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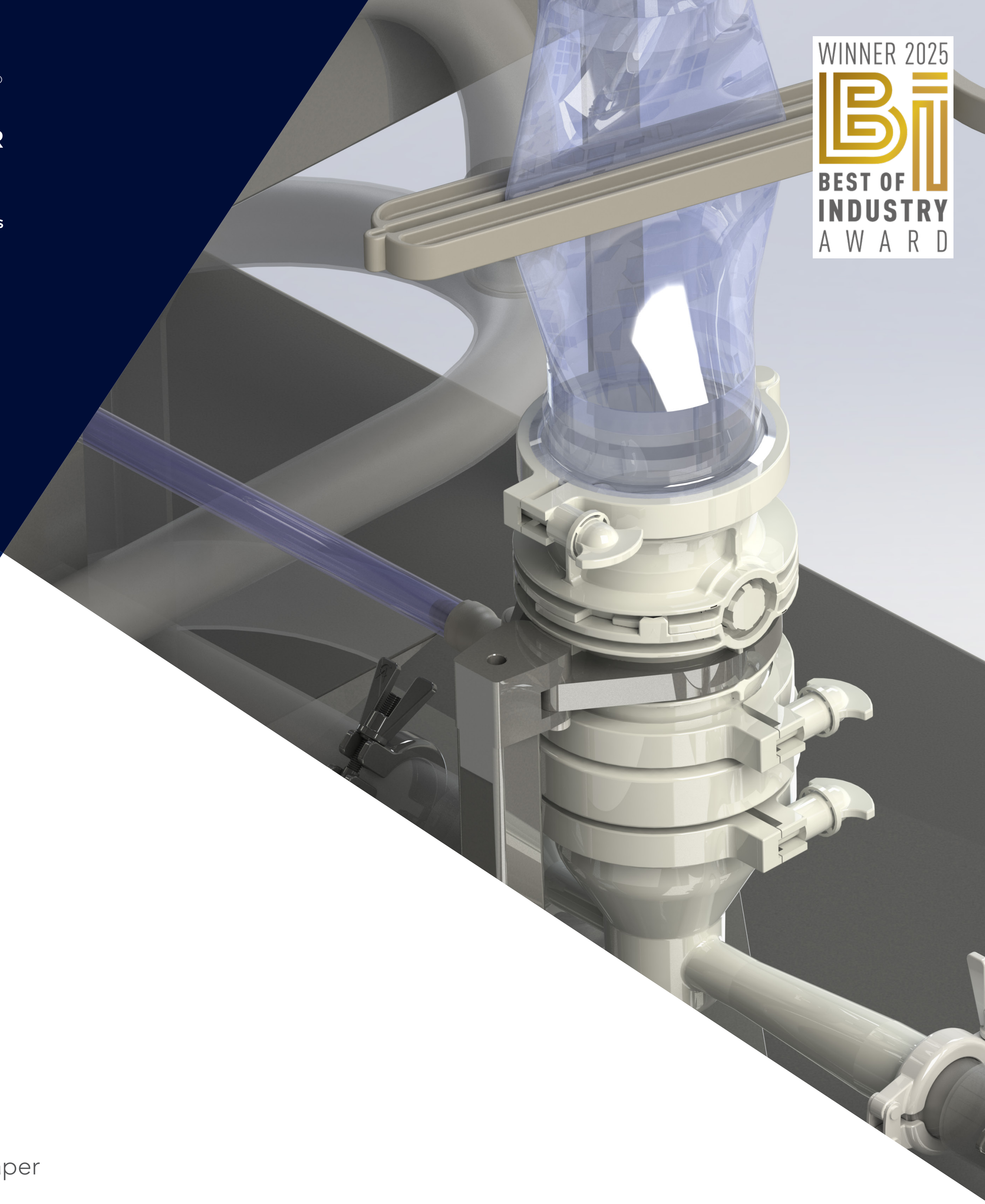

Whitepaper

Enhancing Biopharmaceutical Production Through Advanced Mixing: Boosting Performance with EZJetFlo™ Technology

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INTRODUCTION

As the demand for monoclonal antibodies (mAbs) continues to grow across therapeutic, diagnostic, and industrial applications, biomanufacturers face mounting pressure to achieve higher productivity, increased process robustness, and improved scalability.

Upstream and downstream operations, particularly media and buffer preparation, ingredient dissolution, and process homogeneity, play a critical role in ensuring consistent performance and maximizing overall yield. However, traditional mixing technologies often struggle to meet the evolving needs of intensified and flexible bioprocessing strategies while keeping operators safe and protecting the products from contamination risks.

CRITICAL CHALLENGES AFFECTING POWDER HANDLING PROCESSES

Charging a vessel in biopharmaceutical applications is an inherently complex operation, especially when evaluated through an end-to-end risk assessment. Many raw materials are hygroscopic, tend to form lumps, or have a low bulk density. These properties often lead to inconsistent mass flow, particularly when powders are transferred through funnels, nozzles, or manways.

Beyond material flow behavior, operators' safety considerations play a major role. Lifting raw materials from floor level to the charging nozzle introduces risks of falls, musculoskeletal strain, and poor ergonomics, all of which can increase injuries, fatigue, and broader HSE complications. Additionally, operators are exposed to dust emissions during connection, transfer, and disconnection steps, an especially critical concern when handling sensitizing, toxic, or micro-size powders. During these tasks, the dust will escape and enter the operators breathing zone, potentially causing harmful exposure.

Another significant challenge is the build-up of electrostatic charge, which can cause powders to adhere to low-quality bags or internal equipment surfaces. This adhesion not only complicates material transfer and prevents full product recovery but also contributes to unwanted product retention. Last but not least, during gravity charging of low-density and fluffy powders, these solids can remain above the wetted surface of the equipment, causing further complications from retention.

These accumulations reduce overall yield, increase the risk of cross-contamination, challenge recipe accuracy, and ultimately diminish process efficiency by requiring additional handling steps, longer charging times, and repeated cleaning or recovery operations.

CROSS-CONTAMINATION: A PERSISTENT AND CRITICAL REGULATORY TOPIC

If the HSE risks were not substantial enough on their own, an equally critical concern must be emphasized: the risk of cross-contaminating the production batch, an issue heavily scrutinized by global regulatory authorities. Cross-contamination can arise from multiple sources, including residues left behind due to inadequate cleaning, foreign particles entering the process, shared tools, and even operators inadvertently transferring materials between vessels or areas due to gowning contamination or improper handling practices. The risk escalates significantly as the level of manual intervention increases, a fact consistently recognized in GMP regulations.

Regulatory agencies worldwide impose strict expectations to control cross-contamination. The FDA requires robust prevention measures under cGMP, including full separation or validated technical controls for sensitizing compounds, supported by structural isolation, dedicated HVAC, and documented procedures grounded in quality risk management. The EMA mandates a risk-based approach using Health-Based Exposure Limits (HBELs/PDEs) to define cleaning limits, facility design, and operational controls in shared-use environments. PIC/S aligns closely with EMA, requiring systematic, well-documented cross-contamination risk assessments and verification of control effectiveness during inspections. The 2023 revision of EU GMP Annex 1 further strengthens expectations through a mandatory Contamination Control Strategy (CCS), pointing out segregation, continuous monitoring, and minimizing human intervention—particularly relevant to manual powder charging operations.

In biopharmaceutical processing, contamination typically becomes evident long before the final product stage, it leads to slower cell multiplication, reduce titer yields, and in severe cases, halt cell expansion altogether, resulting in complete batch loss.

MIXING: A BATCH PREPARATION CHALLENGE

Once the powder is charged, the next major challenge is achieving rapid, consistent dissolution. Many biopharmaceutical raw materials tend to form lumps (“fish eyes”), hydrophobic clumps that float on the surface. Low-density powders, such as sodium carbonate, are particularly prone to floating and resisting wetting, which complicates mixing and extends dissolution time. These conditions increase the risk of creating a non-homogeneous solution and often drive the need for higher-energy agitation strategies. However, excessive mixing intensity can elevate temperature and shear forces, potentially degrading particles or compromising the functionality of sensitive components.

These dissolution and dispersion issues can cascade into downstream problems, including filtration blockages, inconsistent chromatography performance, variability in fermentation or cell-culture processes, and overall longer batch cycle times. Ensuring efficient, controlled mixing is therefore essential to maintain process robustness, product quality, and schedule reliability in biopharmaceutical manufacturing.

EZJETFLO™: THE SMARTEST WAY TO CHARGE MEDIAS AND BUFFERS

Image 1 : EZJetFlo™ Mobile Skid

The EZJetFlo™ is an advanced in-line mixing system, engineered from the proven JetMixer™ and purpose-built to address the most critical challenges in media and buffer preparation. By delivering rapid, energy-efficient, and highly uniform mixing across vessels of varying scales, the system ensures reliable dissolution performance even for complex, cohesive, or shear-sensitive raw materials commonly used in mAb and other biologics manufacturing. Its unique hydrodynamic and geometric design supports both single-use and stainless-steel facilities, aligning with modern biopharmaceutical facility design principles.

Beyond enhancing product quality, the EZJetFlo™ system delivers notable sustainability benefits through its compact, high-efficiency motor, powered by the Levitronix LPM-2000.8. The 2 kW bearingless, seal-free motor consumes significantly fewer kilowatt-hours than the larger drives, typically required by conventional top-entry or magnetic-mixing technologies, lowering overall energy use without compromising mixing performance. Its contact-free magnetic drive eliminates mechanical wear components and prevents contamination within the sealed pump casing, resulting in a highly reliable, low-maintenance solution.

The system supports the process of powder dissolution, suspensions, and liquid-liquid blending, producing a homogeneous mixture that is returned directly to the destination vessel.

HOW THE EZJETFLO™ WORKS?

A Closed, Efficient, and High-Performance Powder Delivery and Mixing Solution

1. The liquid is continuously recirculated through a closed loop, using a single-use pump, ensuring consistent flow and optimal mixing conditions.
2. The unique geometry of the EZ JetFlo™, inlet nozzle accelerates the liquid without causing splashing inside the mixing chamber, avoiding the clogging of the chamber.
3. This acceleration creates a vacuum (based on the Venturi principle) within the mixing chamber, which draws the powder directly into the jet stream for seamless integration.
4. As the mixture enters the expansion chamber, intense turbulence rapidly disperses and dissolves the powder, resulting in a fast and highly efficient mixing process.

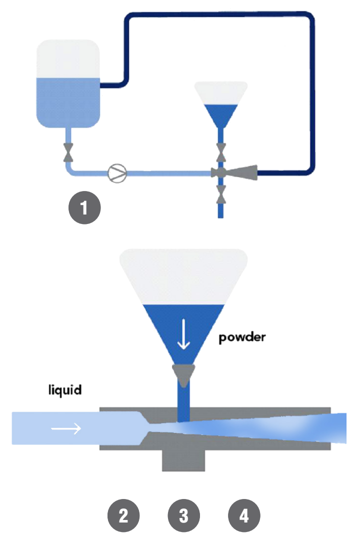


Image 2 : EZJetFlo™ Work Principle

ELIMINATES CROSS-CONTAMINATION RISKS

The process is fully closed and powder addition is completely contained, with liquid recirculated through the EZJetFlo™, while powders are introduced via the contained EZBioPac® system made of ArmorFlex® film. Since all wetted parts are single-use, the system not only eliminates the need for cleaning but also removes the contamination risks typically associated with poor, incomplete, or inconsistent cleaning procedures. This design dramatically reduces or eliminates the potential for cross-contamination between batches, supporting GMP-aligned workflows and enabling rapid, reliable changeovers.
By removing cleaning operations, including labor-intensive CIP/SIP steps, chemical consumption, water usage, and the energy required for heating and sanitization, the solution contributes to a significantly more sustainable process. These efficiencies translate into shorter turnaround times, lower resource consumption, and a reduced environmental footprint, while maintaining strict containment and high process integrity.

INCREASED PRODUCTIVITY

Its unique design, has been fine-tuned to optimize the suction of the powders. The vacuum generated by the Venturi principle (~900 mbar), drags the raw materials almost particle by particle instantaneously beginning the dissolution and mixing, while keeps the process very smooth, without generating heat or high shear, that could damage the product. This stands while it keeps contrast to rotor-stator based systems, which often generate excessive shear and heat, particularly problematic for biologics raw materials.

SMART DESIGN

Designed for practical use across manufacturing suites, the EZJetFlo™ includes:

- A mobile trolley with a manual lifting system for ergonomic handling of powder bags up to 50 kg
- Tool-free assembly of all product-contact parts
- A compact footprint for easy movement through corridors, airlocks, and between equipment trains

These features simplify operation, reduce ergonomic risks, and accelerate batch changeover.

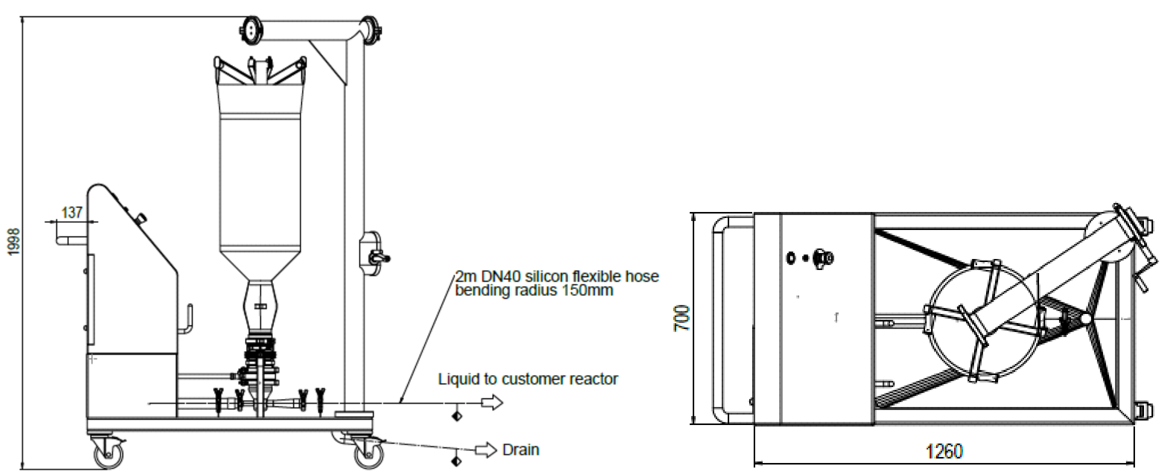


Image 3 : EZJetFlo™ foot print

EZJETFLO™ MIXING PERFORMANCE IN BIOPROCESS APPLICATIONS

The performance of the EZJetFlo™ was evaluated using mixing applications representative of routine biopharmaceutical operations. The goal was to assess dissolution efficiency, mixing speed, and handling capability across a range of challenging raw materials typically encountered in upstream and downstream processing.

- Highly concentrated sodium hydroxide (NaOH) buffer
  Selected as a worst-case scenario due to its exothermic dissolution behavior, and frequent use in purification steps.

- Serum-free CHO cell culture media
  Chosen as a representative formulation widely prepared in monoclonal antibody (mAb) production facilities. These powders often contain components with variable particle size, wettability, and dissolution kinetics.

- Glucose and corn starch
  Included to test the system's ability to disperse and dissolve carbohydrate-based powders, which can exhibit poor wettability, clumping behavior, or swelling during hydration.

Several mixing tests were performed across multiple configurations, including mixer EZJetFlo™ on recirculation mode, with and without additional agitation on the vessel. Each configuration was tested at different flow rates. Instrumentation, including pump settings, flow rates, agitator speed, weight, pH, temperature, and pressure were monitored and recorded, with all devices calibrated and pH probes standardized before testing. The volume was 900 L of Deionized (DI) water, with 36 kg of solids and phenolphthalein quantities scaled accordingly. An agitator speed of 100 RPM was used for all tests.

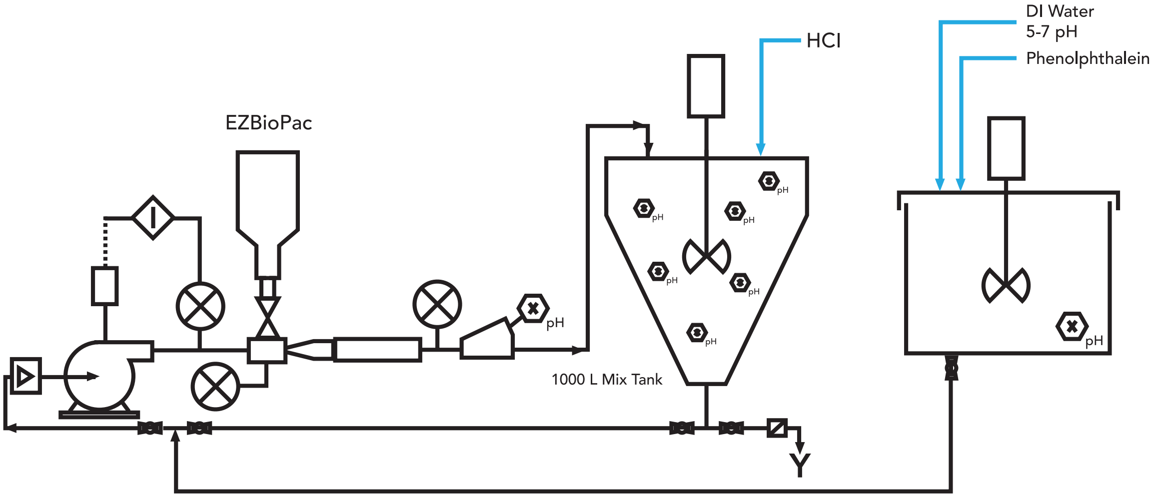
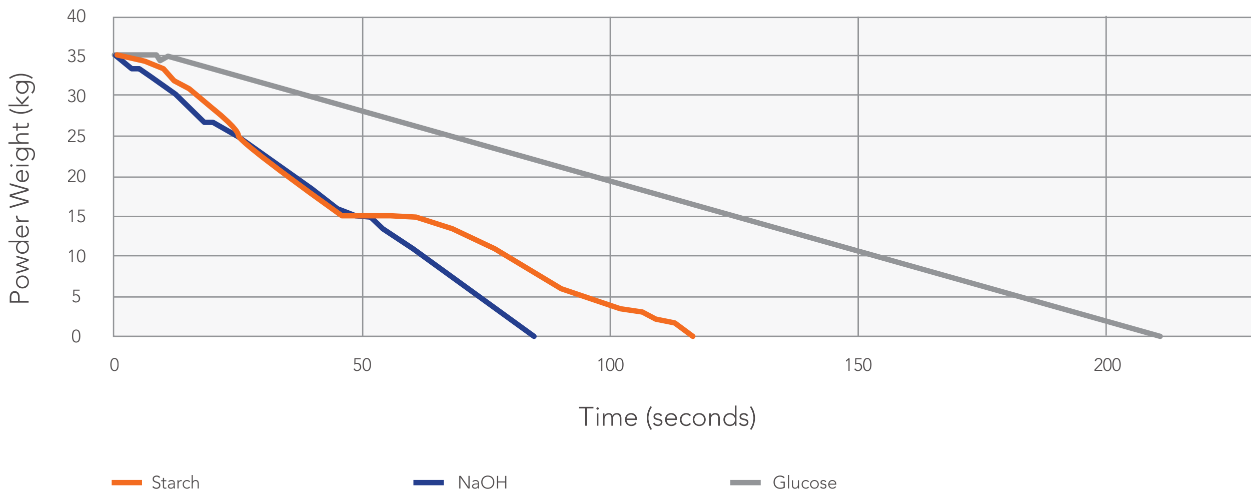


Image 4 : EZJetFlo™ Test arrangement

RESULTS

Effect of Powder Flowability on Solid Delivery Performance:
The throughput of the EZJetFlo™ powder delivery system is closely linked to the intrinsic flowability characteristics of each powder. Powders with higher flowability are conveyed and dispersed more efficiently, enabling faster and more consistent feeding rates. In our evaluation, NaOH displayed significantly better flow behavior than glucose, leading to a markedly higher introduction rate. Nevertheless, all tested powders were successfully delivered without any major operational issues. Additionally, the negative pressure (-900 mbar) generated by the EZJetFlo™ effectively prevents vapors rising from the jet stream, avoiding potential nozzle clogging or lumps generation.

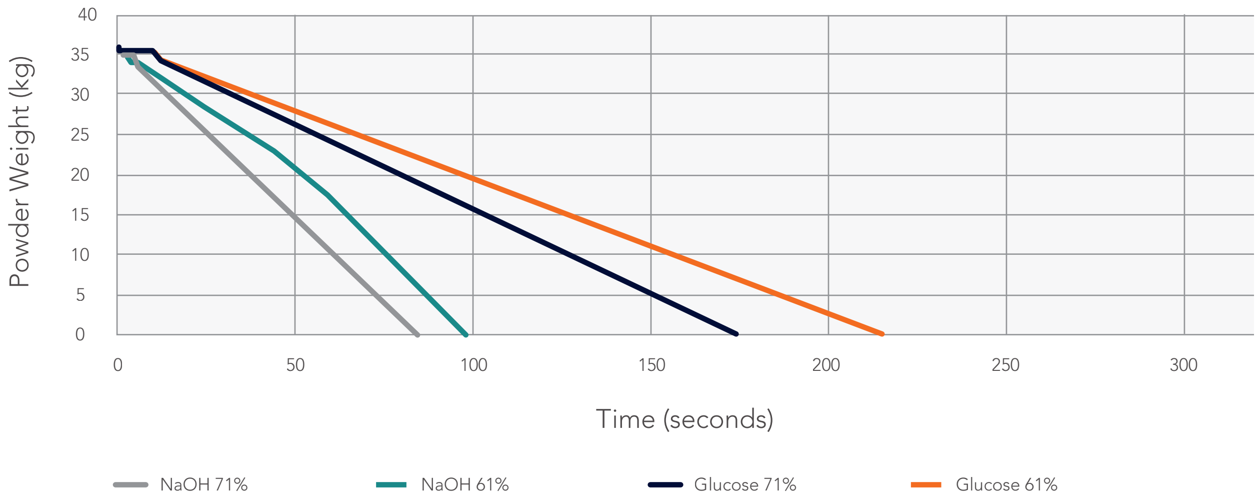


Graph 1 : Weight-Loss Powder Flow Rate Comparison (kg/s)

INFLUENCE OF OUTFLOW CONDITIONS ON POWDER DELIVERY PERFORMANCE

As expected, the outflow rate has a direct impact on the powder delivery performance of the EZJetFlo™ system. When operating at 71% of the pump speed limit, the system delivered powder approximately 25% faster compared with operation at 61%, as shown in the graph below. This behavior is consistent with the Venturi effect generated within the chamber: higher outflow increases the vacuum draw, thereby enhancing powder entrainment and accelerating delivery.

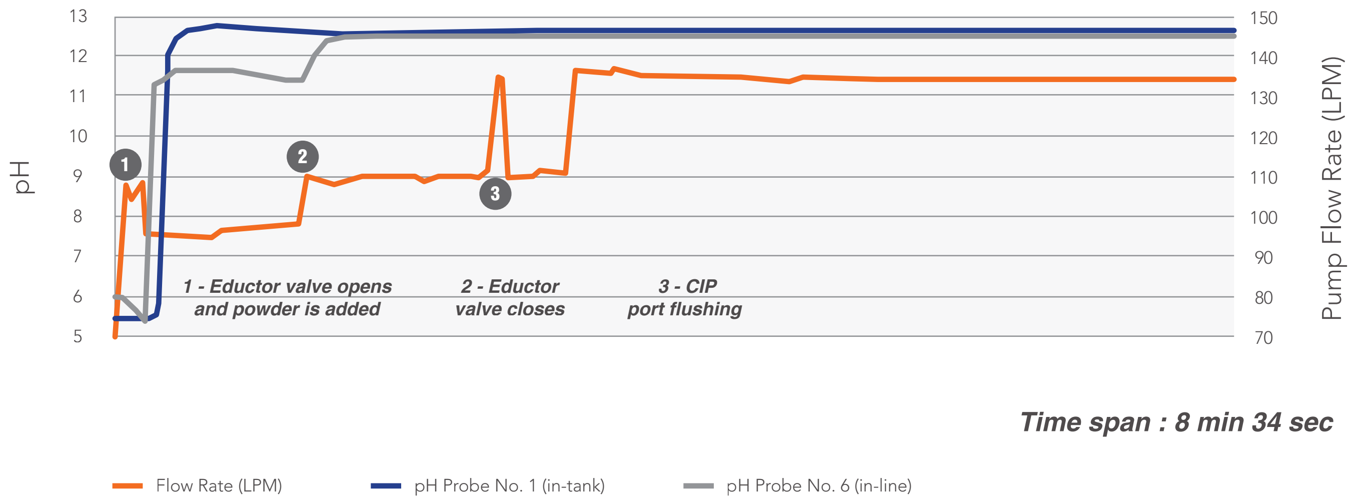
Despite this performance gain, the outflow must remain carefully controlled. Excessive outflow can induce splashing inside the mixing chamber, which may ultimately lead to blockages or instability in powder feeding. The optimization of this process, maximizing delivery speed while avoiding operational disturbances, is part of the process knowledge refined over decades of experience at ILC Dover in developing and supplying the JetMixer™ technology.



Graph 2 : Influence of the Pump Speed on Weight-Loss Powder Flow Rate (kg/s)

MIXING PERFORMANCE

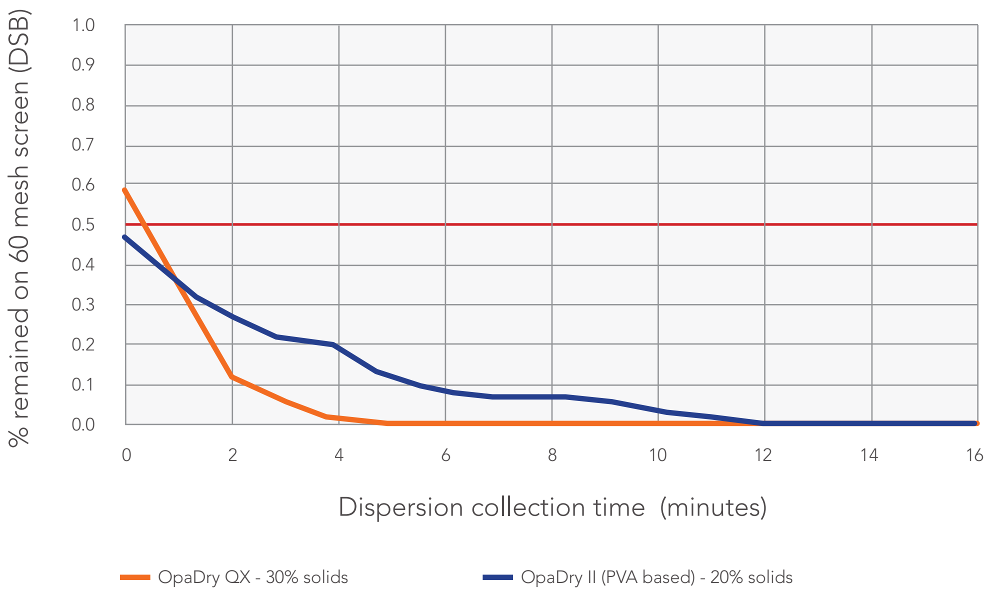
Mixing efficiency was assessed by monitoring the pH profile of the NaOH solution during powder introduction. Across all evaluated pump speeds, the system essentially demonstrated instantaneous increase in pH from an initial baseline of approximately 6 to a stabilized value near 12. This rapid shift indicates that the hydrodynamic conditions generated by the EZJetFlo™ are sufficient to achieve near-immediate dissolution and homogenization of highly soluble powders such as NaOH, without the need for supplemental mechanical agitation within the vessel. It should be noted, however, that the extent to which similar performance can be expected for other materials will depend strongly on the inherent solubility and dissolution kinetics of the specific powder.



Graph 3 : Mixing Performance of NaOH with pump speed at 61%

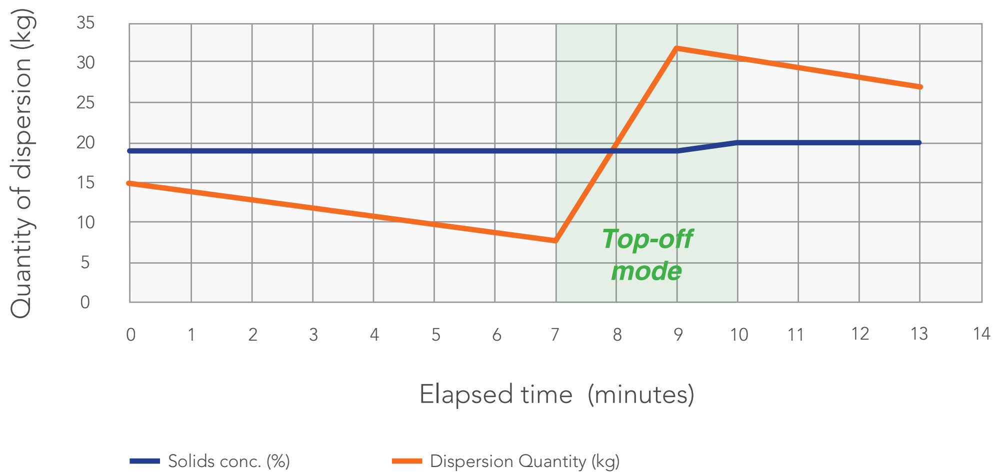
PERFORMANCE OF THE JETMIXER™ FOR COATING DISPERSION PREPARATION

A second study was performed using different analytical methodology. This study uses a powder that is added to a tank using the JetMixer™ technology at two concentration levels. The dispersion (solution with solid dispersed homogenously) was tested on a mesh screen over time. The powder was dispersed immediately reaching full solubilization in minutes. The goal of this study was to qualify the JetMixer™ system to feed a process On-Demand. This allows for a small tank to be used and the solids and liquid are added based on the feed rate of the mixed solution to a process, with the perfusion in mind.



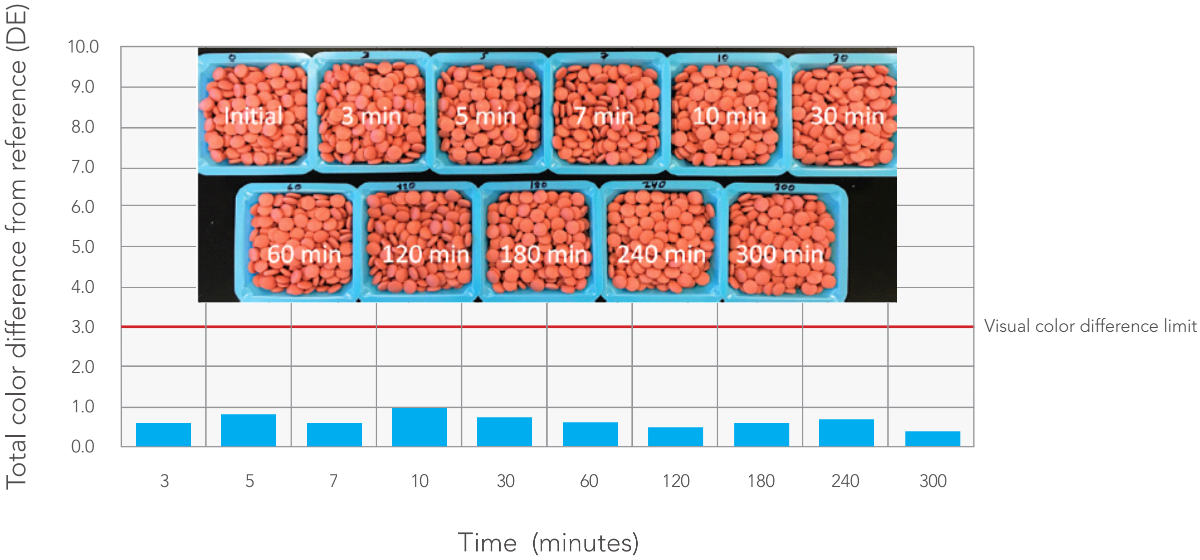
Graph 4 : Screen Retains vs Recirculation time

The coating formulations were rapidly incorporated into the water stream and fully dispersed within a short recirculation interval. Both low-viscosity systems reached an acceptable level of uniformity, exhibiting less than 0.5% retained material on a 60-mesh screen within 2–3 minutes of powder addition, with no visible lumps or undissolved particulates.



Graph 5 : Tank volume vs Solids Concentration During Constant Use and Top-Off (OpaDry QX)

As the dispersion volume in the holding tank decreased, the top-off process was readily performed by metering additional coating powder and water at the required ratio directly into the system. Samples collected throughout this operation showed no measurable change in the solids concentration of the recirculating dispersion, confirming that the system maintained consistent composition during continuous replenishment.



Graph 6 : Five-hour Recirculation Test - Visual and Instrumental Color Uniformity (Opadry QX 30% Solids Concentration)

Tablets coated at intervals over a 5-hour continuous recirculation period showed no detectable differences in color, either visually or by instrumental measurement. This consistency included tablets coated within 3 minutes of the initial powder addition. These results confirm that the dispersion was free of undispersed particles large enough to obstruct the spray nozzle and that the polymer achieved sufficient hydration early in the process to produce a uniform film comparable to that obtained after extended hydration times. Furthermore, the findings indicate that the shear environment within the liquid dispersion was low enough to avoid altering the pigment's color characteristics.

The system enabled rapid preparation of fully formulated coating dispersions using a compact equipment footprint. In this evaluation, the total dispersion mass circulating in the system at any time was relatively low (15–43 kg), demonstrating the feasibility of producing coating dispersions on demand or in a continuous mode, rather than relying on large batch vessels with extended hold times. The system can be readily automated through flow-meter integration, loss-in-weight control, and connection to a large-scale powder delivery system. Both low-viscosity coating formulations—Opadry II and Opadry QX—hydrated rapidly and performed well within this processing approach, confirming their suitability for JetMixer™-based dispersion preparation.

CONCLUSIONS

Plant operations are under constant pressure to streamline operational efficiencies to boost production capacity while gaining agility with response to market demands. The EZJetFlo™ provides a new system that combines the proven JetMixer performance with single use technology to win these efficiencies. Extensive testing across multiple powders and configurations yielded several important findings. At the 900 L scale, agitation was not necessary when operating in recirculation mode and introducing only one component, as mixing performance was adequate. Overall, the studies provides clear proof of concept for the EZJetFlo™, the results demonstrate robust performance across all successful tests and validate the technology's relevance for biopharmaceutical powder-handling applications. The second test demonstrated that the powder into liquid delivery and "on demand mixing" extends beyond biopharmaceutical powders and the technology has broad possibilities for solids handling.

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