Is Wurster Processing the Right Choice for My Multiparticulate Modified Release Dosage Form?

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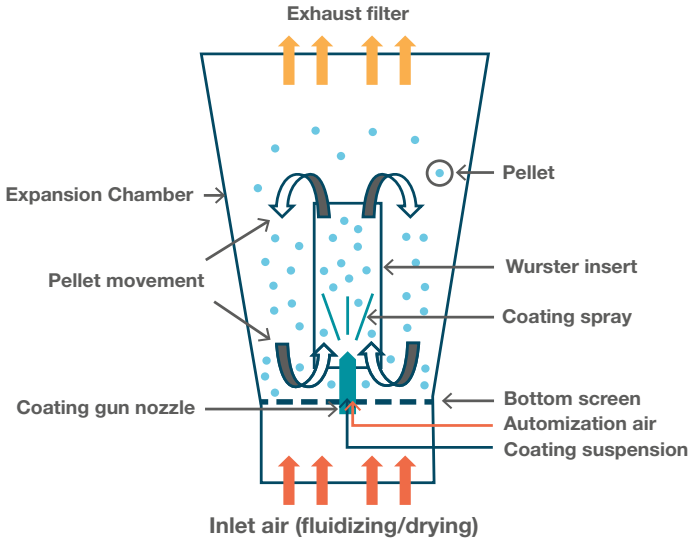
Multiparticulate formulations offer numerous benefits for modified release dosage forms. They allow for the delivery of multiple active pharmaceutical ingredients (APIs) with different dissolution profiles. They make it possible to create a modular and tunable capsule finished product where pellet populations with different APIs or different API release profiles may be filled separately. This allows adjustment of API contents and makes release rates relatively simple, facilitating adjustments to pharmacokinetic and clinical performance. These formulations can also reduce the effect of food on absorption and lessen side effects, such as gastrointestinal irritation. For these reasons, you may have already decided that a multiparticulate format is the best way to get the performance you need for the modified release dosage form you are developing. Now all you have to do is make it.

Wurster processing is a common and appropriate choice for this purpose. But is it the best one? This paper outlines what you need to consider when determining whether Wurster processing is right for your multiparticulate modified release dosage form, as well as general information to assist in discussions with your CDMO.

What Is Wurster Processing?

Wurster processing is a bottom-spray fluidized bed process. It is a one-step, enclosed operation designed to evenly coat individual particles such as pellets with an atomized spray solution or suspension. Core particles — for example, sugar spheres — are fluidized via airflow rising from the bottom of the chamber. An air distribution plate, typically covered with a fine mesh screen, supports the product in the bowl. This chimney-like configuration allows the fluidizing air to flow at higher velocity in the central zone and lower velocity around the periphery of the product chamber. The airflow creates a suspended, fluidized bed of product at the sides with a faster moving central air stream that pulls product particles from the outer zone to the center where they are spouted upwards. In this central spout, a liquid coating is simultaneously sprayed upward into the stream of particles to coat them. The continuous airflow mixes, coats, and dries the particles as they rise in the center of the chamber and fall again at the periphery to be recirculated.



The liquid spray may be an aqueous- or solvent-based solution, a suspension, or a melt. In a well-controlled process, each particle receives a similar quantity of coating, resulting in a uniform population of coated particles. Multi-step processes in which the same or different coatings are layered to achieve desired film thickness and functionality increase the range of possibilities.

Equipment Setup Parameters

Wurster processing equipment must be selected and adjusted for optimal performance in any given task. Proper setup parameters for the air distribution plate, column height, filter material, nozzle aperture, and overall scale depend on chemical and physical attributes of the material to be coated as well as the desired performance of the coating layer.

Setup Considerations for Wurster Processing Equipment

Parameter	Considerations
Scale	Chamber size selection depends on desired batch size and can range from 100 g to 800 kg. Successful coating, especially at larger scales, will rely on understanding of process parameters.
Air distribution plate and product retention screen	Air distribution plate size and hole patterns are designed for a wide range of substrates (from 50 µm particles to pellets and tablets). These parameters affect the fluidization of the particles. Smaller particles call for greater resistance at the plate to achieve optimal product distribution in the chamber.
Nozzle	The binary nozzle tip diameter is an important variable. Smaller nozzles atomize spray more consistently but are prone to clogging. Fine atomization is necessary even at high flow rates, as large droplets lead to agglomeration and lack of consistency.
Column height	The column height, along with the air velocity differential, determines how strongly the particles are pulled into the coating zone. Particle size, shape, bulk density, and the desired velocity of particles as they enter the coating zone all affect optimal column height. In general, it's a good starting point to adjust the column height to maximize product differential pressure without seeing bubbling in the down-bed.
Product filter material	The filter bag prevents loss of material while allowing airflow. An appropriate porosity must be selected based on particle size and experience. The wrong size pores will either lead to excessive loss of material or a clogged bag, either of which affects process efficiency and yield.

Process Parameters

Variables such as airflow, temperature, humidity, and spray rate have a direct effect on coated particle characteristics. It's important to monitor finished particles for particle size, surface morphology, fines, and agglomerates to ensure effective processing for reproducible production.

Processing Considerations for Wurster Microencapsulation

Parameter	Considerations
Airflow	The proper airflow is required to circulate the material and dry the coated particles. If insufficient, agglomeration will occur, especially in longer processes. If excessive, attrition can increase from over-drying and erosion of the cores, or coating stress fractures that alter API release rates.
Inlet air temperature	This temperature affects the rate of drying and must be adjusted to dry slowly enough to let coating material accumulate on the core but not so slowly that agglomeration occurs.
Inlet air dew point	Humidity also affects drying rate as well as the propensity for the accumulation of electrostatic charge. If the humidity is too low, static can cause the bed to seize, resulting in poor coating uniformity and pellet agglomeration.
Nozzle spray rate	Spray rate should be optimized to be as fast as good coating behavior and the drying capacity of the process air flow allow. Slower rates tend to achieve greater uniformity but risk over-drying or spray drying; higher rates improve productivity but risk agglomeration and lower uniformity.
Nozzle spray angle	The spray nozzle plume should be adjusted to achieve efficient atomization and good coverage across the product spout (the spray zone) without hitting the sides of the Wurster column.

Key Formulation Considerations of Wurster Processing

Wurster processing is used in a variety of ways to create multiparticulate modified release dosage forms with a range of functionality. Frequently, gelatin capsules are filled with one or more populations of coated pellets that deliver one or more APIs and have customized release characteristics. But, multiple unit particle systems (MUPS) offer other ways to use coated particles. For example, particles may also be compressed into pellets, or delivered as sachet or stick-pack sprinkles for pediatric or geriatric formulations.

Substrate (primary particle coating)

Wurster coating is typically used to coat individual particles without agglomeration. In this application, it is not a granulation process. A variety of core materials ranging from fine powders to larger pellets can be coated. The outcome should be highly consistent batches with high uniformity and film quality. In general, the particles to be coated should be as close to spherical as possible, nonporous, and reasonably strong. Sharp edges or high particle aspect ratios will lead to more attrition and breakage, as well as inconsistent coating thickness. The most commonly used substrate for Wurster coating is sugar spheres in the range of 250 to 1,000 microns in diameter. Both larger and smaller particles can be coated, depending upon the downstream application, but the process development, particularly for smaller particles, becomes more challenging.

Drug layering

In pharmaceutical applications, the first coating process is typically drug loading. This may be preceded by a seal coat if the core substrate needs preparation or isolation from the drug. Generally, a low-viscosity combination of a water-soluble polymer, possibly a plasticizer, and an antiadherent is used to thinly coat the core in preparation for further additions.

Drug layering is accomplished by creating a solution of the drug in a suitable solvent along with a binder and antiadherent, and sometimes a plasticizer. If drug solubility is a limitation, suspensions can also be used for the drug layering process. Every drug layering solution or suspension should be carefully designed to form a good film after drying that has sufficient drug content, adheres well to the substrate, and isn't too tacky or prone to static charging. Optimizing performance often involves trade-offs. For instance, higher drug or solids content will allow shorter processing times but may lead to poor spray atomization and inconsistent coating or particle agglomeration. Similarly, higher binder or plasticizer content may make a better film at the expense of a lower drug load.

Polymer coating

Once pellets have been loaded with API, secondary or tertiary coats of different polymers can be applied to modify the drug release behavior. A variety of polymers and polymer combinations have been developed to achieve specific release characteristics. For example, polymers such as ethylcellulose or polymethylmethacrylate can be used to form pH-independent, diffusion-controlled release profiles. These are useful options when a longer, steady release of the drug is desired. Alternatively, methacrylic acid polymers are useful to provide pH-dependent release, if, for example, you want to create a pulsed release of the drug after gastric emptying. The formulation decision of what polymers to use should be driven not just by the desired release profile, but also by the expected clinical application, the drug's pharmacokinetic variability, gastrointestinal absorption behavior, chemical stability, and solubility.

The same considerations as for developing a drug layering solution also apply here. The polymer solution or suspension needs to be uniform, of a sprayable viscosity, sufficiently non-tacky to avoid pellet agglomeration, and form a good film with sufficient flexibility to avoid cracking, yet still adhere well to the substrate.

Limitations of Wurster Processing

While Wurster processing is often a promising and adaptable solution, certain situations make it impractical. Your development partner can help you determine whether this method is feasible not just for achieving the desired pharmacokinetic profile with a stable formulation, but also for commercializing it — and if it is, the best process and formulation parameters for scalability and reproducibility.

Batch scale

Wurster processing may work well in small batches but scaling it up successfully requires skill and experience. In general, the Wurster process is more forgiving at batch scales from 1–10 kg. Starting development with a batch size smaller than 1 kg makes it more difficult to scale up to commercial levels. When the desired final scale is in the hundreds of kilograms, a very robust process is needed. The scientist must take care during development to keep scaling parameters and equipment process ranges in mind. Sometimes this means that a process that works nicely at 1.5 kg scale is unacceptable because the larger equipment is incapable of achieving the appropriate air flows, spray rates, or heat transfer rates dictated by the smaller-scale process. Likewise, it's important to keep in mind that an optimized Wurster process will get longer in duration with scale up because the drying capacity of the equipment scales with the cross-sectional area of the air distribution plate (square) while the batch size scales with volume (cubic).

Speed

The batch size limitations of Wurster equipment and duration of spray mean that for complex formulations with multiple coatings or large batch sizes, overall processing times can be much longer than for other oral solid dose processing methods. If high-volume production is expected, you should ask whether a simpler process approach could still achieve the desired product performance. If a high drug load for the core pellet is needed, a tangential-spray powder layering process may be a better choice.

Drug load

In multiparticulate modified release formulations, total drug load versus excipient load must be considered. For one thing, as described above, the manufacturing speed can be affected when many steps are involved. Wurster processing equipment is typically capable of accommodating about 4x weight gain from the initial charge of cores. Accounting for antiadherent, binder, and core weight, the top drug load in a single process pass is limited to about 50%–70%. This pellet potency will be reduced further with the addition of rate-controlling polymer coating. In practice, a finished modified release pellet will contain no more than 50% drug, and often significantly less.

For hard gelatin capsules, taking into account capsule sizes (e.g., 0.91 mL for a 00 capsule) and bead bulk density (often about 0.7 g/mL), the practical, top-end dosage strength is around 300 mg. There are certainly examples of approved multiparticulate modified release capsules with doses higher than 300 mg; this calculation is just a starting point. A high dose may necessitate multiple coating passes and careful optimization (minimization) of other excipient contents. Without careful design, the final dosage form size can turn out to be prohibitive.

Planning for Scale-Up

The FDA focuses on quality by design (QbD) as an approach to scale-up based on preliminary, foundational work done at lab scale. Before scale-up, key variables and their effects on output must be determined. Regulatory authorities expect full documentation of developmental and scale-up batches so the relationship between clinical and commercial processes can be ascertained.

Without experience, scaling up fluid bed processes can be notoriously challenging. The key is to correctly calculate the new process parameters according to the proper geometry of the equipment. Doing this early during small-scale development will help avoid a situation where you later discover proper scaling takes you outside the range of the larger equipment's capability.

Summary

Wurster processing is an extremely versatile technique for developing and manufacturing multiparticulates for use in modified release dosage forms. However, it does have certain limitations and in some cases, other strategies would be better. The Recro® team can help you determine whether Wurster processing is the best option for your project.

If it is the best strategy, Recro is your go-to CDMO for modified release. Recro's organization in Gainesville, GA has been developing and manufacturing multiparticulate dosage forms since the mid-1980s and has used Wurster processing specifically since the late 1990s. Our scientists share decades of experience developing and manufacturing modified release multiparticulate formulations using Wurster processing. With this extensive history, a deep understanding of modified release is ingrained in our organization; our development and commercial teams are ready to leverage their experience to help you design a product that works. With right-sized, proactive management and a proven track record of tackling the most complex formulations, our specialists will deliver a modified release formulation and process that exceeds your expectations.

When You're Looking for the Right Size, Right Partner, and Right Expertise — Recro Is Your Go-To for Modified Release.

About Recro

Recro® provides oral solid dosage form development, regulatory support, clinical and commercial manufacturing, and packaging and logistics services to the global pharmaceutical market. Specializing in modified release oral solid dose and DEA controlled substances, Recro has the experts to deliver our clients' most complex pharmaceutical development and manufacturing projects in our best-in-class facilities, totaling 120,000 square feet. For more information about Recro's flexible CDMO solutions, visit recrocdmo.com.

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