SMART4FABRY

Smart Functional GLA—nanoformulation for Fabry disease

Facing the scale-up of nanomedicines

A large variety of nanoparticle-based delivery systems have become increasingly important for therapeutic applications. A critical issue lies in the challenge of scaling-up the synthesis and formulation of the nanomaterial from the lab to pilot and then to the industrial scale, while maintaining control over their quality attributes, such as particle mean size . The DELOS Platform is a robust procedure to overcome these challenges, delivering consistent, high quality, therapeutic nanoformulations. In the frame of Smart-4-Fabry, the DELOS procedure has been successfully scaled-up to the pilot plant and consistent, high-quality nanoliposomes loaded with GLA enzyme have been delivered for preclinical GLP toxicology assays.

While a first generation of nanocarriers have been successfully brought to market, notably in the oncology field, new classes of therapeutic agents making use of polymers, proteins, polysaccharides and other biomolecules have emerged for the treatment of numerous diseases.

Unfortunately, these new types of nanocarriers are facing difficulties in their translation to the clinics due to an absence of realistic industrial production, lack of reproducibility and insufficient cost-effectiveness. Controlling the nanoformulation attributes in a reproducible manner over intricate structures can be problematic, as well as difficult to bring to the required industrial pharmaceutical manufacturing standards such as Good Manufacturing Practices (GMPs). Accordingly, there is an important need in developing simple and robust nanotherapeutics manufacturing methods that can be readily implemented at industrial scale.

Main challenges on the scale-up of nanomedicines

- Physical and chemical parameters that influence their properties are poorly understood
- Inconsistencies on delivering robust and well-defined products (lack of reproducibility, poor batch-to-batch consistency)
- Lack of available pharmaceutical grade constitutive materials
- Challenging adaptation of facilities to GMP
- Insufficient cost-efectiveness

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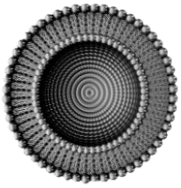
The DELOS Platform: scaling-up a robust method for the production of therapeutic nanovesicle-based systems

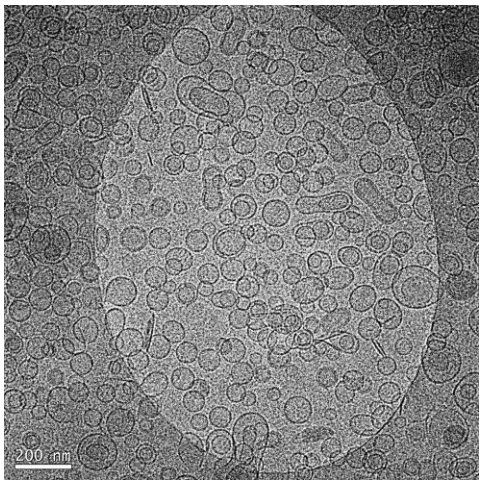
In the framework of the Smart-4-Fabry project, we scaled-up the DELOS platform for the production of GLA-loaded nanoliposomes (nanoGLA) from the lab to the pilot plant scale.

DELOS is a compressed fluid-based method, owned by the SME project partner NANOMOL TECHNOLOGIES, that allows the reproducible and scalable production of nanovesicular systems with remarkable physicochemical characteristics, in terms of homogeneity, morphology, and particle size. These nanovesicles can protect and transport from small molecules to biomolecules, such as the GLA protein. DELOS is a green and sustainable platform, that uses compressed CO_2 as solvent.
During the Smart-4-Fabry project, the DELOS manufacturing process has been succesfully scaled-up from 25 mL to 2 L batch of nanoGLA formulation. During this development, in addition to maintaining the physico-chemical and biological properties of the nanovesicular system, the concentration of GLA enzyme in the nanoformulation has been increased up to 10-fold, which represents an important milestone for the project since the nanoformulation became suitable for in vivo administration, thus unlocking further pharmaceutical development.

NANOMOL TECHNOLOGIES



PARTICLE TECHNOLOGIES FOR HEALTHCARE: DELOS™



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Quality by Design (QbD) implementation for the development of a robust manufacturing process

In order to develop a robust process for the preparation of nanoGLA, a Quality by Design (QbD) approach was applied, following the ICH Q8 Pharmaceutical Development Guideline, which summarizes the principles of QbD and shows how concepts and tools (e.g. the design space) could be put into practice.

QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and `process understanding and process control. Here design spaces serve as multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. Finally, control strategies which are planned set of controls, derived from current product and process understanding, ensures process performance and product quality. This methodology is encouraged both by the FDA and the EMA to develop robust drug manufacturing methods and controls.

Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) were identified, as well as Critical Quality Attributes (CQAs) of the nanoGLA formulation. The potential risk factors which might influence the quality of the product were identified through Risk Analysis assessment, and four formulation factors were considered relevant to be included in the subsequent Design of Experiments (DoE).

As a result, a design space within which the DELOS process operates in a way that the nanoGLA product obtained fulfills all required quality specifications, in terms of controlled particle size, polydispersity index, surface charge, and enzyme concentration, among others; allowed us to produce an optimal nanoGLA test material for the scheduled preclinical GLP trials of the project.

Successful scale-up of the DELOS Platform to deliver high quality enzyme-loaded liposomes

- DELOS is a green, sustainable nanoformulation and manufacturing platform, based on compressed CO_2 as solvent
- Consistent, reproducible, Enzyme-loaded liposomes for the potential treatment of Fabry disease have been delivered for regulatory preclinical testing
- Process was sucessfully scaled up to pilot plant scale (Liter scale)
- Quality by Design approach was followed obtaining a Design Space where the nanoformulation meets all quality criteria

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Conclusions: overcoming scale-up challenges

In the particular case of the Smart-4-Fabry project, high degree of process control and understanding have been achieved by implementing QbD methodology in the development of new enzyme- loaded nanoformulations prepared by DELOS, a scalable compressed fluid-based formulation and manufacturing platform.

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