1 **Introduction: Nanoparticles in medicine**

1.1 Polymeric colloids

1.1.1 Functionalization for protein binding

1.1.2 Polymerization consequences (initiator, co-monomer, surfactants...)

1.2 Liposomal nanocarriers (formation for amphiphilic lipids)

1.2.1 phospholipid bilayer (typical molecules HSPC, DPPC, cholesterol, PEG...)

1.2.2 polydispersity control (extrusion, paper w/ Zoltan)

1.2.3 Drug carrier, SSLs (stealth function, bilayer stabiliy, filling)

1.3 Physicochemical characterization

1.3.1 Dimensional metrology and traceability

1.3.2 Characterization tools

1.3.2.1 Single-particle (AFM, TEM, SEM, TSEM...)

1.3.2.2 Ensemble (DLS, DCS, SAXS)

2 **Theoretical Background**

2.1 Interaction of light and matter

2.2 Small Angle X-ray Scattering (SAXS)

2.2.1 Physical Process

2.2.2 Evaluation of the scattering intensity (Form factor * S(q) , electron density, number of colloids)

2.2.2.1 What is q?

2.2.2.2 Modelling

2.2.2.2.1 Sphere (Gudrun polymeric colloids)

2.2.2.2.2 Core-shell (interface effects???)

2.2.2.2.3 Vesicle model (5 gaussian) ????

2.2.2.2.4 Inclusion of background ??? (a+b*q^-4)

2.2.2.3 Guinier approach (deviation when using few points, polydispersity...)

2.2.3 Contrast variation (solvent variation, ASAXS...)

2.2.3.1 Isoscattering point

2.2.3.1.1 Polydispersity and elipticity smearing (simulation, calculation)

2.2.3.2 Basic functions approach

2.2.3.2.1 Shape factor

2.2.3.2.2 Guinier rule

2.2.3.2.3 I (0) for polydisperse systems

3 **Experimental setup**

3.1 BESSY II

3.2 FCM Beamline

3.2.1 Transmission measurements (calibrated diodes)

3.3 SAXS

3.3.1 Pilatus detector (high dynamic range, noise free...)

3.3.2 HZB SAXS setup

3.3.2.1 distance calibration (10^-4 uncertainty)

3.3.3 Radial integration and error propagation

3.3.4 Absolute intensity calibration

3.3.4.1 Flux monitor (thin diode)

3.3.4.2 Detector efficiency (pilatus, thin diode)

3.4 Continuous contrast variation

3.4.1 Filling of capillaries (galden at bottom, reference layer)

3.4.1.1 Capillary homogeneity (Hilgenberg)

3.4.2 Calibration of solvent density and finding of main axis

3.4.3 Limitations

3.4.3.1 Density range (sucrose, fructose, iodixanol)

3.4.3.2 Background, induced aggregation (heavy salts)

3.4.3.3 Comparison to SANS / RSoXS in polymeric Nps (H. Abe, 2006)

4 Contrast variation in SAXS with the density gradient technique (1st paper)

4.1 Materials and methods

4.1.1 Particle and chemicals

4.1.2 Diffusion time and calibration height (sucrose mass fraction formula)

4.2 Continuous contrast variation in SAXS on PS-PMMA nanoparticles

4.3 Model dependent evaluation

4.3.1 Core-shell form factor fit

4.4 Model-free approach to contrast variation data

4.4.1 Isoscattering point

4.4.1.1 Relative standard uncertainty

4.4.2 Guinier Region analysis

4.4.2.1 Average electron density

4.5 Summary

5 Simultaneous size and density determination of polymeric colloids (2nd paper)

5.1 Materials and methods

5.1.1 Particle and chemicals

5.1.2 Differential Centrifuge Sedimentation (DCS)

5.2 Technique validation for the determination of the particle size distribition

5.2.1 Inter-laboratory comparison of the mean particle size
5.2.2 Colloidal size distribution
5.3 Considerations about contrast variation data evaluation
5.3.1 Shape factor formalism (simulation, depending on number of curves)
5.3.1.1 Advantages / disadvantages
5.3.2 Isoscattering point formalism (simulation, dependent of many things)
5.3.2.1 Advantages / disadvantages
5.4 Determination of the particle physical density
5.4.1 Validation through comparison with DCS
5.4.1.1 Uncertanties (physical density inaccuracy, beam size)
5.4.2 Use for homogenous polymeric colloids (PMMA-COOH)
5.5 Summary
6 Continuous contrast variation applied to relevant relevant bio-materials (3rd paper)
6.1 Materials and methods
6.1.1 Caelyx: PEGylated liposomal doxorubicin
6.1.2 Iso-osmolar contrast agent: Iodixanol
6.1.3 Sterically Stabilized Liposomes (SSLs) of different sizes
6.1.4 Lipoproteins (HDL&LDL)
6.2 Traceable size determination of a liposomal drug
6.2.1 Isoscattering point approach
6.2.2 Shape factor calculation
6.3 Osmotic effects in liposomes
6.3.1 Application to drug-stabilized liposomes
6.3.2 Size dependency of the osmotic activity
6.4 Application to blood plasma components
6.4.1 HDL
6.4.2 LDL
6.4.3 Literature comparison
6.5 Protein-coated low-density nano-particles
6.5.1 Single-SAXS experiments (C. Minelli Paper)
6.5.2 Contrast variation (Isopoint subtraction)
6.6 Summary