Innovation to Resolve Challenging Microsphere Drug Delivery Systems Formulation Process

PEER REVIEWED

Due to their ground-breaking benefits and market share opportunity, the production of polymeric microsphere drug delivery systems is experiencing a fast-growing demand worldwide but remains a very challenging formulation process. New drug delivery devices such as PLA, PLGA, PLG or PEG polymeric microspheres have revolutionary applications. These biodegradable particles work as miniature sustained release capsules for injectable drugs, to treat various conditions from cancer to diabetes, hormonal disorder, mental illness and addictions.

This revolutionary drug delivery platform is one of the most attractive vehicles for drug delivery systems. They provide valuable benefits such as less frequent injections thanks to the long-term sustained release they provide. They also improve greatly the patient comfort and lifestyle, as well as compliance. Reducing the logistic costs and providing drug protection are also significant advantages. Finally, microsphere products allow for a tailored drug release rate according to the application. Formulation of microspheres is a ground-breaking technology for patients, pharmaceutical companies, and governments and public organisations. The polymer-based drug delivery systems market was estimated at US$60Billion in 2010[1] Major blockbuster drugs such as Lupron Depot or Bydureon make up this growing market; patents are running out and there are significant unmet needs with only a dozen FDA approved drugs currently in the market.

The formulation of such polymeric microspheres can be a very challenging process. The particles formulation must be controlled to achieve a specific particle size, distribution and morphology. The particles must be in the range 5-25µm up to 90-150µm. Too small or too large particles will not have the desired effect once injected into the bloodstream. In addition to strict parameters to control, these drug delivery systems have difficult characteristics to work with during the formulation process. They are by nature sticky, soft and fragile, sensitive to temperature and humidity, and most of all sterility must be maintained at all time. For all of these reasons, the manufacturing of microsphere drug delivery devices on a commercial scale has been very challenging. Scaling up from small-scale batches of a few grams to large-scale production above 20kg batches has been almost unmanageable.

Problem-free Downstream Formulation Process

There are two main steps during the formulation of microspheres medicine: first the upstream process which consists of creating the polymeric microsphere particles containing the active ingredient; then the downstream process which consists of filtering, classifying, drying and recovering the micro size particles in a sterile manner ready to be filled, packed and stored (Image 1).

The devices used to inject these treatments can be vials or prefilled syringes. In any case, the microspheres must stay separate from a liquid phase due to their biodegradable characteristic, they are more stable in a solid form and last longer.

During the production of polymeric microspheres, the particles need to be classified per size to only retain specific sizes for the final products. The microspheres need to then be washed from the solvent and dried under restricted conditions and recovered. All these processes require sterile handling. The downstream process became a problem for manufacturers to control because of the following challenges:

- To accurately control the particle size,
- To maintain the sterility envelope during the whole process,
- To efficiently scale-up the R&D process to commercial manufacturing,
- To maintain reproducibility with maximum yield.

The existing technologies developed so far such as sieving or

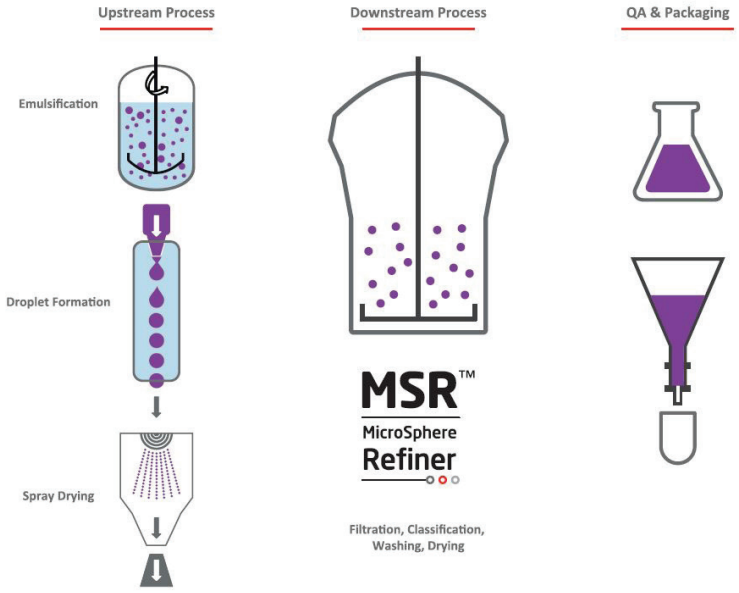

Image 1: Formulation process of polymeric microsphere drug delivery systems

screen filtering, centrifugal sifting and lyophilisation were causing many problems. Amongst the difficulties mentioned by manufacturers, the below were the most common:

- Filtration mesh blocking causing difficult size classification,
- Long drying time,
- Breach of sterility resulting in batch loss,
- Difficult process scale-up,
- Insufficient yield performance,
- High investment for several capital equipment.

Image 2: MicroSphere Refiner technology for drug delivery devices formulation

The MicroSphere Refiner (MSR™) technology has been developed to address these challenges as the demand for efficient microsphere formulation process became greater. Previous processes caused manufacturing issues impacting the finished drug delivery devices' quality. They could not guarantee the correct size distribution, the sterility, and provide an acceptable yield. By working with drug producers, process specialist, PSL, innovated with a unique technology (Image 2) able to perform all the required process steps, and achieve:

- an accurate size classification using a unique filtration technique that avoids the mesh to be blocked by keeping the particles in suspension;
- a homogenous drying through vacuum drying, that gently dries the microspheres at low temperature;

Image 3: MSR vessel with PAT and instrumentation

- high yield thanks to a unique product offloading method resulting in almost 100% of the final product being harvested;
- aseptic recovery with a discharge method that doesn't require the intervention of an operator, being automatically controlled and confined;
- process scale-up capability by providing the same technology from laboratory scale to pilot plant up to commercial scale;
- process repeatability for constant batch quality;
- one-step process to reduce total investment.

For pharmaceutical manufacturers, it is essential to have a proven technology used during process development that can be scaled up to large-scale production, especially to respect the FDA (Food & Drug Administration) regulations and approval. The MicroSphere Refiner technology helps them to greatly reduce costs by using one piece of equipment instead of several process systems and sterile containment isolators. The operative and maintenance costs have been reduced considerably while the quality of each batch is uniform and reliable. The innovation also has a smaller footprint. The MSR technology has been developed and refined over 20 years and it has been adopted by blue chip pharma groups around the world. After successfully installing production lines in USA and Europe, five production lines have recently been installed in Asia. These installations consist of MSR formulation lines suitable for an aseptic production of 10 to 20L of final product. The installations were completed with process skids, modular process systems contained with individual frame for each process equipment. Such process skids include all of the valves and pipework, sterile filters, sterilisation and clean-in-place lines, heat transfer and utilities systems.

The microsphere formulation installations feature full automation of the MSR vessels and process skids through dedicated software and HMI/PLC systems. A variety of process analytical technologies (PAT) in-line or off-line are necessary to ensure a problem-free formulation process. Automated process sampling is available along with a process camera, level sensor and cake volume indicator (Image 3). Temperature probe, mass spectrometer and particle analysers can be also added to the facility.

Feasibility Study and Process Optimisation

Before commercially producing microsphere drug delivery devices, manufacturers are required to work on process optimisation at small scale. Such feasibility studies ensure a successful scale-up approach to larger batch quantity. Process expertise is paramount and can be in-house, fully outsourced or supported by consultancy when required. R&D trials and feasibility studies of filtration and drying downstream formulation ensure an optimum product quality and repeatability. To address this increased demand for process support, the Center Of Process Excellence (C.O.P.E.) opened in 2016 in Philadelphia, USA.

The centre hosts feasibility studies, trials and process development for laboratory and pilot plant. Drug developers are able to use the facility and work with process specialists to develop new microsphere drugs and optimise their manufacturing process.

Polymeric drug delivery systems are revolutionary devices with a wide range of applications providing numerous benefits to patients, public health organisations and pharmaceutical manufacturers. Innovation in formulation process

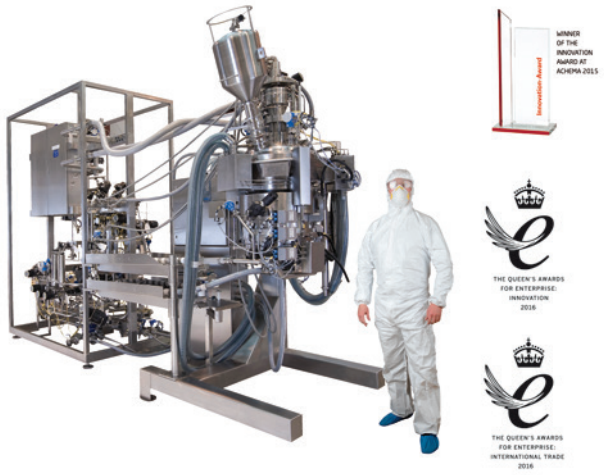

Image 4: Award-winning MSR technology and process skid

was desperately needed to address a challenging manufacturing process and to market faster new treatments. With the MSR technology now available, cGMP standards are met and high yield with low operational costs are achievable. The MicroSphere Refiner™ range was awarded the best Mechanical Process Innovation at the ACHEMA 2015 Awards and best Innovation in 2016 by the Queens Awards for Enterprise in Great Britain (Image 4). Proven track records by blockbuster manufacturers have brought generic manufacturers to adopt MSR technology, who will also contribute to the production and commercialisation of controlled drug release medication in a targeted manner that will improve the wellbeing of millions of suffering patients.

REFERENCES

Trademarks and IP for MSR™ and GFD® are the property of Powder Systems Ltd.

1. Zhang L, Pornpattananangku D, Hu CM, Huang CM. Development of nanoparticles for antimicrobial drug delivery. Curr Med Chem. 2010;17:585–594. [PubMed]

Camille Flores-Kilfoyle

Business Development Manager Camille is the Business Development Manager of Powder Systems Limited (PSL) a process specialist company. She has been working on the development and market launch of the MSR technology, addressing existing challenges in the marketplace when it comes to the production of microsphere drug delivery systems.

Email: info@powdersystems.com

Sartorius Stedim Biotech launches two Single-use Sartocon® Loop Assemblies with Integrated Polyethersulfone (PESU) Membrane

Assemblies save up to 60 percent on processing time and offer a safe approach to ultrafiltration of biologics and vaccines

Sartorius Stedim Biotech (SSB), a leading international supplier for the biopharmaceutical industry, announced its polyethersulfone membrane (PESU) is now integrated into two new, sterile Sartocon® benchtop and production scale filtration assemblies. Using these assemblies guarantees rapid and safe ultrafiltration of biologics and vaccines. Due to the fully enclosed design, the Sartocon® assemblies are ideal for safely purifying vaccines and recombinant proteins, as well as monoclonal antibody manufacturing. This makes them suitable for use in cGMP environments for process development, clinical trials and small-scale production batches.
The new single-use Sartocon® Self-contained Filter Loop Assembly has been developed for use with SSB's unique control unit, the FlexAct® UD. While the Sartocon® Slice Self-contained Bag Loop Assembly has been designed for SSB's benchtop crossflow system SARTOFLOW® Alpha plus SU. Both assemblies are supplied gamma sterilized and ready to use. The integrated PESU membrane is pre-wetted and flushed which saves hours in set-up and validation time, as well as eliminates the costs of using buffers and purified water to prepare the membrane.

The single-use Sartocon® Self-contained Filter Loop Assembly has been developed for use with SSB's control unit, the FlexAct® UD.

Since the Sartocon® assemblies are designed with the same hydrodynamic flow path as SSB's larger production scale filter devices and all device materials and accessories are manufactured to the same industrial quality-assured specifications, linear scale-up and process transfer is a simple process.
The PESU membrane inside the Sartocon® assemblies is available in several sizes and 10-300 KDa molecular weight cut-offs and is robust enough for use in broad pH and temperature ranges. These features combined with the Sartocon® assemblies' single-use design, which prevents product cross-contamination, means they are perfect for use in R&D applications, Contract Manufacturing Organizations and multi-product facilities.

"Following on from the successful introduction in 2015 of the Hydrosart® membrane in our single-use Sartocon® filter loop assemblies, we made our PESU membrane for these applications available as well. Now customers can select from a broader range of membrane polymers and cut offs for ensuring optimal parameter for their specific process. When compared with reusable filter cassettes, we estimate that using these new single-use, PESU membrane-based assemblies will reduce processing time by around 60 percent and could save up to 2,000€ per batch on buffer and water costs", Frank Meyeroltmanns, expert for crossflow-filtration at SSB explains.

The Sartocon® Slice Self-contained Bag Loop Assembly has been designed for SSB's benchtop crossflow system SARTOFLOW® Alpha plus SU.

Contact:
Sartorius Stedim Biotech GmbH
August-Spindler-Str.11
7079 Göttingen
www.sartorius-stedim.com

sartorius stedim biotech