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TECHNOLOGIES

White Paper

MASTERING THE ART OF MICRODISPENSING- ESSENTIAL TIPS FOR DOWNSCALING YOUR REACTIONS

INTRODUCTION

The precise downscaling of reactions is a critical factor in the successful research and development of cost-effective assays. Downscaling offers numerous advantages:

- Reduced reagent usage by scaling reactions down to the nanoliter (nl) and picoliter (pl) level.
- Lower system costs by eliminating the need for large laboratories.
- Enhanced production capabilities for high-throughput manufacturing of biochips and biosensors.

While the benefits of downscaling are significant, the process of development is crucial and comes with specific challenges. These include handling very small volumes, ensuring reproducibility, and adapting to diverse material and environmental conditions.

This white paper provides an overview of the essential considerations for downscaling chemical reactions and offers practical recommendations for leveraging modern dispensing systems effectively.

MOST IMPORTANT PARAMETERS

When precisely downscaling chemical reactions, a variety of factors play a crucial role. Adapting the process to small volumes requires a deep understanding of the materials involved, environmental conditions, and fluid properties. The following are the key parameters that should be considered:

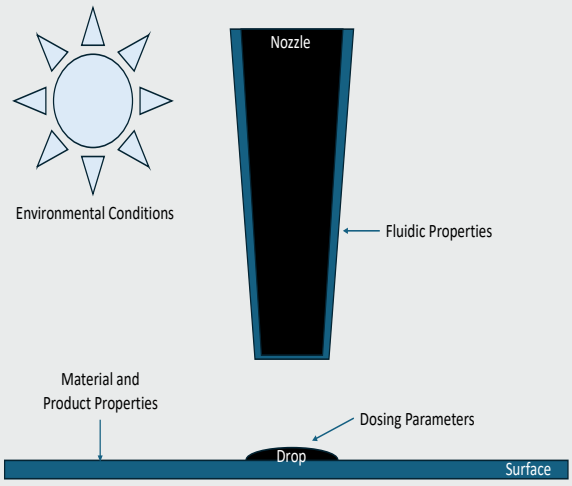

Figure 1: Important parameters to consider when downscaling.

1. Material and Product Properties

- **Reagents:** Is there prior experience with the substances to be processed? Can they be handled without issues? Prior experience with the substances makes dispensing more reliable.
- **Product**: What are the requirements of the product? This includes properties such as dispersion characteristics, stability, and compatibility with end formats like biochips or sensors.

2. Fluid Properties

- **Viscosity and Surface Tension:** Liquids with high viscosity or special surface properties can present challenges in dispensing and distribution.
- **Vapor and Evaporation Behavior:** With small volumes, the risk of evaporation or bubble formation due to vapor is particularly high. These effects can impair the stability of the dispensing process and cause missing droplets.

- **Homogeneity:** To achieve a stable outcome and have the same droplet formation repeatedly, it is important that the liquid properties do not change during the dispensing process.
- **Sensitivity towards the environment:** Some substances are light-sensitive or prone to crystal growth and clumping, which complicates their handling.

3. Environmental Conditions

- **Temperature:** Fluctuations in ambient temperature can affect both the physical properties of the fluid and the functionality of the system.
- **Air Purity:** Dust particles or electrostatic influences can unintentionally disturb small volumes. A controlled environment is advantageous here.
- **Humidity:** can significantly impact dispensing and overall results and droplet evaporation.

4. Dispensing Parameters

- **Dispensing Accuracy:** The drop size and speed must be reproducible and stable to ensure consistent results.
- **Desired Throughput:** Systems must be optimized to deliver the desired output without compromising precision in order to allow efficient scaling

SELECTING THE OPTIMAL SYSTEM

Choosing the right system is crucial for the success of the downscaling process. Modern dispensing systems offer a variety of features specifically tailored to the requirements of small volumes. Depending on the application and material properties, different technologies can be used. Some examples can be found in the microdrop portfolio.

1. Valve-based systems that dispense in the nl range by opening and closing valves

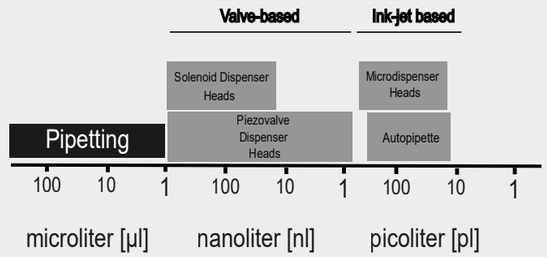

Figure 2: Dispensing options and ranges in the microdrop Technologies product portfolio.

- **Nanojet Solenoid Dispenser Heads**
  Properties: These systems combine capillaries and are easy to clean. They can produce larger jets (0.1–1 µl) and are suitable for larger volumes.
  Advantages: Particularly efficient for applications with higher throughputs or mixing processes.

- **Piezovalve Dispenser Heads**
  Properties: These systems can handle liquids with high viscosity and large particles. They are solvent-resistant and work precisely in the range of up to 8,000 mPas and can dispense more than 200 µl per cycle.
  Advantages: High flexibility and adaptability for demanding applications.
  Limitations: High-throughput systems can be louder and require maintenance after up to 80,000,000 cycles.

2. Ink-jet based systems that use glass capillaries with piezo crystals to generate small droplets in the pl range

- **Autopipettes**:
  Properties: These systems are particularly suitable for aqueous solutions and solvents like Dimethylformamid and with low viscosity (under 20 mPa) and small volumes (20 to 500 pl). They allow the generation of reproducible drops. Various source and destination vessels can be used.
  Advantages: Precise control allows drop sizes in the nanoliter range and offers low-maintenance liquid dispensing. Moreover, their design allows for external cleaning with e.g. a washing station
  Application Examples: Ideal for use in biological assays or the production of biochips.

- **Microdispensing Heads:**
  Properties: These systems are like pipettes. Drops are dispensed from a reservoir vessel as opposed to being taken from a dedicated source vessel. Reservoir sizes of up to 12 ml are possible.
  Advantages: Thanks to their large supply, dispensing heads allow quick dispenses over large areas. They can be heated, or cooled, or stirred and thereby dose a wide variety of solvents.
  Application Examples: Ideal for use in biological assays with more challenging solvents- e.g. paraffin.

PRACTICAL TIPS FOR PROCESS OPTIMIZATION

Ensuring success in downscaling reactions requires a well-thought-out approach. The following steps and strategies can help maximize efficiency and reproducibility:

1. Assessing the Feasibility of the Dispensing Process

- **Leverage prior knowledge:** If there is already experience with dispensing the liquids, this step can be skipped. Otherwise, it is crucial to establish whether the liquid is dispensable and whether the outcome aligns with the product goals.
- **Improve feasibility through solvent adjustments:** Changing the solvent can improve the dispensability of substances, especially for those prone to crystallization or clumping. Such substances should be processed under optimized conditions using appropriate solvents or additives
- **Ensure proper cleaning:** The functionality of dispensing systems depends heavily on cleanliness. Residues can compromise accuracy and lead to clogging or contamination. Establishing a suitable cleaning procedure is essential to prevent such issues.

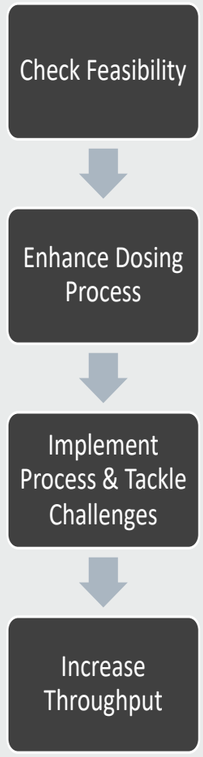

Figure 3: Practical process for downscaling optimization.

2. Enhancing Dispensing Processes

- **Ensure reproducibility:** The stability of the droplet formation process is criti-

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cal. Tests under various conditions (e.g., temperature, viscosity) help achieve consistent results. A feasibility study can support this process and prevent wasted time and resources on suboptimal processes.

- **Optimize droplet size:** Droplets that are too small may evaporate, while oversized droplets can cause inaccuracies. Selecting the optimal droplet size ensures uniform dispensing. Continuous processes minimize interruptions and reduce the risk of droplet detachment.
- **Temperature control:** Heated or cooled dispensing systems help maintain stable fluid properties and ensure consistent dispensing performance.

3. Proactively Addressing Challenges

- **Avoid gas bubbles:** Vapor or gas bubbles can disrupt the dispensing process. Degassing samples before use can help mitigate this issue.
- **Adhere to maintenance schedules:** High-performance systems like piezo valves require maintenance after several million cycles to prevent malfunctions.
- **Control environmental factors**: Dust, electrostatic influences, or microstructures on dispensing surfaces can cause disruptions. Enclosures can help mitigate these effects and protect the dispensing environment.
- **Establish end controls:** Reliable end controls are essential to validate the process and ensure that all parameters are being met.

4. Increasing Throughput

- **System integration:** Using automated systems with multiple heads or pipettes can double throughput without compromising dispensing quality.
- **Optimize labware:** Selecting appropriate labware and ensuring precise droplet positioning can accelerate workflows and improve overall efficiency.

CONCLUSIONS

Downscaling reactions can unlock significant advantages, from reducing reagent consumption to enabling cost-effective production of biochips and biosensors. However, achieving success requires careful consideration of material properties, environmental conditions, and dispensing technologies. By implementing the tips and strategies outlined in this document, you can optimize your processes for efficiency and reproducibility and furthermore this holds the potential for further method and workflow development.

For more detailed advice, tailored solutions, or to explore how advanced dispensing systems can support your specific requirements, please contact microdrop Technologies. Our experts are ready to assist you in finding the ideal system to meet your needs and help you achieve precision and reliability in every step of your process.

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