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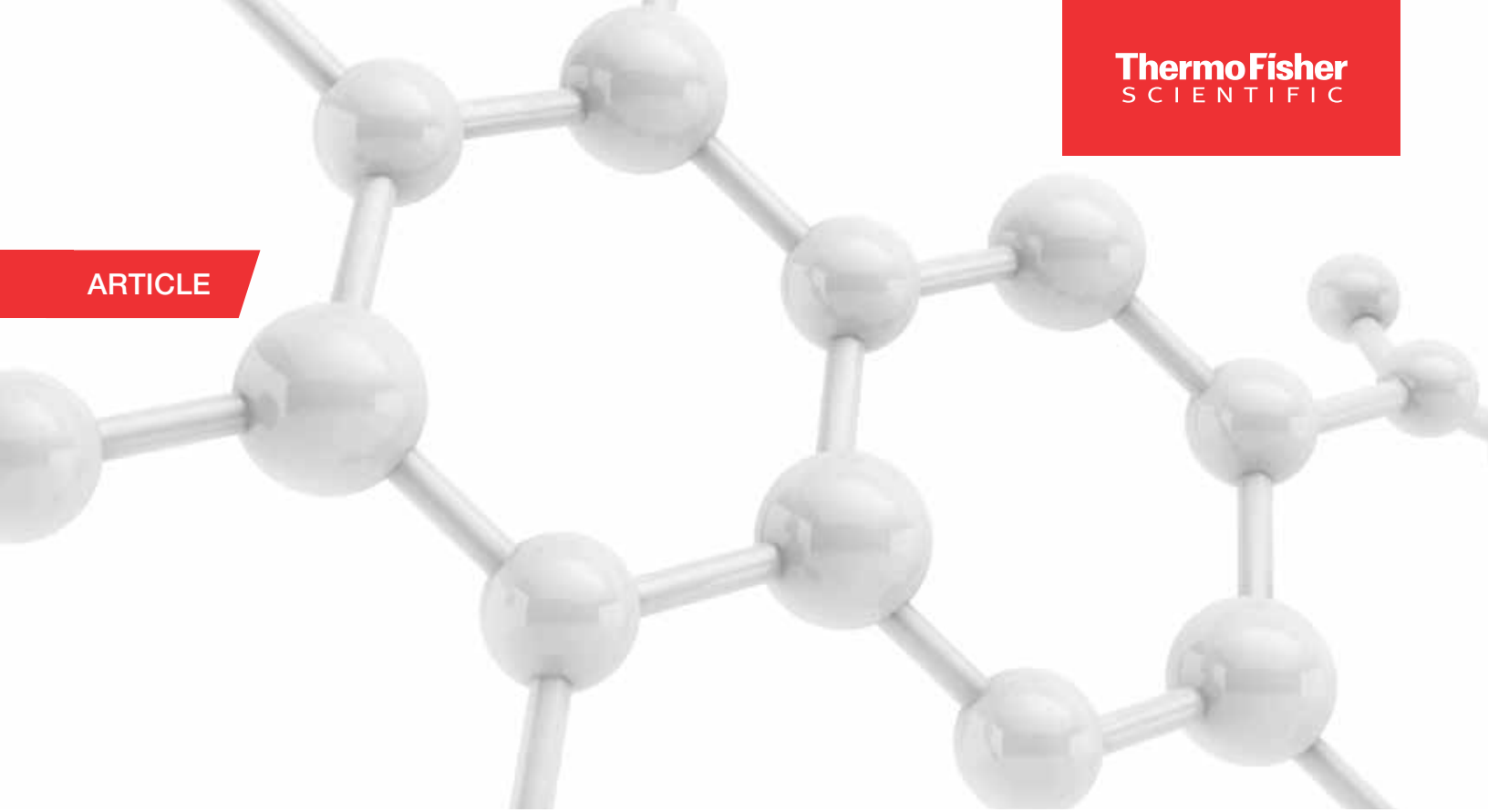

A comprehensive approach to improving solubility and bioavailability: Spray drying

Spray drying is a well-established manufacturing process with applications in foods, industrial products, and pharmaceuticals. Having come a long way from the first patent in 1865 (US patent 51,236),[1] spray dryers today support the development of some of the most advanced drug formulations, meeting the most precise morphological requirements to ensure performance, stability and manufacturability.

Stabilizing amorphous form: Worth the effort

Amorphous form materials have high levels of free energy and require a driving force to ensure their stability. Spray drying is one method of stabilizing the amorphous form via amorphous solid dispersions (ASDs). ASDs improve availability of poorly water-soluble molecules.[2] In these systems, drug-polymer interactions inhibit recrystallization both in a solid state and in a dissolving media. In the latter, drug-polymer interactions can increase free drug in solution which in most cases results in a higher *in vivo* exposure. Thus, one of the initial steps in spray drying is to identify the optimal drug-polymer combination for the most successful levels of interaction.

Computational modeling programs, such as the Patheon™ Quadrant 2™ program, can predict optimal drug-polymer combinations and ratios by assessing compatibility between functional groups. This process generally yields four to five drug-polymer combinations from which a series of prototypes are developed and evaluated at different drug loadings to determine which one(s) provide the best combination of solubility enhancement and stability.

Spray drying is one method of stabilizing the amorphous form via amorphous solid dispersions (ASDs).

Overview of the spray drying process

Once identified, the optimal drug-polymer system is dissolved in an appropriate solvent and this solution is introduced into the drying chamber of the spray dryer. The spray solution (or slurry) is then atomized with an appropriate spray nozzle along with a hot drying gas (e.g. nitrogen) being introduced co-currently. Due to coupled heat and mass transfer, the solvent evaporates, causing the droplets to dry and resulting in a spray-dried solid dispersion powder. The particle morphology and particle size can be highly controlled throughout the entire spray drying process. The spray-dried powder typically undergoes a secondary drying step where the solvent content is reduced to meet ICH guidelines.

Keeping an eye on the critical quality attributes of the product

Several quality attributes of the product are monitored throughout the spray drying process and can be categorized as either formulation-dependent or process-dependent. Formulation-dependent attributes depend on type of polymer selected and the relationship of the drug to the polymer. These include amorphicity, dissolution performance, physical stability, purity, and potency.

Process dependent attributes are directly influenced by the equipment used and include yield, particle size, flow properties, residual solvent content, and particle morphology. Importantly, process-dependent attributes can be engineered to take on specific properties by adjusting various processing conditions and equipment parameters.

Comprehensive spray drying services from early development through commercialization

An experienced spray drying manufacturer will be able to contribute to all stages of drug development—from formulation to clinical trial manufacturing to commercialization. Comprehensive spray drying services also should also include downstream processing of the spray-dried materials, including further conversion, compacting, and spray coating of the spray-dried powder into tablet or capsule formulations. Coating for clinical trial blinding purposes should also be available.

Specialized equipment is designed to support varying batch sizes. Smaller dryers are used in early development to conserve material, and larger dryers support commercialization with batch sizes measured in megatons. Having the right equipment saves time and resources. For example, smaller equipment is used to help understand the sensitivity of the product to process parameters prior to investing in the larger batches necessary at scale-up.

Considerations for scale-up and technology transfer

Scale-up and technology transfer between sites is typically done by a combination of thermodynamic process modeling and targeted statistical experiments relating the critical quality attributes of the drug with the critical process parameters. The design space is established by studying the scale independent process variables that are verified at the new scale. These studies can also serve as a basis for process validation.

In addition to the obvious requirement of having equipment capable of handling larger batches of material, several factors should be considered prior to scale-up. These include analytical method validation, process fit/cycle time optimization, cleaning validation (including studies and method validation), vendor qualification, shipping qualification, stability, etc. An experienced spray-drying service provider needs to understand the impact of each of these factors before initiating scale up to prevent costly errors and delays.

Analytical and downstream capabilities

Spray drying services need to include specific analytical capabilities for characterization of the spray-dried products. A well-equipped characterization lab includes comprehensive analytical testing of the product. These include differential scanning calorimetry, X-ray powder diffraction, particle size analysis, residual moisture/solvent, moisture sorption, dissolution testing, ICH storage stability and other analytical tools to fully characterize the products. Having these capabilities onsite increases speed and streamlines development.

Downstream processing to convert the spray-dried intermediates into solid oral dosage forms involve manufacturing capabilities such as blending, roller compaction, milling, tablet compression or encapsulation, and coating.

The benefit of a streamlined, comprehensive approach to spray drying

The poor water solubility of many of today's new chemical entities[3] in pharmaceutical research requires enabling technologies such as spray drying to achieve the desired bioavailability. CDMOs such as Thermo Fisher Scientific who have breadth and depth of experience in spray drying formulation and processes can expedite product development along with successful technology transfer and scale-up. In-house analytical and solid-state capabilities allow for rapid development and release testing. Spray-dried amorphous dispersions expand the possibilities for therapeutic options for patients by making otherwise poorly soluble compounds suitable for drug delivery. A detailed understanding of the complexities associated with spray drying coupled with in-house expertise and capabilities can leverage this enabling technology to speed drug development.

References

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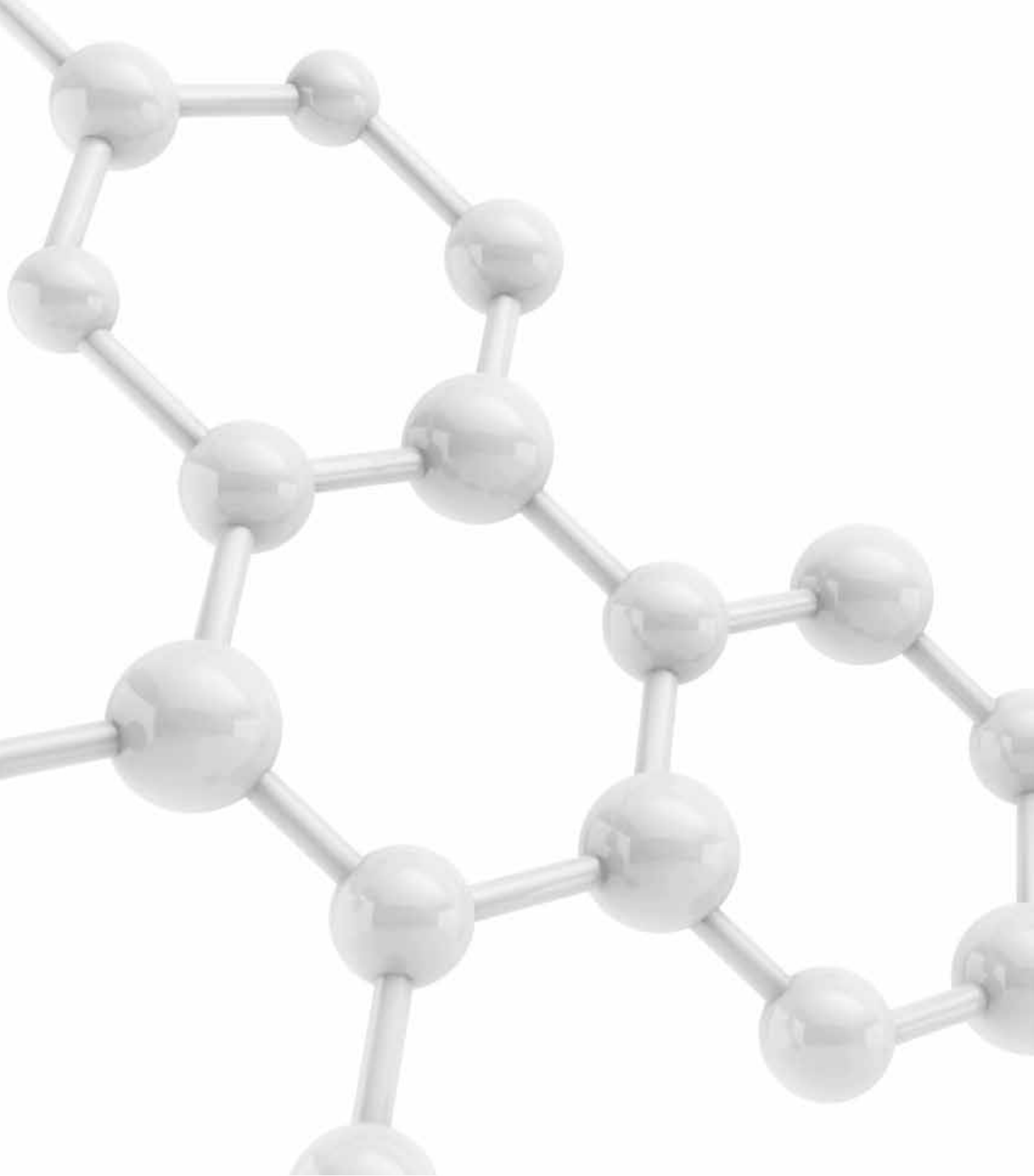

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