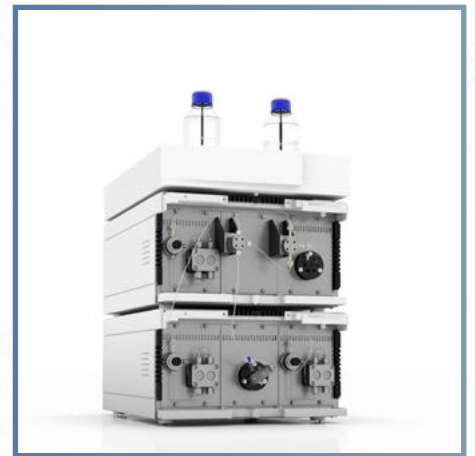


Science with Passion



# Systems for lipid nanoparticle (LNP) production

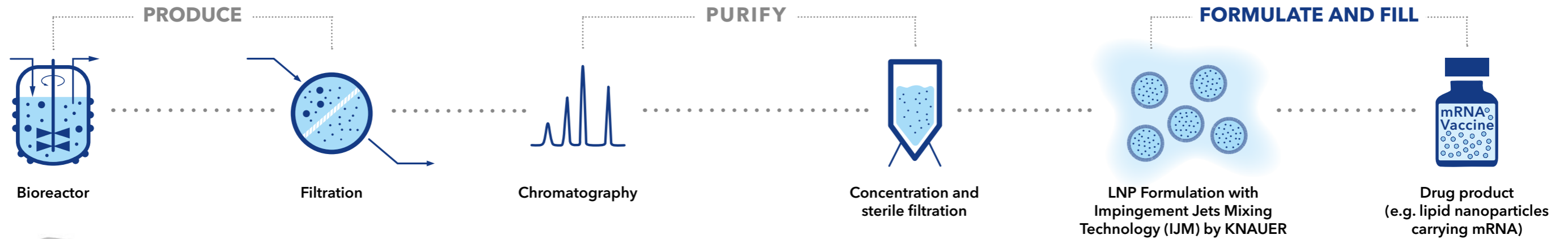


Impingement Jets Mixing units for high flow production of nanoparticles (LNP, microemulsions, etc.)

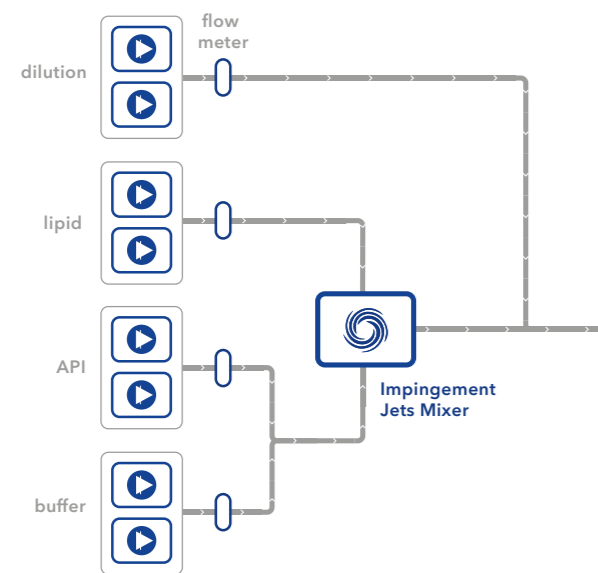
**PANDEMIC PROVED**

think **LNP** | think **KNAUER**

## PROCESS OVERVIEW



Customized IJM NanoProducer for lipid nanoparticle production



Flow scheme for example for mixing of lipids and API

## SYSTEMS FOR LIPID NANOPARTICLE (LNP) PRODUCTION AND FORMULATION

The number of parallel units depends on the application. Also, the number of pumps, flow meters, jets mixers and pipes can be adapted to the required conditions and scale. All IJM NanoProducers are built in a stainless steel frame on casters and are suitable for CIP cleaning procedures in pharmaceutical production. The IJM DoubleCore NanoProducer contains two parallel mixing units. Each unit consists of four pumps. Concentrated Active Pharmaceutical Ingredient (API) solution is diluted first and then mixed with the organic phase. Finally, the mixture is quenched in a third mixer. Both units can be operated independently. The IJM NanoProducer can be configured with up to eight parallel mixing units depending on the customer requirements. Each unit consists of two pumps to deliver lipid and API streams, two flow meters for flow control and one jet mixer. Depending on the configuration, the predilution of the API and quenching can be performed for the combined flow of all units in one process step outside the Impingement Jets Mixing (IJM) NanoProducer.

### LOOKING FOR LIQUID CHROMATOGRAPHY?

As experts in liquid chromatography KNAUER offers a large variety of systems, solutions and applications for **analytical HPLC**, **preparative HPLC** and **FPLC**.

Find out more: [www.knauer.net](http://www.knauer.net)

## THE TECHNOLOGY

**Impingement Jets Mixing Technology (IJM)** enables the formulation and production of high-quality lipid nanoparticles carrying API (e.g. for **mRNA vaccines**). The encapsulation process of active pharmaceutical ingredients with lipids is based on Impingement Jets Mixing Technology, where two streams collide at high velocity in a jet mixing chamber. One of the streams contains the lipids in organic solvents and the other stream the API in water.

The mixing at high velocity reduces the solubility of the lipids so that homogenous nanoparticles are formed. The quality of nanoparticles depends on the streams' flow stability, the mixer geometry and the fluid velocities. As a final step, the mixture is quenched to stop particle growth.

**System for LNP formulation consisting of:**

- KNAUER high-pressure dosing pumps 80P
- Coriolis flow meters
- KNAUER IJM mixers
- Inlet manifolds for lipid/ethanol mixture and API/buffer mixture
- Outlet manifold for LNP solution
- Back-seal washing system
- Frame (stainless steel system 1.4301)
- Installation & familiarization by KNAUER
- A customized technical documentation which is order- and article-related
- Customer Service before, during and after the set up
- Capillary customization and labeling
- FAT (Factory Acceptance Test at KNAUER Berlin)
- SAT (Site Acceptance Test at customer site)

### WHAT THE EXPERT SAYS

"I am delighted that we have been able to successfully deliver all our systems for vaccine production on time. It makes our team proud that we are helping to combat COVID-19 in this way."

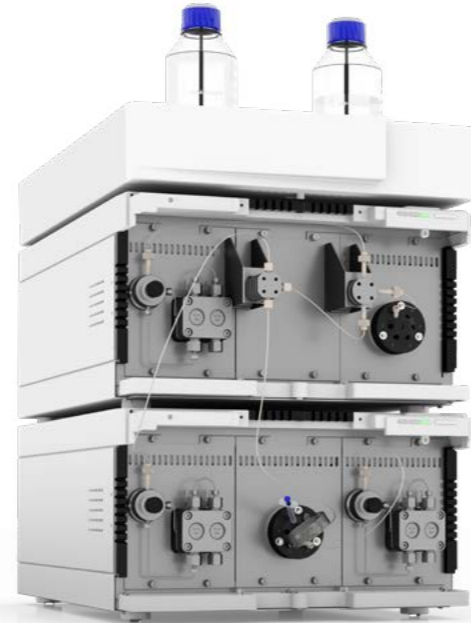
**Lilit Avagyan**, Senior Business Development Manager



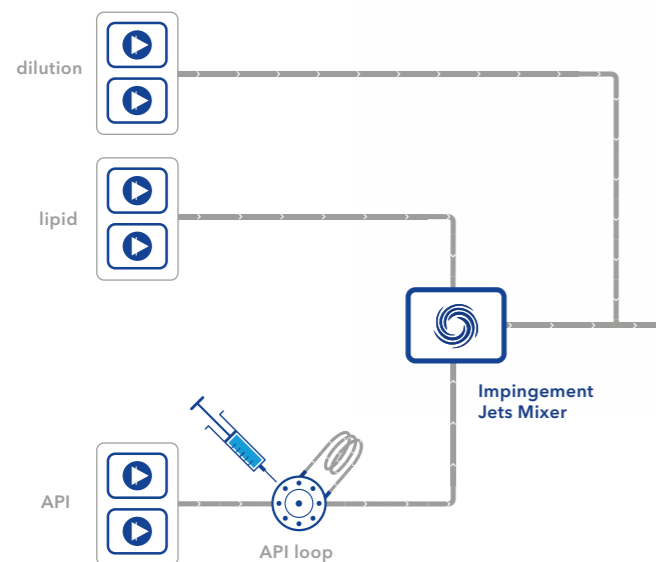
# THE IJM NANOSCALER: A BENCHTOP SYSTEM FOR LIPID NANOPARTICLE FORMULATION

KNAUER's new benchtop IJM NanoScaler system is designed for lab-scale lipid nanoparticle formulation - allowing scientists to screen for optimal process parameters to formulate API-containing lipid nanoparticles.

The IJM NanoScaler is made for research and development as well as pre-clinical and small-scale production of lipid nanoparticles. Equipped with our lipid nanoparticle producing Impingement Jets Mixing (IJM) technology the NanoScaler allows researchers to optimize encapsulation conditions for their API-based therapy before scaling up the process to run on a larger IJM NanoProducer unit.



 IJM NanoScaler



Flow scheme of the NanoScaler

The NanoScaler is made for low sample consumption so as not to waste valuable API. Its small footprint means it can comfortably sit on the benchtop of a research and development lab. The system comes with five different KNAUER Impingement Jets Mixers to help researchers determine which conditions result in the optimum level of API encapsulation. These active pharmaceutical ingredients include complex or delicate API like RNA, mRNA, siRNA, and DNA-based molecules, or products that need specific entry into target cells. In addition researchers can use their own custom mixing unit and benefit from the flexibility of the system set-up. The formulation process can be remotely controlled by software; ran from a conventional PC or laptop, or even a tablet.

## WHAT THE CUSTOMER SAYS

"With the help of the NanoScaler we can meet the various demands and requirements of our customers. The flexibility of the system and the achieved nanoparticles are the perfect choice for our formulations."

### Key parameters

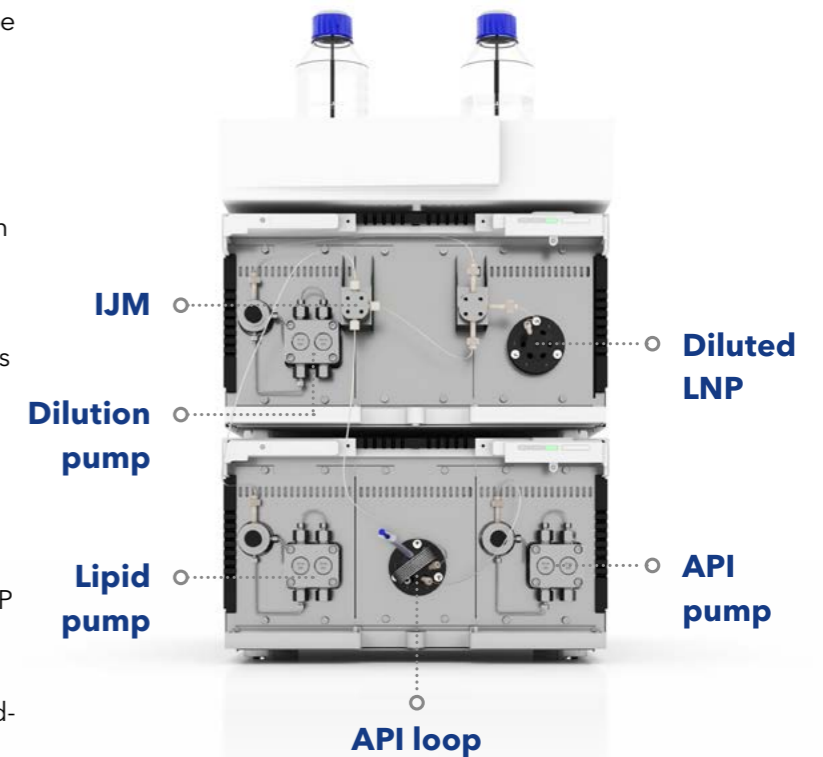
PDI	between 0.1 and 0.2
Particle size	80-90 nm
Encapsulation Efficiency	> 90%



# LNP FORMULATIONS FOR PRE-CLINICAL RESEARCH AND PRODUCTION

The NanoScaler can be used to produce lipid-encapsulated nucleotides at a range from 1 ml to hundreds of milliliters meaning the system is perfect for:

- **Proof of concept testing and process optimization** - pure nucleotides are an expensive resource. Carry out proof of concept testing and process optimization at the 1,000 µl scale to avoid wastage.
- **Pre-clinical trials** - Pre-clinical testing can be carried out using 100 ml of nucleotides such as, for *in vitro* studies to determine the tolerability, efficacy and potential toxicity of the mRNA therapy of interest.
- **Small scale production** - Once proof-of-concept and safety testing have been successfully conducted, production of LNP encapsulated APIs can even be carried out at up to 0.1 Liter per minute with the IJM NanoScaler or using KNAUER's scaled-up IJM-NanoProducer Units.



## Which formulation parameters can be tested using the NanoScaler?

The IJM NanoScaler enables the scouting of several key process parameters during the lipid nanoparticle encapsulation stage.



**Mixing unit** - The five different Impingement Jets Mixer geometries, plus the opportunity to integrate a custom mixing unit, allow determination of the process conditions required to achieve maximum efficiency, optimal particle size and homogeneous size distribution.

**Mixing flow rate and ratio** - Determine how the specific physicochemical properties of the lipid nanoparticle are impacted by the mixing flow - find out which flow rates and ratio provide optimum lipid nanoparticle encapsulation.



**Lipid formulation** - Testing of new lipid formulations, for example lipids with embedded antibodies for targeted medicines, is possible using the NanoScaler. Determine the conditions required to ensure lipid nanoparticle encapsulation takes place before producing the therapy at scale for trials.

**Dilution protocols** - The liquid flow path of the NanoScaler can be configured to either include or bypass the dilution step following lipid nanoparticle formation - allowing scientists to produce formulations at the exact concentration required.

# IMPINGEMENT JETS MIXING UNITS BY KNAUER

	IJM NanoScaler	IJM SingleCore NanoProducer
		
<b>Number of impingement jets mixers</b>	5, IJM 1-5 manual selection	1
<b>Number of pumps</b>	3	4
<b>Number of flow meters</b>	on request	4
<b>Number of valves</b>	2	1
<b>Process connection inlet**</b>	1/8" OD, 2.1 mm ID FEP tubing (UNF 1/4-28 thread, flat bottom)	1/2" Tri-clamp (4 inlets)
<b>Process connection outlet**</b>	1/16" OD, 0.5 mm ID PEEK tubing (UNF 10-32, thread coned)	1/2" Tri-clamp (1 outlet)
<b>Volumetric flow rate</b>	up to 0.1 l/min	up to 1 l/min
<b>Volumetric flow rate</b>	up to 6 l/h	up to 60 l/h
<b>Maximum operating pressure***</b>	140 bar (2030 psi)	95 bar (1378 psi)
<b>Liquid temperature range</b>	4-60 °C (39.2-140 °F)	4-60 °C (39.2-140 °F)
<b>Wetted materials</b>	stainless steel, PEEK, titanium, FFKM, PTFE (GFP 55), aluminum oxide, ruby, sapphire, ETFE, PETP, zirconium oxide, Hastelloy, FEP	stainless steel, PEEK, titanium, FFKM, PTFE (GFP 55), aluminum oxide, ruby, sapphire, EPDM, zirconium oxide, POM, hastelloy
<b>Software</b>	CDS optional available 21 CFR part 11 and Gamp 5 compliant	CDS, 21 CFR part 11 and GAMP 5 compliant
<b>Interfaces</b>	LAN, pin header connectors	pump: LAN, RS-232, pin header connectors; flow meter: RS-232 + FLOW-BUS™; valve drive: LAN
<b>Power supply</b>	docking station (including pumps and valves): 100-240 VAC single phase, 50/60 Hz; PC: 100-240 VAC single phase, 50/60 Hz; Monitor: 100-240 VAC single phase, 50/60 Hz; Network switch: 100-240 VAC single phase, 50/60 Hz, 12V DC Power supply	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; PC: 100-240 VAC single phase, 50/60 Hz; monitor: 100-240 VAC single phase, 50/60 Hz; network switch: 100-240 VAC single phase, 50/60 Hz, 12 V DC Power supply
<b>Power consumption (per device)</b>	docking station (including pumps and valves): maximum 130 W; PC: 1000 W; monitor: 380 W; network switch: 50 W	pump: maximum 320 W; flow meter: 3 W; valve drive: 65 W; PC: 1000 W; monitor: 380 W; network switch: 50 W
<b>Ambient conditions</b>	temperature range: 4-40 °C; 39.2-104 °F; below 90 % humidity (non-condensing)	temperature range: 4-40 °C; 39.2-104 °F; below 90 % humidity (non-condensing)
<b>Dimensions (W x H x D)</b>	361 x 501 x 603 mm	900 x 915 x 700 mm
<b>Net weight (approx.)</b>	35 kg	150 kg
<b>API-predilution and quenching</b>	only quenching	Yes
<b>Customized technical documentation, order-and article-related</b>	on request	Yes
<b>Factory acceptance test</b>	on request	Yes
<b>Site acceptance test</b>	on request	Yes
<b>Purchase order lead time</b>	about 3 months	about 4 months

\*design of the skid on customer requirements \*\*different connections on request \*\*\*depends on specific pump configuration and application

	IJM DuoCore NanoProducer	Customized NanoProducers
		
<b>Number of impingement jets mixers</b>	2	up to 8
<b>Number of pumps</b>	8	up to 16
<b>Number of flow meters</b>	8	up to 16
<b>Number of valves</b>	2	-
<b>Process connection inlet**</b>	1/2" Tri-clamp (6 inlets)	Sanitary Clamp Connector (2 inlets)
<b>Process connection outlet**</b>	1/2" Tri-clamp (2 outlets)	Sanitary Clamp Connector (1 outlet)
<b>Volumetric flow rate</b>	up to 2 l/min	depending on configuration
<b>Volumetric flow rate</b>	up to 120 l/h	depending on configuration
<b>Maximum operating pressure***</b>	95 bar (1378 psi)	50-70 bar (725-1015 psi)
<b>Liquid temperature range</b>	4-60 °C (39.2-140 °F)	4-60 °C (39.2-140 °F)
<b>Wetted materials</b>	stainless steel, PEEK, titanium, FFKM, PTFE (GFP 55), aluminum oxide, ruby, sapphire, EPDM, zirconium oxide, POM, hastelloy	stainless steel, PEEK, titanium, FFKM, PTFE (GFP 55), aluminum oxide, ruby, sapphire, EPDM, zirconium oxide, POM, hastelloy
<b>Software</b>	CDS, 21 CFR part 11 and GAMP 5 compliant	CDS, 21 CFR part 11 and GAMP 5 compliant
<b>Interfaces</b>	pump: LAN, RS-232, pin header connectors; flow meter: RS-232 + FLOW-BUS™; valve drive: LAN	pump: LAN, RS-232, pin header connectors; flow meter: RS-232 + FLOW-BUS™
<b>Power supply</b>	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; PC: 100-240 VAC single phase, 50/60 Hz; monitor: 100-240 VAC single phase, 50/60 Hz; network switch: 100-240 VAC single phase, 50/60 Hz, 12 V DC Power supply	pump: 100-240 VAC single phase, 50/60 Hz; flow meter: 115/230 VAC single phase; depending on configuration
<b>Power consumption (per device)</b>	pump: maximum 320 W; flow meter: 3 W; PC: 1000 W; monitor: 380 W; network switch: 50 W	pump: maximum 320 W; flow meter: 3 W; PC: 1000 W; monitor: 380 W; network switch: 50 W
<b>Ambient conditions</b>	temperature range: 4-40 °C; 39.2-104 °F; below 90 % humidity (non-condensing)	temperature range: 4-40 °C; 39.2-104 °F; below 90 % humidity (non-condensing)
<b>Dimensions (W x H x D)</b>	1000 x 1290 x 700 mm	depending on configuration
<b>Net weight (approx.)</b>	250 kg	depending on configuration
<b>API-predilution and quenching</b>	Yes	depending on configuration
<b>Customized technical documentation, order-and article-related</b>	Yes	Yes
<b>Factory acceptance test</b>	Yes	Yes
<b>Site acceptance test</b>	Yes	Yes
<b>Purchase order lead time</b>	about 3 months	minimum 6 months, depending on customer requirements

Depending on the process the end user must consider the legal situation of patents and intellectual property. KNAUER is designing the customized hardware solution on customer's request, process and chemistry are not included. Technical information are subject to change.

KNAUER is the proud winner of the German Innovation Award 2022 in the category of medium-sized businesses.

**(U)HPLC • FPLC • SMB • Osmometry and units for the production of lipid nanoparticles (LNP)**



**Innovation**

Own hardware and software development



**Customized solutions**

Pumps, detectors, valves and systems adapted to your needs



**Made in Germany**

Independent and family-owned since 1962

think **LNP** | think **KNAUER**

**KNAUER Wissenschaftliche Geräte GmbH**

Hegauer Weg 38 • 14163 Berlin  
+49 30 809727-0 • +49 30 8015010 (Fax)  
info@knauer.net • www.knauer.net

