



IMPROVING OPHTHALMIC DRUG DELIVERY WITH NOVEL EMULSION TECHNOLOGIES FOR STERILE SUSTAINED-RELEASE INJECTABLES

In this article, Robin de Bruijn, MSc, Chief Technology Officer, and Frank de Jong, MSc, Chief Executive Officer, both of EmulTech, describe the company's ET4ME micro-encapsulation process, and its suitability as a particle formation technology for enhancing and enabling injectable ophthalmic pharmaceutical products.

In the ophthalmic pharmaceutical world, there is a large need for and challenge to develop effective long-term delivery systems to solve problems with the retina. Typically, only systemic doses by administration directly into the eye are the only way to deliver sufficient concentrations of drugs. These are done by injections which

(fluocinolone acetonide), Ozurdex® (dexamethasone), and Iluvien® (fluocinolone acetonide). Unfortunately, the aforementioned complications as a result of these (often non-absorbable) implantations are still not fully resolved.

Micro-encapsulation of small- and large-molecule APIs is a very advanced solution

to injectable delivery problems. Micro-encapsulation is one of the most interesting areas in modern pharmaceutical technology. It is a complex, interdisciplinary field requiring specialist knowledge of polymer science and familiarity with emulsion technology. It includes the process in which the active pharmaceutical ingredient is trapped in small microparticles. Due to its complexity, micro-encapsulation is extensively studied inside major pharmaceutical companies, universities and research institutes. Encapsulation in biodegradable matrices is used for controlling the release of all

“Encapsulation in biodegradable matrices is used for controlling the release of all kinds of compounds. Demand for the process has led to the creation of advanced emulsion solvent evaporation/extraction based micro-encapsulation technologies. It is advanced process knowledge that can translate the formulation complexity into to a successful drug product”

can be very problematic. An increasing number of drugs designed to prevent or treat these diseases require repeated and high-dose injections due to the high ocular clearance rate, leading to clinical challenges in the form of side effects (infections, haemorrhages and cataract formation). One successful approach has been the surgical implantation of drug-releasing devices, such as Vitrasert® (ganciclovir), Retisert®

kinds of compounds. Demand for the process has led to the creation of advanced emulsion solvent evaporation/extraction based microencapsulation technologies. It is advanced process knowledge that can translate the formulation complexity into to a successful drug product.

The process of micro-encapsulation can address complex modern drug delivery issues. EmulTech has developed, and put to use in



Mr Robin de Bruijn
Chief Technology Officer
T: +31 40 751 6162
E: DeBruijn@EmulTech.nl

Mr Frank de Jong
Chief Executive Officer
T: +31 40 751 6160
E: DeJong@EmulTech.nl

EmulTech BV
De Lismortel 31
NL-5612 AR Eindhoven
The Netherlands.

www.EmulTech.nl

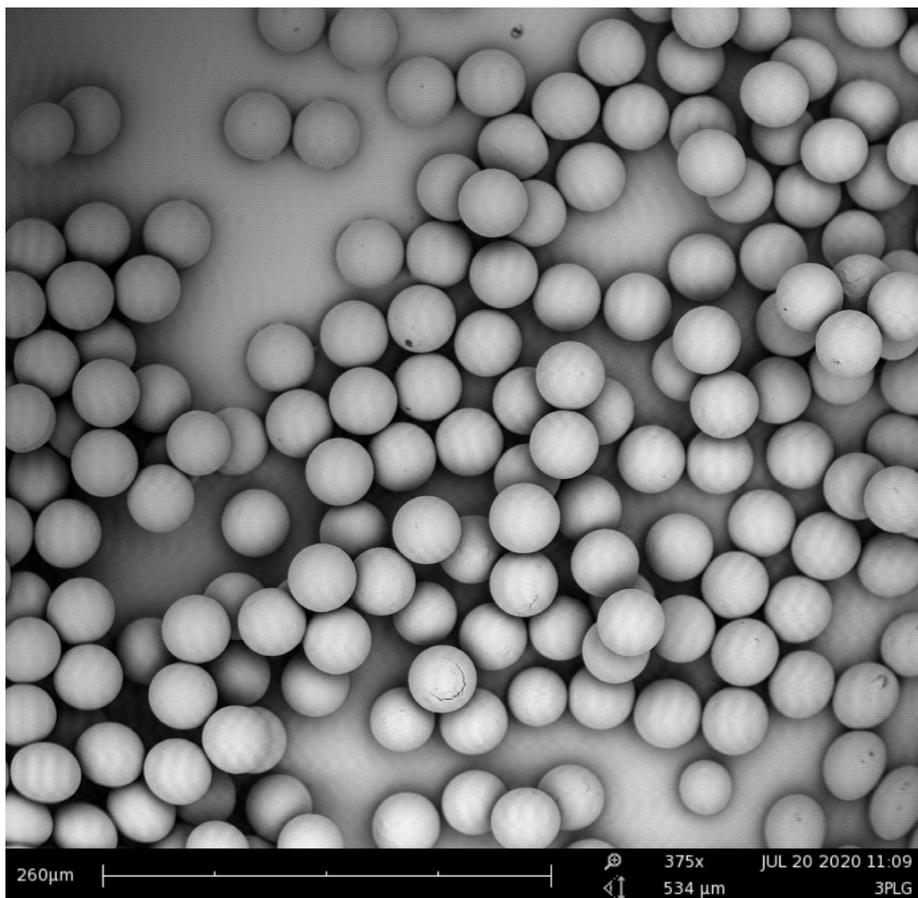


Figure 1: SEM image of 40 µm PLGA particles created with ET4ME.

the formulation of drugs for clinical trials, a microfluidic process that creates a measurable microparticulate suspension where particle size is uniform and reproducible.

This novel emulsion technology for micro-encapsulation, ET4ME, is usable in the formulation of multiple APIs, from small molecules right through to complex biomolecules, with high levels of batch consistency and reproducibility upon scale-up.

By utilising a closed system, sterile formulations can be achieved, coupled with resistance to oxidative degradation. After validation for several biodegradable microparticulate systems and successful aseptic process simulation trials using the ET4ME process, the technology's potential for pharmaceutically acceptable, sterile injectable product formulation has been demonstrated.

BUSINESS MODEL BRINGING EMULSION TECH TO LIFE

EmulTech has adopted a flexible and professional model to pool collective experiences and co-operate in a multi-disciplinary network to advance the use of innovative technologies in product formulation. For example, EmulTech has the capability to test formulations together

with world experts in partnered academic institutions that require small volumes. The company offers a parallel strategy for swift and reproducible scale-up whilst providing product and process support throughout a product's development cycle. CMOs in the network provide a varied palette of formulation development expertise, analytics and GMP services and expert guidance through the processes of new medicine and material development for Phase I and Phase II clinical trials.

"This novel emulsion technology for micro-encapsulation, ET4ME, is usable in the formulation of multiple APIs, from small molecules right through to complex biomolecules, with high levels of batch consistency and reproducibility upon scale-up"

By collaborating, such companies are able to maximise budget effectiveness and minimise experimentation without sacrificing quality levels, and enhance productivity, thereby providing increased value to customers and achieving significantly shorter development times.

Following the preclinical formulation and lab-scale process development, EmulTech is in the process of installing the capability to validate the equipment further and to formulate products according to cGMP requirements.

EMULSION TECHNOLOGY BENEFITS

Droplet formation in microfluidic devices has always been an interesting approach. EmulTech has made a breakthrough by modelling droplet formation on the cross-intersection of a microfluidic channel structure. Process parameters can be identified by feeding measurable material specific parameters (e.g. viscosity, interfacial tension) and particle characteristics (e.g. particle size) into the model. When the process parameters are set correctly, each droplet is formed to the same characteristics, ensuring the uniformity of the batch and thus its quality. This way ET4ME translates the trial-and-error approach of many processes into a quality-by-design approach.

Scale-up is done through process intensifications (more channels per device) and numbering out (cartridges containing multiple devices). Process parameters identified in a single-channel setup can easily be translated to a multi-channel setup to create larger volumes (up to Phase II clinical depending on the application).

In principle, the technology is a highly controlled emulsification technology having various applications in different markets, such as the food industry (taste masking, protection of additives against its surrounding, delivery to the gastro-intestinal system), cosmetics (stability enhancement of uniform micro-emulsions), chemicals

(increased control over reactions), pharmaceutical industry (drug delivery, markers, radiotherapeutics, etc). EmulTech's prime markets are the inhaled and injectable drug delivery markets, because of the significant added value ET4ME provides in these markets.

| Parameter | Benefit |
|---------------|--|
| Quantifiable | Based on measurable parameters, particle formation is now “measure-and-make.” |
| Compatible | APIs ranging from small molecules to complex biomolecules can be used. |
| Uniform | Particles are individually formed in the same way, leading to uniform size, loading and morphology. |
| Consistent | Droplet formation is based on a physical process: fixed process parameters give fixed product characteristics. |
| Scalable | Highly reproducible using mass parallelization. |
| Closed system | Degradation by air/oxygen can be eliminated. |
| Aseptic | Inline filtration in a closed system ensures sterility. |
| Static system | No moving parts, no high temperatures or high shear. Very reliable and stable. |

Figure 2: Benefits of ET4ME as a particle formation process.

The inhaled market requires particles in the range 1-5 μm , preferable 2-3 μm for optimal lung deposition. ET4ME, because of its uniformity, is well suited to meet these requirements.

The ophthalmic injectable market requires sterile suspensions with high syringability, preferably with very small gauge needles (>28G). The closed system, combined with the 0.22 μm inlet filters, ensures the creation of sterile suspensions. Also the uniform particle size reduces the suspension's viscosity, making it more syringable and thus less painful for the patient. Also the uniform particle-size distribution of ET4ME ensures that large particles that may block the needle are not present. Very small particles that may result in immune response dose dumping are also absent. In short, the optimal particle size both to ensure release and deliver by small-gauge needles is now possible to achieve (see Figure 1).

Main advantages of the technology are:

- Quality-by-design approach
- Reproducibility between batches and during scale up
- No end sterilisation as a result of closed system with inlet filters
- Benign process; no shear, no heat increase.

Product benefits include:

- Microparticles with a very narrow particle size distribution
- Improved injectability
- Broad variety of APIs and carrier materials possible
- New products are feasible

The technology is a highly versatile particle formation technology based on a microfluidic process (see Figure 2). The process enables the particle size, loading and carrier material to be changed so as to create an optimal drug delivery system by offering a high level of control over droplet formation. Size ranges of 1–1000 μm (with a distribution of <1%) are possible, with up to 100% encapsulation in perfect spheres with no porosity.

The process is applicable to small molecules and biomolecules, is highly reproducible during scale-up and offers reliable batch-to-batch consistency.

Parameter optimisation is of critical importance with such emulsion technologies, particularly for criteria such as size, API load and morphology. ET4ME, for example, facilitates the combination of two fluids that cannot be mixed using

standard droplet formation techniques. Particles in this purely physical process are produced in separate microchannels, which protect APIs during particle formation.

The particles in this versatile process are formed under very low shear conditions and the absence of temperature modifications. With the ability to process any two liquids in a drug delivery system, the optimal excipient and active blend can be achieved, resulting in the optimised product.

BIOMOLECULES

Highly potent biologically active ingredients are often easily deactivated and are a challenge to deliver in a pharmaceutical formulation. Technologies like ET4ME preserve the fragile three-dimensional structure of these actives; and the ability to define the optimal composition and release properties, via superior particle formation control, meaning that the challenges that accompany these highly potent active drug substances can be overcome.

FASTER DEVELOPMENT, BETTER PRODUCTS

This type of technology enables products to be developed with better therapeutic effects and improved patient compliance in a cost-efficient and timely manner. By eliminating poor batch-to-batch consistency, variable particle formation and numerous rounds of inaccurate, costly and time-consuming screening, ET4ME allows for more rapid, reliable and efficient prototyping. Such versatile enabling technologies are used for the non-destructive testing of fragile compounds, inhalables, injectables (including for ocular injection) and solid dosage forms.

Many different formulations and multiple parameters can be scanned and tested, facilitating more efficient R&D and accelerating the development, scale-up and commercialisation of highly potent APIs in the product pipeline.

CONCLUSION

The important development steps made by EmulTech resulting in the ability to produce sterile suspensions and reducing the need for end-sterilisation provide the pharmaceutical world with a new tool in their development programs.

INJECTABLE PLGA DELIVERY SYSTEMS

Current APIs often exhibit poor solubility and/or a short half-life, requiring novel approaches such as sustained release to achieve acceptable bioavailability. Injectable biodegradable and biocompatible polymer systems that utilise copolymers of lactic and glycolic acid (PLGA) are a promising advanced delivery system for week- to month-long controlled release and have been around for decades.

ET4ME type technologies address head-on the challenges of large-scale manufacturing/scale-up needs and convoluted production schemes. Polymer microspheres can be formulated with a highly defined size, encapsulating the API in a polymer matrix. The correct matrix sets the release duration (from weeks to months) and perfecting the mono-dispersed particle size establishes the zero order kinetics of the release.

The system operates under aseptic, closed conditions and eliminates the need for complex work-up steps. Scale-up is achieved by massive parallelisation, ensuring product consistency throughout the pharmaceutical development pipeline.