Science with Passion

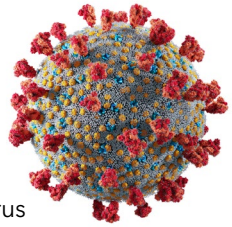
KNAUER

Systems for lipid nanoparticle (LNP) production

From early stage to commercial scale

think **LNP.** think **KNAUER.**

Our contribution to combating the COVID-19 pandemic



December 2019
The outbreak of COVID-19 begins in Wuhan, China. A new coronavirus is identified, but its global impact is not yet understood.

30 January 2020
The World Health Organization (WHO) declares the outbreak a Public Health Emergency of International Concern (PHEIC). The situation escalates rapidly.

11 March 2020
The WHO officially declares COVID-19 a global pandemic. The world enters crisis mode, and the race for a vaccine begins.

Spring 2020
The pandemic spreads across the globe. No vaccine exists at this stage, and the need for a rapid solution becomes urgent.

Spring–Summer 2020
Leading pharmaceutical companies begin developing mRNA-based vaccines. mRNA must be encapsulated in lipid nanoparticles (LNPs) for effective delivery into the body.
However, LNP formulation is available only at laboratory scale. No industrial system exists to meet the urgent, large-scale production requirements.

3 MONTHS

May 2020
KNAUER is approached with a challenge
We are contacted by a major pharmaceutical company and asked whether we can develop a customized, scalable LNP production system – based on our expertise in high-pressure dosing and laboratory systems engineering.

Our response is clear
We commit to delivering a tailored, production-ready solution in record time, despite the complexity and urgency of the task.

July 2020
Less than 3 months later
Together with our client, we design, build, and deliver the first LNP production system – ready for immediate deployment in vaccine manufacturing.

11 December 2020
The U.S. Food and Drug Administration (FDA) grants Emergency Use Authorization (EUA) for BioNTech/Pfizer's mRNA-based COVID-19 vaccine BNT162b2.

21 December 2020
The European Commission grants Conditional Marketing Authorisation (CMA) for the BioNTech/Pfizer COVID-19 vaccine, making it the first approved COVID-19 vaccine in the EU.

2021–2022
Global vaccine rollout and increased LNP demand
As global vaccination campaigns scale-up, the demand for LNP production systems continues to grow. KNAUER releases first standardized production systems **IJM Single Core NanoProducer** and **IJM DuoCore NanoProducer.** KNAUER's systems are used in multiple production facilities worldwide, ensuring consistent quality and scalability.

10 September 2021
Dr. Angela Merkel visits KNAUER and acknowledges the company's important role in the race to produce the COVID-19 vaccine on a large scale.

2022–2023
IJM NanoScaler and IJM NanoScaler Pro
KNAUER launches the **IJM NanoScaler** for early-stage LNP development and, in 2023, the **IJM NanoScaler Pro** with full automation for high-throughput formulation screening.

Today
Our technology continues to support global vaccine production. What began as an emergency response has evolved into a scalable solution that helps protect lives worldwide.

KNAUER product solutions in nanoparticle processing: From purification to formulation to quality control

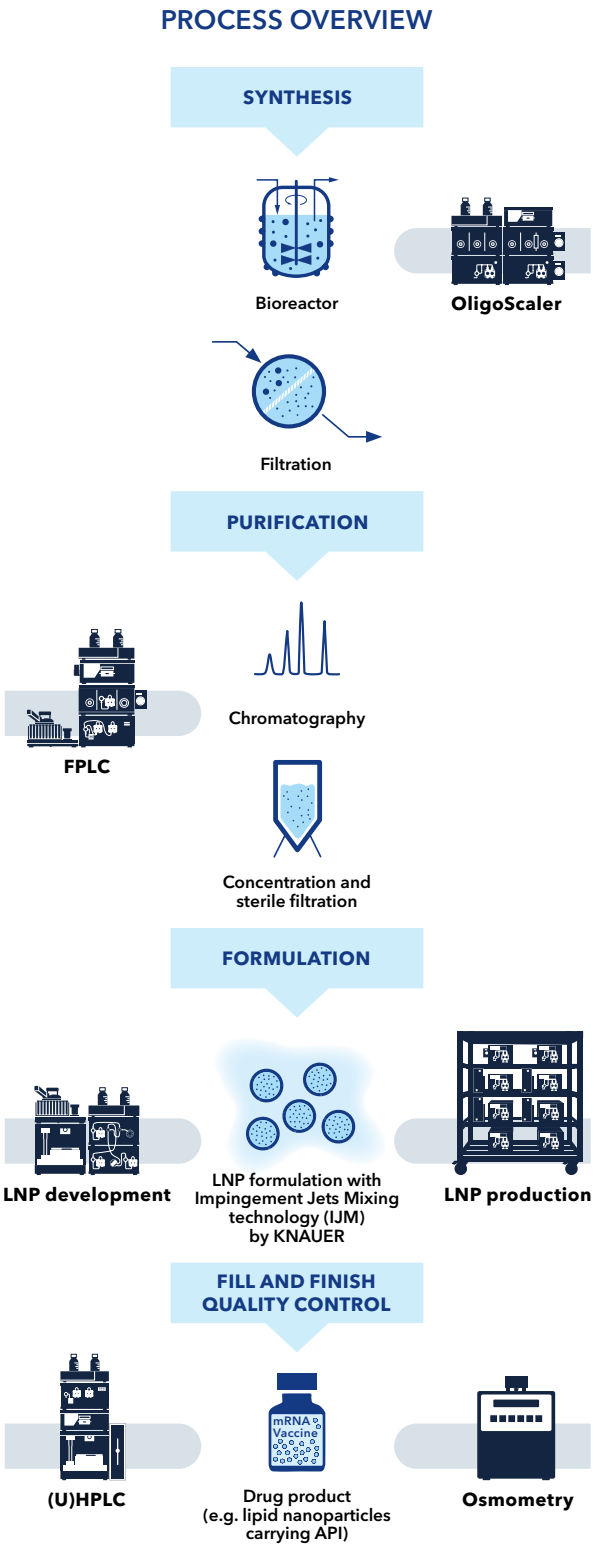
Since 2020, lipid nanoparticles (LNPs) have been the focus of research and industry as a robust platform for drug delivery and gene therapy, with wide-reaching potential.

The API can range from nucleic acid (mRNA, pDNA) to polypeptides (proteins/enzymes). Lipid encapsulation of these components leads to LNP formation, providing stability to the cargo and offering options for directionality and absorption to target specific tissues. In the field of LNP formulation, the industry standard is the KNAUER Impingement Jets Mixing (IJM) technology.

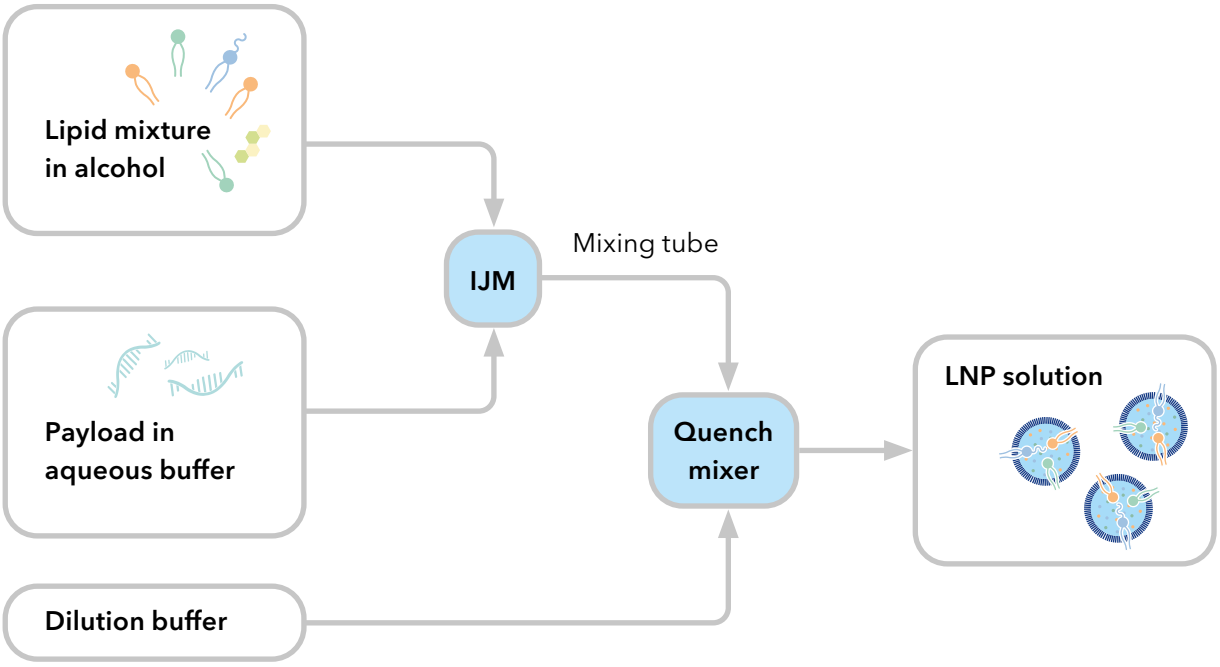
The KNAUER IJM technology relies on the rapid mixing of two high velocity streams in the IJM mixing chamber. Turbulent mixing leads to an oversaturation of the lipids, resulting in self-assembly of the LNPs. A further integrated quenching step stabilizes the formulated LNPs until they undergo further processing.

KNAUER's IJM technology is customizable and can be implemented across all formulation scales. The benchtop systems allow for small-scale development of LNP formulation parameters, thereby reducing waste of valuable lipids and mRNA. Automation with integrated, programmable software enables high-throuput screening while streamlining and optimizing research. The IJM technology can be smoothly transferred from R&D to preclinical scale in one system, while KNAUER's IJM production skids enable seamless scale-up from R&D to production and GMP manufacturing.

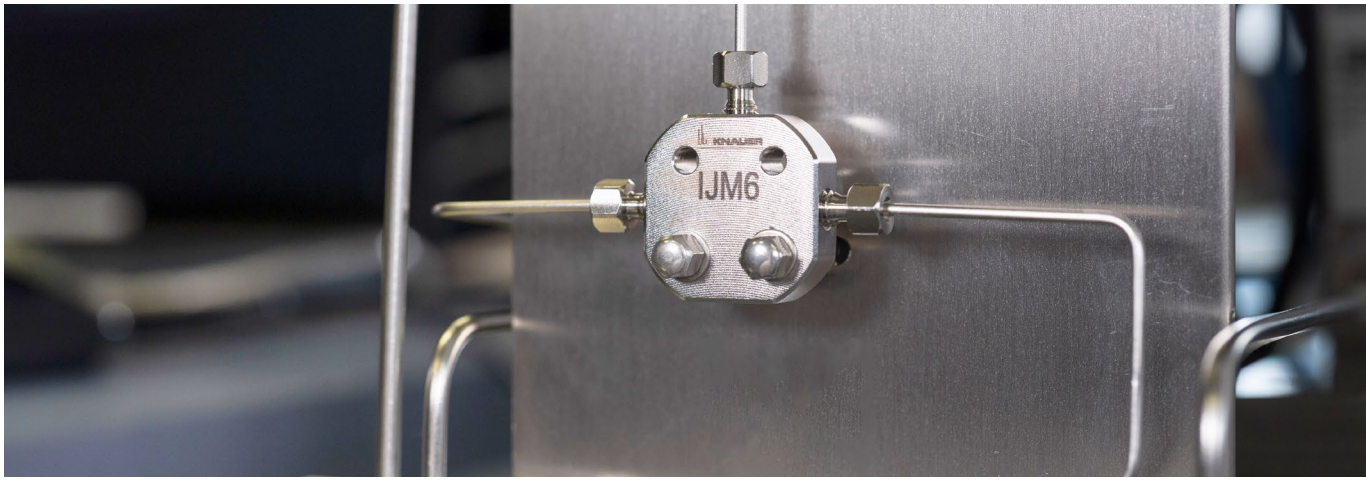
KNAUER enhances the LNP production process not only with the innovative IJM formulation skids but also by offering its synthesizer for oligonucleotide synthesis, the OligoScaler. KNAUER also provides advanced preparative HPLC systems designed for the purification of both mRNA and oligonucleotides. To ensure the highest quality of the final particles, KNAUER's analytical HPLC systems and osmometers enable thorough analysis, safeguarding the integrity of the formulation process. Notably, KNAUER's IJM systems are GMP-ready, facilitating a seamless transition into regulated environments.



Impingement Jets Mixing Technology



For the formation of lipid nanoparticles, two streams are required: The payload (e.g. mRNA) is dissolved in an aqueous buffer. The lipid mixture is dissolved in an organic solvent, e.g. ethanol. When both streams are mixed, the solubility of the lipids in the mixture decreases, leading to oversaturation and causing the lipids to form structures which encapsulate the payload. The composition of the lipid mixture allows the production of defined structures like lipid nanoparticles. Key achievement of the mixer is a fast and reliable mixing. In Impingement Jets Mixers, fast mixing is achieved by a collision of the two liquid streams. Turbulent flow conditions in the mixing chamber and the following tube ensure a completely homogeneous mixture of nanoparticles with a monodisperse size distribution. After a defined mixing time, the mixture is diluted/quenched in a quench mixer. This final step further reduces solvent concentration and prevents agglomeration of nanoparticles. The size of the IJM and diameter and length of the mixing tube are chosen according to flow rates and chemistry of the formulation components.



IJM advantages:

KNAUER's Impingement Jets Mixer (IJM) combines reliability, scalability, and flexibility to meet the demands of modern nanoparticle production.

Designed for performance in both research and large-scale manufacturing, the IJM offers proven benefits across all stages of development.

Performance

- **Capable of producing monodisperse particles (PDI < 0.05)**
- **Pressure resistant**
- **CIP capable**
- **Simple, reliable technology**

Cost & flexibility

- **No license fee**
- **Multi-use, no exchange required after each batch**
- **Customized versions available**

Scalability

- **Scalable from method development to commercial manufacturing**
- **Proven in large-scale vaccine production**
- **Many sizes available**

Materials

- **316L stainless steel or PEEK (Life-sciences grade)**

LNP - PRODUCTPORTFOLIO

Development & screening, preclinical, clinical

Scalability assurance with KNAUER's Impingement Jets Mixing technology

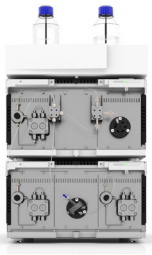
IJM NanoScaler

designed for
METHOD DEVELOPMENT AND SCALE-UP

- ✓ Scale-up with 5 IJMs
- ✓ Encapsulation at a range of 500 µL to hundreds of milliliters
- ✓ Small-scale production up to 70 mL/min

INCLUDES

- ✓ 5 KNAUER IJMs
- ✓ 3 pumps
- ✓ 2 valves
- ✓ 3 different API sample loops



IJM NanoScaler Pro
IJM NanoScaler Ultra

designed for
AUTOMATED SCREENING AND SCALE-UP

- ✓ High-throughput screening with up to 108 samples
- ✓ Automated premix of different lipid compositions to screen early-stage API candidates
- ✓ Minimal sample volume of 300 µL
- ✓ up to 70 mL/min

INCLUDES

- ✓ 5 KNAUER IJMs
- ✓ 3 pumps
- ✓ Autosampler with cooling option:
- ✓ Pro: one autosampler
- ✓ Ultra: two autosamplers
- ✓ UV detector

IJM Benchtop NanoProducer

designed for
CLINICAL TRIALS

- ✓ Compact, GMP-ready design for benchtop use in labs or clinical trials
- ✓ From concept to clinic: Supports development, scale-up, and GMP batch production
- ✓ LNP formulation up to 700 mL/min

INCLUDES

- ✓ 3 KNAUER IJMs
- ✓ 3 pumps
- ✓ Benchtop module with one flowmeter, PC, switch, valves and mixers

commercial

Scalability assurance with KNAUER's Impingement Jets Mixing technology

IJM SingleCore NanoProducer

designed for

COMMERCIAL PRODUCTION

- ✓ API predilution
- ✓ Online flow and pressure monitoring
- ✓ Large-scale production up to 1 L/min

INCLUDES

- ✓ 1 KNAUER IJM
- ✓ 4 pumps
- ✓ 4 flowmeters
- ✓ 1 valve
- ✓ GMP ready documentation
- ✓ 21 CFR part 11 and GAMP 5 compliant software

IJM DuoCore NanoProducer

designed for

LARGE-SCALE COMMERCIAL PRODUCTION

- ✓ Parallel LNP formulation with 2 KNAUER IJMs
- ✓ Online flow and pressure monitoring
- ✓ Large-scale production up to 2 L/min

INCLUDES

- ✓ 2 KNAUER IJMs
- ✓ 8 pumps
- ✓ 8 flowmeters
- ✓ 2 valves
- ✓ GMP ready documentation
- ✓ 21 CFR part 11 and GAMP 5 compliant software

IJM Customized NanoProducer

CUSTOMIZE YOUR PRODUCTION-SCALE UNIT

- ✓ Scale-out up to 8 KNAUER IJMs
- ✓ Flexible pump configuration
- ✓ Interfaces for the integration into PLC available

INCLUDES

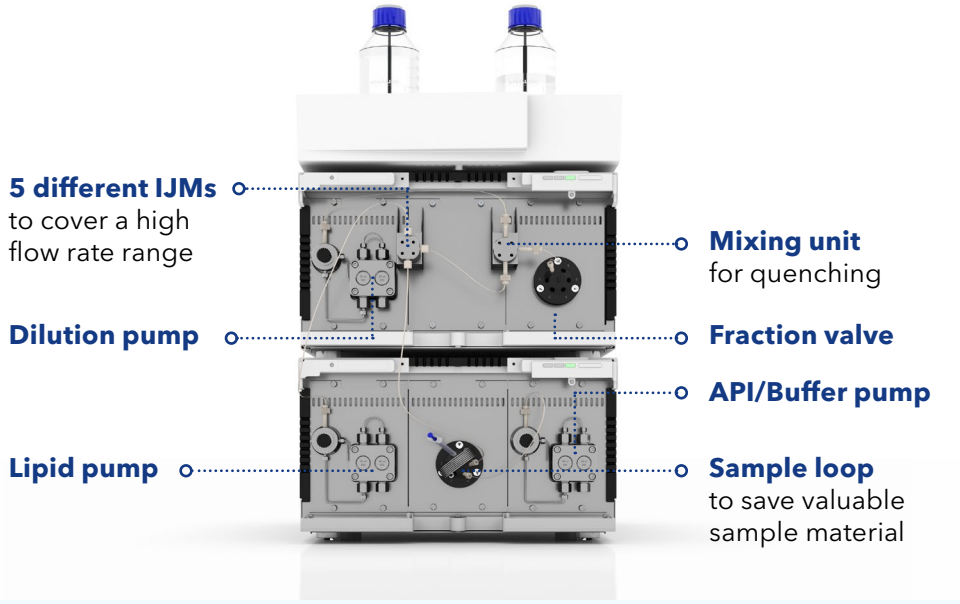
- ✓ Up to 8 KNAUER IJMs
- ✓ Up to 16 pumps
- ✓ Up to 16 flowmeters
- ✓ GMP ready documentation

OPTIONAL

- ✓ 21 CFR part 11 and GAMP 5 compliant software
- ✓ Advanced detection options

The IJM NanoScaler: The most versatile LNP formulation system

The IJM NanoScaler offers a flexible solution for the production of lipid-encapsulated nucleotides in volumes ranging from 500 µL to several hundred milliliters. This flexibility makes the NanoScaler ideal for early-stage development, including proof-of-concept studies, process optimization, and pre-clinical testing – where minimizing the use of costly API material is essential. Once initial results are validated, the NanoScaler also supports small-scale GMP-compliant production, with throughput rates of up to 70 mL/min, and offers seamless scalability using KNAUER's NanoProducer systems.



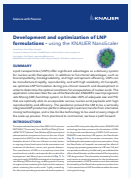
WHAT THE CUSTOMER SAYS

"Having already a robust LNP production process in place, we were looking out for alternative techniques to support our scale-up activities. The **Impingement Jets Mixing (IJM)** equipment provided by KNAUER was the right fit for us! Even from early runs we were able to produce **LNPs of high quality** with a high encapsulation efficiency and low PDI values. We will further build on this and expand our knowledge into GMP production to further support our projects and partners by delivering high quality LNP production."

eTheRNA
engineeringRNA

Iris Bombeke
Research Associate Drug Product Development
eTheRNA, Ghent, Belgium

KNAUER Application Notes
For more information on the KNAUER AppNotes visit:
https://www.knauer.net/vph0078

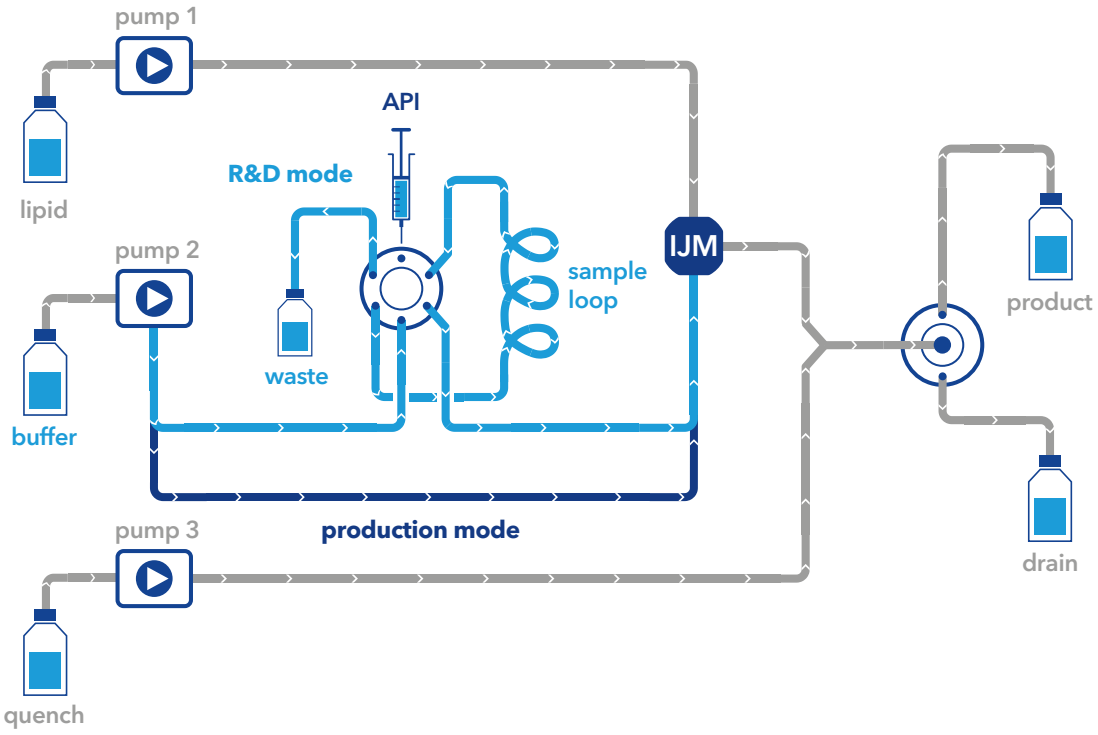


IJM NanoScaler

A formulation system that scales with your research

The IJM NanoScaler is a formulation system that scales with your research, bridging R&D and small-scale production. It features both modes to support each stage of development.

Its modular design and five interchangeable IJMs ensure precise control across the full flow rate range, enabling a smooth transition from lab experiments to preclinical scale.



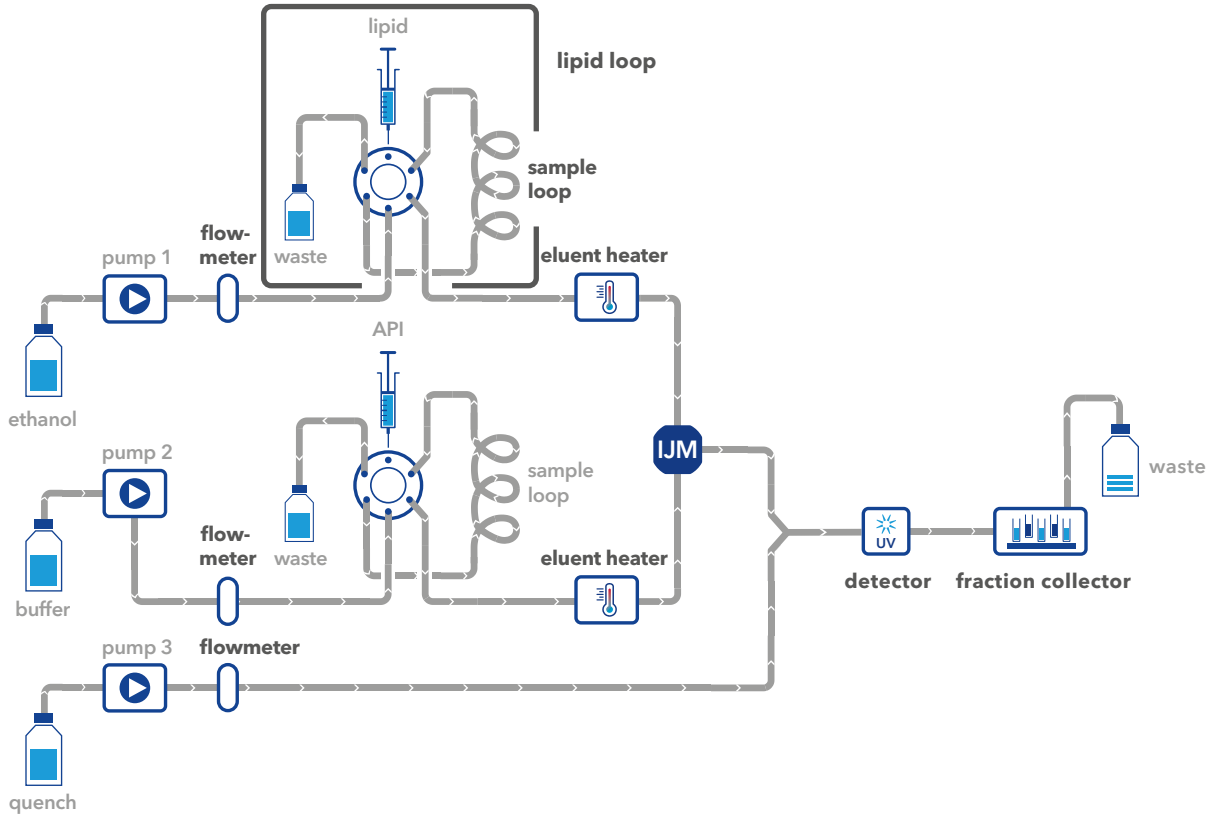
	R&D mode	Production mode
Intended use	Screening, optimization, and feasibility testing	Batch production after process optimization
Sample volume	500 µL to 2 mL	Unlimited (up to 70 mL/min)
Sample handling	Sample loop-based pumping	direct flow delivery, loop bypass
IJM	Test multiple IJMs for best performance	Apply optimal mixer selected in R&D
Efficiency focus	Minimizes waste, precise process control	Reproducible, time-efficient encapsulation

IJM NanoScaler

Upgrade kits

The modular design of the IJM NanoScaler allows flexible integration of various upgrade kits to meet specific application needs. Whether you're aiming to reduce sample volume, improve process control, or add advanced monitoring, the system is easily configurable to support your workflow.

All upgrade kits are seamlessly integrated into the PurityChrom® 6 software environment, ensuring smooth operation from setup to execution.



SYSTEM CONTROL

- ☐ A71104 - Upgrade kit **NanoScaler eTC** (elevated Temperature Control)
- ☐ A71107 - Upgrade kit **NanoScaler UV detector**
- ☐ A71109 - Upgrade kit **NanoScaler conductivity monitor**
- ☐ A71114 - Upgrade kit **NanoScaler 3x flowmeter**

SAMPLE HANDLING

- ☐ A71103 - Upgrade kit **NanoScaler lipid loop**
- ☐ A71105 - Upgrade kit **NanoScaler Pro**
- ☐ A71106 - Upgrade kit **NanoScaler fraction collector**
- ☐ A71108 - Upgrade kit **NanoScaler Ultra**

FLOW PATH

- ☐ F48040X97 - Upgrade kit **SST capillaries NanoScaler**
- ☐ A71101 - Refill kit **API/Lipid supply by syringe**
- ☐ A71125X97 - Upgrade kit **High-Flow Inlet NanoScaler**

IJM NanoScaler

Upgrade kits

SYSTEM CONTROL

Flowmeter (PID control)

Coriolis flowmeter
with integrated temperature and density measure-ments

PID control
enables automatic flow adjustment

eTC – Elevated Temperature Control

Eluent heater
with two independent heat channels

controls fluid temperature up to 100 °C (212°F)

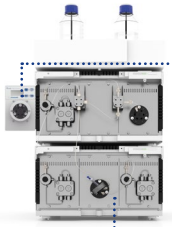
Detectors

UV- or conductivity monitor
enables real-time fractionation

assists with CIP validation

SAMPLE HANDLING

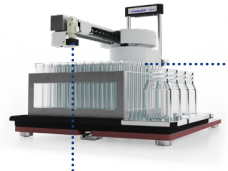
Lipid loop



Additional sample loop
minimizes sample consumption

ideal for R&D-scale experiments

Fraction collector



Fraction collection
up to 165 samples per rack

enables precise inline fractionation

FLOW PATH

Stainless steel capillaries

Upgrade to stainless steel (SST) capillaries for improved chemical resistance and cleanability – ideal for GMP environments and sensitive LNP formulations.

IJM NanoScaler Pro

IJM NanoScaler Ultra

Automated screening systems for lipid nanoparticle formulation

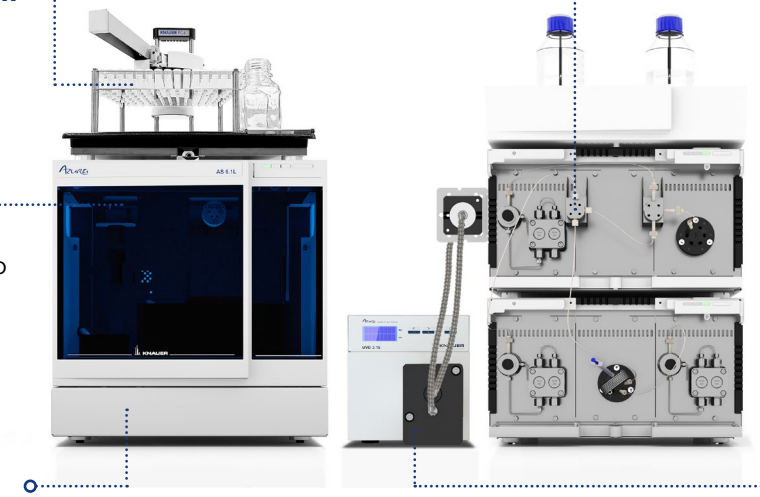
KNAUER's IJM NanoScaler Pro & Ultra systems are designed for automated lab-scale formulation of lipid nanoparticles – allowing scientists to screen early-stage API candidates with different lipid compositions.

Unique in the market, these systems are the only ones that offer automated premixing of lipid compositions, providing a distinct advantage for rapid LNP development.

Scalability assurance
with KNAUER's proven IJM technology

Efficient research
integrated LNP collection

Formulation discovery
high-throughput screening with up to 108 samples



Integrated **UV monitoring** facilitates the controlled collection of your formulation sample and minimizes sample loss

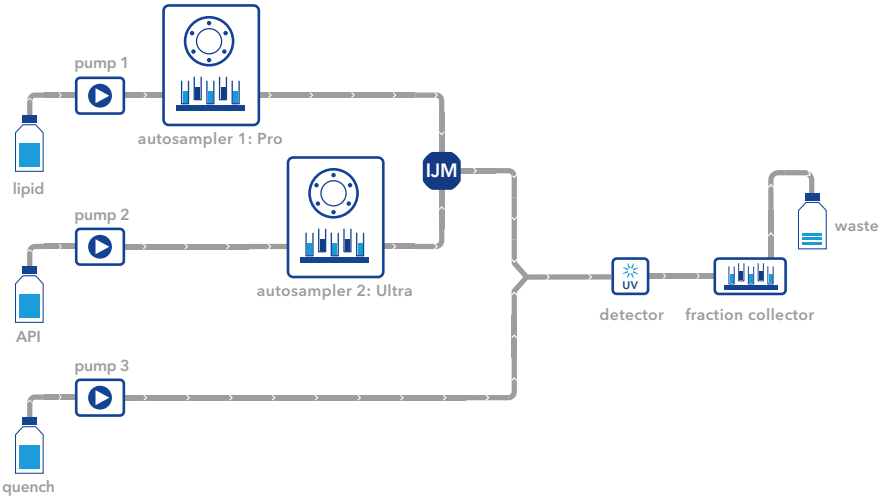
Ensure stability
maintain sample stability with cooling options

IJM NanoScaler Pro

Equipped with a single autosampler, this system enables automated screening of either API or lipid candidates.

IJM NanoScaler Ultra

The enhanced Ultra version features two autosamplers, enabling full automation for high-throughput workflows and complex libraries.



Flow scheme of the IJM NanoScaler Pro & Ultra

IJM NanoScaler Pro

IJM NanoScaler Ultra

Options

With four configurable operating modes, the NanoScaler Pro allows users to adapt the system to different formulation tasks without changing hardware. Whether screening APIs or lipids, with or without quench, the system enables quick switching between workflows while maintaining consistent operation.

The NanoScaler Ultra builds on this platform by adding an additional autosampler that enables fully automated, high-throughput screening of APIs and lipids. This upgrade further reduces manual handling, increases process efficiency, and supports consistent and reproducible formulation results.

	IJM NanoScaler Pro		IJM NanoScaler Ultra
	Sample loop refill	Additional quench step	
Compatible with lipid/API screening workflows	✓	✓	✓
Automated refill of both injection valves	✓	×	✓
Manual injection of either API or lipid required	×	✓	×
Quench step after formulation	×	✓	✓
Screening of API or lipid individually	✓	✓	×
Screening of API and lipid in combination	×	×	✓

Art. No.	Description
A71105	Upgrade kit NanoScaler to NanoScaler Pro
A71108	Upgrade kit NanoScaler Pro to NanoScaler Ultra

Introducing the newest feature: Lipid Mixing Smarter. Faster. More capable.

The NanoScaler Pro helps you advance your nanoparticle formulations with the latest in precise mixing and formulation technology. Designed for researchers and process developers alike, the IJM NanoScaler Pro offers exceptional versatility and performance. The new NanoScaler Pro version comes with a built-in lipid pre-mixing function, allowing for even more streamlined workflows and improved reproducibility.

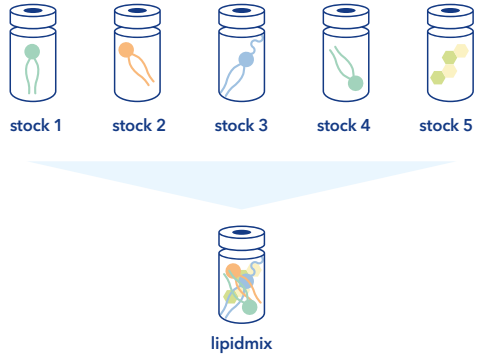
This smart feature enables you to:

- Save time by combining two steps into one seamless process
- Ensures excellent mixing before nanoparticle formation
- Reduce preparation errors caused by manual handling
- Improve batch-to-batch consistency

Efficiency meets precision.

With advanced software control, real-time monitoring, and a user-friendly interface, the IJM NanoScaler Pro is the ideal solution for small-scale development and rapid scale-up.
Experience the future of nanoparticle preparation.

Whether you're working with mRNA lipid nanoparticles, liposomes, or other complex formulations, the NanoScaler Pro gives you full control from start to finish.



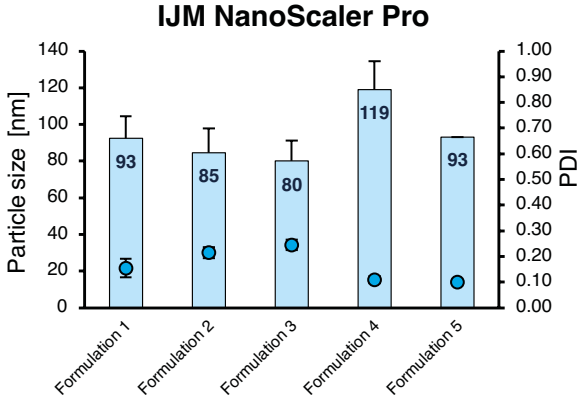
- Up to five lipids or other solutions can be mixed
- Volumes of single components ≥ 1 µL
- Customizable wash routine
- Optional use of inserts to save lipids

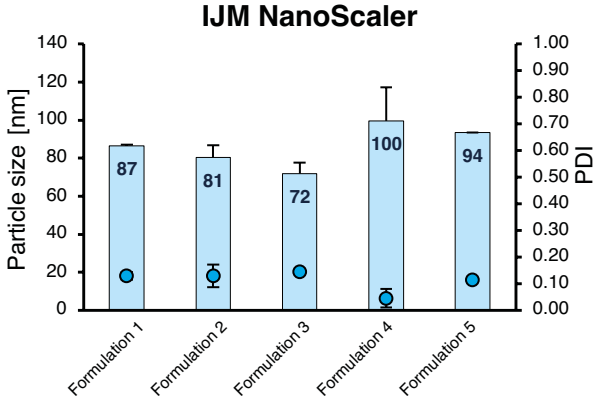
The autosampler is used to premix the lipid solutions, which is then injected into a loop to minimize lipid consumption. The payload (mRNA in our case) is injected directly from pump 2. Both solutions are then mixed in the IJMs, quenched with buffer, and collected by the fraction collector.

We demonstrate the system's robustness by preparing three formulation replicates. Additionally, we showcase its ability to automate the screening of various LNP compositions. All tested formulations match those produced with the established NanoScaler basic system.

Sample	TFR (mL/min)	Payload	Ionizable lipid	Helper lipid	Cholesterol	Shielding lipid	N/P
Formulation 1	7.5	mRNA	45 %	10 %	41.5 %	3.5 %	8.7
Formulation 2	7.5	mRNA	25 %	22 %	50.5 %	2.5 %	8.7
Formulation 3	7.5	mRNA	25 %	22 %	49.5 %	3.5 %	8.7
Formulation 4	7.5	mRNA	35 %	10 %	53.5 %	1.5 %	8.7
Formulation 5	7.5	mRNA	35 %	19 %	46.5 %	2.5 %	8.7

The implementation of high-throughput screenings is of pivotal importance because it allows the search of the optimal ranges of LNP molar ratios, such as the ones designed in DoEs. Lipid molar ratios were varied.





In this test, by comparing mean sizes of the five LNPs obtained with IJM NanoScaler Pro and the non-automated IJM NanoScaler, all batches match comparable sizes and PDI. In addition, LNPs showed no free mRNA detected by gel electrophoresis (data not shown).

IJM Benchtop NanoProducer

Designed for clinical trials

The IJM Benchtop NanoProducer is a compact system developed for the formulation and small-scale production of lipid nanoparticles (LNPs), specifically tailored to meet the demands of clinical trial manufacturing. Designed for effortless integration into any lab or cleanroom, the system minimizes complexity through small footprint, minimal cabling, reduced power requirements and a clean, clearly traceable capillary layout.

Compact, GMP-ready design for benchtop use in R&D or clinical trials

Low setup complexity with benchtop module

Embedded control system and switch reliable and space-saving solution

Integrated coriolis flowmeter regulates consistent flow regardless of fluid density or composition

Automated quench system ensures stability and reproducibility

Easy mixer exchange enables flexible and scalable mixing

Recycling valve minimizes sample loss efficient recirculation of valuable materials

The standard setup includes three high-precision pumps – two for delivering API and lipid solutions, and one for the quenching solution. A flowmeter ensures accurate flow adjustment and monitoring. At its core, the compact benchtop module houses all essential components: valves, IJMs, flowmeter, quench mixer, capillaries, PC, and network switch.

IJM Benchtop NanoProducer

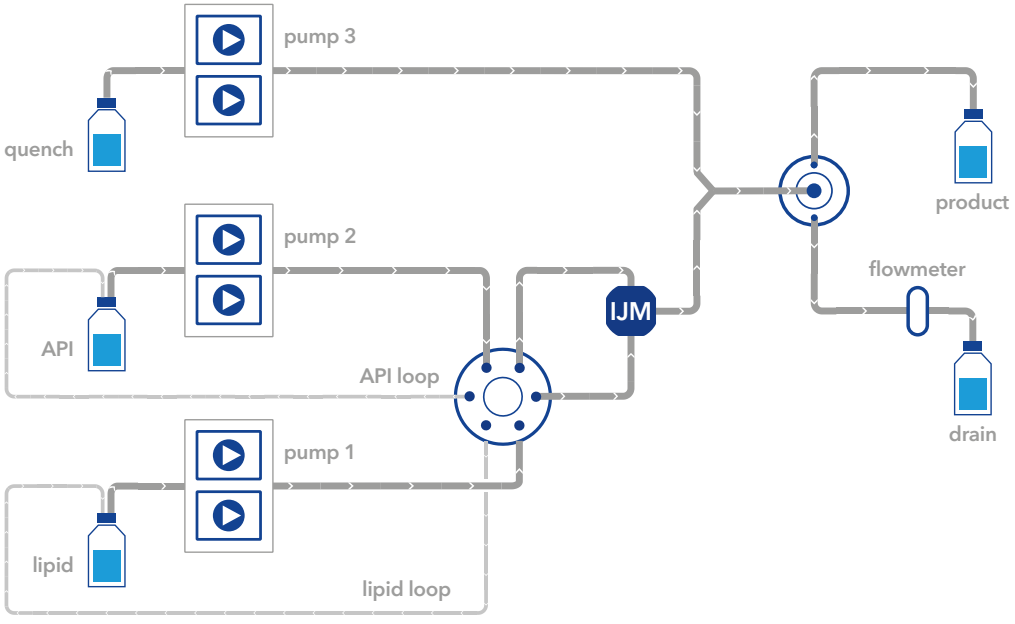
Bridging the gap from development to GMP manufacturing

The IJM Benchtop NanoProducer is equipped with the same IJM No. 5 as the NanoScaler, allowing for a seamless scale-up of your validated formulation process from development to benchtop scale. Additionally, the Benchtop NanoProducer also integrates IJM No. 6, identical to that used in the large-scale IJM NanoProducer for GMP production. This dual compatibility ensures a smooth and efficient transition from clinical trials to full-scale commercial manufacturing.

Valve design minimizes sample loss

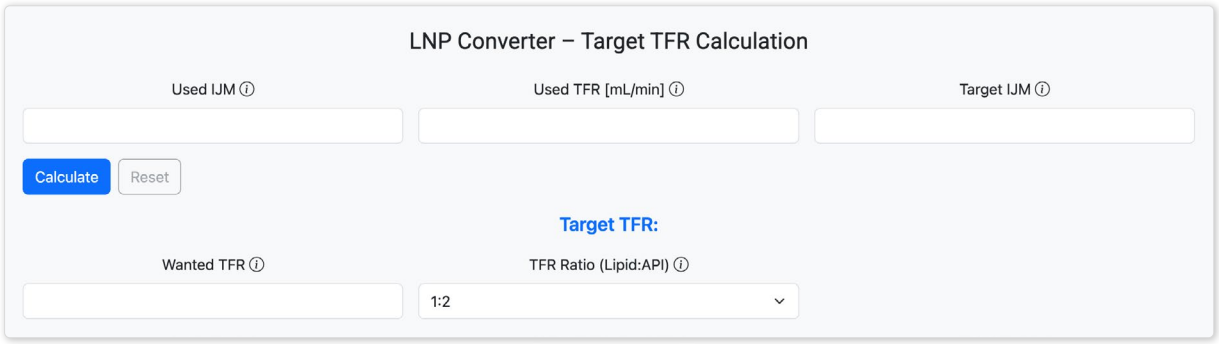
Valuable samples such as lipids and APIs can be efficiently recirculated through the valve system. The flow streams can be switched simultaneously to the Impingement Jets Mixer, enabling low-loss processing and precise control of the mixing process. This feature is exclusive for the IJM Benchtop NanoProducer.

With operating pressures up to 100 bar and flow rates up to 0.7 L/min, the IJM Benchtop NanoProducer covers a wide range of process parameters and formulation conditions. The system features three manually selectable Jet Mixers, providing unmatched flexibility to support a wide range of formulation conditions and process parameters for scale-up purposes.



Helping the transfer: The IJM NanoCalculator tool

Our new IJM scale-up tool is a practical online guide for customers who already have an established process and are looking to scale-up to higher flow rates or larger IJMs. At the same time, it provides valuable orientation for those who need support in identifying the right parameters for their method development.



Two ways to find your perfect IJM solution

Our NanoCalculator makes it simple to choose the right system for your needs.

Start with your goal:
Enter your desired throughput, and the NanoCalculator instantly recommends the ideal IJM and KNAUER system.

Scale with confidence:
Seamlessly transition from one IJM to another: scale-up to larger mixers or scale down for smaller batch sizes.

IJM Benchtop NanoProducer

Target total flow rate [mL/min]	Recommended mixer and system
120	IJM 6

IJM NanoScaler

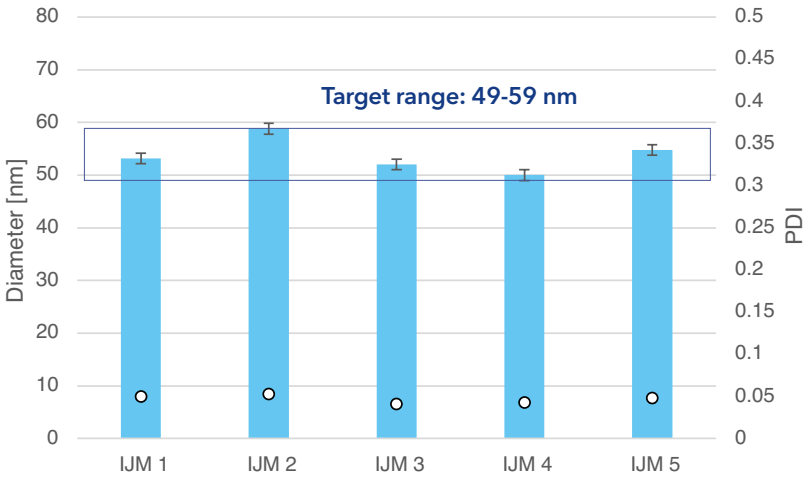
Used TFR [mL/min]	Target IJM
8	3
Used IJM	**Minimal target flow rate [mL/min]**
1	20 mL/min

From R&D to full-scale production, the NanoCalculator guides you every step of the way.

KNAUER LNP Converter – IJM NanoCalculator Tool
For more information visit the KNAUER website:
https://www.knauer.net/ijm-nanocalculator-tool

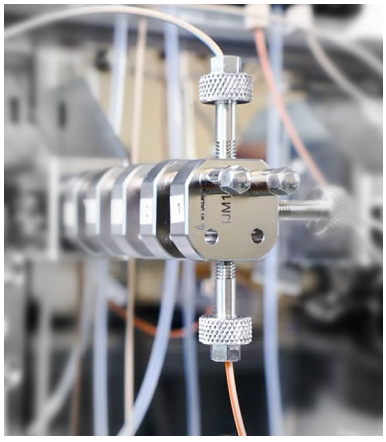
Scalable lipid nanoparticle production: From lab to GMP

Our platform is designed with scalability at every step. We extensively tested all five IJMs which are part of the NanoScaler to produce LNPs. By maintaining a constant Reynolds number across all mixers, we achieve highly consistent particle sizes with an exceptionally low polydispersity index. This reproducibility demonstrates the robustness and scalability of the IJM technology.



Conditions

IJM	1-5
Flow rates	5-27 mL/min
Flow rate ratio (lipid : API)	1 : 3
Lipids	DLin-MC3/DSPC/Cholesterol/DMG-PEG
Lipid molar ratios	50 %/10 %/38.5 %/1.5 %
Particle sizes	50-58.8 nm
PDI	0.04-0.05
Batch size	2 mL
Cargo	no



Acuitas achieved excellent results with the IJM NanoProducer, demonstrating its capability to deliver high-quality lipid nanoparticles with consistent performance. The process was initially developed at production scale and was seamlessly and efficiently transferred to a larger IJM, confirming the scalability and robustness of the formulation.

ACUITAS THERAPEUTICS

	Standard process	Scaled-up process
Impingement Jets Mixer	IJM 6	IJM 15
Combined flow rate (lipid + payload streams)	480 mL/min	960 mL/min
Total production	4.3 g mRNA/h	8.6 g mRNA/h
Particle size	62-64 nm	60-63 nm
PDI	0.04-0.08	0.03-0.05
Encapsulation efficiency	> 99%	> 99%

IJM SingleCore NanoProducer

Designed for commercial production of lipid nanoparticles

The IJM SingleCore NanoProducer enables efficient high-flow production of lipid nanoparticles, making it a robust choice for commercial manufacturing processes. The system includes four precise, low pulsation, high-pressure pumps that support all key process steps: predilution of concentrated Active Pharmaceutical Ingredients (APIs), Impingement Jets Mixing of the lipid and API phases, and final quenching of the concentrated nanoparticle solution.
The system is mounted in a mobile stainless-steel frame (grade 1.4301) and is compatible with Cleaning-In-Place (CIP) procedures, making it ideal for use in pharmaceutical production environments.

License-free technology for LNP encapsulation
with one KNAUER IJM

Process control
online flow and pressure monitoring

GMP - Software
21 CFR part 11 and GAMP 5 compliant

Complete mixing unit
API predilution
encapsulation
quenching

Precise flow streams
with total flow rate up to 1 L/min and pressure up to 95 bar

Process connections
sanitary clamp connectors

One core of the NanoProducer is equipped with four high-pressure dosing pumps, each paired with a coriolis flowmeter and assigned to a specific process step. One pump delivers the lipid phase, another the API, while the third predilutes the API and the fourth quenches the concentrated LNP solution. This setup ensures precise and reliable flow control throughout the entire process.

The lipid and API phases are injected at high velocity into the Impingement Jets Mixer, where nanoparticle encapsulation occurs. This step is followed by controlled post-dilution to reach the target concentration. A downstream valve enables seamless switching between product collection and waste, offering maximum flexibility and operational safety.

IJM DuoCore
NanoProducer

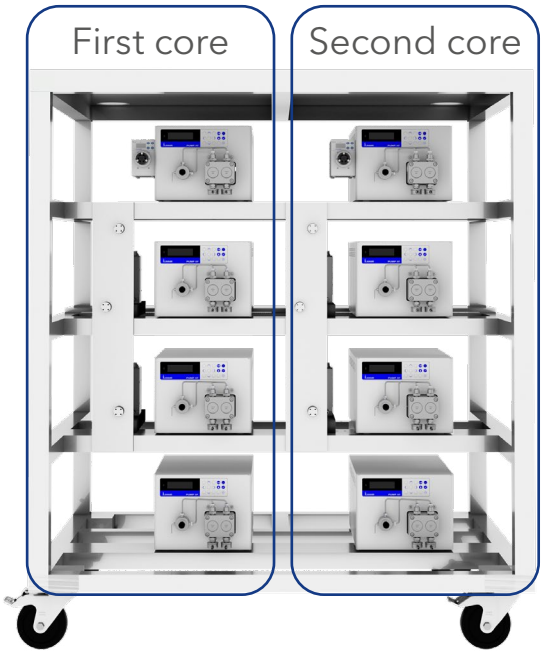
Scale-out for high-flow production of lipid nanoparticles

The IJM DuoCore NanoProducer is designed for parallelized, high-flow production of lipid nanoparticles enabling significantly increased throughput for commercial manufacturing. By integrating two independent IJM process lines into a single compact unit, the DuoCore system allows for simultaneous production runs – doubling capacity without compromising precision or process control. Each process line features a SingleCore, equipped with one KNAUER IJM, four high pressure pumps, two mixers for predilution of API and postdilution of the concentrated LNP solution.

One software – multiple systems
consistent operation across SingleCore and DuoCore

Integrated process control
real-time flow and pressure data

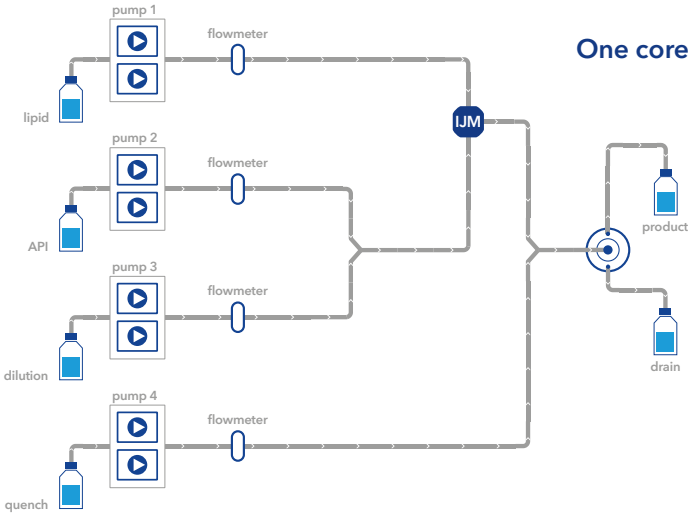
Flexible mixer configuration
optional use of different IJMs



Scalable and license-free technology
with two KNAUER IJMs

High-flow streams
with total flow rate up to 2 L/min and pressure up to 95 bar

Space-saving design
for GMP production facilities



IJM Customized NanoProducer

Customized equipment

KNAUER's IJM systems can be customized for specific customer applications. Since the introduction of the KNAUER IJM systems, the engineering team at KNAUER has implemented numerous customizations.

Examples of projects that have been successfully implemented include:

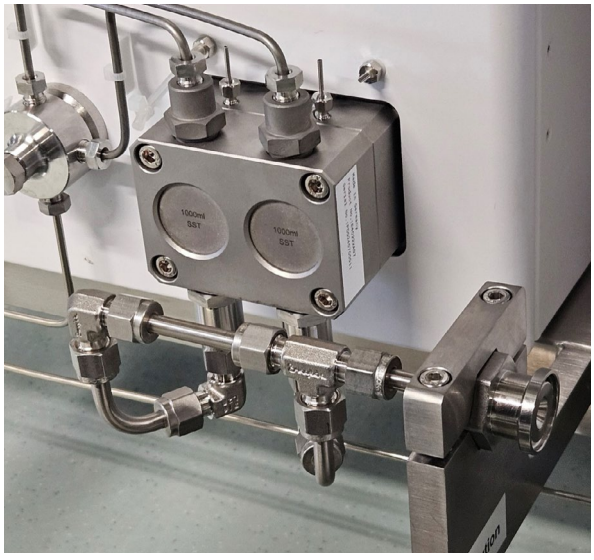
- Scale-out with parallel mixers
- High-flow (>1 L/min TFR)
- Preparation for single-use consumables
- Two-step dilution
- Integration of additional sensors, e.g. conductivity
- Integration of peristaltic pumps
- Integration of balances for liquid reservoirs
- Integration of custom mixers
- Integration into industrial automation environments

Customization
Large-scale production
Task
Production of lipid nanoparticles on a large scale without upscaling the mixer
Solution
A system with eight parallel mixers and 16 pumps was designed, including distribution and collection system for liquids. Integration with further upstream and downstream equipment was coordinated with an engineering company.

Customization service exclusively by KNAUER Germany: sales@knauer.net

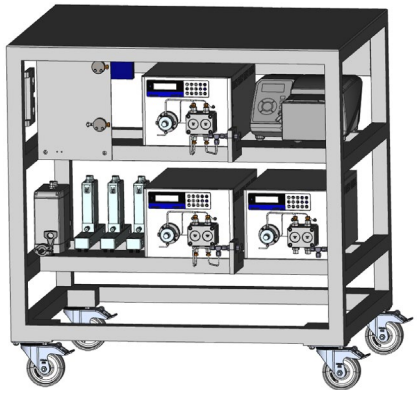
IJM Customized NanoProducer

Customization
Cleaning monitoring
Task
Final water flushing after CIP should reach <5 µS/cm
Solution
A sensor and flow cell for low conductivity in biopharma quality were integrated and a piping adapter was designed for combining both system outlets into the conductivity flow cell.



Customization
High-flow modification
Task
Using a SingleCore NanoProducer for total flow of > 2 L/min
Solution
The inlet piping system was extended from 1/8" to 1/4" piping. This avoids cavitation at high-flow while maintaining turbulent flow for cleaning. Mixer and internal piping were enlarged to allow for higher flow without increasing back pressure.

Customization
High-flow quenching
Task
Final dilution (quenching) required flow rates beyond KNAUER's pumping capabilities
Solution
A peristaltic pump was integrated into the system and drivers for the pump in PurityChrom® software were implemented.



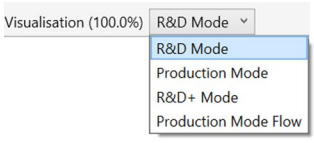
Software solutions

PurityChrom® 6

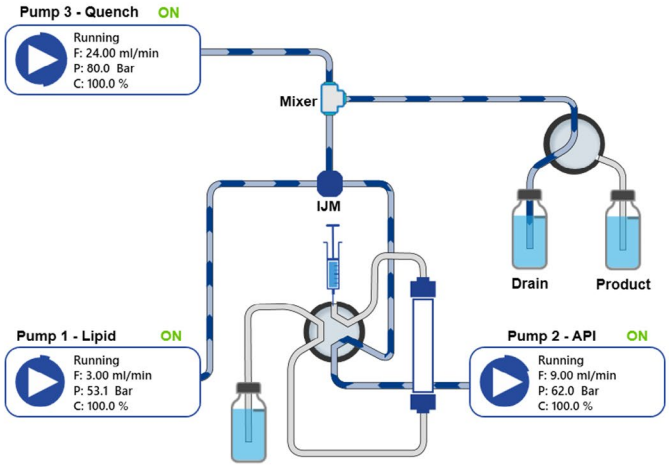
Our software solution fully compliant with GAMP 5 and 21 CFR Part 11

PurityChrom® 6 is an all-in-one software solution for controlling all KNAUER IJM systems, from the IJM NanoScaler up to customized NanoProducers. It features a modern user interface, powerful new functionalities, and significantly improved usability. The software is developed according to GAMP 5 guidelines and is 21 CFR part 11 compliant.

Switch between **multiple configurations** with just a click



Animated flowpath visualization improves usability and method writing

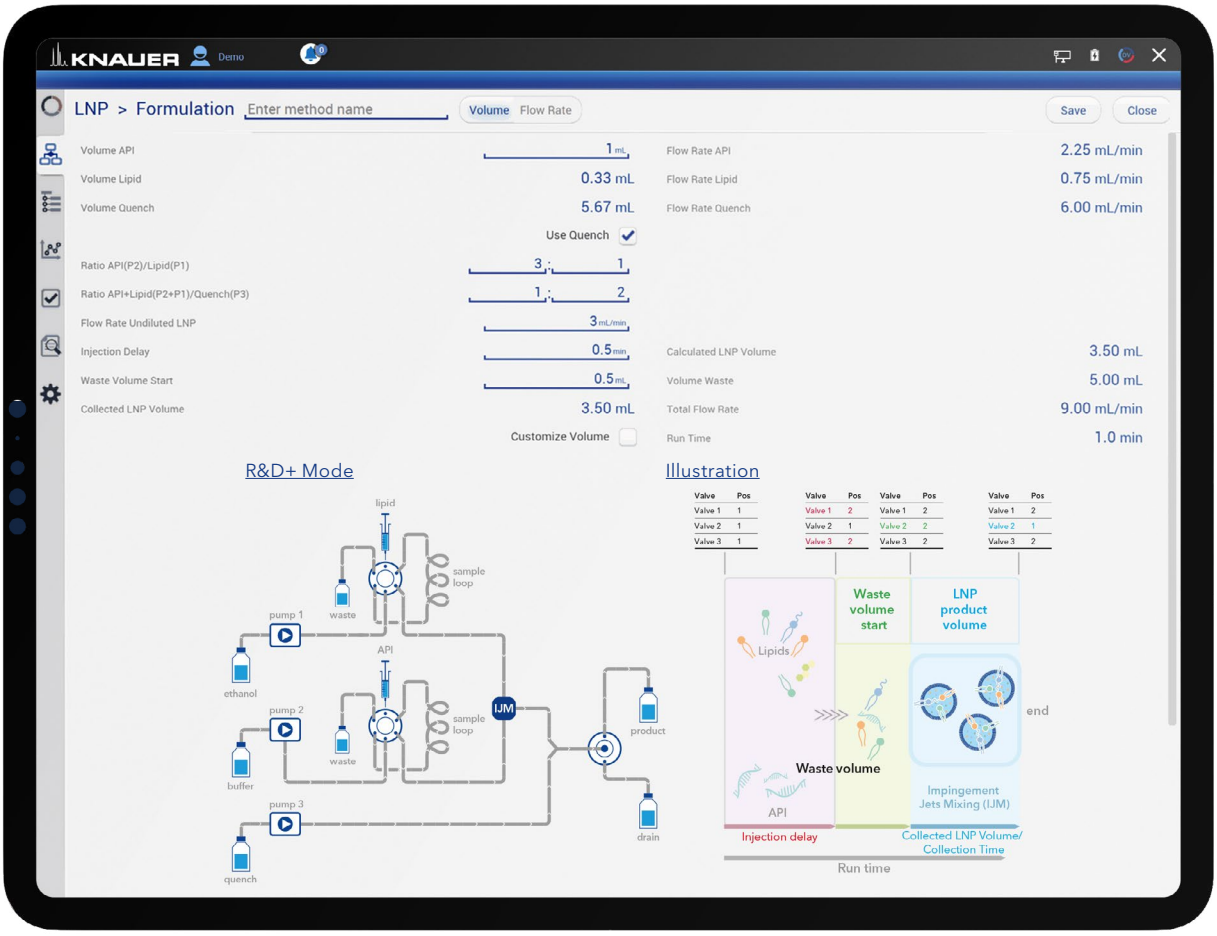


- **Advanced user management:** Role-based access simplifies administration. Full traceability with audit trail and run protocol of each batch
- **Alarm management**
  - Emergency pause option
  - Threshold/trigger option
  - Definition of notifications and warning texts
- **Security settings:** Customizable password policies, login restrictions, and automatic lockout/inactivity rules
- **Audit trail and batch history:** Version control allows detailed tracking of all method changes
- **OPC-UA compatibility:** Enables secure and platform-independent communication between industrial devices

Mobile Control LNP for IJM NanoScaler

The LNP license of Mobile Control is designed to control the IJM NanoScaler system. The software is adapted to the formulation workflow featuring a special LNP user interface and predefined method structures. Formulation methods can be created using familiar LNP parameters like volumes and ratios of API and lipid.

LNP formulation with intuitive user interface



- Predefined method structure and writing with familiar LNP formulation parameters
- Fast system startup and user-friendly interface
- Ready-to-use workflow for easy formulation

The user interface is adapted to the needs of LNP formulation method writing. There are two different types of methods. **Pre-/aftercare methods** are used to prepare the system for formulation or to clean it afterwards. **Formulation methods** are created by entering flow rates or volumes of API, lipid and quench. Depending on the system composition, different formulation workflows are executed by the software.

For each mode the LNP user interface shows the input fields, the calculated parameters, a flowchart of the system configuration and a profile of the formulation. The R&D+ mode is ideal for small volumes of both API and lipid.
For small API volumes but larger lipid volumes, the R&D mode is well-suited. The production mode is designed for large volumes of both API and lipid.

Regulatory and quality considerations

General quality standards and certificates by KNAUER

KNAUER is committed to delivering high-quality production and laboratory equipment that meets international regulatory and quality standards. The companys Quality Management System is certified according to:

DIN EN ISO 13485:2016

Supporting the development and manufacturing of medical devices with enhanced product and process safety

DIN EN ISO 9001:2015

Ensuring consistent product and continuous improvement

DIN EN ISO 14001:2015

Reflecting KNAUER's commitment environmental sustainability

These certifications and documents ensure that KNAUER products are suitable for use in GMP-regulated environment, and support customers in meeting their own regulatory and quality assurance obligations.

KNAUER provides GMP-ready documentation:

- ✓ User requirement specification
- ✓ Design qualification
- ✓ Installation qualification
- ✓ FAT/SAT
- ✓ Material certificates
- ✓ Test certificates and protocols
- ✓ P&ID and drawings
- ✓ Customer training and familiarization with the equipment
- ✓ Service concept, including annual preventive maintenance plan
- ✓ Traceability and change control
- ✓ General cleaning recommendation

Visit KNAUER in Berlin:

Meet and Greet with the

IJM NanoScaler (Pro)

Experience firsthand how the IJM NanoScaler (Pro) can help you formulate high-quality LNPs with precision and efficiency. Join a live demonstration to explore the system's capabilities and see how it can support your formulation needs. We offer free demos at our locations in Berlin (Germany), Cambridge (MA, USA), and at selected sites worldwide.

Interested?

Get in touch with us to learn more about the IJM NanoScaler (Pro) and its key features – or to schedule your personalized demo.

- Low volumes
- Minimal residual carry over with high precision
- Reproducibility
- Automated screening and scalability

Roadmap of a KNAUER demo:

If you want to bring your own material let us know upfront!

1. Introduction

- Overview of KNAUER IJM NanoScaler Pro equipment and Impingement Jets Mixing considerations
- Delving into key points of LNP formulation and critical parameters

Introduction to our partner Evonik providing lipids for the demo

2. Live demonstration

- Overview of equipment capabilities and key benefits for research applications
- Setting up the NanoScaler Pro for LNP formulations
- Running automated formulation process
- Reviewing real-time data collection and analytical characterization of particles generated (size, PDI, zeta potential)

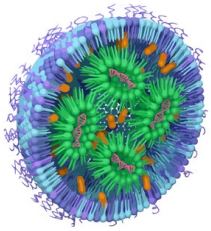
3. Q&A session and wrap-up

- Open floor for questions and discussions

For Booking Request/
more Info via E-Mail: sales@knauer.net

KNAUER worldwide:

Assisting your LNP formulation development and analysis



Starting an LNP formulation from scratch can be overwhelming.
To help you with this process, KNAUER can connect you with the right formulation experts.

Our partners **EVONIK** Industries (North-America), **Curapath** (Spain and Europe), **Monash** University (Australia) and **Fraunhofer IPK** (Germany and Europe) are experts in LNP formulation using KNAUER's IJM technology.

KNAUER partners will share their expertise and support you as you begin the formulation process, streamlining your development. Working together, you will become familiar with the KNAUER instrument while taking a deep dive into LNP formulation steps, with subsequent particle processing and analysis of LNP size, PDI and encapsulation efficiency. These three key parameters should be evaluated during the formulation process to assess LNP quality and viability under in vivo conditions.

For those looking to receive intensive LNP formulation training, KNAUER offers industry training, together with Monash University's accredited mRNA Workforce Training Center. This center is a dedicated mRNA workforce training center that provides pilot phase training with a particular focus on LNP formulation. Participants will receive guided instruction in LNP formulation and encapsulation protocols, and operation of KNAUER instruments with state-of-the-art software.

Our partner EVONIK Industries has a lot of experience in the field of lipids and LNP formulation. Evonik offers its services in Cambridge, (MA, USA) and Vancouver, (BC, Canada).

Work packages
SMALL package formulation development assistance (3 days in the lab): Sleeves up: You bring your cargo and our experts help you to optimize your formulation. Method adaptation, adjustment of flow rate and direct read out of particle quality with different methods.
LARGE package formulation development assistance (5 days in the lab): Still sleeves up: More time to develop your formulation. Run more repetitions to test reliability and reproducibility with your cargo. Take home your particles and the confidence to run the system yourself at your lab site without skipping a beat. With this package you hit the ground running at your facility.
Lipid kits for formulation (different quantities available), send to your lab

Our partner Curapath offers the whole spectrum from research and development over production to fill-and-finish.

Work packages
All around LNP package: From research to fill-and-finish, the whole process from the CDMO
Need mRNA? mRNA production and quality control for your research and own production
Lipid kits for formulation

Our partner, Fraunhofer IPK, offers advanced analytical studies, such as nanoparticle tracking analysis and cryoelectron microscopy (cryo-EM). These analyses provide valuable insight into the morphology and behavior of your particles. All characterization is conducted at Fraunhofer IPK's state-of-the-art facilities in Berlin, Germany.

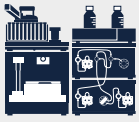
Work packages	Order number
Encapsulation study including determination of simple particle characteristics (particle size/PDI)	WP1
Determination of the encapsulation efficiency of generated LNP	option 1
Stability analysis of generated LNP	option 2
Nanoparticle tracking analysis	option 3
Cryo-EM	option 4

Disclaimer: All contract work is done by external third parties. The terms and conditions are beyond KNAUER's scope. KNAUER has no influence on the results of the studies and must not be accounted for warranty of quality.

Business areas

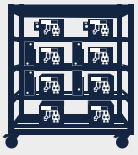
Formulation development

IJM NanoScaler
IJM NanoScaler Pro
IJM NanoScaler Ultra



Commercial LNP production

IJM Benchtop NanoProducer
IJM SingleCore NanoProducer
IJM DuoCore NanoProducer
IJM NanoProducer Customized

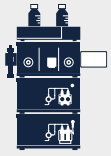


Analytical solutions

HPLC
(U)HPLC
LC MS/MS
GPC
IC

Prep.-HPLC solutions

SMB
Peptides
Oligonucleotides
Cannabis



FPLC solutions

SEC
BIO-SMB
Proteins
HIC
Affinity
IEX

Osmometry

Freezing point osmometer

Science with Passion

Worldwide partner in science since 1962

Based in Berlin, KNAUER is a medium-sized, owner-managed company that has been serving the sciences since 1962. We develop and manufacture scientific instruments of superior quality for liquid chromatography. The range includes systems and components for analytical HPLC/UHPLC, preparative HPLC, fast protein liquid chromatography (FPLC), multi-column chromatography/simulated moving bed (SMB), gel permeation chromatography/size exclusion chromatography (GPC/SEC), osmometry and skids for the production of lipid nanoparticles (LNP).

Independent and family owned

It all started with a soldering iron, a jigsaw and an ingenious idea for a highly accurate electronic thermometer.

Chemist Dr.-Ing. Herbert Knauer founded the company together with his wife Roswitha in 1962. The couple's daughter, Alexandra Knauer, is managing director and owner of the company since the year 2000. As of April 2021, she leads KNAUER together with CEO Carsten Losch.

Today, KNAUER is an established company with about 190 employees that successfully develops, manufactures and markets chromatography instruments worldwide.

think **LNP.** think **KNAUER.**

Technical specifications

	IJM NanoScaler	IJM NanoScaler Pro/Ultra
		
Number of Impingement Jets Mixers	5, IJM 1-5 manual selection	5, IJM 1-5 manual selection
Number of pumps	3	
Number of flowmeters	on request (Upgrade Kit Flowmeter)	
Number of valves	2	Pro: 3, Ultra: 4
Number of loops	3 (500 µL, 1 mL, 2mL)	
Number of benchtop module (includes two valve drives, one flowmeter, switch, PC)	-	
Number of autosamplers	-	Pro: 1, Ultra: 2
Number of fraction collectors	-	1
Process connection inlet	1/8" OD, 2.1 mm ID FEP tubing (UNF 1/4-28 thread, flat bottom); optional: High-Flow Inlet Kit 3/16" OD, 1/8" ID PTFE (UNF 5/16-24 thread, flat bottom)	1/8" OD, 2.1 mm ID FEP tubing (UNF 1/4-28 thread, flat bottom);
Process connection outlet	1/16" OD, 0.5 mm ID PEEK tubing (UNF 10-32, thread coned)	fraction collector with rack for 165 tubes 1/1.5/2 mL each (11 mm) and rack for 99 tubes 15 mL each (17 mm)
Volumetric flow rate	up to 70 mL/min*	
Volumetric flow rate	up to 4.2 L/h*	
Maximum operating pressure	140 bar (2030 psi)	
Maximum flow rate single pump	30 mL/min	
Liquid temperature range	4–60 °C (39.2–140 °F)	
Wetted materials	stainless steel, PEEK, titanium, FFKM, UHMW-PE, aluminum oxide, ruby, sapphire, ETFE, PETP, zirconium oxide, Hastelloy, FEP	stainless steel, PEEK, titanium, FFKM, UHMW-PE, aluminum oxide, ruby, sapphire, ETFE, PETP, zirconium oxide, Hastelloy, FEP; Pro/ Ultra additional: glass, Kel-F, PPS, EPDM
Software	CDS optional available 21 CFR part 11 and GAMP 5 compliant	
Interfaces	LAN, pin header connectors	
Power supply	docking station (including pumps and valves):100–240 VAC single phase, 50/60 Hz	docking station (including pumps and valves):100–240 VAC single phase, 50/60 Hz; fraction collector 100-240 V AC single phase, 50/60 Hz, autosampler 95 – 240 V AC single phase, 50/60 Hz, detector: 100–240 V
Power consumption (per device)	docking station (including pumps and valves): maximum 130 W	docking station (including pumps and valves): maximum 130 W, fraction collector maximum 100 W, autosampler 200 W, detector: 60 W
Ambient conditions	temperature range: 4–40 °C; 39.2–104 °F;	
	below 90 % humidity (non-condensing)	
Dimensions (W x H x D)	361 x 501 x 603 mm	
Net weight (approx.)	35 kg	Pro: 70 kg, Ultra: 100 kg
API-predilution and quenching	only quenching	
GMP version	optional	not available

* depends on IJM, in production mode up to 70 mL/min

**without monitor

IJM Benchtop NanoProducer	IJM SingleCore NanoProducer	IJM DuoCore NanoProducer
		
3, IJM 5-7 manual selection	1	2
3	4	8
1	4	8
2	1	2
-		
1	-	
-	-	
-	-	
7 mm OD, 5 mm ID silicon tubing (hose connector)	1/2" Triclamp (4 inlets)	1/2" Triclamp (8 inlets)
"1/8" OD, 2.1 mm ID FEP tubing (1/4-28 UNF coned)"	1/2" Triclamp (1 outlet)	1/2" Triclamp (2 outlets)
up to 700 mL/min*	up to 1 L/min	up to 2 L/min
up to 42 L/h*	up to 60 L/h	up to 120 L/h
100 bar (1450 psi)	95 bar (1378 psi)	
API & lipid pump 200 mL/min, Quench pump 400 mL/min	400 mL/min	
4–60 °C (39.2–140 °F)		
stainless steel, PEEK, FFKM, UHMW-PE, aluminum oxide, ruby, sapphire, zirconium oxide, hastelloy, silicon, FEP	stainless steel, PEEK, FFKM, UHMW-PE, aluminum oxide, ruby, sapphire, zirconium oxide, hastelloy, EPDM, FEP	
CDS optional available 21 CFR part 11 and GAMP 5 compliant	CDS, 21 CFR part 11 and GAMP 5 compliant	
pump: LAN, RS232, pin header connectors; benchtop module: LAN, USB	pump: LAN, RS232, pin header connectors; flow meter: RS232 + FLOWBUS™; valve drive: LAN	
Pump: 100-240 V AC single phase, 50/60 Hz; benchtop module 100-240 V AC single phase, 50/60 Hz	pump: 100–240 VAC single phase, 50/60 Hz; flow meter: 115/230 VAC single phase, 50/60 Hz 24V DC Power supply; valve drive: 115/230 VAC single phase, 50/60 Hz 24V DC Power supply; Touch Industrial PC: 100–240 VAC single phase, 50/60 Hz, 12-24 VDC Power supply; network switch: 100–240 VAC single phase, 50/60 Hz, 12 V DC Power supply	
pump: maximum 320 W; benchtop module: 240 W	pump: maximum 320 W; flowmeter: 3 W; valve drive: 65 W; Touch Industrial PC: 80 W; network switch: 50 W	
temperature range: 4–40 °C; 39.2–104 °F		
below 90 % humidity (noncondensing)		
360x 630 x 550 mm**	900 x 915 x 700 mm	1000 x 1290 x 700 mm
50 kg	150 kg	250 kg
only quenching	✓	
✓	✓	

LNP glossary

	Term	Definition
A	Active pharmaceutical ingredient	Active pharmaceutical ingredient (API) is the biologically active substance in drugs that is responsible for the therapeutic effect (→ Payload).
	Aqueous phase	The aqueous phase in the synthesis of LNPs contains the dissolved payload/API, which is to be encapsulated in the particles during synthesis.
B	Brownian motion	Brownian motion is the random movement of particles in fluids or gases due to thermal motion.
C	Cationic lipids	Cationic lipids are charged amphiphilic molecules that form positively electrostatic interactions with the negatively charged backbone of nucleic acids and thus enable high encapsulation efficiencies in LNP formulations. The permanently charged, polar head group is connected to the non-polar hydrophobic domain by a linker.
	Cholesterol	Cholesterol belongs to the steroid lipids and is found in all animal cells due to its numerous functions (e.g. lipid metabolism, membrane structure). In LNP formulations, cholesterol serves as a structuring component and is responsible for the density and fluidity of the particle membrane.
D	Dynamic light scattering	Dynamic light scattering (DLS) is a measurement method for determining the particle size distribution in a sample. The method is based on the different degrees of scattering of light on the particles according to their size. The Stokes-Einstein equation is used to determine the particle size via the detected light scattering.
E	Electrophoretic light scattering	Electrophoretic light scattering (ELS) is a method for determining the zeta potential of nanoparticles. During the measurement, an electric field is generated in which the particles move according to their surface potential. Electrophoretic mobility and thus the zeta potential is determined via shifts in the frequency of the scattered light.
	Encapsulation efficiency	The effectiveness of the encapsulation of a molecule in nanoparticles is referred to as encapsulation efficiency (EE) and is expressed as a percentage of the encapsulated concentration compared to the concentration used.
F	Flow rate ratio	The flow rate ratio (FRR) indicates the ratio between the aqueous and organic phase.
H	Helper lipids	Another important component of LNP formulations are phospholipids, also known as helper lipids. Their function is to support and stabilize the formation of nanoparticles. Phospholipids consist of a polar head group linked to a phosphate residue and two hydrophobic fatty acid tails.
I	Impingement Jets Mixer	An IJM (Impingement Jets Mixer) is a mixing chamber in which two liquid streams collide at high velocity; one of the streams contains the lipids in an organic solvent, and the other stream contains the API in an aqueous solution.
	Ionizable lipids	Like cationic lipids, ionizable lipids are amphiphilic molecules with a polar head group and a hydrophobic tail. In contrast to cationic lipids, ionizable lipids are neutral under physiological conditions and only acquire their positive charge at lower pH values. Due to the possibility of protonation in an acidic environment, non-permanently charged lipids usually exhibit lower toxicity while maintaining high encapsulation efficiencies.
L	Laminar flow	Laminar flow refers to a type of flow in which the movement is orderly in parallel layers. Laminar flow conditions are realized at low flow velocities without mixing between the layers. This flow condition is characterized by low Reynolds numbers.
	Lipid-phase polymorphism	Lipids can form different structures when hydrated. Depending on the lipids and the environmental conditions (temperature, pH or ionic strength), different structures, so-called phases, can be formed, e.g. spherical (micelles), lamellar (bilayers), hexagonal or cubic phases.
	Liposome	Liposomes are spherical vesicles consisting of a lipid bilayer surrounding an aqueous core. Liposomes are divided into unilamellar and multilamellar vesicles.
	LNP	Like liposomes, lipid nanoparticles belong to the lipid-based transport systems for encapsulating various cargoes. The difference to liposomes is the usually solid lipid core, surrounded by a lipid shell. This structure is made up of four main components: ionizable lipid, cholesterol, helper lipid and PEGylated lipids.

M	Microfluidic	Microfluidics is a technology in which small volumes of fluids are manipulated using microscale channels. The microfluidic-based mixing of two or more flows uniformly is achieved by using microscale microfluidic chips.
N	Nanoparticle	Nanoparticles are understood as nanometer-sized particles in a size range of 1-100 nm and form the overlap for a range of structures with different shapes such as liposomes, dendrimers or nanotubes. The particles are classified based on their composition into organic-, inorganic- and carbon-based nanoparticles and are used in various fields such as medicine and pharmaceuticals, electronics, agriculture or the food industry.
	Nanoprecipitation	Nanoprecipitation or flash nanoprecipitation (FNP) occurs when an organic solvent containing the particle components is rapidly mixed with an aqueous phase in which the components are not soluble. The change in the solvent when the two phases collide leads to local supersaturation and particle nucleation. Accordingly, FNP is a fast and effective method for producing nanoparticles.
	N/P ratio	The N/P ratio describes the molar ratio between the amines of the ionizable lipids and the phosphates of the backbone of the nucleic acids to be encapsulated.
O	Organic phase	The organic phase contains the hydrophobic precursors (ionizable lipid, cholesterol, helper lipid and PEGylated lipid) for the synthesized lipid nanoparticles dissolved in organic solvents such as ethanol or chloroform.
P	Payload	Nanoparticles are suitable as a delivery system for a wide range of molecules such as mRNA, siRNA, plasmids or proteins which are referred to as payload (→ API).
	PEGylated lipids	PEGylation of lipids means that the hydrophobic alkyl chain of lipids is linked to polyethylene glycol (PEG) derivatives to increase the stability of LNPs ('stealth effect').
	Polydispersity	Polydispersity or the polydispersity index (PDI) describes the degree of heterogeneity of a particle size distribution. The greater the PDI, the broader the distribution and the more different particle sizes there are in the sample.
R	Reynolds number	The Reynolds number, named after Osborne Reynolds, is a dimensionless quantity used to distinguish between laminar and turbulent flow conditions. The parameter helps to predict fluid flow patterns in different situations by measuring the ratio of inertial and viscous forces.
S	Stealth effect	In LNP formulations, PEGylated lipids are also referred to as 'stealth lipids'. Due to its hydrophilic properties, PEG forms a hydration shell on the surface of nanoparticles, which prevents the absorption of molecules by steric hindrance and thus prolongs the circulation time of the particles.
T	Total flow rate	The total flow rate (TFR) defines the volume per unit of time with which the flow in the system pass a position.
	Turbulent flow	In contrast to laminar flows, turbulent flow conditions do not exhibit a fixed, constant flow pattern. The irregular, chaotic movement of the fluid form constantly changing vortices and is characterized by high Reynolds numbers.
Z	Zeta potential	In ionic solutions, two ionic layers form around the nanoparticles, the electrical double layer. The electrical potential of the double layer, the zeta potential, is measured via the electrophoretic mobility of the particles and is directly related to the surface charge, which determines the stability of a colloidal solution.

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