Recro Gainesville is a contract development and manufacturing organization (CDMO) that provides oral solid dosage (OSD) form development, regulatory support, clinical and commercial manufacturing, and packaging and logistics services to the global pharmaceutical market. Based in Gainesville, GA, the company operates facilities totaling 120,000 square feet and specializes in modified-release OSD products and DEA-controlled substances.

Recently, a new customer asked the CDMO to reformulate an immediate-release OSD with a dosing regimen of 3 times per day to create an extended-release product with a complex release profile and a dosing regimen of twice per day. Drug product manufacturers often want to reformulate multidose products into once- or twice-daily dosage forms because reducing the dosing regimen can increase patient convenience and adherence and may also reduce potential side effects.

**A complex reformulation**

The customer's reformulation presented a challenge, because the product carried a high drug load and contained two chemically incompatible active pharmaceutical ingredients (APIs), each requiring both immediate- and modified-release components. Because of the specific and elaborate pharmacokinetics (PK) requirements, the formulation team conducted multiple feasibility PK studies.

To allow formulators to easily adjust the dosage strength and the ratio between immediate and modified API release, the product's dissolution profile needed to be tunable and the dosage form needed to be modular. Also, because the APIs were chemically incompatible and required different dissolution profiles, they would need to be isolated from each other in the dosage form.

The formulation team quickly determined that matrix and bilayer tablets would be difficult to fine-tune, and a mini-tablet format would be impractical, so they decided to pursue a multiparticulate capsule dosage form. Multiparticulate capsules are a common solution for products with complex PK profiles because they can be filled with multiple populations of pellets, allowing formulators to easily adjust the API content and release rates.
The team needed to develop four pellet types using different amounts of various polymers to produce the release rates required for the specified PK. The formulators could then vary the type and amount of polymer and the quantities of each pellet population in each capsule, making the dosage strength and release rates modular and tunable.

With the dosage form selected, the next step was to determine how to form pellets with large API loads. To create multiparticulate pellets, companies often use Wurster coating, in which a solution or suspension containing the API and a film-forming agent is sprayed onto a substrate such as sugar spheres, creating pellets with a high-quality coating.

The Wurster coating process is relatively slow, however, and the pellets may require multiple coatings to achieve a high enough drug load. Multiple coating steps create larger pellets, which can increase the size of the final dosage form, making it too large for patients to easily swallow. Also, because this product required four separate populations of high-drug-load pellets, the formulators would need to split each batch into sub-lots for additional coating, and the process would have been prohibitively time consuming.

An efficient solution

For a more efficient method of creating the multiparticulate pellets, Recro turned to the Granurex GX-40 rotary granulation system from Freund-Vector, a global supplier of processing equipment and services to the pharmaceutical, nutraceutical, and other industries.

“Recro’s ongoing relationship with Freund-Vector is very collaborative,” said Myke Scoggins, director, product development at Recro Gainesville. “Freund-Vector provides specific equipment recommendations and troubleshooting assistance during formulation and process development as well as expert assistance when scaling from development-scale batch sizes to commercial volumes.”

The Granurex system can be used for spherical granulation, dry powder layering, and Wurster-like coating, either separately or in combination for fast, efficient processing.

“When the Granurex was first introduced to the market, it was designed as a stand-alone system,” said Ryan Crawford, process development scientist at Freund-Vector. “Later, its design was modified to be an insert into the VFC Flo-Coater product line. This allows the Granurex to be interchanged with Wurster and top-spray granulation processing.” While the system used for this project is one of the original, stand-alone designs, Recro also has VFC Flo-Coater technology available for projects where these additional processing applications would be useful.

The system uses a conical rotor to spin a core substrate material—in this case 30/35-mesh sugar spheres—inside a chamber. The system then sprays powdered API into the chamber via a powder spray gun on one side of the chamber, while spraying a binder solution from a spray gun on the other side of the chamber. Both spray guns are completely submerged in the rotating material bed. This process simultaneously layers and adheres the API powder directly onto the cores.

The benefits of this method are that it typically requires little binder, quickly applies a large amount of API to each sphere, and produces reliably uniform pellets. In this case, the system’s powder layering function greatly simplified and accelerated the production of the four high-drug-load pellet populations required. The pellets can achieve a 500 percent weight gain in a relatively short time, while maintaining a very narrow particle-size distribution.

“This allows for the coating material to be applied at a 100 percent concentration as opposed to a typical 10 to 30 percent when applying the coating using a liquid carrier. As a result, the coating process is completed more rapidly.”

To finish the multiparticulates, the company uses the system’s solution/suspension coating mode to add a high-quality functional polymer coating to the pellets and achieve the modified-release profile. The team could have completed this step as a separate Wurster coating process, but the one-pot method was much more efficient than transferring the pellets to a different type of equipment and having to develop another set of processing parameters.

A successful outcome

The reformulation required efficient production of a dosage form with high drug loads, complex dissolution profiles, and incompatible APIs. The conical rotor powder layering process enabled significantly higher API loading than a typical Wurster process, achieving a 400 percent weight gain in 8 hours at commercial scale. The ability to coat the pellets in the same vessel further increased production efficiency. The uniformity of the resulting particulate pellets was evident by the narrow particle size distribution after processing. The result was a high-quality, modular, and tunable OSD that exceeded the client’s expectations.

“Working with Freund-Vector has contributed to a more seamless development cycle, helping us to keep the project on track with customer expectations,” said Scoggins. “The Granurex rotor processing equipment is very useful for reproducible production and coating of high-drug-load pellets. Recro will use this process and equipment for other client projects.”

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