1. **The control of size and morphology in the preparation of catalytic particles for Ziegler-Natta olefin polymerization**

**Project objective**

Develop a method for the preparation of catalytic particles of defined size for the large scale polyethylene production. Special focus will be on the evaluation of very high shear rates on the particle size and particle size distribution and what implications it has for an integrated precipitation process.

![Fig 1.1: Integrated precipitation and high pressure homogenizer.](image1.png)

**Fig 1.1: Integrated precipitation and high pressure homogenizer.**

**Project description**

This project aims at gaining knowledge about how an industrially relevant heterogeneous Ziegler-Natta catalyst particle forms. The focus is put on the evolution of the size of the particles during their synthesis by reactive precipitation. The fundamental knowledge gained will then be used in order to devise a process enabling to control the final size of the catalyst and to minimize the width of the size distribution. Such a process will then be put into comparison with the standard precipitation method prevailing in industry. The project is carried out in collaboration with SABIC (Geleen, NL).

![Fig 1.2: Particle size distribution measured by SASLS (Mie-fit).](image2.png)

**Fig 1.2: Particle size distribution measured by SASLS (Mie-fit).**

**Work description**

80% experimental, 20% computational

**Contact person**

Antoine Klaue, antoine.klaue@chem.ethz.ch, +41 44 633 63 87, HCI F130
2. **Investigation of the polymerization kinetics of ionizable monomers**

**Project objective**

Ionizable monomers are widely used to synthesize polyelectrolytes: they are very interesting materials which find application in a large variety of fields, from waste water treatment and paper-making industry to the manufacturing of cosmetics and pharmaceuticals. The presence of ionized groups in the polymer determines the peculiar solution and surface properties of these materials. On the other hand, predicting the polymerization behavior of ionizable monomers is a challenging task due to the effect of the electrostatic interactions between the charges on the reaction kinetics.

![Graph showing polymerization kinetics](image)

**Project description**

The master thesis project is aimed at the investigation of the free-radical polymerization and copolymerization of systems with ionizable monomers, such as acrylic / methacrylic acid and ammonium salts. The kinetic study is carried by both experimental analysis, through the implementation of the novel in-situ NMR technique, and by the development of advanced models of polymerization accounting for the electrostatic effect on the reaction rate parameters.

**Work description**

60% experimental, 40% computational

**Contact person**

Dr. Danilo Cuccato, danilo.cuccato@chem.ethz.ch, +41 44 633 10 83, HCI F137
3. HPMA-based materials for protein delivery and cell encapsulation

Project objective

Polymers find many applications in the biomedical field due to the possibility to easy control their properties both at the macro- and nano-scale. In this light, there is a big request of biocompatible materials that can offer both biocompatibility and reproducible behavior compared to the system nowadays used (e.g. collagen). The aim of the project is to exploit the possibility offered by the FDA approved poly(HPMA), a water soluble, non immunogenic and biocompatible polymer, which, can be easily functionalized pre- and post-polymerization even leading to complexes 3D structures.

Fig 3.1: Scheme of HPMA activation for the production of lipophilic nanoparticles.

Project description

Two different applications will be investigated in the project, from one side, it will be explored the possibility to produce HPMA-based nanoparticles, with tunable properties as size, surface charge and lipophilicity/hydrophilicity balance. This polymeric dispersion will be destabilized to obtain a yogurt-like material for the controlled protein delivery. From the other side, polymer chains will be produced through solvent polymerization and then functionalized to obtain a 3D hydrogel upon cross-link formation. The adoption of the polymer as environment for the cell growth should first ensure the reproducibility of the cell growth and proliferation. To get this achievement a well-controlled polymer synthesis is required and, in addition, the gelation process should happen in mild condition thus ensuring cell encapsulation and proliferation.

The project mainly focuses in the production of materials for drug delivery applications by using techniques related to polymer synthesis (emulsion polymerization, ring opening polymerization, chemical modification, controlled aggregation) and characterization (DLS, NMR, SEC, MALDI).

Work description

100% experimental, 0% computational

Contact person

Dr. Raffaele Ferrari, raffaele.ferrari@chem.ethz.ch, +41 44 632 30 29, HCI F135
4. **Role of polysaccharides as stabilizer/grafting agent during emulsion polymerization**

**Project objective**

The project covers the investigation of the detailed reaction mechanism and kinetics of polymerization processes in the presence of polysaccharides as a low cost, renewable alternative to the ionic stabilizers.

![Possible grafting reaction pathway](Image)

*Fig 4.1: Picture of the possible grafting reaction pathway occurring during emulsion polymerization in the presence of polysaccharides.*

**Project description**

As a first step, the project aims to elucidate the adsorption mechanism of the polysaccharide on the polymer particles. Evidences in the literatures shows also the possible grafting of the polysaccharides to the polymer chains leading to a system with an increased steric stabilization. However, the presence and the impact of this process over the polymerization reaction are still unclear. Then, the same approach adopted to evaluate the polysaccharide adsorption will be exploited to evaluate the impact of the grafting in the case of particles produced in the presence of polysaccharide. Specific experiments will be also performed to general reactivity of the polysaccharides. And aimed to quantify the tendency of the polysaccharides to degrade as well as to form branches, reactions that could take place during the emulsion polymerization. The project mainly focuses in the area of polymer reaction engineering covering different aspects (emulsion polymerization, adsorption, chemical modification) and various characterization techniques (UV, DLS, NMR, SEC, MALDI).

**Work description**

100% experimental, 0% computational

**Contact person**

Dr. Raffaele Ferrari, raffaele.ferrari@chem.ethz.ch, +41 44 632 30 29, HCI F135
5. **Ring-opening Polymerization for 100% “green” renewable resource-based PEF as a substitute for PET**

**Project objective**

Development of a novel synthesis route to produce bio-based polymers suitable as PET-substitutes.

**Project Description**

Limited fossil resources on the planet and environmental pollution require new and more sustainable solutions to replace existing fossil resource-based materials, one of which is polyethylene terephthalate (PET). Polyethylene Furanoate (PEF) has been named a “top-chemical from biomass” by the US-Department of Energy, and can substitute PET as it is 100% renewable resource-based and possesses even superior properties to PET. Due to increased consumer and political interest, as well as the large CO₂ reduction potential by a large existing PET market of >60M tons/year, this field of research is a current hot-topic for the chemical industry. While all recent efforts were focused on synthesis via polycondensation that is burdened with by-product removal and long reaction times (days), we are exploring a novel route via ring-opening polymerization that offers fast reaction times (minutes) without byproduct removal necessary.

Thus far, we have established different synthesis routes to produce the cyclic monomers and convert them to the final PEF polymer. We have shown that the synthesis of PEF with sufficiently high molecular weight for bottle applications is feasible, and that the thermal properties of the ring-opening polymerization based product are indeed favorable over the ones of PET.

**Work Description**

This master thesis project will focus on either part of 1) the experimental optimization of cyclic monomer synthesis with potential “green” solvents, investigation of selective precipitation behavior and kinetic studies for modelling, as well as 2) synthesis of high molecular weight PEF from the produced cyclic species of different size, kinetic studies and modelling of the latter, optimization of reaction conditions for high yields, and finally the testing of PEF material properties such as strength, oxygen and CO₂ barrier, opacity etc. We are working in a productive and highly motivated team of 2 PhD students and usually 2-4 master and research project students, supervised by Prof. Storti during weekly progress meetings.

**Contact person**

Jan-Georg Rosenboom, jan-georg.rosenboom@chem.ethz.ch, +41 44 632 61 23, HCI F136
6. **Design of aggregation processes of binary colloids towards the preparation of nanocomposite materials**

**Project objective**

Nanocomposite materials find large applications in various fields such as biomedicine, drug delivery, photovoltaic industry and enhanced membranes and are considered to be very promising in many other sectors. In this direction, there is an increasing interest in the scientific community towards the incorporation of nanoparticles into polymer matrices. To guarantee the achievement of optimal performance, a precise and homogeneous distribution of nanoparticles into the framework is required, while their aggregation has to be limited (Fig 6.1). For many specific applications, on the other hand, the formation of a continuous network of interconnected nanoparticles within the polymer matrix is highly desirable, thus leading to a bi-continuous system (Fig 6.2).

![Fig 6.1 Homogenous distribution of Nanoparticles.](image1)

![Fig 6.2 Continuous network of interconnected nanoparticles.](image2)

**Project Description**

This project aims at designing effective macro-scale nanocomposite materials through a controlled aggregation of a colloidal dispersion of polymer and organic/inorganic nanoparticles. Depending on the desired final architecture of the nanofillers (homogeneously dispersed or interconnected), different aggregation strategies will be thoroughly studied to produce innovative, functional nanocomposite materials. Moreover, investigation of the active role of the nanoparticles together with the optimisation of their composition, size and amount in the polymer matrix is object of this study. The master thesis will mainly involve experimental work, including the use of analytical techniques such as static and dynamic light scattering, SEM and TEM as well as rheology.

**Work description**

100% experimental, 0% computational

**Contact person**

Stefano Caimi, stefano.caimi@chem.ethz.ch, +41 44 633 32 59, HCI F138
7. Noble metals incorporation on microporous nitrogen-doped carbon material for catalysis

Project objective

Development of a protocol for the incorporation of noble metals during the synthesis of polyacrylonitrile nanoparticles. In addition, the control of the reduction in the polymer matrix to achieve a stable single-site metal.

Project Description

The scope of the project is the production of polymeric support for catalysis aiming an industrial application. This requires a well-defined pore size distribution: on one side macropores to ensure good path across the material and on the other side micropores to permit the access to the active sites.

Polyacrylonitrile is a well-known semi-crystalline polymer synthetized by free radical polymerization of acrylonitrile, which is our nitrogen precursor and the bonding site for noble metals. Via emulsion polymerization, we are able to produce non-porous nanoparticles in a range of 100-200 nm in diameter. When polymerizing the acrylonitrile with the salt of the metal, it will be trapped inside the polymeric matrix of the nanoparticle and will become difficult to reduce in liquid phase. The polyacrylonitrile is then pyrolyzed (N₂-atmosphere) on one hand to reduce the metal and on the other hand to create microporosity, which will permit the access of the adsorbate towards the active sites. The following catalyzed reaction will take advantage of the high porosity of the pyrolyzed polymer (high mechanical and thermal resistance) and the high loading as single-site metal.

Work description

100% experimental, 0% computational

Please be aware that the lecture “Polymer Reaction & Colloid Engineering” given by Prof. Morbidelli is highly recommended in order to be familiar with colloidal science.

Contact person

Anna Beltzung, anna.beltzung@chem.ethz.ch, +41 44 632 56 88, HCI F130
8. **Kinetic study of the digestion and purification of an antibody on columns**

**Project objective**

In this project, antibody fragments should be generated by a process which directly yields purified product. Among other uses, antibody fragments are used as therapeutics and diagnostic reagents. Fragments can be generated by digestion with a wide variety of digestion agents.

**Project description**

In this study, papain will be used to cleave a monoclonal antibody in three fragments, namely two Fab fragments and one Fc fragment. The papain is immobilized on an agarose resin packed in a chromatographic column. The reaction will be studied experimentally and by modelling. Subsequent to the papain column, two different columns are installed. The products of the reaction are directly purified and captured with these columns. The operating parameters of these two columns will be designed. The final goal is to have a system running on optimal conditions for the digestion of monoclonal antibodies and capturing of fragments.

![Flow sheet of the digestion and purification process.](image)

**Work description**

70% experimental, 30% computational

**Contact person**

Nicole Ulmer, nicole.ulmer@chem.ethz.ch, +41 44 633 45 38, HCI F126
9. **Dynamic metabolic modeling in mammalian cell perfusion culture**

**Project objective**

Driven by the availability of new technologies, continuous mammalian cell culture regained tremendous interest in the biopharmaceutical industry for the production of therapeutic proteins, such as monoclonal antibodies (mAbs). The application of mathematical modelling drives the further understanding of intracellular processes such as metabolism and N-linked glycosylation.

**Project description**

The goal of this project is the understanding of mammalian cell dynamics in continuous perfusion processes. The master thesis project focuses on mathematical modelling in combination with state-of-the-art analytical technologies. By combining metabolic and mAb glycosylation modeling, the dynamic regulation of cell metabolism and glycosylation as well as their interplay will be investigated.

![Flow sheet of the integrated experimental and modeling process.](image)

**Work description**

20% experimental, 80% computational

**Contact person**

Daniel Karst, daniel.karst@chem.ethz.ch, +41 446334642, HCI F133 (Morbidelli-group)
Sandro Hutter, sandro.hutter@chem.ethz.ch, +41 446330659, HCI F104 (Gunawan-group)
10. Applying Omics technologies for industrial continuous manufacturing of biopharmaceuticals

Project objective

- Combining engineering expertise for technical understanding, bioinformatics for data mining and database usage as well as biotechnology to gain insights into cellular mechanisms
- Characterizing biopharmaceutical production processes by transcriptome and proteome analysis – Compare fed-batch and continuous steady state mammalian cell processes

![Schematic overview of the omics application to industrial cell culture processes.](image)

Fig 10.1: Schematic overview of the omics application to industrial cell culture processes.

Project description

Steady state verification in terms of process performance and quality attributes on the molecular level is the next step for long time consistency and consequently building quality into the process. Further, the project will not only focus on the process consistency of continuous manufacturing but also highlight the differences between fed-batch and perfusion. As model process an industrial CHO cell line producing a monoclonal antibody (mAb) was chosen. The comparison of the intracellular mechanisms is done by the analysis of the proteome time profile. Further transcriptomics will be performed in order to investigate the time evolution of the mRNA abundance and compare the transcribed genes to the expression of the corresponding proteins. To capture existing correlation or discrepancies between transcribed mRNA and the expressed protein bioinformatics analysis will be applied for data mining and database handling. In particular profiling of the produced mAb and the corresponding quality attributes will be discussed in detail as productivity and quality are the most important process parameters of biopharmaceutical manufacturing.

Work description

0% experimental, 100% computational

Contact person

Vania Bertrand, vania.bertrand@chem.ethz.ch, +41 44 633 45 13, HCI F135
11. Hybrid models for protein aggregation during formulation of biopharmaceuticals

Project objective

Therapeutic proteins are increasingly used for the treatment of autoimmune diseases, diabetes and cancer. Proteins are affected by aggregation, which is arguably the most common and impeding manifestation of protein instability, encountered in almost all stages of protein drug development including formulation.

Project description

As protein aggregates may affect drug efficacy and trigger undesirable immunogenicity it is important to ensure satisfactory product quality during production and long-term storage. In the final formulation step a preparation of the drug is developed which ensures both, stability for storage and acceptability for the patient. There is still a gap in the process understanding to meet the complex requirements for formulation in industry. The goal of this thesis shall be to combine well-understood first principle mechanisms with flexible statistical approaches to build an overall hybrid model for product quality in formulation based on the dynamic effect of selected process parameters. Motivated from collaboration work with an industrial partner, the results of this project will be of great interest for academia and industry, and shall provide an important basis to reduce the experimental effort.

![Hybrid Model Diagram](image)

*Fig 11.1: Hybrid model approach for protein aggregation during formulation of biopharmaceuticals.*

Work description

0% experimental, 100% computational

Contact person

Michael Sokolov, michael.sokolov@chem.ethz.ch, +41 44 633 77 56, HCI F135
12. Development of a scaling-up platform for the ex-vivo expansion human stem cells spheroids

Project objective

- Achieve a robust expansion of human stem cells as suspended aggregates
- Screening of different culture conditions to promote proliferation/differentiation

Project description

Many cell therapies and tissue engineering applications require large numbers ($10^9$-$10^{10}$) of stem cells, which are commonly not achieved by means of biopsies on patients. For successful clinical applications it is therefore required to develop first robust and scalable expansion strategies. The use of multicellular spheroids has been shown to better mimic the microenvironment in which cells reside physiologically, and allows the cultivation of adherent cells in suspension system, such as stirred tank bioreactors. The project aims to overcome the limitations in scalability offered by static monolayer cultivations by expanding human stem cells as aggregates in suspended systems.

![Fig 12.1: Schematic description of the project.](image)

Work description

100% experimental, 0% computational

Contact person

Ernesto Scibona, ernesto.scibona@chem.ethz.ch, +41 446334669, HCI F123
13. Synthesis of Monodisperse, Spherical Macro-Porous Particles for Separation Application

Project Objective

The major aim of this Master Thesis is to produce macro-porous materials in the form of particles with specific porosity and pore size distribution finding application in separation of proteins and other bio-derivatives.

Project Description

Currently these materials are synthesized through a combination of aggregation and breakup of primary polymeric particles in the presence of turbulent flow i.e. using a micro-fluidizer. In order to obtain mechanically stable materials, an additional reactive step is applied to “freeze” the aggregate structure, thus performing the so-called “reactive gelation”. Accordingly, before the aggregation step the primary particles are swollen with additional monomer and initiator and right after it a post-polymerization reaction is run. Obtained micro-particles have irregular shape with rather broad size distribution. Since porosity, micro-particle size and polydispersity of the distribution have strong effect on the final application, i.e. protein separation, other techniques have to be used. As it was experimentally demonstrated, generation of mono-disperse distribution of spherical micro-particles can be achieved applying microfluidic technique. Therefore, the goal of this Master Thesis is to explore the possibility of using microfluidic techniques to generate a reasonable amount of macro-porous micro-particles with regular spherical shape of various sizes and running controlled aggregation of polymer particles and reactive gelation in a small droplet.

Work Description

Since several phenomena are taking place during the synthesis of these macro-porous particles, few challenges have to be overcome during this project. It will be carried out in collaboration of two groups, i.e. Professor de Mello’s and Professor Morbidelli’s group. Potential candidate will be involved in the complete procedure of synthesis starting from preparation of primary polymer latex particles, measurement of its stability followed by the testing and modification of various microfluidic devices up to final characterization of the produced macro-porous micro-particles. The work will be therefore mainly experimental. The characterizations of such particles will be performed via light-scattering (SLS) optical and electron microscopy (SEM, TEM), BET analysis, Hg intrusion and inverse chromatography of tracers with different molecular size (iSEC).

Contact persons

Alberto Cingolani (alberto.cingolani@chem.ethz.ch) +41 44 632 31 13
Ioannis Lignos (ioannis.lignos@chem.ethz.ch) +41 44 633 43 14
Dr. Stavros Stavrakis (stavros.stavrakis@chem.ethz.ch) +41 632 33 39