Nano-structure Development of Oral Pharmaceutical Formulations in Simulated Intestine – D-contrast SANS and DLS

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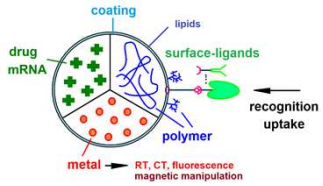
Therapeutic Nanoparticles as Drug carriers:

Mixed nanoparticles bearing material domains



Combination : DLS and SAXS and D-contrast Neutron scattering 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.

Pharmaceutical drug application:

therapy, cancer

parenteral (injection) :

study of formulations and interactions

for details: see contribution 238

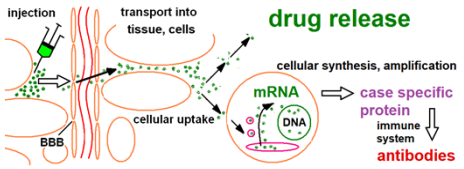
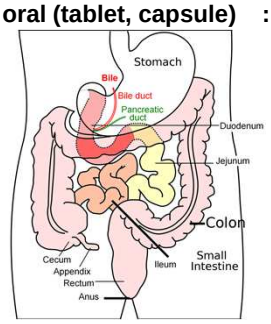


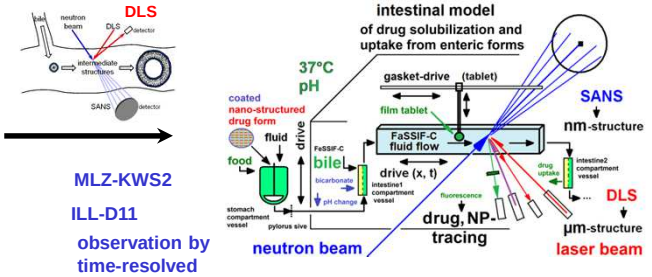
Fig.1:Drug nanoparticles for parenteral application (injection): The drug (pharma agent, mRNA) in lipid, liposomes or polymer nanoparticles release the drug, **if the structure is sufficient**.

oral (tablet, capsule) :



study in a Gastro-Intestinal simulator model (GI Sim)

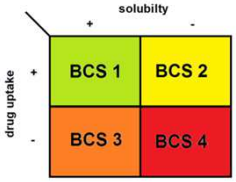
for details: see contribution 241



DLS: large particles 0.1 - 100 µm

- **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, i.e. stepwise solid drug form **disintegration and dissolution**, 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 (200x12x1mm) as position-time resolved **xtr-SANS+DLS** with a SM-drive (KWS2)

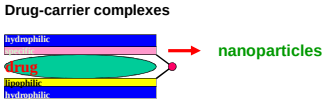
Application simulation and structure investigation : DLS + SANS



Deuterium-contrast variation:

The pharmaceutical components differ in the hydrogen content and can be thus distinguished by SANS, Deuterium-matching:

Lipids, RNA, protein, PLGA polymer, drug



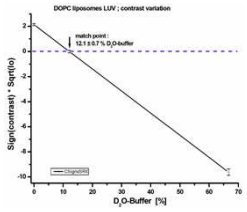
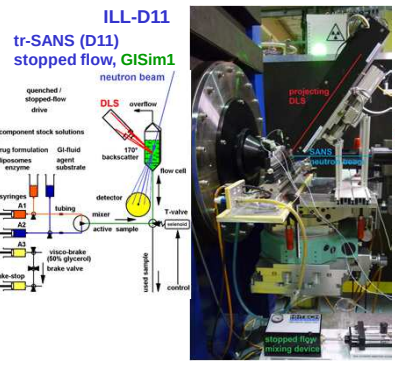
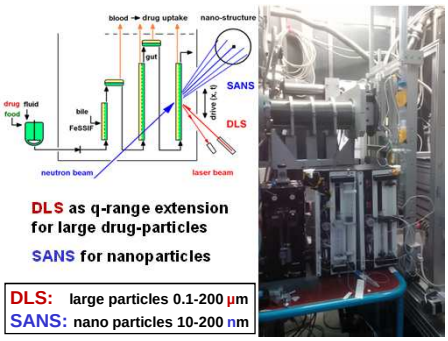


Fig.2-7: SANS of **drug-nanoparticles** for **oral therapy** by deuterium-contrast variation



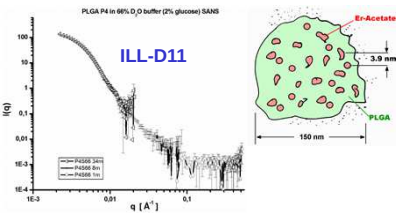


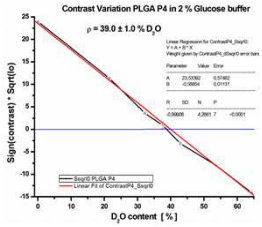
DLS as q-range extension for large drug-particles

SANS for nanoparticles

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

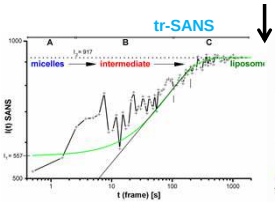
PLGA polymer particles for oral, parenteral and radio- therapy

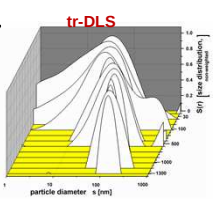


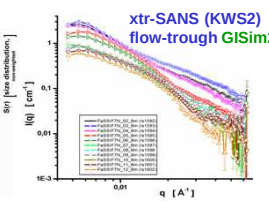


Polymer nanoparticles as drug carriers: **PLGA** w/o/w **double suspension NP,** 150nm resemble proteins (42%)

Fig.16-20: Therapeutic polymer nanoparticle for parenteral and oral therapy are inverstigated by SANS + DLS). For tissue and cell targeting the can be coated by a specific protein shell (cell recognition).

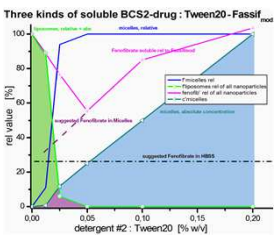






Results:
1) novel **Cholesterol-containing intestinal model fluid „**FaSSIF-C" [13] : 7%C ↔ female, 10%C ↔ male humans;
2) **Cholesterol-Lipid drug formulations** of BCS2/4-drugs and their nano-solution structure - dynamics in GI-fluids;

studied drugs: Fenofibrate, Amphotericidin B, Danazol, Carbamazepine, Griseofulvin, Paracetamol, Gemcitabine, Curcumin
in nano-forms: drug-lipid-cholesterol-NP, drug-PLGA-nanoparticles, drug solid-lipid particles (SLP), liposomes, micelles

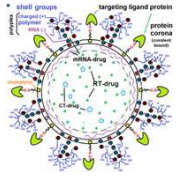


GI model	stomach	intestine	technology	drug form development
GiSim 1	mixing, stiring	vessel, cuvette	Stopped flow, fast mixing	Solid to disintegration and dissolution, nanoparticles, time
GISim 2	mixing, stiring	Flow through closed channel	Continuous flow, syringe pumps	Solid to dissolution to nanoparticles, localized
GISim 3	stiring, pH-sift, pressure	flow through series of vessels	GI-Batch flow, peristaltic pumps for micro-particles	Stepwise tablet (solid) **nano-disintegration** and dissolution to nanoparticles
GISim 4	stiring, pH-sift, pressure	Flow through series of vessels	GI-Batch flow, spiral pumps for large particles	Stepwise **coated tablet** disintegration to **µm particles**, later intestine dissolution to NP
GISim 5	stiring, pH-sift, pressure	Flow through open channel, then vessels	GI-Batch flow, spiral pumps, solid form transfer	**Enteric coated tablet** (solid) disintegration in intestine, dissolution to nanoparticles

Fig.8-15: Therapeutic nanoparticle test and structure investigation by a combination of time resolved neutron scattering and dynamic light scattering (tr-SANS + DLS) .

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 on targeting).
- The surface **protein coating** was attached to semi-synthetic lipid (cholesterol) and polymer (PLA) by sulfur-bridges (amido-**S-S**).



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