LESS MESS, LESS STRESS, BEST EXPRESSED: **A SUPERIOR ALTERNATIVE TO SPRAY DRYING**

By Chris Brough, AustinPx

Spray drying is a well-established process, and it is the de-facto standard in pharmaceutical amorphous solid dispersion (ASD) formulation and manufacturing today. Hot-melt extrusion (HME) was developed as a more environmentally friendly production alternative, but it cannot be used for thermolabile APIs and polymers, greatly limiting its applicability.

KinetiSol™ — a fusion-based process for the manufacture of amorphous solid dispersions — has existed in the plastics industry for decades, yet only in the past ~15 years has it become available and competitive within the pharmaceutical industry. In that relatively short time, it has proven to outperform competing technologies by numerous metrics, including bioavailability, cost-savings, manufacturing speed, environmental impact, and more.

Excipient innovation and IP opportunity

Spray drying generates ASDs by dissolving the crystalline drug and a water-soluble polymer in an organic solvent, then rapidly evaporating the solvent to create a molecular mixture of the drug and the polymer. By eliminating the crystal structure of the drug and covering its hydrophobic surface with a hydrophilic polymer, the drug's solubility and bioavailability are greatly improved. However, contemporary development pipelines are rife with molecules that are insoluble in both water and organic solvents.

For spray drying to succeed, the drug must be reasonably soluble in one of the few volatile organic solvents suitable for pharmaceutical spray drying. Drugs with limited solubility in such solvents either present volumetric inefficiencies that preclude large-scale production, or simply cannot be spray dried at all. Moreover, the polymer must also be soluble in the same organic solvent. This requirement greatly limits the formulator's polymer toolbox and thereby limits performance of the resulting product. Also, when confined to a limited formulation space, there is essentially no opportunity to obtain formulations IP as the space has been exhausted by the prior art.

In principle, the spray drying process involves converting the drug-polymer organic solution into a mist of fine droplets (atomization) within a continuous stream of hot nitrogen gas to rapidly evaporate the solvent from each droplet, leaving behind very small, hollow drug-polymer spheres. The evaporative process of ASD formation carries the risk of drug-polymer phase separation according to the affinity of the drug for the solvent over the polymer. The

resulting formation of drug-rich domains inside the particles leads to formulation instability and reduced performance. Also, the very high surface area of the spray dried powder can negatively impact drug release in the body. The active compound can release from the particle before the polymer dissolves, negating the polymer's intended solubility-enhancing function.

Alternatively, KinetiSol™ forms ASDs by dissolving the drug in the polymer (i.e., the polymer acts as the drug's solvent). This mechanism eliminates the possibility of phase separation and ensures the formation of a perfect molecular mixture, which is paramount to maximizing product stability and performance.

This process generates very dense, low surface area particles whereby drug release is controlled by polymer dissolution. Congruent drug-polymer release promotes prolongation of supersaturated drug concentration in the intestines — key to enhanced bioavailability — by maintaining the amorphous drug in close proximity to the stabilizing polymer, which delays precipitation, nucleation, and crystal growth. In fact, a majority of insoluble compounds exhibit rapid crystallization and precipitation kinetics, where polymer protection of the amorphous payload is key, so KinetiSol™ often produces superior formulation performance over spray drying.

The formulation toolbox enabled by KinetiSol is substantially larger than spray drying and HME. Polymer selection with KinetiSol is not limited by organic solvent solubility as with spray drying, nor thermal stability and viscosity as with melt extrusion. Hence, KinetiSol provides formulators access to essentially any pharmaceutical polymer. Furthermore, KinetiSol allows for combinations of polymers and incorporation of ancillary excipients that work synergistically to enhance performance and/or stability. The KinetiSol toolbox thus enables formulators to easily generate complex drug delivery systems to maximize product performance. Substantial IP potential is inherent to these complex and superior formulations. Furthermore, KinetiSol products cannot be duplicated by other technologies, creating perpetual protection against generic competition.

Minimize thermal stress

KinetiSol generally is considered a thermal technology and, as such, it can be inaccurately associated with the same shortcomings as HME. For example, HME typically is considered inferior to spray drying because of its narrow breadth of possible formulations and incompatibility with thermolabile APIs and polymers. However, because KinetiSol™ is based on shear, it can process both drugs and polymers well below their melting points.

How? For polymers, a range exists above the glass transition temperature and below the melting point where they exhibit viscoelastic behavior (often referred to as the "leathery range"). Viscoelasticity is when a material exhibits both viscous (fluid-like) and elastic (rubber-like) characteristics when undergoing deformation. The shear forces in the KinetiSol™ technology deform the polymer while the mixing kinetics molecularly disperse the drug into the polymer. Because this process occurs in a matter of seconds, thermal stress is minimized by reducing the duration of exposure to heat as well as the overall temperature.

Thus, KinetiSol™ creates opportunities for thermolabile drugs by enabling rapid drug solubilization within the leathery polymer to form ASDs in seconds and at temperatures well below the compound's melting point and the polymer's degradation point. The result is stable and chemically pure ASDs of drugs that would otherwise substantially degrade from thermal processing. Polymer combinations are also key toward success with thermolabile compounds. For example, if a drug has a natural affinity for a polymer that does not increase its solubility, a co-polymer can be introduced to drive good performance. These co-polymer systems cannot be duplicated by spray drying or HME, providing inherent IP protection.

Combine sustainability with profitability

By 2026, the world is expected to use about 33 million metric tons of solvent, of which the United States will account for ~9 million metric tons and China is expected to use ~6 million metric tons.[1] Pharmaceuticals and healthcare waste are becoming a bigger part of that total, and 80% to 90% of pharmaceutical waste is solvents. While not all these solvents come from spray drying, the process often demands thousands of liters of organic solvents and countless tanks of nitrogen to complete large batches.

In addition to its environmental impact, spray drying also comes with a huge up-front facility capital expenditure (CapEx). The spray dryer requires a multi-story building, outfitted at a cost of tens to hundreds of millions of dollars. Solvents and nitrogen must be sourced and purchased. Then, solvent recovery farms and nitrogen recovery farms must be constructed and operated.

By comparison, KinetiSol™ uses no solvents and no nitrogen: no chemicals to acquire, store, or dispose of. Due to the up-front and operational cost savings, compared by equivalent throughputs, a $1M to $3M scale KinetiSol™ line would match a $150M spray drying line.

KinetiSol™ also helps to reduce operating costs by eliminating the multiple manufacturing steps associated with spray drying. For instance, this includes but is not limited to secondary drying, powder densification to enable tablet compression, and the excessive addition of tableting agents.

KinetiSol-produced ASDs exit the process as a solid mass that, when milled, form a dense, freely flowing, and compressible powder. The excellent compression properties of KinetiSol™ particles lend themselves to tableting with the addition of minimal tableting excipients. Thus, the final drug product can contain significantly higher doses per unit and/or fewer or smaller dose units versus spray dried tablets. This reduction of pill burden provides a significant benefit to patients, ensuring therapy compliance and improving therapeutic outcomes

Critically, KinetiSol™ is a fee-for-service technology. No licensing is required to access it and no royalties are required. It has been installed at multiple CDMOs and can be added as part of companies' in-house production lines.

Streamline scale-up

Using both spray drying and HME, base parameters selected at the lab scale change as they are scaled up. For example, it is important to limit the amount of time the drug is molten when using HME. On lab-scale units, residence time — when materials are in the heated barrel — may be one minute. When scaled up, residence time may climb to five minutes. This introduces risk of drug degradation on processing and impurity concentrations in the final drug product that are beyond the allowable limits.

Scale up in spray drying has a different but similarly disruptive challenge. Particle size increases often coincide with an increase in scale. This influences not only downstream tablet production but also drug release and product performance. A late-stage product change of this nature can put timelines and clinical outcomes at risk.

Additionally, at lab and pilot scale, spray drying production does not focus much on solids loading in the organic solution feed because the product volume is relatively small. Hence, the waste solvent burden is manageable, even at very low solids load. Thus, many companies advance an inefficient spray drying process into Phase I and even Phase II clinical trials. However, on scale-up for Phase III and commercialization where product demand increases by orders of magnitude, the amount of solvent necessary to produce the drug product grows exponentially. Thus, low solids loading at this late development stage cripples manufacturing efficiency, sometimes to an extent that spray drying is no longer viable.

During R&D, KinetiSol™ can be used to establish feasibility with any given molecule using single-digit gram quantities. Given 50 to 100 grams, the technology can exhaustively map a formulation space to find the optimum formulation. Research-scale KinetiSol™ can also be applied in GMP as a way to accelerate a drug product entry into a human pharmacokinetic (PK) study, eliminating the need for engineering batches and expediting tech transfer.

Scaling is linear at that point to the manufacturing equipment, which can produce first-in-human (FIH) supplies all the way to commercial. At all scales, residence time stays the same, minimizing risk by ensuring base parameters remain unchanged. Also, the ASD particle properties remain unchanged, ensuring consistent downstream production and biopharmaceutical performance.

Add speed and reduce risk simultaneously

To produce a single drug and polymer combination effective in spray drying, one must dissolve both in a common solvent, evaporate the solvent, collect the powder product, then fully clean and reset the equipment. That process takes four to eight hours. So, a week's worth of work could result in just a few potential formulations.

Using a KinetiSol™ research compounder, up to 25 unique ASD formulations can be produced in a day. This enables an empirical approach to ASD development that directly tests the key quality attributes and accelerates formulation development. Its use eliminates any discussion of computer modeling validity or what theoretically works best and focuses efforts on finding tangible solutions.

Once appropriate chemistries have been discovered, the grade of polymer, different molecular lengths, and other attributes must be pinned down. KinetiSol™ can rapidly screen all the possible grades and within a week, the formulation space can be mapped. KinetiSol™ also enables a low drug load approach to establish compatibility of the drug with the process in general. Then, the drug's compatibility with all types of polymer chemistries can be determined quickly as a preformulation step, prior to consuming significant volumes of API.

You owe yourself an objective comparison

KinetiSol™ broadens the formulation design space relative to other technologies by offering the ability to process polymers that are thermally sensitive or lack a common solvent with the API. Versus spray drying and HME, KinetiSol™ has proven its bioavailability superiority in numerous cases.

Moreover, to ensure regulatory success with KinetiSol™, AustinPx has worked closely with the FDA during its development, producing registration batches and writing CMC sections for filing. As the first commercial product using KinetiSol™ nears approval, we are excited about the future of this innovative technology in today's industry. To learn more, contact the author and visit www.austinpx.com.

References

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About the author

Chris Brough is the co-founder and chief technical officer of AustinPx and one of the key inventors of the technology. He has an M.S. in mechanical engineering with a material science emphasis and a Ph.D. in pharmaceutical sciences. He is responsible for the design and build of the KinetiSol equipment at AustinPx.

About AustinPx

AustinPx Pharmaceutics and Manufacturing is a contract development and manufacturing organization (CDMO) providing analytical and formulation development services and cGMP manufacturing for small molecule drugs. They specialize in phase-appropriate development strategies, speed to clinic and market strategies, and bioavailability enhancement of poorly soluble molecules — including the next-generation amorphous dispersion platform, KinetiSol™ Technology.