De-Risking API Potency

High potency APIs (HPAPIs) drugs are difficult to mix, handle, and process. This introduces significant risk for pharmaceutical companies due to poor uniformity, increased toxicity, and uncertain scale up. ResonantAcoustic® Mixing (RAM) solves these problems, reducing risk and creating reliable, safe results quickly.

Pharmaceutical brands are under more pressure than ever before to create drugs that are effective, inexpensive, safe, and quick to market. This pressure is building from many sources, including consumers, governments, and competition. A new pain point contributing to this pressure is the growing trend of high potency APIs, known as HPAPI.

Growth in the larger pharmaceutical industry has been largely driven by oncology and obesity drugs. PCI[1] reports, “Around 41% of new drug compounds are considered highly potent, which is unsurprising considering that oncology and GLP-1 therapies are among the industry’s major growth drivers, and those molecules tend to be highly potent.” Furthermore, a 2023 research report published by Pharmaceutical Research2 shows a long-standing trend, “Data from 2022 alone showed that 41% of all newly approved drug compounds and 45.5% of small molecule new chemical entities now fall into the category of “highly potent” drug molecules.”

While this represents advancements in medicine that have very positive implications for many, increased potency carries with it significant new risks. Traditional mixing technology is a weak point that exposes these risks, namely poor mix uniformity, cross-contamination, and difficult scale-up. This threatens the successful development of HPAPI drugs. Adopting mixing technology that specifically addresses these risks is critical.

Thankfully, new mixing technology exists to mitigate these concerns. ResonantAcoustic® Mixing alleviates the pressure from this rapidly growing trend. Implementing this advanced mixing technology reduces risk for drug discovery, pilot testing, and production.

Uniformity Concerns

As demand for these drugs rise, so do research and development efforts, but not without significant risk. High potency directly affects drug formulation, forcing a low-dose API compared to the excipient. Homogenous dispersion is critical for proper drug delivery and has proven challenging to formulation scientists and process engineers. The Pharmaceutical Research report further details, “The predicament faced becomes how to achieve blend and content uniformity in oral solid dosage forms for these compounds, for which there has been no easy solution.”

Handling Risks Increasing

Even when a good process is found, proper handling is paramount and challenging.

According to Aragen[3], “The biggest risk of high-potency active pharmaceutical ingredients (HPAPIs) is cross-contamination.” Maintaining sealed containers and other specialized handling techniques increases complexity and production cost. In addition to cross-contamination concerns, worker safety and proper disposal of waste carry additional concern as potency increases. These risks weigh heavily as the trend is expected to continue and as standardization catches up to the increased need for safer practices.

Scaling Challenges

Producing high potency drugs in a lab is the first hurdle, but scaling lab practices to higher production volumes can be difficult. Even if proper dispersion can be achieved at the lab, and it can be done safely, scale up to production processes may not translate, especially as API dosages get smaller. HPAPIs are generally produced on a smaller scale when compared to standard API drugs. However, the scale varies, and production technology needs to be flexible to match.

News Medical[4] reports, “The potency and high value of HPAPIs present a variety of manufacturing scales and batch volumes when compared to APIs. Meeting market demand generally requires fewer volumes and smaller batches to minimize financial risk related to batch loss.” The concern over batch loss is a clear indicator that producing at higher volumes is difficult and results in quality issues. Scaling any drug is challenging, but doing so with high-potency APIs has proven to be a consistent concern.

Mixing at the Heart of Challenges

The processing equipment tied directly to uniformity, material handling, and scaling to production is the industrial mixer that combines the API with the excipient material. This key piece of equipment is vital to the success of the drug, and selecting the right mixer should be done with great care. The most advanced mixing technology on the market today is ResonantAcoustic® Mixing, which solves mix uniformity issues, improves handling of sensitive materials, and provides a secure path for scale up from bench to production.

Uniformity at Ultra-Low-Dose APIs

The working principle of ResonantAcoustic® Mixing (RAM) is ideal for creating unmatched uniformity, even in very difficult circumstances. This effect has been studied extensively, proven both in research and in the field. The Pharmaceutical Research[2] paper by Frey, et al studied this very issue: RAM technology for ultra-low-dose blends. Their concern for properly blending medicine with HPAPIs, particularly for oral delivery, led them to test this mixing method in one of the most difficult scenarios. They chose anhydrous caffeine as their API, given its notorious nature for uniform blending. Its morphology is acicular, prone to low flowability and agglomeration.

In addition to using a difficult API, they used it in ultra-low doses, testing all the way down to concentrations of 0.05% and 0.0125% by weight. Despite stacking the odds against RAM, the results were overwhelmingly positive, “In this report, using RAM technology we present the first instance of a <0.1% blend homogenously blended in a single step dry powder process, where concentrations as dilute as 1 part per 8,000 were confirmed to meet USP standards for passing BU criteria with only 135 seconds of mixing.”

ResonantAcoustic® mixing is the premier choice for homogeneously mixing HPAPIs. These results prove to offer the highest performing mixer for ultra-low-dose formulations.

Eliminating Cross-Contamination at the Mixer

While RAM technology can be configured to mix in either batch or continuous processing, the batch process offers a sealed container option. Mixing with resonance is non-contact, meaning there are no impellers, paddles, or scraper involved. This alone is a significant advantage when cross-contamination and worker safety are concerned. Cleaning is simplified, taking less time and resulting in much less waste.

If fast high-volume production is required, continuous processing versions offer a 100% effective clean-in-place option. These flexible processing methods available with RAM make it uniquely capable of mixing HPAPI blends.

Both methods support isolation, automation, and various other tools to protect employees handling hazardous materials.

Seamless Scalability from Lab to Production

Frey, et al[2] acknowledge the seamless scaling options available with RAM technology, “Attractively, RAM is inherently well suited for positioning at any stage of a drug product manufacturing process – process optimization

and formulation development can be carried out on the benchtop using minimal amounts of materials and the resulting procedures directly applied to scaled-up batches on an industrial scale. Scale-up is reported to be seamless, with little to no adjustments in parameters, and similar mixing time requirements".

This is due to the consistency of the operating principles. The mechanical mixing forces generated by the resonator are perfectly tuned at different payloads, with models created for anything from a 1 mg batch mix up to 2,000 kg/hr with continuous mixing. Therefore, the parameters developed in the lab translate directly, with few adjustments, to a production scale model.

For HPAPIs specifically, where scale varies but is often on the lower end, this flexibility is key. Process engineers can reliably predict performance at different scales, reducing risk. Engineers can prove a process on a smaller scale and present the opportunity for management to increase scale as the specific scenario allows, and as the surrounding processes can support.

For formulations scientists, this means optimizing with confidence that the scale up will not be a problem. They can run tests at a minute scale to use as little API as possible, taking advantage of high-throughput practices and reducing costs, knowing that the same principles that work at the lab scale will translate directly.

Meeting Modern Demands

ResonantAcoustic® Mixing is a revolutionary, research-backed technology that is ideally suited for modern challenges that increasingly push the boundaries of what's possible. Older, well-established mixing technologies are failing to keep up, lacking the uniformity, speed, and inherent safety of resonant mixers. In the case of HPAPIs, the trend is both concerning and exciting. New medicines are improving outcomes for patients all over the world. But risks and costs are increasing for pharmaceutical manufacturers. RAM processing technology offers a unique way to operate with unparalleled performance and quality, reducing risks and costs at the same time.

For more information about RAM, visit https://resodynmixers.com/.

Citations:

PCI Pharma Services, The High Potent Pathway, https://pci.com/resources/the-high-potent-manufacturing-pathway/

Frey, K.A., Baker, H., Purcell, D.K. et al. Use of Resonant Acoustic Mixing Technology for Ultra-Low-Dose Blending in a Single-Step Mixing Process. Pharm Res 41, 165–183 (2024), https://doi.org/10.1007/s11095-023-03629-3

Aragen, The Rise of High Potent APIs: Trends, Technologies, and Manufacturing Best Practices. (2024), https://www.aragen.com/the-rise-of-high-potent-apis-trends-technologies-and-manufacturing-best-practices/

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