# Pharmaceutical Drug Carriers – Study by Neutrons, SAXS and DLS

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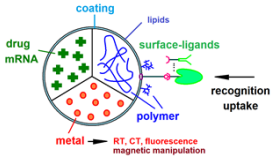
## Application simulation and structure investigation : DLS + SANS

- Specific target **Nanoparticles for therapy** of cancer and other diseases were assembled from lipids, polymers, and pharmaceutical drugs or mRNA. For cell targeting proteins were bound to the surface (corona). The structure in solution is analyzed by dynamic light scattering DLS and SAXS combined with neutron small angle scattering SANS, SAXS, metal specific X-ray scattering ASAXS. Material sub-domains in the nanoscaled drug carriers (~100 nm) were localized by **Deuterium-contrast variation in SANS** and by **ASAXS**. [7, 2-4] of nanoscaled drug carriers (liposomes, solid lipid particles, micelles, magnetic oxide, and polymer-protein particles).
- The power of D-contrast SANS is the **specific detection of material domains** with different hydrogen content, e.g. of **drug, mRNA, lipid, polymer, protein**.
- The **mixed nanoparticles** (100 nm), e.g. biodegradable polymer (PLGA, protein, carbohydrates), intestinal lipid-bile nanoparticles, lipid particles, surface-proteins and optional bio-target domain are ampiphilic and partly charged. Thus the internal particle structure forms **sub-domains of different material and scattering power**, enabling a localization by contrast. For several medical cases we construct and study pharma nanoparticles for parenteral and oral applications, which contain soluble or hydrophobic drugs, or nucleic acid drugs, e.g. **mRNA** for immunotherapy of cancer and vacination.

## Therapeutic Nanoparticles as Drug carriers:

**Mixed nanoparticles bearing material domains**




**Combination : DLS and SAXS and D-contrast Neutron scattering SANS**

## Pharmaceutical drug application:

**cancer therapy, vaccination**

### parenteral (injection) :

**study of formulations and interactions**

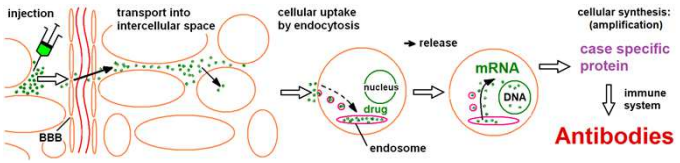
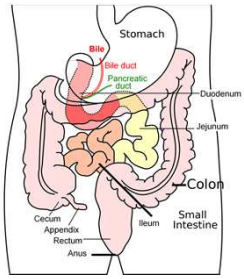


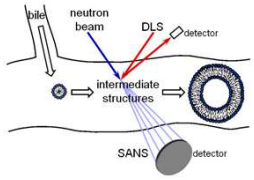

**Fig.1:Drug nanoparticles for parenteral application** (injection): The drug (pharma agent, mRNA) is entrapped in lipid, liposomes or polymer nanoparticles. After transfer to the relevant body region the particles are taken up into cells and release the drug, **if the structure is sufficient**. Structure and drug loading is investigated by D-contrast variation neutron small angle scattering SANS and DLS, structure details by high flux SAXS. In case of mRNA the active agent (protein) is formed by local bio-synthesis.

- **Parenteral nano-drug application** (injection): **mRNA nano-complexes for immune-vaccination and cancer therapy** [15-18] work by cellular synthesis of the corresponding case specific protein (not the antigen, but the genetic information for it is supplied). The cells and immune system of the patient work as biological drug amplifier.
- mRNA and synthetic pharmaceutical drugs can be applied in mixed nanoparticles bearing a molecular organization (domains of drug, excipients, carrier, surface ligands). Two classes cover the main drug nanoparticle forms: polymer-drug nanoparticles and liposome-lipid-drug nanoparticles. For therapeutic mRNA both classes were investigated by d-contrast SANS ant the FRM2 reactor of the MLZ (KWS2 instrument), by SAXS at the DESY PETRA III (P12 instrument) and projecting DLS (backscattering NIBS at 170°). At the MLZ, all samples were investigated by projecting DLS in the SANS cuvettes (1 mm Q), immediately after the neutron study. The SAXS investigation at high flux revealed highly resolved substructures, while the D-contrast SANS studies yielded differentiation and identification of domains.

### oral (tablet, capsule) : study in a simulator model (GI-Sim)




**MLZ-KWS2**
**ILL-D11**




**DLS:** large particles 0.1 - 300 µm
**SANS:** nano particles 10 - 200 nm

**for details: see contributions 239, 241**

**observation by time-resolved SANS + DLS**

- **Oral nano-drug application** (tablets, capsules) is tested with a simulator device of the gastro-intestinal tract with SANS+DLS observation of drug nanoparticles and intermediates. The structure optimized drug-carriers shall improve the application of **hydrophobic and difficult drugs** (BCS-classes 2-4), food-drug interaction problems and side effects. A specific development was the introduction of a **cholesterol**-containing medium **FASSIF-C**.
- At the MLZ (KWS2) and ILL (D11), all samples were investigated by **projecting DLS** (backscattering NIBS at 170°) in the SANS cuvettes (1 mm Q), immediately after the neutron study. The projecting DLS system contains two separate optical benches in a common carrier shining on the same focus, 120 mm in front of the device, with sufficient space for the SANS.
- **Time dependent processes** in the gastro-intestinal fluid system were studied by time resolved tr-(SANS+DLS) with a) stopped flow mixing and static sample (MLZ KWS2 and ILL D11); and b) with a constant flow through channel cuvette (200x12x1 mm Q) as position-time resolved xtr-SANS+DLS with a SM-drive (KWS2 at MLZ).

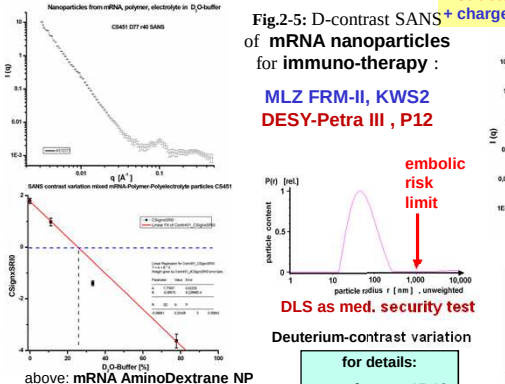
## mRNA-Nanoparticles for immuno-therapy : two forms

**mRNA polymer-nanoparticles:**

**mRNA** (protein/antibody coding)
**+ structure polymer excipient**
**+ charged poly-electrolyte**

**mRNA lipid-layer nanoparticles:**

**mRNA** (protein/antibody coding)
**+ structure lipid excipient**
**+ charged lipid exipient**




above: **mRNA AminoDextrane NP**

**Fig.2-5:** D-contrast SANS of **mRNA nanoparticles** for **immuno-therapy** :

**MLZ FRM-II, KWS2**
**DESY-Petra III , P12**

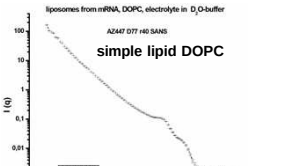



**embolic risk limit**

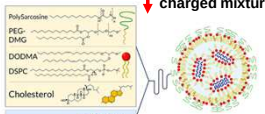
**DLS as med. security test**

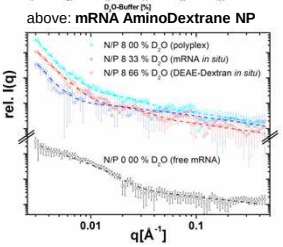
**Deuterium-contrast variation**

**for details: see reference 15-18**

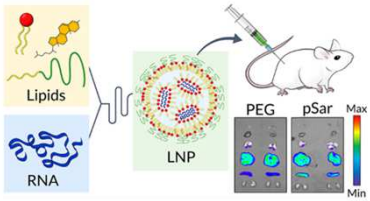



**improved lipid charged mixture**

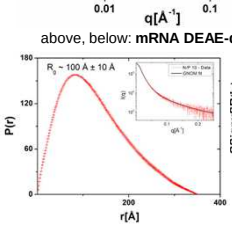


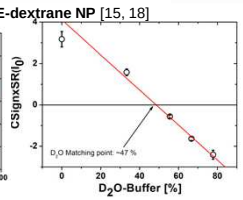




above, below: **mRNA DEAE-dextrane NP** [15, 18]




above: **mRNA charged lipid-NP** [16,17]




**mRNA immuno Nanoparticles:**

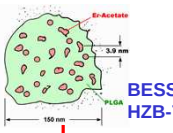
**Medical use for :**
a) vaccination, e.g. Covid-19
b) cancer immuno therapy

**Structure based development :**
variant coding for luciferase
SANS, SAXS, DLS, animal tests

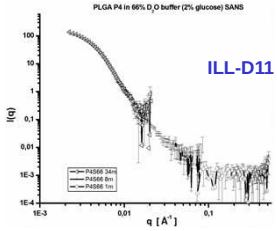
## Targeting drug excipients for nanotherapy

- **Tissue and cell targeting:** Intestinal, cell or tumor recognition and uptake of the drug carriers can triggered by a surface protein or ligand head (see method sub-page targeting).

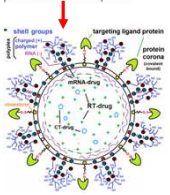
**polymer PLGA-cholesterol-lipid particles for parenteral, oral, pulmonary and radio- therapy**




**BESSY-HZB-7T**




**ILL-D11**

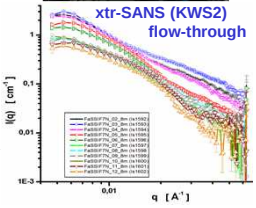



Polymer nanoparticles as drug carriers: **PLGA** w/o/w **foam NP,** 150nm size result: the PLGA polymer in w/o/w double emulsion NP resembles proteins

**Fig.6:** Therapeutic polymer nanoparticle for parenteral and oral therapy are inverstigated by SANS + DLS). For tissue and cell targeting they can be coated by a specific protein shell (cell recognition).

**FRM-II-KWS2 and ILL-D11**

**xtr-SANS (KWS2) flow-through**

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