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# Drug-Lipid Structure Development upon Oral Drug Delivery in simulated Intestine - Time resolved SANS and DLS

The active substance resolution in oral application of badly soluble drugs of the BCS classes 2 and 4 depends on the drug interaction with micelles and liposomes formed from bile and pharmaceutical formulation in the duodenum part of the small intestine. During the passage of the second duodenum half, i.e. after bile influx, the native and drug lipid nanoparticles depict a sequence of structure conversions from 1 nm micelles to 100 nm liposomes, additionally to cholesteric phase particles of some 10 µm size. The success of the pharmaceutical product depends on the kinetic and structural interaction with the different lipid phases, forming the uptake-competent drug-excipient complex.

At ILL-D11 we have developed a method of time resolved estimation of those wide size spectrum particle samples by parallel application of SANS and DLS, both with time resolution of the suspensions in a model system (Gastro-Intestinal Simulator GISim). The dynamic sample, which represents the fluid in the second half of the Duodenum after influx of bile, was produced by rapid mixing of pre-diluted bile ("FeSSIF") with drug-lipid suspension in buffer solution (transfer medium TM), forming the late intestinal fluid "FaSSIF" with a stopped-flow device (HiTech Scientific UK). The sample is injected into a flow-through SANS cuvette (2 mm). A trigger signal starts the SANS detection film at D11, and the estimation of the DLS sequence film by a controller. The SANS and DLS beams meet at the same point of the flow cell. The SANS operates in transmission (foreward scattering. 0-30°), but the DLS in backscattering mode (173°, non invasive back scattering "NIBS" from the front 100 µm sample layer) using a dual beam projecting DLS device (ProSpecD, Nanovel).

By the novel method intermediates during the structural transition of the intestinal fluid upon addition of pharmaceutical solution were detected. The particle size scale was extended by the method combination to 1nm – 100µm in parallel, in this case of micelles, liposomes and cholesteric particles. The method is used for the study of pharmaceutical nanoparticles.

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