MSR™

MicroSphere Refiner

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The MSR™ MicroSphere Refiner is an all-in-one solution that combines all the individual stages required for microsphere processing, offering unique features and process designs. It addresses the major manufacturing challenges of microspheres and removes operator variability, reduces plant footprint and optimises capital investment.

Microspheres or micro-particles are complex drug formulations that combine an Active Pharmaceutical Ingredient (API) with an FDA-approved polymer such as PLGA. Microsphere drugs enable the sustained release of APIs into patients over prolonged periods of time, from weeks up to several months, helping to make novel therapeutics safer and more effective.

At PSL, we have developed a unique method of downstream processing microspheres, which condenses the multi-stage process within a single instrument. The MSR™ Microsphere Refiner is an innovative, automated solution with predictive scale-up to the kilogram level with a high product yield. This allows users to optimise batch reproducibility and to streamline production.

PSL's pioneering MSR™ technology is disrupting the way microsphere drugs are developed and manufactured around the world.

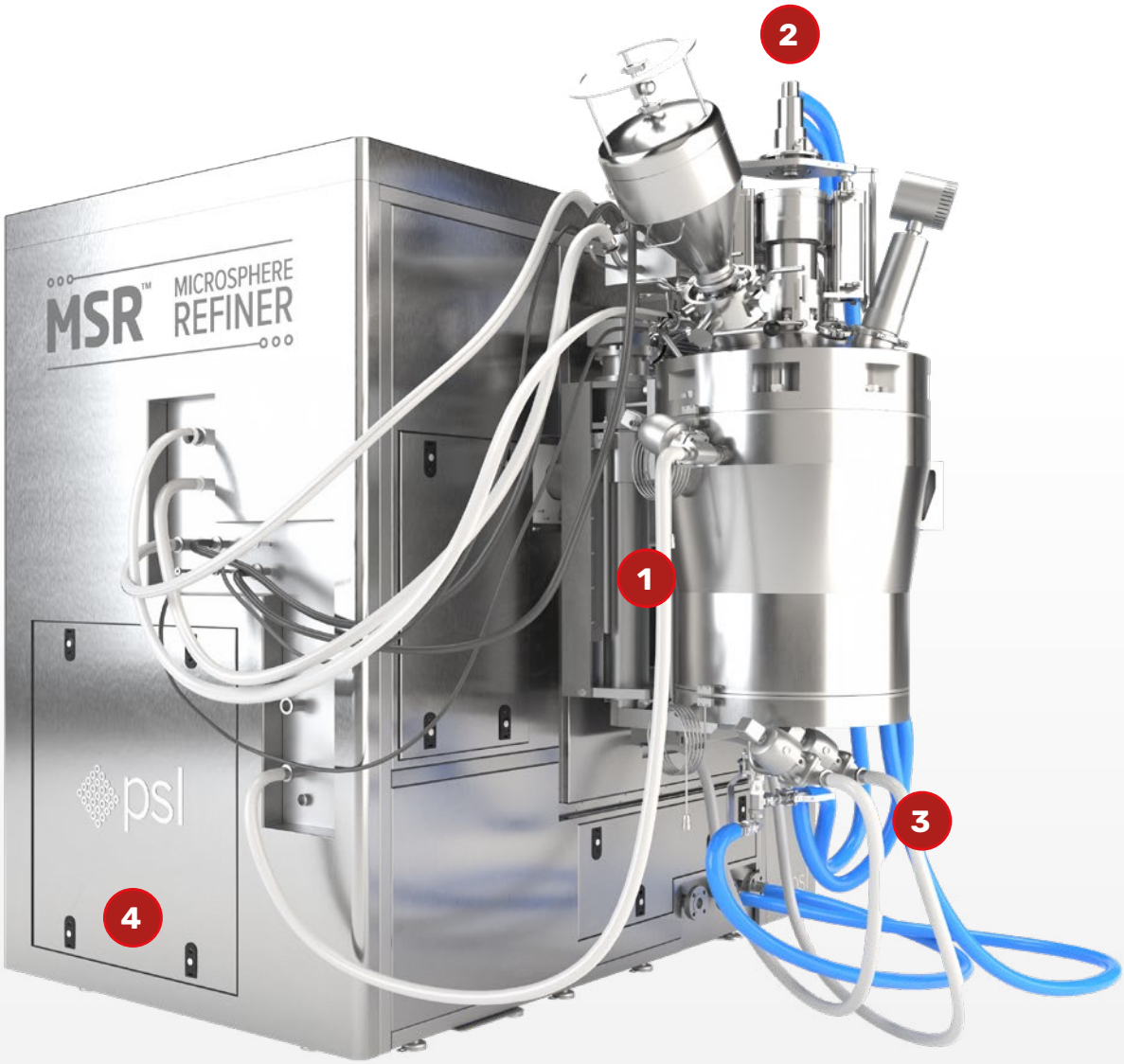
Features and Benefits

- **All-One-Solution**
  Combined processing steps, increasing overall yield
- **Batch Reproducibility**
  Robust, automated processing, removing operator variability
- **Process Automation**
  Configurable recipes for repeatability and traceability
- **PAT-Verified**
  Fast-tracks qualification and process optimisation
- **Successful Scale-up**
  Easy transition from early R&D to commercial batch sizes

Microsphere Drug Production: Redefined

The MSR™ MicroSphere Refiner condenses multi-stage microsphere processing within a single, Current Good Manufacturing Practice (cGMP) instrument. It naturally maximises product recovery, batch repeatability and production flexibility of the microspheres as it can complete the following processes in one single system:

- Microsphere Classification/Filtration/De-watering
- Microsphere Washing
- Microsphere Drying, including Freeze-Drying if required
- Microsphere Aseptic Sampling
- Microsphere Aseptic Discharge/Product Recovery



1: Pressure Vessel **2: Agitator** **3: Filtration Areas** **4: Process Support Module**

Key Features

1: Pressure Vessel

Filtration and drying occur within the MSR™ vessel, operating to secure maximum product discharge.

Pressure capability results in efficient filtration. Vacuum proficiency optimises drying and, where more complex formulation is required, product freeze-drying can be used.

- 316L Stainless Steel construction
- Pressure Directives: PED, ASME “U” Stamp, SELO, etc.
- Temperature controlled, insulated base and side walls

2: Agitator

The specially engineered blades are designed for distinct functionality, depending on the direction of rotation.

Clockwise rotation means the microspheres are kept in suspension during filtration stages and gentle mixing occurs during drying.

During anti-clockwise rotation the product cake top surface is smoothed for efficient pressure filtration.

- Single- piece blade design
- Temperature-controlled
- Top drive electrical motor and belt arrangement
- Pneumatic raise/lower cylinders

3: Filtration Areas

Specifically engineered filtration areas offer precise control of the end product particle size distribution.

Removable filtration elements allow change-over of mesh porosity to match the desired product quality.

- Metallic sintered mesh benchmarked specifically for polymeric microsphere particles
- Interchangeable for multi-product capability

4: Process Support Module (PSM)

Complete process flexibility is achieved with the MSR™ Process Support Module.

It provides full automation of each step, with prebuilt recipes and is customisable using the MSR™ sequence configurator.

- Entry point for upstream process and utilities
- Process distribution pipework, valves and control/monitoring instrumentation
- Built-in CIP and SIP features, including sterile boundaries (in place WIT capable)

Meeting the Challenges: The MSR™ Way

Various upstream methods exist for creating microspheres, but it is their downstream processing which is challenging using traditional methods. The MSR™ MicroSphere Refiner has revolutionised how effective microsphere processing is achieved using unique technology.

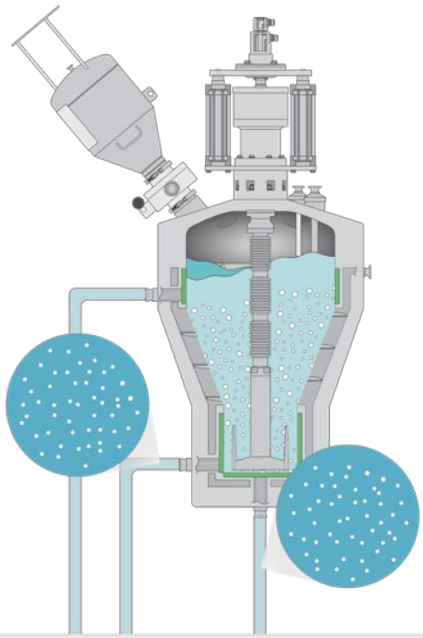
De-watering and Size Classification

Nascent microspheres typically undergo a solvent extraction in a buffer or quench tank. This highly diluted suspension transfers into the MSR™ vessel in a controlled manner for initial solid-liquid separation.

The MSR™ vessel contains specially engineered filtration areas, coupled with a unique suspension introduction method that maintains high filtration throughput.

The filtration mesh element also provides a size cut-off point for removing undersized particles, retaining only the desired particle size distribution.

In specific cases, recirculation loops are implemented to maintain filtration efficiency.

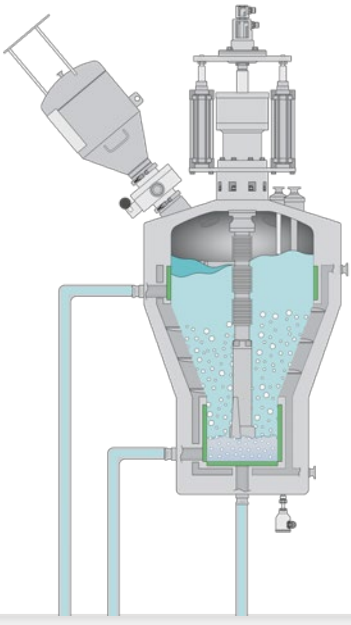


Product Washing

Upstream microsphere creation relies on the use of solvents and surfactants which must be washed to ensure high product quality.

Specific product washing solvents are used to obtain product quality and/or anticipate optimisation of the subsequent drying step by using more volatile elements.

The agitator helps the process by putting the microspheres back into suspension.



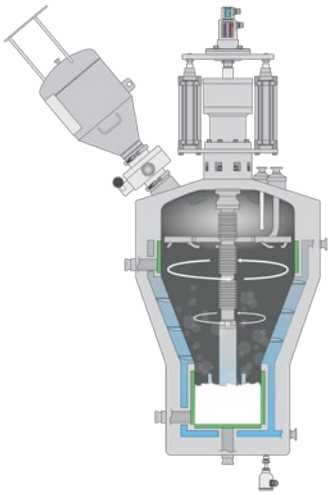
Product Drying

Polymeric microspheres are dried to evaporate the final solvent traces and achieve final product quality.

Various elements in the MSR™ can be temperature controlled, including the agitator. Cooling down the product throughout the process, avoids polymer degradation.

The fully sealed vessel is put under low vacuum to help with solvent evaporation and reduces drying times.

Agitating the product during drying ensures a homogeneous product batch.

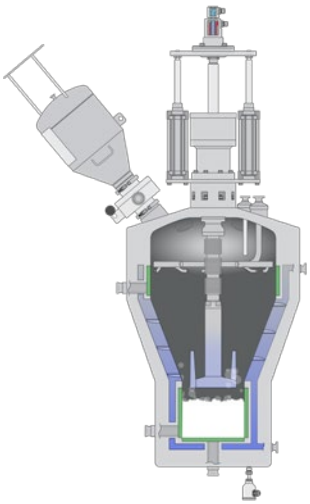


Freeze-Drying

Where a more complex formulation is required, product freeze-drying can be performed in bulk, inside the MSR™ vessel.

The quality of the vessel design and ancillary specification allows low vacuum levels to be reached and the freezing temperatures required for sublimation to be reached.

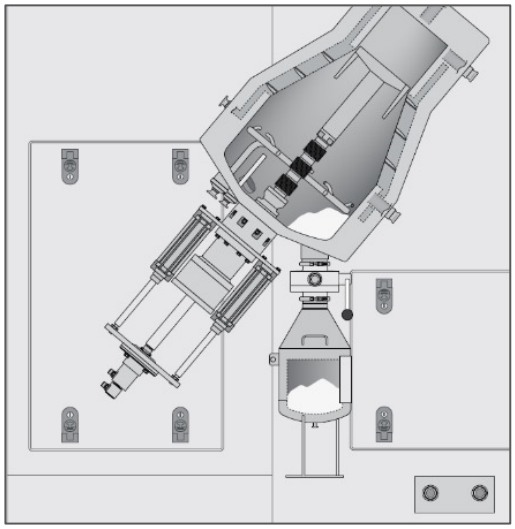
The agitator breaks down the bulk product back into a free-flowing powder form, for final discharge.



Aseptic Discharge/Product Recovery

The MSR™ vessel tilts to discharge the final powder into a harvesting container.

Connections between the MSR™ and the container are aseptic, to ensure product sterility and operator safety.



Process Flexibility: The PSM

If the vessel is the heart of the MSR™ technology, then Process Support Module (PSM) is the brain, allowing precise control and functionality.

A Centralised Hub

Cleanroom environments need to be controlled and maintained which is why the PSM is designed so utilities can connect to it via a single point of entry.

Internal distribution pipework and diverting valves link utilities and process lines, for example: correct distribution of process nitrogen during filtration or drying steps.

Monitoring and Control

An array of instruments and transmitters within the PSM monitor and control processing, providing an accurate indication of system health.

Adjustments to flow, pressure, temperature etc. can be implemented, as necessary.

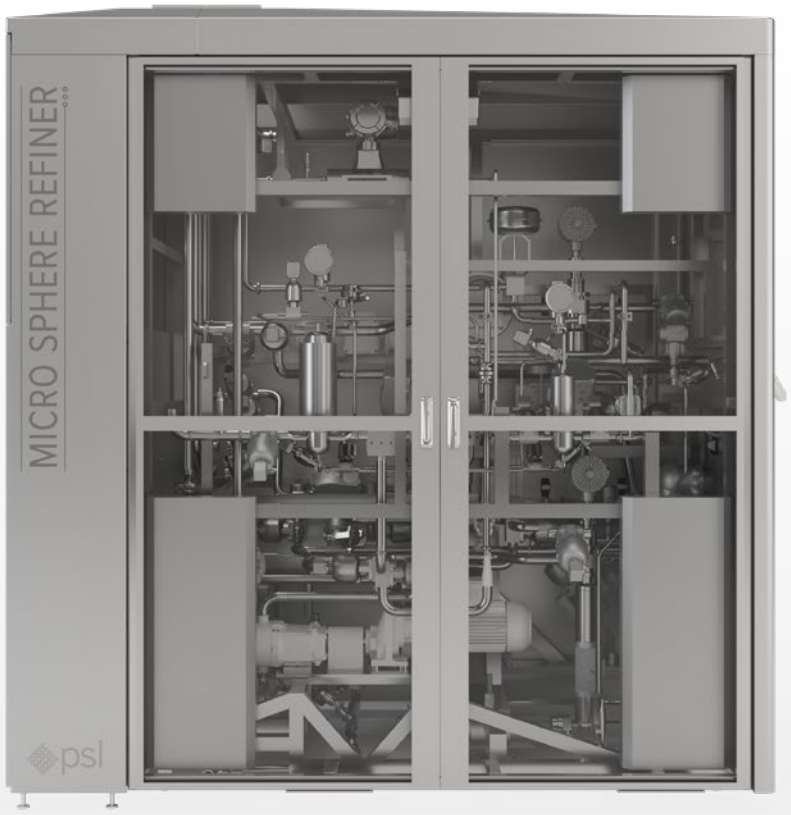
Flexible Hoses

The MSR™ vessel is connected to the PSM via flexible hoses and tubing to allow for rotation during final product harvesting.

Special manifold and hose lengths are engineered to address draining angles by shortening lines as much as possible.

Controlling Filtration

Variable speed drive filtrate pumps are integrated for controlling filtration rates.



Process Support Module Features

Process Analytical Technology (PAT)

Various additional instrumentation can be added for closer monitoring of the process.

- Processing Camera for visual inspection inside the vessel from a remote location
- Particle Size Analyser for product particle size distribution
- Dew Point Sensor for determining drying end points
- Conductivity Meters for optimising product washing cycles and/or CIP cycles

Sterile Boundaries

Polymeric microspheres, as injectable drugs, require sterile conditions.

The PSM incorporates sterile boundaries with 0.2µm filters.

These filters have built-in WIT (Water Intrusion Test) capability.

Integrated Ancillaries

The MSR™ process steps rely on surrounding utilities such as vacuum and temperature control – precise control being central to product quality, the following ancillaries are integrated to the MSR™ scope and software package:

- Vacuum Pump and Skid (with condenser)
- Temperature Control Unit

A Plug & Play Solution

By nature of the drugs being developed and manufactured in the MSR™, batch repeatability and traceability are critical.

The MSR™ automation package has been developed and undergoes continuous improvement to support market and regulatory requirements including GAMP5 (Good Automated Manufacturing Practice, version 5 by ISPE) and 21 CFR Part 11 established by the US FDA for electronic records and signatures.

Software Automation

- The MSR™ includes a software and automation package developed by PSL on a Siemens interface
- Architecture relies on a Safety PLC, Field Remote I/O and Field Touchscreen Colour HMI
- Provides access and monitoring to all areas within the PSM and Vessel for either manual, semi-automatic or fully automated control

Sequence Configurator

Removing operator variability is central to a robust process. The MSR™ Software comes with pre-built sequences, such as:

- Vacuum and pressure hold test (pre-batch checks)
- De-watering Filtration
- Product Washing
- Product Drying
- CIP
- SIP

Parameters can be entered and modified for each sequence to suit product and process characteristics. Storage and retrieve functions allow for quick changeover in manufacturing needs.

Reporting

- An industry standard built-in audit trail captures modifications to the system and electronic signatures
- Built-in SCADA (Supervisory Control And Data Acquisition) with redundant server configuration for fail-safe storage of batch records, to satisfy regulatory requirements

Predictive Microsphere Scale-up

Due to their characteristics and properties, polymeric microspheres have traditionally been known to be difficult to process for manufacturers – especially as the batch size gradually increases as part of the microsphere product development. The unique features of our MSR™ were developed following a Quality-by-Design (QbD) approach, taking into account the microspheres characteristics and process behaviour throughout scaling-up.

LabMSR™

The LabMSR™ is a GLP piece of equipment developed to enable global drug manufacturers to carry out R&D activities, product scale-up, and refinement of process parameters in laboratory conditions.

It offers some of the process benefits of PSL's full scale production MSR™ MicroSphere Refiners but was specifically designed for laboratory activities and early clinical phase batch requirements.

	LabMSR™	MSR™	
Nominal Filtration Area Size (m²)	**0.01**	**0.05**	**0.125**
Typical Operating Liquid Volume (L)	4	120	120
Recommended Min/Max Cake Batch Volume (L)	0.2 / 0.4	0.8 / 9.0	2 / 21
Freeze-Drying Capability	Y	Y	Y
Aseptic Processing Capability	Y	Y	Y
Suitable for use in Hazardous Area (ATEX/NFPA)	Y	Y	Y
Integrated with Process Support Module (PSM)	n/a	Y	Y
Full Automated Recipes with Process Configurator	n/a	Y	Y
SCADA and Batch Records	n/a	Y	Y

Taking your process further, together.

For over 35 years, Powder Systems Limited (PSL) has been at the forefront of designing and engineering advanced technology to support process development. We are a globally recognised, award-winning business with expertise in pharmaceutical and chemical processing.

Our focus is to help clients and partners address challenging manufacturing processes by providing fit-for-purpose solutions from our wide range of Microsphere Processing, Filtration and Drying ranges.

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