug applications

Fluid-Bed Innovation

Science-of-scale was used to scale and transfer a fluid-bed spray-layering technology by developing a miniaturized fluid-bed process for early feasibility programs. This established technology continues as a key formulation approach in modified and targeted drug delivery, as well as paediatric drugs. Again, this scaled down process required only minimal quantities of API. Modelling work with the miniaturized process has made the transition to larger batch sizes on larger equipment seamless.

Equipment Innovation

A specialized and proprietary encapsulation machine was developed for laboratory scale to support the evaluation of liquid-filled hard capsules (LFHC) used in addressing solubility issues for highly lipophilic compounds, and for oral solid dosing of highly potent compounds. Lonza's proprietary capsule filling system (CFS 1200™) precisely fills and seals up to 1,200 capsules per hour for early-stage development and rapid advancement to human studies. With science of scale principles in mind, the filling and sealing mechanisms and equipment used for this machine are the same as those used on the commercial liquid-fill encapsulation machines, which can manufacture more than 100 million LFHC units annually, thus simplifying the scale-up process.

SUMMARY

Effective technology scaling requires in-depth knowledge of problem statements, process parameters, tools, and equipment. Lonza scientists and engineers have been instrumental in the development, characterization, production, and scale-up of SDDs as drug-product intermediates. In addition to equipment suitable of all phases of development (drug discovery through commercial manufacture under Good Manufacturing Practice [GMP] conditions), Lonza has developed proprietary modelling techniques and equipment to ensure that scaling of processes is as seamless as possible. We also provide integrated formulation and product development, analytical method development, and manufacturing services. To learn more, please visit our website.